AstraZeneca

Revised Clinical Study Protocol

Drug Substance	TC-5214
Study Code	D4130C00008
Edition Number	1
Date	[redacted]

An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

Sponsor: AstraZeneca [redacted]

AstraZeneca Research and Development site representative [redacted]

[redacted]

Date

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

[redacted]

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PROTOCOL SYNOPSIS

An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

Coordinating Principal Investigator

[redacted]

Study center(s) and number of subjects planned

The study will be a multi-center study conducted at up to 3 centers in the United States. Eight subjects in each category of mild, moderate renal impairment, end stage renal disease requiring dialysis, and 8 male or female subjects without renal impairment will be dosed for a total of approximately 32 evaluable subjects to complete the study.

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Phase 1
Estimated date of last subject completed	[redacted]	

Primary Objective

To assess the pharmacokinetics of a single dose of TC-5214 in subjects with renal impairment and to compare the results with those in subjects with normal renal function

Secondary Objective

- To assess the effect of hemodialysis on TC-5214 pharmacokinetics
- To assess the safety and tolerability of TC-5214 in subjects with renal impairment compared with those subjects with normal renal function

Exploratory Objectives

To collect samples for potential pharmacogenetic testing, which will allow future investigation of the influence of genotype on drug disposition and pharmacodynamic response

Study design

This is a Phase I single dose, multi-center, open-label study designed to evaluate the safety, tolerability and pharmacokinetics of TC-5214 in renally impaired subjects compared with subjects with normal renal function.

Based on an interim review of the safety and pharmacokinetics data, subjects with severe renal impairment (previous Group 4) will not be recruited for this study, and the study will be conducted in 2 parts.

Subjects will be enrolled into 1 of 4 groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate (eGFR), determined using the abbreviated, 4-variable Modification of Diet in Renal Disease formula as follows:

Group 1: control subjects with normal renal function: eGFR greater than 80 mL/min

Group 2: mild renal impairment: eGFR greater than or equal to 50 to 80 mL/min

Group 3: moderate renal impairment: eGFR greater than or equal to 30 to less than 50 mL/min

Group 5: end stage renal disease: eGFR less than 30 mL/min, currently receiving dialysis

Part 1, Groups 1 through 3:

Subjects in Groups 1 through 3 will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 4. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period. During Part 1, subjects in Groups 1 through 3 will have pharmacokinetic blood and urine samples collected through 72 hours postdose.

Part 1, Group 5:

The first 4 subjects enrolled into Group 5 will participate in 2 treatment periods, and receive a single oral dose of TC-5214 on each occasion. For Treatment Period 1 subjects will be admitted into the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will receive a single dose of TC-5214 on Day 1 after completion of a dialysis session and will remain in the

clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. Subjects who are unable to remain in the clinic during this time may have their samples collected as outpatients. Subjects will return to the clinic after a washout period of at least 2 weeks to start Treatment Period 2. Subjects will be admitted to the clinic the morning of Day -1 or on Day -2 at the discretion of the Investigator for Treatment Period 2. Time-matched vital signs will be collected on Day -1. Subjects in Treatment Period 2 will receive a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects will remain in the clinic until the start of their next dialysis session. Blood samples will be collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Safety assessments will be performed periodically throughout the treatment period. Dialysis fluid will be collected in 1-hour intervals. Subjects who are unable to remain in the clinic through the entire treatment period may have their samples collected as outpatients. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from Treatment Period 2. Subjects who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor.

Part 2, Groups 1 through 3:

Subjects in Groups 1 through 3 will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 6. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

During Part 2, subjects in Groups 1 through 3 will have blood and urine samples collected through 120 hours postdose.

Part 2, Group 5:

The remainder of subjects enrolled into Group 5 will participate in 1 treatment period, and receive a single oral dose of TC-5214. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 after completion of their first inpatient dialysis session, and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 6.

Pharmacokinetic blood samples will be collected after a single oral dose (Day 1) for up to 120 hours postdose. Samples will be collected through 72 hours postdose (assessment between dialysis) and between 72 and 120 hours (assessment during dialysis). Pharmacokinetic urine samples will be collected for up to 120 hours postdose from subjects who are able to produce urine.

Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects who withdraw from the study prior to completion of all pharmacokinetic sample collections may be replaced at the discretion of the Sponsor.

Target subject population

The target population will include male and female nonpregnant, nonlactating subjects with normal, and mild, moderate, and end stage renal impairment on dialysis, aged 18 to 80 years with a body mass index between 19 and 40 kg/m^2. The demographics of healthy subjects with normal renal function will be matched for age ± 10 years, and body mass index ± 3 kg/m^2, to the mean age and body mass index of subjects across the 3 renal impairment groups. Sex will be matched to achieve similar distribution between male and female subjects.

Investigational product, dosage and mode of administration

TC-5214 will be administered orally with 240 mL of water on Day 1. All subjects in Groups 1 and 2 will receive a single oral dose of 8 mg TC-5214 on 1 occasion. All subjects in Groups 3-4 will receive a single oral dose of 2 mg TC-5214 on 1 occasion. Subjects in Groups 5 will receive a single oral dose of 2 mg TC-5214 on 2 occasions separated by an at least 2 week washout period.

Duration of treatment

For Groups 1 through 3 the duration of each subject's participation will be approximately 47 days, including a screening period of up to 30 days, a treatment period consisting of 6 to 7 nights (depending on the admission day) and a follow-up visit, 7 to 10 days after discharge from the treatment period.

For the first 4 subjects in Group 5 (Part 1) participating in the 2-period portion of the study, duration of each subject's participation will be approximately 55 days. These subjects will be given the option to remain at the clinic between samplings for the off dialysis assessment (post dialysis dosing) at the discretion of the Investigator.

For the remaining subjects in Group 5 (Part 2) participating in a single treatment period, duration of each subject's participation will be approximately 47 days.

Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.

Outcome variable(s):

- Pharmacokinetic
  - Primary plasma pharmacokinetic parameters: AUC and C_{max},
  - Secondary plasma pharmacokinetic parameters: CL/F, $t_{1/2}$, t_{max}, and V_z/F in all subjects; Ae, CL_D, and fe in Groups 1 to 4; $A_{d(4-8)}$, Cl_R, and $fd_{(4-8)}$ in Group 5 during Period 2

- Safety

  Adverse events and serious adverse events including severity, vital signs, physical examinations, laboratory parameters, electrocardiograms, and the Columbia-Suicide Severity Rating Scale.

Statistical methods

Tabulations and listings of data for vital signs, physical examinations, clinical laboratory tests, and electrocardiograms will be presented. Results from the Columbia Suicide Severity Rating Scale will be presented separately in a listing only. For clinical laboratory tests, listings of values for each subject will be presented with abnormal or out-of-range values flagged (other than those associated with renal impairment and /or stable chronic condition). Plasma and urine concentration data and the derived pharmacokinetic parameters will be summarized by renal function group using descriptive statistics.

Regression models will be used to assess and quantify the relationship between renal function, as measured by the eGFR, and TC-5214 dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The initial model will specify a linear relationship between primary pharmacokinetic parameters and the eGFR, and will be estimated using ordinary least squares. Log-transformations may be used to improve model fit. Models which are non-linear in the model parameters will be used in the event that linear models do not yield an adequate fit. Model parameters, 90% CI and p-values will be reported. From the final models, estimates of the mean pharmacokinetic parameters and 90% CI will be made at the median eGFR of each of the renal function groups, as will the differences (or ratios) and 90% CI relative to the control subjects with normal renal function.

As an exploratory analysis, the renal function groups will be compared using a one-way analysis of variance model on the log-transformed dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The renal impairment groups will be compared to the control subjects with normal renal function (Group 1), with the latter as reference. Geometric least-squares means with corresponding 95% CI and ratios of geometric least squares with corresponding 90% CI will be presented. While this study is not statistically powered in terms of claiming no effect of renal impairment on TC-5214 exposure, interpretation of the effect of renal impairment will be based on point estimates and associated 90% confidence intervals.

Comparisons of pharmacokinetic parameters for subjects in Group 5 with endstage renal disease on a nondialysis day with those on a dialysis day will be performed using a paired t-test (C_{max} and AUC).

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
$Ad_{(4-8)}$	Cumulative amount of drug extracted unchanged into the dialysate over the dialysis period from 4 hours postdose to 8 hours postdose
AE	Adverse event (see definition in Section 6.3.1)
AUC	Area under plasma concentration time curve from zero to infinity
$AUC_{(0-t)}$	Area under plasma concentration time curve from zero to last quantifiable time point
$AUC_{(4-8)}$	Area under plasma concentration time curve from 4 to 8 hours postdose
%AUCex	Percentage of AUC obtained by extrapolation
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent plasma clearance
CL_D	Dialysate clearance
Cl_R	Renal clearance
C_{max}	Maximum plasma concentration
CPA	Clinical Pharmacology Alliance
CRF	Case Report Form (electronic/paper)
CL_{CR}	Creatinine clearance
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation (%)
DAE	Discontinuation of Investigational Product due to Adverse Event
DES	Data Entry Site
DMP	Data Management Plan
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ESRD	End stage renal disease
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
f_e	Fraction of dose excreted as unchanged drug into urine
$f_{d(4-8)}$	Fraction of dose extracted unchanged into the dialysate over the dialysis period from 4 hours postdose to 8 hours postdose
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
LIMS	Laboratory Information Management System
LH	Luteinizing hormone
LLOQ	Lower Limit of Quantification
MDRD	Modification of Diet in Renal Disease
OAE	Other Significant Adverse Event (see definition in Section 11.1.1)
pCRF	paper case report form
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex.
QRS	ECG interval measured from the onset of the QRS complex to the J point.
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	The time between corresponding points on 2 consecutive R waves on ECG
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.3.2).

Abbreviation or special term	**Explanation**
SD	Standard deviation
SOP	Standard Operating Procedure
$t_{1/2,\lambda z}$	Terminal half-life
Vz/F	Apparent volume of distribution

1. INTRODUCTION

1.1 Background

Mecamylamine HCl (Inversine®) was originally developed as a nicotinic ganglion-blocking agent and was approved in the United States in 1956 for the treatment of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension. The safety and tolerability profile of Mecamylamine HCl has been established during its decades of clinical use as an antihypertensive agent. At the high doses (greater than 10 mg/day up to 90 mg/day) used in antihypertensive therapy, the most common Adverse Events (AE) of the drug include constipation, orthostatic dizziness, urinary retention, and blurred vision. At dosages of 2.5 to 10 mg/day (one-tenth of the dosages used in the treatment of hypertension) the mecamylamine antagonizes central nervous system neuronal nicotinic receptors with no effect on those in the periphery and no impact on blood pressure.

TC-5214 is the S-(+)-enantiomer of racemic mecamylamine and is the more active enantiomer. A single ascending dose (SAD) study (TC-5214-23-CLP-001) has been conducted with TC-5214 in healthy male volunteers. In this study, TC-5214 was generally well tolerated across 4 dose cohorts (single doses of 2 mg, 4 mg, 8 mg and 16 mg; 6 volunteers per cohort). There were no serious adverse events (SAEs) in the SAD study. Additionally, a Phase 2b study (TC-5214-23-CRD-001) was conducted to evaluate the efficacy and safety of TC-5214 including evaluation of the level of exposure to TC-5214 in the target patient population. In this Phase 2b study, a flexible dose titration design was used, and doses from 1 mg twice daily (2 mg total per day) through 4 mg twice daily (8 mg total per day) TC-5214 was administered to the active treatment arm. There were 2 serious adverse events (SAE) in the study: possible seizure and menorrhagia. For further details, see the Investigator's Brochure (Investigator's Brochure TC-5214)

1.2 Research hypothesis

The hypothesis in this study is that renal impairment may affect the plasma pharmacokinetics (PK) of TC-5214, by decreasing the renal clearance (Cl_R) of TC-5214, leading to increased exposure.

1.3 Rationale for conducting this study

The human absorption, metabolism, elimination study (TC-5214-23-CLP-002) has shown that the mean recovery of total radioactivity in urine was 96.1%. In urine, the individual total percent of dose corresponding to parent ranged from 89.5% to 93.9%. After oral administration, TC-5214 was systematically cleared by renal excretion mainly as unchanged drug and non-renal clearance was very minimal. Thus renal impairment is likely to significantly affect the PK of TC-5214. This study is being conducted as a standard approach to determine the effects of renal impairment and dialysis on the PK of TC-5214.

1.4 Benefit/risk and ethical assessment

There will be no benefit for subjects participating in this study. Given the observed pharmacological and toxicological profiles in nonclinical studies and previous clinical experience, it is judged that TC-5214 can be given in carefully monitored clinical trials.

The doses selected for subjects with moderate and severe renal impairment have been reduced to a single dose well below the highest single doses shown to be safe and well tolerated in healthy subjects.

Inclusion and exclusion criteria as well as study restrictions are chosen to ensure that the selected subjects are exposed to minimal risk.

The major risk for subjects who participate in the study is from AEs induced by TC-5214. The most likely safety concern for subjects receiving TC-5214 will be orthostatic hypotension, based on clinical data on mecamylamine and its mechanism of action. Orthostatic hypotension may occur when vascular volume is depleted, for example when fluid is withdrawn during the dialysis session. A low TC-5214 dose of 2 mg has been chosen for these subjects as an additional measure of safety.

There is a slight risk of infection or bruising that may occur as a result of phlebotomy. Treatment-emergent adverse events in the previous SAD study included vertigo, decreased neutrophil count, and somnolence in the TC-5214 4 mg group; vertigo in the TC 5214 8 mg group; nausea, xerosis, dizziness, eating disorder, and decreased appetite in the TC-5214 16 mg group. For further information regarding an overall risk benefit assessment, see Investigator's Brochure TC-5214.

2. STUDY OBJECTIVES

2.1 Primary objective

To assess the pharmacokinetics of a single dose of TC-5214 in subjects with renal impairment and to compare the results with those in subjects with normal renal function

2.2 Secondary objectives

- To assess the effect of hemodialysis on TC-5214 PK
- To assess the safety and tolerability of TC-5214 in subjects with renal impairment compared with those subjects with normal renal function

2.3 Exploratory objectives

To collect samples for potential pharmacogenetic testing, which will allow future investigation of the influence of genotype on drug disposition and pharmacodynamic response

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a Phase I single dose, multi center, open-label study designed to evaluate the safety, tolerability and PK of TC-5214 in renally impaired subjects compared with subjects with normal renal function.

Based on an interim review of the safety and pharmacokinetics data, subjects with severe renal impairment (previous Group 4) will not be recruited for this study, and the study will be conducted in 2 parts.

Subjects will be enrolled into 1 of 4 groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate (eGFR), determined using the abbreviated, 4-variable Modification of Diet in Renal Disease (MDRD) formula as follows:

Group 1: control subjects with normal renal function: eGFR greater than 80 mL/min

Group 2: mild renal impairment: eGFR greater than or equal to 50 to 80 mL/min

Group 3: moderate renal impairment: eGFR greater than or equal to 30 to less than 50 mL/min

Group 5: end stage renal disease (ESRD): eGFR less than 30 mL/min, currently receiving dialysis

3.1.1 Part 1

3.1.1.1 Part 1, Groups 1 through 3

Subjects in Groups 1 through 3 will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 4. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period. During Part 1, subjects in Groups 1 through 3 will have pharmacokinetic blood and urine samples collected through 72 hours postdose.

3.1.1.2 Part 1, Group 5

The first 4 subjects enrolled into Group 5 will participate in 2 treatment periods, and receive a single oral dose of TC-5214 on each occasion. For Treatment Period 1 subjects will be

admitted into the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will receive a single dose of TC-5214 on Day 1 after completion of a dialysis session and will remain in the clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. Subjects who are unable to remain in the clinic during this time may have their samples collected as outpatients. Subjects will return to the clinic after a washout period of at least 2 weeks to start Treatment Period 2. Subjects will be admitted to the clinic the morning of Day -1 or on Day -2 at the discretion of the Investigator for Treatment Period 2. Time-matched vital signs will be collected on Day -1. Subjects in Treatment Period 2 will receive a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects will remain in the clinic until the start of their next dialysis session. Blood samples will be collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Safety assessments will be performed periodically throughout the treatment period. Dialysis fluid will be collected in 1-hour intervals. Subjects who are unable to remain in the clinic through the entire treatment period may have their samples collected as outpatients. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from Treatment Period 2. Subjects who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor.

For details on Part 1, see the Study Flow Charts (Figure 1 and Figure 2) and the Study Plan Table 1 below.

3.1.2 Part 2

3.1.2.1 Part 2, Groups 1 through 3

Subjects in Groups 1 through 3 will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 6. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

During Part 2, subjects in Groups 1 through 3 will have blood and urine samples collected through 120 hours postdose.

3.1.2.2 Part 2, Group 5

The remainder of subjects enrolled into Group 5 will participate in 1 treatment period, and receive a single oral dose of TC-5214. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 after

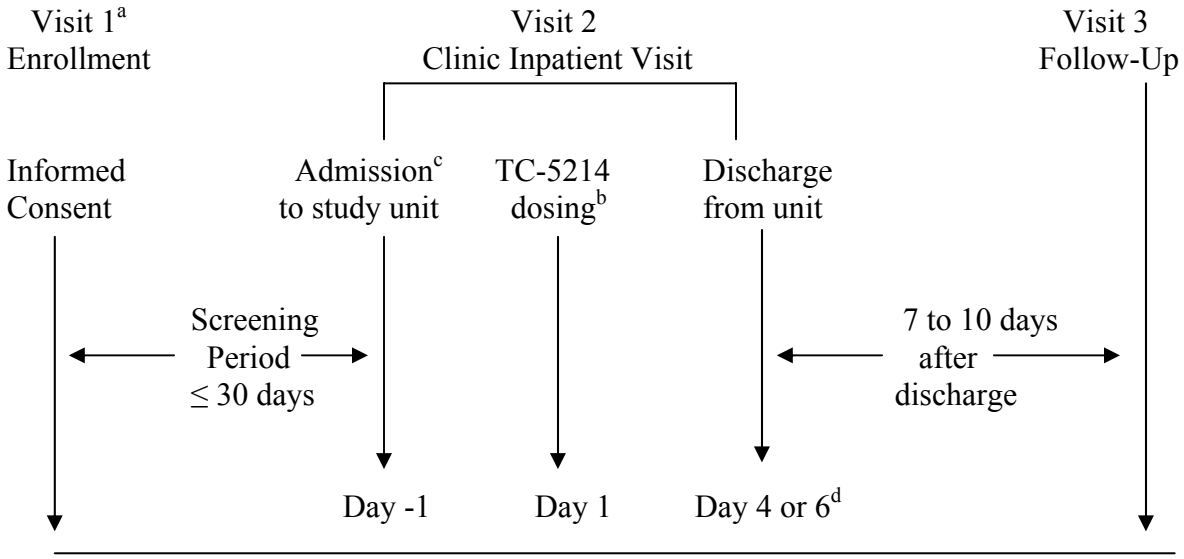
completion of their first inpatient dialysis session, and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 6.

Pharmacokinetic blood samples will be collected after a single oral dose (Day 1) for up to 120 hours postdose. Samples will be collected through 72 hours postdose (assessment between dialysis) and between 72 and 120 hours (assessment during dialysis). Pharmacokinetic urine samples will be collected for up to 120 hours postdose from subjects who are able to produce urine.

Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects who withdraw from the study prior to completion of all pharmacokinetic sample collections may be replaced at the discretion of the Sponsor.

For details on Part 2 see the Study Flow Charts (Figure 1 and Figure 3) and the Study Plan Table 2 below.

Figure 1: Study Flow Chart Groups 1 through 3



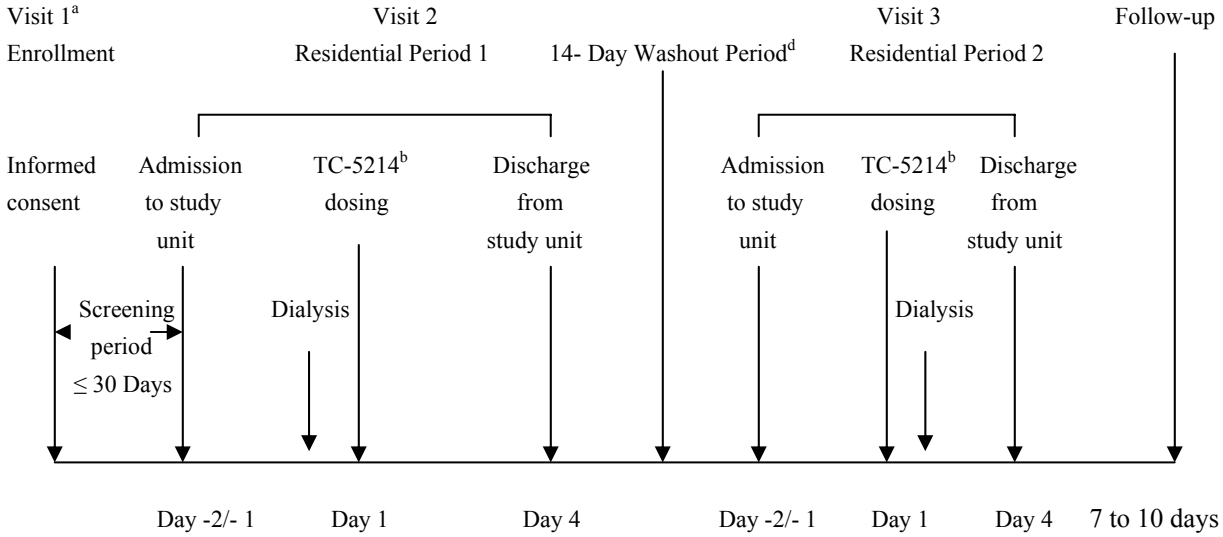
[a] Visit 1 may be conducted over 1 or more days during the screening period.

[b] A single dose of TC-5214 8 mg will be administered for Groups 1 and 2, 2 mg will be administered for Groups 3 on Day 1.

[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.

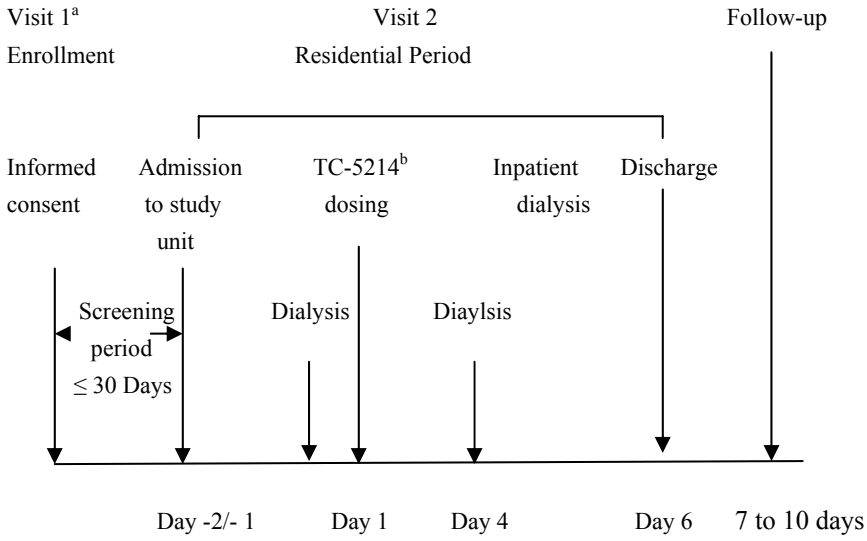
[d] For subjects in Groups 1 through 3, during Part 1 blood and urine samples are collected through 72 hours postdose, and for Part 2, blood and urine samples are collected through 120 hours postdose.

Figure 2: Study Flow Chart Group 5, Part 1



[a] Visit 1 may be conducted over 1 or more days during the screening period.
[b] A single dose of TC-5214 2 mg will be administered to Group 5 on Day 1 of each residential period
[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.
[d] At least 14 days between TC-5214 administrations.

Figure 3: Study Flow Chart Group 5, Part 2



[a] Visit 1 may be conducted over 1 or more days during the screening period.
[b] A single dose of TC-5214 2 mg will be administered to Group 5 on Day 1**.**
[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.

Table 1: Study Plan, Part 1

Visit number	**1**	**2** **Residential Period** **(For Group 5, Part 1 – 2 Residential Periods)**					**3**	
Activity/ Day	**-30 to -2** **Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**Follow-Up** **7 to 10 days following discharge**	**Details in Section**
Informed consent	X							8.4
Demography	X							6.2
Inclusion/exclusion criteria	X	X						4
Physical Examination	X	X[i]				X[i]	X	6.3.6
Height and weight [a]	X	X				X		6.3.6
Medical and Surgical History	X							6.2
Columbia Suicide Severity Rating Scale	X	X				X	X	6.2
Clinical chemistry	X	X				X	X	6.3.5
Hematology	X	X				X	X	6.3.5
Urinalysis	X	X				X	X	6.3.5
HIV and HBV Serology	X							6.3.5
Drugs of Abuse Screen	X	X						6.3.5
Alcohol Screen		X						6.3.5

Visit number	**1**	**2** **Residential Period** **(For Group 5, Part 1 – 2 Residential Periods)**					**3**	
Activity/ Day	**-30 to -2** **Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**Follow-Up** **7 to 10 days following discharge**	**Details in Section**
Blood pregnancy test for female subjects of childbearing potential	X	X				X		6.3.5
Orthostatic blood pressure (supine, seated, and standing) and pulse[b]	X	X	X	X	X	X	X	6.3.7
Oral temperature and respiration rate	X	X	X	X	X	X	X	6.3.5
12-lead ECG [c]	X	X	X			X	X	6.3.6.1
Admission to the clinic		X						NA
Pharmacogenetic sampling (optional)[k]		X						6.5.1
TC-5214 administration [d]			X					5.5.2
Blood sample collection for PK [e]			X	X	X	X		6.4.1.1
Urine sample collection for PK [f]			X	X	X	X		6.4.1.2
Dialysis Period / Dialysate Collection			X[j]					6.4.1.4
Discharge from clinic						X[g]		NA

Visit number	**1**	**2** **Residential Period** **(For Group 5, Part 1 – 2 Residential Periods)**					**3**	
Activity/ Day	**-30 to -2** **Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**Follow-Up** **7 to 10 days following discharge**	**Details in Section**
Concomitant medications	X	X	X	X	X	X		5.6
Adverse Events	X	X	X	X	X	X	X	6.3

[a] Height will be measured during the screening visit only.
[b] Orthostatic blood pressure and pulse will be measured at the Screening Visit, on Day -1 (time to correspond with the planned predose and 4 hour postdose timings for Day 1), on Day 1 at predose and 4 hours post dose, each morning during the residential period and at the Follow-up Visit.
[c] Subjects must rest in the supine position for 10 minutes prior to the 12-lead ECG evaluation to be performed at screening, on admission on Day -1, on Day 1 at 4 hours postdose, before discharge on Day 4, and at the Follow-up Visit
[d] Study drug will be administered with 240 mL room temperature water
[e] For detailed timings of blood PK sampling times see Section 6.4.1.1.
[f] Urine collection times for Groups 1 to 3: Urine will be collected for 72 hours postdose in the following intervals: 0-12, 12-24, 24-48 and 48-72 hours.
[g] Subjects will be discharged from the unit after all study procedures have been completed.
[h] Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.
[i] Abbreviated physical examination.
[j] Applies only to Group 5, Part 1, Treatment Period 2. Subjects will start their scheduled dialysis at 4 hours post TC-5214 administration. Dialysate will be collected over 1 hour intervals throughout the entire (approximately 4 hour) dialysis session (eg, 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours).
[k] Subjects must agree to sign a separate, optional informed consent for genetic research in order for this sample to be collected.

Table 2: Study Plan, Part 2

Visit number	**1**	**2 Residential Period**							**3**	
Activity/ Day	**-30 to -2 Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**5**	**6**	**Follow-Up 7 to 10 days following discharge**	**Details in Section**
Informed consent	X									8.4
Demography	X									6.2
Inclusion/exclusion criteria	X	X								4
Physical Examination	X	X[i]						X[i]	X	6.3.6
Height and weight [a]	X	X						X		6.3.6
Medical and Surgical History	X									6.2
Columbia Suicide Severity Rating Scale	X	X						X	X	6.2
Clinical chemistry	X	X						X	X	6.3.5
Hematology	X	X						X	X	6.3.5
Urinalysis	X	X						X	X	6.3.5
HIV and HBV Serology	X									6.3.5
Drugs of Abuse Screen	X	X								6.3.5
Alcohol Screen		X								6.3.5
Blood pregnancy test for female subjects of childbearing potential	X	X						X		6.3.5

Visit number	**1**	**2 Residential Period**							**3**	
Activity/ Day	**-30 to -2 Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**5**	**6**	**Follow-Up 7 to 10 days following discharge**	**Details in Section**
Orthostatic blood pressure (supine, seated, and standing) and pulse[b]	X	X	X	X	X	X	X	X	X	6.3.7
Oral temperature and respiration rate	X	X	X	X	X	X	X	X	X	6.3.5
12-lead ECG [c]	X	X	X					X	X	6.3.6.1
Admission to the clinic		X								NA
Pharmacogenetic sampling (optional)[j]		X								6.5.1
TC-5214 administration [d]			X							5.5.2
Blood sample collection for PK [e]			X	X	X	X	X	X		6.4.1.1
Urine sample collection for PK [f]			X	X	X	X	X	X		6.4.1.2
Dialysis Period			X			X				6.4.1.4
Dialysate Collection						X[j]				6.4.1.4
Discharge from clinic								X [g]		NA
Concomitant medications	X	X	X	X	X	X	X	X		5.6
Adverse Events	X	X	X	X	X	X	X	X	X	6.3

[a] Height will be measured during the screening visit only.

[b] Orthostatic blood pressure and pulse will be measured at the Screening Visit, on Day -1 (time to correspond with the planned predose and 4 hour postdose timings for Day 1), on Day 1 at predose and 4 hours postdose, each morning during the residential period and at the Follow-up Visit.

[c] Subjects must rest in the supine position for 10 minutes prior to the 12-lead ECG evaluation to be performed at screening, on admission on Day -1, on Day 1 at 4 hours postdose, before discharge on Day 6, and at the Follow-up Visit.

[d] Study drug will be administered with 240 mL room temperature water.

[e] For detailed timings of blood PK sampling times see Section 6.4.1.1.

[f] Urine collection times: Urine samples for PK will be collected for 120 hours postdose in the following intervals: 0-12, 12-24, 24-48, 48-72, 72-96, and 96-120 hours. Urine will be collected for subjects in Part 2 for Groups 1 through 3, and for subjects in Group 5 who produce urine.

[g] Subjects will be discharged from the unit after all study procedures have been completed.

[h] Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.

[i] Abbreviated physical examination.

[j] For Group 5 (Part 2), dialysate will be collected over 1 hour intervals throughout the entire (approximately 4 hour) dialysis session (eg, 72 to 73, 73 to 74, 74 to 75, and 75 to 76 hours postdose).

[k] Subjects must agree to sign a separate, optional informed consent for genetic research in order for this sample to be collected.

3.2 Rationale for study design, doses and control groups

The purpose of this study is to determine if renal impairment will affect the PK of TC-5214. The study is designed using the principals embodied in the Food and Drug administration guidance on drug renal impairment studies (Cockcroft 1976).

For control subjects with normal renal function and subjects with mild renal impairment, a 8 mg dose of TC-5214 was chosen because it is the highest daily dose that will be administered in Phase III trials and was shown to be well tolerated in healthy subjects in previous studies. For subjects with moderate and severe renal impairment, to minimize the effects of compensatory changes such as significant hypotension, a 2 mg dose will be administered.

In order to avoid bias due to demographic differences between the control subjects with normal renal function and subjects with renal impairment, the control group will be matched to the mean demographic characteristics of the **3** renal impairment groups with an allowable variability in age of +/- 10 years and in BMI of ± 3 kg/m^2. Sex will be matched to achieve similar distribution between male and female subjects. Only control subjects with stable chronic medical conditions will be included.

Based on available data to date, the mean terminal half-life ($t_{1/2,\lambda z}$) of TC-5214 in human plasma is approximately 8 to 9 hours. Based on limited interim PK data in 2 subjects with moderate impairment, and 2 subjects with ESRD, renal impairment has been shown to increase the half-life of TC-5214 by approximately 3 and 10 fold, respectively.

For Groups 1 to 3, the study design has been updated to extend the sampling period to 120 hours postdose to adequately characterize the elimination phase of TC-5214 and more accurately determine TC-5214 PK parameters (eg $t_{1/2,\lambda z}$, AUC, and CL/F). For Group 5 it was determined that a single dose of TC-5214 administered after the completion of a dialysis session, with the collection of blood samples for PK through 120 hours postdose (including a 4 hour dialysis session beginning approximately 72 hours postdose) would enhance patient safety.

The PK profile in patients with severe renal failure will be extrapolated from the data in subjects on dialysis obtained between their dialysis sessions, thus subjects with severe renal impairment (eGFR <30 mL/min) will not be recruited for this study.

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Provision of signed, written and dated informed consent prior to any study specific procedures.

2. Males and non-pregnant, non-lactating females 18 to 80 years old inclusive with suitable veins for cannulation or repeated venipuncture

   - Male subjects: Male subjects who are sexually active must be willing to use accepted double barrier method of contraceptive methods (eg condom or diaphragm plus spermicide), avoid unprotected sex, and avoid donating sperm until 3 months after drug administration.

   - Women of childbearing potential: Women of childbearing potential must have a negative blood pregnancy test confirmed by the Investigator, and use a highly effective form of birth control for 3 months before enrollment and until 3 months after their last dose of study drug. The following methods of highly effective birth control include vasectomized sexual partner, tubal occlusion, intra-uterine device (copper banded coils only), intrauterine system (eg, Mirena), Depo-Provera, implants (Implanon, Norplan), normal and low dose combined oral pills, ethinylestradiol transdermal system (Evra Patch), and intravaginal device (NuvaRing). Highly effective birth control can also include true sexual abstinence (starting at the screening visit and through completion of the study) or a double barrier method of contraception (eg diaphragm plus spermicide). The Investigator will capture the method of birth control and compliance at each study visit.

   - Women of non childbearing potential: Women of non childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but excluding bilateral tubal occlusion) or who are postmenopausal. Women will be considered post menopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

     Women under 50 years old would be considered post menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment, and LH and FSH levels in the post-menopausal range.

     Women over 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

3. Regarding renal function, subjects will be classified as either normal or as suffering from mild, moderate or severe renal impairment. Classification of renal impairment

will be based using an abbreviated 4 variable MDRD equation. To ensure the assessment of consistent estimated glomerular filtration rate (eGFR) using the MDRD, a single equation will be used (see Section 6.2)

4. Have a body mass index (BMI) between 19 and 40 kg/m^2 and weigh at least 50 kg.

5. Be able to understand and comply with the requirements of the study as judged by the Investigator.

For inclusion in the genetic component of the study, subjects must fulfill the following additional criterion:

6. Provision of signed, written and dated informed consent for genetic research. If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant medical, neurologic or psychiatric disease or disorder (other than those previously defined as acceptable for these population) which, in the opinion of the Investigator and sponsor, may either put the subject at risk because of participation in the study, or influence the results of the subject's ability to participate in the study: This includes seizure activity and repeated episodes of major depression.

2. Subjects with a history of suicide attempts in the past year and/or seen by the Investigator as having a significant history of risk of suicide or homicide, or considered at risk for suicide or homicide during the study.

3. History of gastrointestinal surgery (with the exception of cholecystectomy and appendectomy) or unintentional rapid weight loss.

4. Subjects with an active renal transplant (subjects who have previously received a renal transplant and are currently undergoing dialysis due to transplant failure may be enrolled)

5. Any clinically significant acute illness or medical/surgical procedure within 4 weeks of the first administration of investigational product (IP) (other than those previously defined as acceptable for these population) as judged by the Investigator.

6. Clinically significant progression of current disease or clinically relevant trauma, as judged by the Investigator, within 2 weeks before the first administration of the IP.

7. Any clinically significant abnormalities (other than those associated with the subject's degree of renal impairment and /or stable chronic condition) in clinical chemistry, hematology or urinalysis results as judged by the Investigator and Sponsor.

8. A positive result on screening for serum hepatitis B surface antigen or human immunodeficiency virus (HIV).

9. Clinically significant abnormal vital signs as judged by the Investigator

10. Any clinically important abnormalities in rhythm, conduction or morphology including abnormalities suggestive of acute changes or recurrent ischemic changes of resting electrocardiograms (ECG) as determined by the Investigator and sponsor

11. Prolonged QTcF (subjects with up to 500 ms prolongation are acceptable with joint approval with investigator and sponsor) or shortened QTcF (less 340 ms), or family history of Long QT Syndrome

12. Current smokers, those who have smoked or used nicotine products within the previous 1 month prior to enrollment are to be excluded only if the investigative site has no accommodation for subjects to continue smoking during confinement.

13. Consumption of alcohol within 72 hours of admission to the clinic.

14. Past or present alcohol or drug abuse within 1 year of enrollment. Excessive intake of alcohol (greater than 15 units/week).

15. Positive test in drugs of abuse screens (except for prescription medications, which are verified by the Investigator), or alcohol on admission to the clinic prior to the administration of the IP

16. Pregnancy, lactation or positive serum pregnancy test in women at screening and at admission to the unit prior to the first administration of IP.

17. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, other than seasonal allergies, as judged by the Investigator

18. Excessive intake of caffeine containing foods or beverages (more than 5 units or equivalent per day). One caffeine unit is contained in the following items: one (6 oz.) cup of coffee, two (12 oz) cans of cola, one (12 oz) glass of tea, ½ (4 oz) cup of energy drink (e.g. Red Bull) or three (1oz) chocolate bars within 48 hours prior to admission to unit.

19. Plasma or blood product donation within one month of screening or any blood donation/blood loss greater than 500 mL during the 3 months prior to screening or intention to donate blood or blood products during the study or within 1 month after the completion of the study.

20. Has received another new chemical entity (defined as a compound which has not been approved for marketing) other investigational drug product within 30 days (if half-life was less than 24 hours) of the first administration of IP in this study. Note subjects consented and screened but not dosed in previous phase I studies are not excluded.

21. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

22. Judgment by the Investigator that the subject should not participate in the study if considers subject unlikely to comply with study procedures, restrictions and requirements

23. History or hypersensitivity or intolerance to drugs with a similar chemical structure or class to TC-5214

For control subjects:

24. Use of prescription medication for a chronic medical condition in this demographically matched control group is acceptable as long as the medical condition is stable and there have been no significant changes in the medical regimen within 6 weeks of Day 1 unless approved by the investigator and sponsor. Accepted drugs include hormone replacement therapy, diuretics, ACE inhibitors, statins, NSAIDS and oral hyperglycemic agents. Unaccepted drugs include beta blockers, vasodilators, calcium channel blockers, nitrates and erectile dysfunction drugs, high dose NSAIDs, probenecid, penicillin G, phenylbutazone, and indomethacin

Subjects with renal insufficiency:

25. Subjects may continue their appropriate accepted (as agreed between the Investigator and sponsor) routine medications as long as there have been no recent (within 28 days) significant changes in, or addition to, routine medications. Subjects on beta blockers, vasodilators, or calcium channel blockers may be included at the discretion of the Investigator and considered for an individualized dose reduction when appropriate. Unaccepted drugs include nitrates, erectile dysfunction drugs, high dose NSAIDs, probenecid, penicillin G, phenylbutazone, and indomethacin.

In addition, the following is considered a criterion for exclusion from the genetic research:

26. Previous bone marrow transplant

27. Whole blood transfusion within 120 days of the date of genetic sample collection

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply from the specified time and throughout the study period:

1. Subjects must fast from at least 2 hours before planned administration of IP. A moderate amount of water is allowed up to 1 hour prior to dosing and may be resumed 1 hour after dosing. A meal may be given as early as 1 hours after dosing. A moderate amount of water is allowed up to 1 hour prior to dosing and may be resumed 1 hour after dosing.

2. Subjects may eat and drink only the standardized diet provided (appropriate for the subject's degree of renal insufficiency) during the residential period in the unit.

3. Subjects should follow instructions with regard to food and fluid intake in relation to samplings of clinical laboratory tests during the study.

4. Abstain from consuming any of the following:

   - Alcohol from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit

   - Energy drinks containing taurine or glucuronolactone eg, Red Bull from 72 hours before admission, during the residential period and for 72 hours before the study follow-up visit

   - Caffeine-containing drinks during the residential period apart from any provided as part of a standardized meal. Excessive intake of caffeine should be avoided between discharge from the unit and the study follow-up visit

   - Poppy seeds found in specialty bread from time of consent until after the final medical examination at the study follow-up

   - Grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges from 72 hours before admission until after the final medical examination at the study follow-up.

5. Unless smoking areas are accessible to subjects who are smokers, abstain from nicotine use, smoking and drugs of abuse from screening until after the final medical examination at the study follow-up.

6. Subjects with normal renal function should adhere to the medication restrictions according to exclusion criteria #24.

7. For subjects with renal insufficiency refer to exclusion criteria # 25.

8. Subjects will remain semi-recumbent or sitting for 4 hours following IP administration.

9. Subjects should refrain from strenuous physical activity, which is not within the subject's normal daily routine, from 48 hours prior to admission to the unit until after the final medical examination at the study follow-up.

10. Abstain from blood or plasma donation until 3 months after the final medical examination at the study follow-up.

11. Abstain from unprotected sex and sperm donation from the first administration of IP until 3 months after the last administration of IP. Subjects should ensure that their partners of child bearing potential use a reliable method of contraception.

5.2 Subject enrollment and initiation of investigational product

The Investigator will ensure:

1. Signed informed consent is obtained from each potential subject before any study specific procedures are performed

2. The eligibility of each subject is determined. See Sections 4.1 and 4.2.

3. Each screened subject is assigned a unique enrollment number or Ecode (eg E0001001) at screening (before any procedures are completed)

4. Subjects who pass all screening procedures will return to the clinic on Day -1

Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

Subjects in Group 5, Part 1, who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor (see Section 5.9). Subjects in Group 5, Part 2 may be replaced.

All replacements must be approved by AstraZeneca. If a subject withdraws his/her participation in the study, then his/her enrollment code cannot be reused. Enrollment codes for replacement subjects will be assigned as follows: the original subject's number plus 1000 (eg, if the original subject being replaced had a subject number of 504, the replacement subject's number will be 1504).

5.2.1 Procedures for randomization (Not Applicable)

5.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances receive study medication. There can be no exceptions to this rule.

Where subjects that do not meet the selection criteria are incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca CPA Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

The AstraZeneca CPA Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the subject should have their study treatment stopped.

5.4 Blinding and procedures for unblinding the study (Not Applicable)

5.5 Treatments

5.5.1 Identity of investigational product(s)

AstraZeneca or a company acting on its behalf will supply the IP to the Investigator. The IP will be supplied as tablets for oral use according to the description in Table 3 below.

Table 3: TC-5214

Investigational product	Dosage form and strength	Manufacturer
TC-5214	2 mg Tablet	[redacted]
TC-5214	4 mg Tablet	[redacted]

The formulation consists of -(+)-mecamylamine hydrochloride (TC-5214) [(1R,2S,4S)-N,2,3,3-tetramethylbicyclo-[2.2.1]heptan-2-amine hydrochloride] provided in hard gelatin tablets at 2 mg dose strengths based on free base equivalents.

5.5.2 Doses and treatment regimens

Investigational product will be administered with 240 mL of water. For details on food and fluid intake surrounding drug administration refer to Section 5.1.

Subjects in Groups 1 and 2 will receive a single dose of TC-5214 8 mg (2 x 4 mg tablets).

Subjects in Groups 3 will receive a single dose of TC-5214 2 mg.

Subjects in Groups 5, Part 1 will receive a single dose of TC-5214 2 mg, on 2 occasions, once during each treatment period. These doses will be separated by a washout period of at least 14 days.

Subjects in Groups 5, Part 2 will receive a single dose of TC-5214 2 mg.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language, where appropriate.

5.5.4 Storage

All study drugs will be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage. All study medications shall be stored in their original containers. Only staff members who are authorized to dispense the drug supplies will have access to them.

5.6 Concomitant and post-study treatment(s)

Concomitant medications allowed and their relation to stable medical conditions are outlined for control subjects with normal renal function in exclusion criteria 24 and for subjects with renal insufficiency in exclusion criteria 25.

No subjects should receive any new chemical entities or other clinical study IP within 1 month of TC-5214 administration.

Medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the Investigator during the residential period. When any medication is required, it should be prescribed by the Investigator who should inform the AstraZeneca CPA Physician. Following consultation with the CPA Physician, the Investigator should determine whether or not the subject should continue in the study.

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the Investigator and recorded on the paper case report form (CRF).

5.7 Treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by supervised administration of the IP by the Investigator or representative. The dose, date, and time of administration of the IP will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject, and return all unused drugs to AstraZeneca for destruction. Certificates of delivery and return should be signed by the appropriate personnel.

5.8 Discontinuation of investigational product

Subjects may be discontinued from IP in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Risk to healthy subjects as judged by the Investigator or AstraZeneca
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca
- Incorrectly enrolled subject, the subject does not meet the required inclusion/exclusion criteria for the study
- Subject loss to follow-up
- If any AE, laboratory, vital sign or ECG changes are seen during or after dosing which would indicate that any further dosing may harm the safety of the subject, dosing must be stopped or further study treatment must be discontinued
- Positive pregnancy test for a female subject

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

If a subject is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

Subjects who are discontinued from IP or withdrawn from the study may replaced as described in Section 5.2.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in the study plans (Table 1 and Table 2).

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the timepoint. The sequence at a particular time point is:

1. ECGs
2. Blood pressure (BP) and pulse rate
3. PK blood sample (Note: PK sampling must be performed at the precise protocol scheduled time.)
4. Urine collections
5. In Group 5 (Part 1, Period 2), dialysis related procedures will follow PK blood sample collections, where appropriate.

Predose assessments may be performed up to 60 minutes prior to dosing.

6.1 Recording of data

The Investigator will ensure that all data collected in the study are recorded as specified by the protocol.

He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the paper case report form (pCRF) and according to any instructions provided. The Investigator will sign the CRF and a copy will be archived at the study site.

The Investigator will provide AstraZeneca with all data produced during the study from the scheduled study assessments.

Procedures for data editing, entry, and handling of the data query process will be described in the data management plan. See Section 10.

6.2 Data collection and enrollment

At enrollment (Visit 1), each potential subject will provide informed consent prior to starting any study-specific procedures.

Demographic data and other characteristics will be recorded and will include date of birth, sex, race, alcohol consumption, smoking history, drug use history and CL_{CR}.

Each subject will undergo screening during the 30 days prior to admission to confirm eligibility. This will consist of:

1. Obtaining written informed consent prior to starting any study-specific procedures are performed;

2. A standard medical, medication, and surgical history with review of the inclusion and exclusion criteria with the subject;

3. A complete physical examination;

4. Height, weight, and calculation of BMI;

5. Recording a resting 12-lead paper ECG;

6. A blood sample for routine clinical chemistry, hematology, and screen for hepatitis B surface antigen and antibodies to HIV;

7. Vital signs – blood pressure, pulse, and oral temperature;

8. A serum pregnancy test (females of childbearing potential only);

9. A midstream urine sample for routine urinalysis;

10. A drugs of abuse screen;

11. Collection of AEs;

12. Prior and concomitant medications;

13. Columbia Suicide Severity Rating Scale (C-SSRS).

The eGFR will be determined for each subject using the following abbreviated 4-variable MDRD equation (National Kidney Foundation 2002):

- $eGFR = 175 \times (\text{serum creatinine})^{-1.154} \times age^{-0.203} \times (1.210 \text{ if African American}) \times (0.742 \text{ if female})$

An online calculator from a reputable source (eg nephron.org) will be used to ensure a consistent calculation across subjects. After admission and before IP administration the Investigator should reassess each subject to reconfirm eligibility. The renal function determination at screening will be used to classify the subject to the renal function Groups 1 through 4; however, the eGFR value determined at check-in on Day -1 or Day -2 will be used for purposes of any statistical correlation of PK data with renal function.

6.2.1 Follow-up procedures

A poststudy medical examination will be performed 7 to 10 days after the final discharge from the study site. This will be similar to the one performed at screening and will include a complete physical examination, vital signs, recording a 12-lead paper ECG, a blood sample for clinical chemistry, hematology, a urine sample for urinalysis, CSSRS, and assessment of any AEs or required medication.

6.3 Safety

The Investigator is responsible for ensuring all staff involved in the study is familiar with the content of this section.

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.3.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect; or
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the Investigator for as long as medically indicated. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE;

- AE (verbatim);
- The date and time when the AE started and stopped;
- Maximum intensity on a scale of 1 to 3 (if the intensity of an AE changes, only the maximum intensity of the event will be recorded):
  - Mild (awareness of sign or symptom, but easily tolerated);
  - Moderate (discomfort sufficient to cause interference with normal activities); or
  - Severe (incapacitating, with inability to perform normal activities).
- Whether the AE is serious or not;
- Investigator causality rating against the IP (yes or no);
- Action taken with regard to IP;
- AE caused subject's withdrawal from study (yes or no);
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to

- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to additional Study Drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note, for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP or if the Investigator insists on reporting them as an AE.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the pCRF.

If any SAE occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs, where important or relevant information is missing, active follow-up is undertaken immediately. The Investigator or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, serology, and urinalysis will be taken at the times indicated in the study plan Table 1 and Table 2. The date and time of collection of all laboratory tests will be recorded.

The following laboratory variables will be measured:

Clinical chemistry

Serum (S)-Albumin

S-Bilirubin, direct

S-ALT

S-AST

S-Alkaline phosphatase

S-Bilirubin, total

S-Bilirubin, direct

S-Blood Urea Nitrogen

S-Chloride

S-Creatinine

S-GGT

S-Protein, Total

S-Potassium

S-Sodium

S-Uric Acid

Hematology

Blood (B)-Hemoglobin

B-Leukocyte

B-Absolute leukocyte differential count

B-Platelet count

B-Red blood cell count

B-Hematocrit

Urinalysis

Urine (U)-Appearance

U-Bilirubin

U-Blood

U-Glucose

U-Ketones

U-Nitrites

U-pH

U-Protein

U-Specific Gravity

U-Urobilinogen

If a urine sample is positive for protein or blood, a microscopic examination of the urine sediment will be performed. Urine safety samples will not be required for anuric subjects.

Additionally, at screening all subjects will be tested for HIV and hepatitis B surface antigen. Subjects will be tested for alcohol using either blood test or a breathalyzer. Subjects will be tested for the following drugs of abuse on admission to the clinic using urine, blood, or saliva samples: amphetamines, barbiturates, cocaine, oxycodone, and tetrahydrocannabinol. For female subjects, a urine or blood pregnancy test will be performed at screening, on admission and at final discharge. The method for ethanol, drugs of abuse, and the pregnancy assessments will be recorded in the pCRF. If a subject tests positive to any of these screening tests he/she will be excluded from the study (except for subjects who are on prescription medications, which are verified by the Investigator).

Laboratory values outside the reference limit (other than those associated with the subject's degree of renal impairment and /or stable chronic condition) suspected to be of any clinical

significance will be repeated. Subjects, in whom suspected clinical significance is confirmed will either not be included or if they have already received treatment, will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the Investigator.

The samples for laboratory testing will be analyzed using routine methods at the site's reference laboratory.

For blood volume see Section 7.1

6.3.6 Physical examination

The timing of individual examinations are indicated in the study plans Table 1 and Table 2. A complete physical examination will include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculo-skeletal, cardiovascular, respiratory and neurological systems. On admission and prior to discharge only a brief physical examination is required.

Height will be measured in centimeters and weight will be measured in kilograms at screening. Measurements should be taken without shoes and will be collected using a calibrated scale to ensure consistency across all measurements. BMI is derived in the database from the height and weight.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the randomization assessment will be reported as an AE.

6.3.6.1 Resting 12-lead ECG

The timing of ECGs are indicated in the study plans Table 1 and Table 2. A 12-lead ECG will be obtained after the subject has been resting in the supine position for at least 10 minutes. If indicated, additional ECG assessments can be made at the discretion of the Investigator. These assessments should be entered as an unscheduled assessment.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded. All ECG readings will be stored as source documents both digitally and as a paper printout. The following variables will be reported: RR, PR, QRS, and QT intervals from the primary lead (V2) of the digital 12-lead ECG. The QTcF will be derived and reported.

6.3.7 Vital signs

For timing of individual measurements refer to study plans Table 1 and Table 2.

6.3.7.1 Pulse and blood pressure

Blood pressure (BP) and pulse (supine, seated, and standing) will be measured using a semi-automatic BP recording device with an appropriate cuff size. The volunteers will be required

to rest in a supine position for at least 10 minutes prior to BP and pulse rate measurements. For the seated evaluation, volunteers will be required to be in the sitting posture for at least 2 minutes for BP and pulse. For the standing evaluation, volunteers will be required to be in the upright standing posture for at least 3 minutes respectively for BP and pulse.

6.3.7.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the study plan.

6.3.8 Other safety assessments

6.3.8.1 Columbia Suicide Severity Rating Scale

The C-SSRS (see Appendix D) will be administered to all volunteers as outlined in the study plans Table 1 and Table 2. The C-SSRS is a low burden, clinician administered tool designed to track suicidal AEs throughout any treatment trial and is considered to be the "gold standard" for assessment (Posner K 2007). The measure succinctly covers the full spectrum of suicidality addressing both behavior and ideation and is now required by the US Food and Drug Administration (FDA) in clinical trials.

6.4 Pharmacokinetics

6.4.1 Collection of samples

All samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual. It must be ensured that samples collected for subjects in Group 5, Part 1 will be clearly labeled with the treatment period information.

6.4.1.1 Blood Samples

Blood samples (approximately 6 mL, split into 2 tubes, collected in K2 EDTA tubes) for determination of TC-5214 in plasma will be taken on the days presented in the study plans Table 1 and Table 2.

Part 1:

For Group 1, Group 2, and Group 3 blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose.

For Group 5, Part 1, blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose. For Treatment Period 2, the timing of sample collections is the same as for Treatment Period 1, however, the sample scheduled for collection at 4 hours must be collected immediately before dialysis start, and the sample scheduled at 8 hours must be collected immediately after dialysis completion rather than strictly adhering to the scheduled sampling times at 4 and 8 hours. For Treatment Period 2, the blood samples during and surrounding the hemodialysis session will be collected from predialyzer lines.

Part 2:

For Part 2, Group 1, Group 2, and Group 3, blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours postdose.

For Group 5, Part 2, blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 74, 76, 96, and 120 hours postdose. The sample scheduled for collection at 72 hours must be collected immediately before dialysis start, and the sample scheduled at 76 hours must be collected immediately after dialysis completion rather than strictly adhering to the scheduled sampling times. Blood samples during and surrounding the hemodialysis session will be collected from predialyzer lines.

The date and time of collection of each sample will be recorded on the pCRF. For blood volume, see Section 7.1.

6.4.1.2 Protein binding

For Groups 1 to **3**, Group 5**, Part 1** for Treatment Period 1**, and Group 5, Part 2,** 2 plasma samples (2.5 and 12 hour postdose) will be initially analyzed for unbound concentrations of TC-5214. After review of these data, if plasma protein binding of TC-5214 appears to be concentration or time-dependent, some or all of the remaining samples from each subject may be analyzed.

Plasma samples from Group 5, **Part 1,** Treatment Period 2, will not be analyzed for unbound concentrations of TC-5214.

The date and time of collection of each sample will be recorded on the pCRF. For blood volume, see Section 7.1.

6.4.1.3 Urine Samples

Urine samples (approximately 10 mL in total, split into 2 tubes) for determination of concentrations of TC-5214 in urine will be taken from the total urine sample provided during each collection period presented in the study plans. The weight, volume, specific gravity, and start/stop time for each interval of each urine collection will be recorded.

For Part 1, urine will be collected in Groups 1 through 3 from predose to 72 hours postdose (see Table 1).

For Part 2, urine will be collected in Groups 1 through 3 and in Group 5 subjects who are able to produce urine from predose to 120 hours postdose (see Table 2).

6.4.1.4 Dialysate Samples

For Group 5, the dialysate will be collected in custom buckets over 1 hour intervals throughout the entire (approximately 4 hours) dialysis period (eg, Part 1, Residential Period 2: 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours; Part 2, Residential Period; 72 to 73, 73 to 74, 74 to 75, and 75 to 76 hours).

The blood flow, dialysate flow rate, dialysate volume, and the make and model of the dialyser will be recorded. The entire dialysate will be collected, its volume recorded, and a sample retained for the analysis of TC-5214 concentrations.

6.4.2 Determination of drug concentration

Samples for the determination of the concentration of TC-5214 in plasma, urine, and dialysate will be analyzed by [redacted] on behalf of AstraZeneca Clinical Pharmacology and Drug Metabolism and Pharmacokinetics. Plasma and urine samples will be analyzed for total concentrations of TC-5214 using liquid chromatography/tandem mass spectrometry (LC/MS-MS). Dialysate and unbound plasma concentrations will be determined using validated bioanalytical methods. All samples should be shipped to:

Full details of the analytical method used will be detailed in a separate bioanalytical report.

All samples will be analyzed within the timeframe for which the stability of TC-5214 have been validated and shown to be acceptable.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites or determine the reproducibility of the analytical results. Any results from such analyses may be reported separately from the CSR.

6.5 Pharmacogenetics

6.5.1 Collection of pharmacogenetic samples

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit for the subject. The subject will not be excluded from any aspect of the main study.

The blood sample for genetic research will be obtained from the subjects on Day -1. If for any reason the blood sample is not drawn on Day -1 according to the study plan, it may be taken at any time up until the last study visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. Only 1 sample will be collected per subject for genetic research during the study.

A record of the date the subject consented to the genetic research and the date of the blood sample collection will be recorded. Samples will be collected, handled, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

6.5.2 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. For all samples irrespective of the type of coding used, the DNA will be extracted from the blood sample.

DNA samples

The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the AstraZeneca genetics laboratories or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.).

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrollment code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Samples will be stored up to a maximum of 25 years, from the date of last subject last visit, after which they will be destroyed. Deoxyribonucleic acid is a finite resource that is used up during analyses. Samples may be stored and used until no further analyses are possible or the maximum storage time has been reached.

6.5.3 Summary of genetic assessments and analysis

The purpose of the genetic research is to enable the generation of data for possible use in future retrospective analyses. Future analyses may explore genetic factors that could influence the disposition, efficacy, safety, and tolerability of TC-5214. The results of the genetic research will not form part of the CSR for this study. The results may be pooled with genetic data from other studies on TC-5214 to generate hypotheses to be tested in future studies.

6.5.4 Derivation or calculation of genetic parameters

The number of subjects who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

6.5.5 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

Subjects who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the subject:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future
- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed.

Procedures for discontinuation are outlined in Section 7.5.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 4: Volume of blood to be drawn from each subject in Groups 1 through 3

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry[a]	8	4	32
	Hematology	4	4	16
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics[b]		6	14 (16)	84 (96)
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	14 (16)	28 (32)
Pharmacogenetics		10	1	10
Total			38 (42)	178 (194)

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.
[b] The total number of samples and associated blood volumes for Part 2 are indicated in parentheses.

Table 5: Volume of blood to be drawn from each subject in Group 5, Part 1

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8	7	56
	Hematology	4	7	28
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics		6	28	168
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	28	56
Pharmacogenetics		10	1	10
Total			72	326

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.

Table 6:Volume of blood to be drawn from each subject in Group 5, Part 2

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8	7	56
	Hematology	4	7	28
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics		6	18	108
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	18	36
Pharmacogenetics		10	1	10
Total			48	246

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data become available. However, the maximum volume to be drawn from each subject will not exceed 450 mL (ie, the same volume as would be drawn

during a regular blood donation), unless additional tests are mandated by the Investigator for safety laboratories or repeat testing.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research will be retained at R&D site, on behalf of AstraZeneca for a maximum of 25 years following the last subject's last visit in the study. The results from future analysis will not be reported in the CSR.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses, see below.

Selected PK samples may be used for TC-5214 identification and/or quantification. These samples will be retained by, or on behalf of AstraZeneca, for a maximum of five years following the finalization of the CSR. The results from any metabolite investigation will not be reported in the CSR.

7.2.2 Pharmacogenetic samples

Refer to Section 6.5.1

7.3 Labelling and shipment of biohazard samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator will keep full traceability of collected biological samples from the subjects while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subject's withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions will taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

The Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable IRB and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any subject into the study.

The IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide the regulatory authority, IRB and Investigator with safety updates / reports according to local requirements, including Suspected Unexpected SAEs, where relevant.

The Investigator will also be responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Investigator so he/she can meet these reporting requirements.

8.4 Informed consent

The Investigator will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, and possible risk of the study.
- Ensure each subject is notified they are free to discontinue from the study at any time.
- Ensure each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the subject.
- Ensure any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by the IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Investigator(s). For distribution to the IRB see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's IRB are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IRB.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or the IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY [redacted]

[redacted] will be managing the study on behalf of AstraZeneca.

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of [redacted] or designee to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the Investigator.

9.2 Training of study site personnel

Before the first subject is entered into the study, an [redacted] representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures system(s) utilized.

The Investigator will ensure appropriate training relevant to the study is given to all of these staff, and any new information relevant to the performance of this study is forwarded to the staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca/[redacted] representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the pCRFs, that biological samples are handled in accordance with the Laboratory Manual and, study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the subject.

The AstraZeneca/[redacted] representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The Investigator should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in the [redacted] and to end by the [redacted].

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the

entire study prematurely if concerns for safety arise within this study or in any other study with TC-5214.

10. DATA MANAGEMENT BY [redacted]

Data management will be performed by [redacted] Phase I Data Management.

When the completed pCRFs have been scanned and indexed, the data are entered into the study database and proofread.

The study Data Management Plan (DMP) will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Furthermore, the DMP will describe the data flow and timelines within the study.

Paper CRFs or electronic case report forms (eCRF)s will be used to record all data except from bioanalysis concentration data and safety lab data or any other data that will be transferred electronically from an external source. For pCRFs data should be recorded legibly onto the pCRFs in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

Paper CRF and eCRF operations are following [redacted] Standard Operation Procedures (SOPs) and data is processed in validated CFR 21 Part 11 compliant systems. Screening failures (subjects who signed consent to take part in the study but were not allocated a screening number) will not be entered into the clinical study database.

In the case of genotypic data, only the date the subject gave consent to participation in the genetic research and the date the blood sample was taken from the subject will be recorded in the pCRF and database.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the CSR for the main study.

Data storage will be done in accordance with AstraZeneca/GCP guidelines.

11. EVALUATION AND CALCULATION OF VARIABLES BY [redacted]

11.1 Calculation or derivation of safety variable(s)

All AEs will be collected for each subject from the time when informed consent is obtained (Visit 1) until the follow-up visit (Visit 3). AEs that occur before dosing will be reported separately.

Change-from-baseline variables will be calculated by [redacted] Inc for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: Day -1 value
- Vital signs (including supine blood pressure and pulse): Day -1 time-matched values
- ECG: Day 1

Baseline values for safety variables during each respective period will serve as the baseline value for that period.

11.1.1 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and Discontinuation of Investigational Product due to Adverse Event (DAE)s. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the TC-5214 plasma, urine, and dialysate concentration data will be performed at [redacted]. Pharmacokinetic analyses will be conducted according to [redacted] SOPs for PK analyses. The actual sampling times will be used in the PK parameter calculations. Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp., Mountain View, California). All PK computations will be performed using WinNonlin Professional® 5.2, or higher; or SAS® Version 9.1, or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared with SAS Version 9.1, or higher; SigmaPlot® 9.0, or higher (Systat Software, Inc., San Jose, California); or WinNonlin Professional® 5.2, or higher. Nominal times will be used for any interim PK analyses, if applicable.

Where possible, the following plasma PK parameters will be determined for TC-5214:

- Maximum plasma concentration (C_{max}, ng/mL), obtained directly from the observed concentration versus time data

- Time to maximum plasma concentration (t_{max}, h), obtained directly from the observed concentration versus time data

- Terminal rate constant (λ_z). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points, with an Rsq of greater than or equal to 0.8 will be used for determination.

- Terminal half-life ($t_{1/2\lambda z}$, h)

- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration [$AUC_{(0\text{-}t)}$]

- Area under the plasma concentration-time curve from 4 to 8 hours [$AUC_{(4\text{-}8)}$] to match the dialysis period, Group 5, Treatment Period 2, Part 1, only

- Area under the plasma concentration-time curve from 72 to 76 hours [$AUC_{(72\text{-}76)}$] to match the dialysis period, Group 5, Part 2, only

- Area under the plasma concentration-time curve from zero to infinity (AUC) calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0\text{-}t)} + C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 30% of AUC, then AUC will not be reported

- Apparent plasma clearance (CL/F, L/h)

- Apparent volume of distribution (V_z/F, L)

The following plasma PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression used to determine $t_{½\lambda z}$

- Number of data points included in the log-linear regression analysis

- Goodness of fit statistic for calculation of λ_z (Regression coefficient)

- Percentage of AUC obtained by extrapolation (%AUC_{ex}).

Where possible, the following urine PK parameters will be determined for TC-5214:

- Cumulative amount of drug excreted unchanged into urine from zero to time t hours ($A_{e(0\text{-}t)}$, mg). The amount will be calculated and reported for each collection interval and cumulatively

- Fraction of dose excreted as unchanged drug into urine (f_e; % dose). The fraction will be calculated and reported for each collection interval and cumulatively

- Renal clearance (CL_R, L/h), calculated as $A_{e(0-t)}$ divided by $AUC_{(0-t)}$

For Group 5, Part 1, Treatment Period 2, the following PK parameters for TC-5214 will be derived using the dialysate concentrations:

- Cumulative amount of drug extracted unchanged into the dialysate over the dialysis period (time: 4 hours postdose to 8 hours postdose) ($Ad_{(4-8)}$, mg). The amount will be calculated and reported for each 1-hour dialysate collection interval, and cumulatively

- Fraction of dose extracted unchanged into the dialysate over the dialysis period ($fd_{(4-8)}$; % dose). The fraction will be calculated and reported for each collection interval and cumulatively.

- Dialysate clearance (CL_D, L/h), calculated as $Ad_{(4-8)}$ divided by $AUC_{(4-8)}$

For Group 5, Part 2, the following PK parameters for TC-5214 will be derived using the dialysate concentrations:

- Cumulative amount of drug extracted unchanged into the dialysate over the dialysis period (time: 72 hours postdose to 76 hours postdose) ($Ad_{(72-76)}$, mg). The amount will be calculated and reported for each 1-hour dialysate collection interval, and cumulatively

- Fraction of dose extracted unchanged into the dialysate over the dialysis period ($fd_{(72-76)}$; % dose). The fraction will be calculated and reported for each collection interval and cumulatively.

- Dialysate clearance (CL_D, L/h), calculated as $Ad_{(72-76)}$ divided by $AUC_{(72-76)}$

Additional PK parameters may be calculated if deemed appropriate.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY [redacted]

12.1 Description of analysis sets

12.1.1 General principles

The statistical analysis will be performed by [redacted] using SAS®, Version 9.1 or higher. The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively. The decision regarding validity of data for each of the analysis sets will be based on a blind review of data.

The as-treated principle will be applied to all evaluations; ie, volunteers who received another treatment than the one assigned will be analyzed as belonging to the actual treatment group.

12.1.2 Safety analysis set

All subjects who received at least 1 dose of IP and for whom any postdose data are available will be included in the safety population.

12.1.3 Pharmacokinetic Analysis Set

The PK analysis set will be a subset of the safety analysis set and will include only subjects who receive TC-5214 and have at least 1 postdose PK measurement without important protocol deviations or violations thought to significantly affect the PK. A strategy for dealing with data affected by protocol violations and deviations will be specified prior to clean file by the study team (eg, the CPA physician, and AstraZeneca/[redacted] pharmacokineticists and statisticians).

12.2 Methods of statistical analyses

12.2.1 General Principles

The statistical analysis will be performed at [redacted], using [redacted] Standard Operation Procedures and Work Instructions.

Study and PK data will be presented by renal function group. Safety data for all TC-5214 treated subjects combined will also be presented.

Since no planned formal testing will be performed in this study, and the confidence intervals that will be calculated are only for descriptive purposes, no corrections for multiplicity will be used.

Missing data will be result in a reduced sample size for that parameter. Since the statistical analyses will be predominantly presentations in tables and individual data listings, no action will be taken to handle missing data.

A volunteer who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

Quantitative continuous variables will be summarized using descriptive statistics, including the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max) values. Additionally, for PK parameters, (except for t_{max}), geometric means and geometric coefficient of variation (CV%) will be reported. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the standard deviation of the data on a log scale. Mean, SD, geometric mean and CV% will not be calculated for t_{max}.

Categorical variables (eg, sex) will be summarized in frequency tables (frequency and proportion of subjects in analysis set).

In general, descriptive statistics will follow the rounding convention in [redacted] Global SOPs.

Baseline characteristics will be summarized across all subjects.

12.2.2 Safety

All safety data (scheduled and unscheduled) will be presented in the data listings.

Safety variables (ie, clinical laboratory values, vital signs, and ECGs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived (eg, QT_c derived from QT interval).

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in data listings. All AEs, ECG outliers, and clinical laboratory outliers that occur following the first dose of study medication will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

All available data from subjects in the safety analysis set will be included in the safety analyses. No adjustment or imputation will be utilized for missing values or for subjects who withdraw prior to completing the study, neither will analyses be restricted to subjects with complete data.

All AEs will be collected for each subject when informed consent is obtained (Visit 1) until the follow-up visit (Visit 3). AEs that occur before dosing will be reported separately.

AEs will be summarized by preferred term and system organ class using MedDRA vocabulary (version 12.0 or higher) by treatment and across all treatments. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized.

Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs, and physical examination findings will be presented. All continuous safety data will be summarized across all treatments for the absolute value at each scheduled assessment and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each subject will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR.

For ECG parameters, the QT correction factor will be based on the Fridericia's formula. Further categorical summaries of absolute QT and QTcF values (greater than 450 ms, greater than 480 ms, greater than 500 ms) and change-from-baseline values in QT and QTcF values (greater than 30 ms, greater than 60 ms) may also be produced.

12.2.3 Pharmacokinetics

Pharmacokinetic concentrations will be reported to the same precision as the source data. For descriptive statistics, concentrations below lower limit of quantitation (LLOQ) values will be handled as follows:

- At a time point where at least 1 value is above LLOQ, but less than or equal to 50% of values are below LLOQ, all values below LLOQ are set to LLOQ and a mean (arithmetic and geometric) value and SD and CV% are calculated
- At a time point where more than half of the observations are below LLOQ only individual values are reported; mean, SD, geometric mean and CV% will be set to NQ (non quantifiable). The min value and the median are set to less than LLOQ
- If all values are below LLOQ, at any time point, no descriptive statistics are calculated for that time point. Write NA (not applicable) in the field for SD and CV% and write less than LLOQ in fields for mean, geometric mean, min, median and max in the table
- The number of observations greater than LLOQ [number of observations above LLOQ (N greater than LLOQ)] will be reported in the table

Pharmacokinetic parameters will be rounded for reporting purposes in the summary tables and subject listings, as per [redacted] SOPs.

Data from subjects excluded from an analysis population will be included in the data listings, but not in the summaries.

Pharmacokinetic data will be presented by renal function group using the primary classification of eGFR determined by the MDRD formula. In addition, as supportive information, a tabular summary of PK parameters will be presented based on an estimate of their creatinine clearance (CL_{CR}) derived using the Cockcroft-Gault equation (Cockcroft 1976), using the following formulas:

For males:

- CL_{CR} (mL/min) = {[(140-age(years)] x weight(kg)} / 72 x serum creatinine (mg/dL)

For females:

- CL_{CR} (mL/min) = {[(140-age(years)] x weight(kg)} / 72 x serum creatinine (mg/dL) x 0.85

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of all concentration-time data, individual and dose-normalized PK parameters will be presented by renal function. Figures of arithmetic mean concentration-time

data and dose-normalized PK parameters will be presented by renal function. Figures of PK parameters will also be presented by dose. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

For Groups 1 through 3 and Group 5, (Part 1,Treatment Period 1 and Part 2), regression models will be used to assess and quantify the relationship between renal function, as measured by eGFR, and TC-5214 dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The initial model will specify a linear relationship between primary pharmacokinetic parameters and eGFR and will be estimated using ordinary least squares. Log-transformations may be used to improve model fit. Non-linear models will be used if there is statistical evidence of departure from linearity at the 0.10 significance level. Further, models which are non-linear in the model parameters may be used if simpler models do not provide adequate fit. Model parameters, 90% CI and p-values will be reported. From the linear and final models, estimates of the mean pharmacokinetic parameters and 90% CI will be made at the median eGFR of each of the renal function groups, as will the differences (or ratios) and 90% CI relative to the normal renal group (at the group median eGFR).

As an exploratory analysis, the renal function groups will be compared using a one-way analysis of variance model on the log-transformed dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The renal impairment groups will be compared to the control subjects with normal renal function (Group 1), with the latter as reference. Geometric least-squares means with corresponding 95% CI and ratios of geometric least squares with corresponding 90% CI will be presented.

Comparisons of PK parameters for subjects in Group 5, Part 1, with ESRD between the two treatment periods (ie on a non dialysis day with those on a dialysis day) will be performed using a paired t-test (C_{max} and AUC).

12.3 Determination of sample size

Due to the exploratory nature of the study, no formal sample size calculation is made and the sample size is not based on any formal statistical criteria. The sample size of 8 subjects per dose group is based on experience from previous similar Phase I studies with other compounds and is considered to be sufficient to characterize the PK of TC-5214 and to gather information on safety and tolerability data of TC-5214 to achieve the objectives of the study while exposing as few subjects as possible to study medication and procedures.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4**

In the case of a medical emergency the Investigator may contact the CPA Physician. If the CPA Physician is not available, contact the CPA Program Director at the AstraZeneca Research and Development (R&D) site shown below.

Name	Role in the study	Address & telephone number
[redacted]	CPA Physician	[redacted] Work: [redacted] Mobile: [redacted]
[redacted]	CPA Program Director	[redacted] Work: [redacted] Mobile: [redacted]
[redacted]	Investigator	[redacted] Phone: [redacted]
[redacted]	Study Project Manager	[redacted] Work: [redacted] Mobile: [redacted] Fax: [redacted]

13.2 Overdose

For TC-5214 program, overdose is defined as a dose ingested (or taken via any other route), confirmed by the subject (if possible), in excess of the total daily dose specified for the subject in their treatment group of the protocol.

Clinical studies have demonstrated that TC-5214 is well tolerated when given to healthy subjects as single doses of up to 16 mg. Multiple dose regimens of TC-5214 starting at 1 mg twice daily titrated up to 4 mg twice daily were well tolerated for up to 8 weeks.

In the event of an overdose the subject should be monitored closely and treated symptomatically. All reports of overdose (with or without associated AEs) are to be collected.

There is no specific antidote to TC-5214. In cases of severe intoxication, intensive care procedures are recommended. Close medical supervision and monitoring should be continued until the subject recovers.

Signs of overdose with mecamylamine include hypotension (which may lead to peripheral vascular collapse), postural hypotension, nausea, vomiting, diarrhea, constipation, paralytic ileus, urinary retention, dizziness, anxiety, dry mouth, mydriasis, blurred vision, or palpitations. A rise in intraocular pressure may occur.

Pressor amines may be used to counteract excessive hypotension. Since subjects being treated with ganglion blockers are more than normally reactive to pressor amines, smaller doses of the latter are recommended to avoid excessive response.

In the event a study subject takes an overdose of study medication, the Investigator in the case of a medical emergency may break the treatment code as outlined in Section 5.4.2.

For recording purposes:

- If an overdose is reported during the course of a study, the subject is evaluated by the Investigator/site staff to determine whether an SAE, non-serious AE, or no symptoms have been experienced after the overdose has been taken

- If the subject experiences an overdose with an associated SAE, the Investigator/site staff will capture details of the SAE and associated information on OVERDOSE, AELOG, and SAE modules

- If the subject experiences an overdose with an associated non-serious AE, the Investigator/site staff will capture details of the non-serious AE and associated information on OVERDOSE and AELOG modules

- If the subject experiences an overdose with no symptoms, the Investigator/site staff will capture details of the overdose and associated information on OVERDOSE module only

- The OVERDOSE module will be used for collecting the overdose information

For reporting purposes:

- If an overdose occurs in the course of an AstraZeneca study, the Investigators/site staff must inform appropriate AstraZeneca representatives immediately, but no later than the end of the next business day of when he or she becomes aware of it.

- The designated AstraZeneca representative or its representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site (DES)

The following timelines will apply on reports of overdose:

- Fatal/life threatening SAEs are sent to DES within one calendar day of initial notification of the overdose

- Other SAEs are sent to DES within four calendar days of initial notification of the overdose

- Overdoses with no symptoms or with associated non-serious AEs are sent to DES within five calendar days of initial notification of the overdose

For overdoses associated with an SAE, standard reporting timelines apply.

All overdoses must be reported. In all instances, the overdose substance and amount ingested if known, must be stated and an assessment whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this should be clearly stated.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

13.3.2 Paternal exposure

Pregnancy of the subject's partners is not considered to be an AE. However, any conception occurring from the date of dosing until 2 weeks after the last dose of IP should be reported to AstraZeneca and followed up for its outcome.

14. LIST OF REFERENCES

Cockcroft 1976
Cockcroft DW, Gault MH (1976). "Prediction of creatinine clearance from serum creatinine". Nephron 16 (1): 31–41.

Guidance for Industry May 1998
Guidance for Industry: Pharmacokinetics in subjects with impaired renal function: study design, data analysis and impact on dosing and labeling. U.S. Department of Health and

Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 1998.

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National Kidney Foundation 2002
National Kidney, Foundation (2002). "K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification". Am. J. Kidney Dis. 39 (2 Suppl 1): S1–266.

Posner K 2007
Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007 Jul;164(7):1035-43.

Clinical Study Protocol Appendix B

Drug Substance	TC-5214
Study Code	D4130C00008
Edition Number	1
Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	TC-5214
Study Code	D4130C00008
Edition Number	1
Date	[redacted]

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between risk groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D

Drug Substance	TC-5214
Study Code	D4130C00008
Edition Number	1
Date	[redacted]

Appendix D
Columbia Suicide Severity Rating Scale (C-SSRS)

1. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline Version 7/19/08

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ____ _____ ***Most Severe Ideation: Type # (1-5) Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.	
Have you made a suicide attempt? ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?***	**Yes** **No** ☐ ☐
What did you do?	
Did you_____ as a way to end your life?	
Did you want to die (even a little) when you_____?	Total # of Attempts
Were you trying to end your life when you _____?	_____
Or did you think it was possible you could have died from_____?	
Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.	
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____

Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:			**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:			**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?			**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

2. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit Version 7/19/08

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). _____ _____ ***Most Severe Ideation: Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply; wish to die only	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____

Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	TC-5214
Study Code	D4130C00008
Date	[redacted]
Protocol Dated	[redacted]

An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

Sponsor:

AstraZeneca [redacted]

Centres affected by the Amendment:

This amendment will affect the principal site of [redacted], and any other center where recruitment may be conducted. For the purposes of this document, the revised text or text added will be presented in **bold** font. Page references are included for the original protocol, and revised protocol where applicable.

Reason for Amendment:

An interim review of the pharmacokinetic (PK) data from 2 subjects from Group 3 (moderate renal impairment eGFR ≥30 to <50 mL/min) and 2 subjects from Group 5, Period 1 [end stage renal disease (ESRD) on dialysis, dose administered after the completion of a hemodialysis session], was conducted 18 January, 2011.

Currently 3 subjects in Group 2, 3 subjects in Group 3, and 4 subjects in Group 5 have received investigational product and completed study procedures based on the original protocol design.

The changes in this amendment will be implemented and apply to the remaining subjects who will participate in this study (planned for 8 healthy volunteers, and 5 mild, 5 moderate, and 4 ESRD subjects).

The analysis of the data from the first 4 subjects demonstrated renal impairment reduces the plasma clearance of TC-5214 in accord with what might be predicted for a drug cleared predominantly via renal elimination. Thus the following changes will be made in order to ensure the adequate characterization of TC-5214 PK and patient safety:

1. The PK profile in patients with severe renal failure will be able to be determined from the data in subjects on dialysis obtained between their dialysis sessions, thus subjects with severe renal impairment (Group 4; eGFR <30 mL/min) will not be recruited for this study.

2. Given the prolonged elimination half-life of TC-5214 in and high percentage of the AUC requiring extrapolation in subjects with renal impairment, the blood and urine sampling collection intervals for TC-5214 PK sampling time will be extended to 120 hours postdose for Groups 1, 2, and 3 to allow for a more reliable estimation of TC-5214 elimination.

3. Urine will be collected for ESRD subjects in Group 5 who are able to produce urine output, which will allow us to obtain a more complete PK profile in these subjects as both total and renal clearance will then be able to be calculated.

4. Due to the greatly reduced TC-5214 plasma clearance in patients on dialysis, it will be possible to estimate TC-5214 PK from data obtained between and during dialysis after a single dose, so a second study period is not required, thus ESRD subjects in Group 5 will participate in only 1 treatment period, and receive only a single dose of TC-5214.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Page 2, Protocol Synopsis, Study center(s) and number of subjects planned

Previous text:

Eight subjects in each category of mild, moderate, severe renal impairment, end stage renal disease requiring dialysis, and 8 male or female subjects without renal impairment will be dosed for a total of approximately 40 evaluable subjects to complete the study.

Revised text:

Eight subjects in each category of mild, moderate renal impairment, end stage renal disease requiring dialysis, and 8 male or female subjects without renal impairment will be dosed for a total of approximately **32** evaluable subjects to complete the study.

Reason for Amendment:

Subjects with severe renal impairment (Group 4) will not be recruited for this study, reducing the number of evaluable subjects to approximately 32.

Section of protocol affected:

Page 3, Protocol Synopsis, Study design

Previous text:

Subjects will be enrolled into 1 of 5 groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate (eGFR), determined using the abbreviated, 4-variable Modification of Diet in Renal Disease formula as follows:

Group 1: control subjects with normal renal function: eGFR greater than 80 mL/min

Group 2: mild renal impairment: eGFR greater than or equal to 50 to 80 mL/min

Group 3: moderate renal impairment: eGFR greater than or equal to 30 to less than 50 mL/min

Group 4: severe renal impairment: eGFR less than 30 mL/min

Group 5: end stage renal disease: eGFR less than 30 mL/min, currently receiving dialysis

Subjects in Groups 1 through 4 will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 4. Study procedures in Group 4 may be extended by 24 hours (1 day) to Day 5 depending on a review of preliminary pharmacokinetic results obtained in Group 5 subjects. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic.

Subjects in Group 5 will be on dialysis. They participate in 2 treatment periods, and receive a single oral dose of TC-5214 on each occasion. For Treatment Period 1 subjects will be admitted into the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will receive a single dose of TC-5214 on Day 1 after completion of a dialysis session and will remain in the clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. Subjects who are unable to remain in the clinic during this time may have their samples collected as outpatients.

Subjects in Group 5 will return to the clinic after a washout period of at least 2 weeks to start Treatment Period 2. Subjects will be admitted to the clinic the morning of Day -1 or on

Day -2 at the discretion of the Investigator for Treatment Period 2. Time-matched vital signs will be collected on Day -1. Subjects in Treatment Period 2 will receive a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects will remain in the clinic until the start of their next dialysis session. Blood samples will be collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Safety assessments will be performed periodically throughout the treatment period. Dialysis fluid will be collected in 1-hour intervals. Subjects who are unable to remain in the clinic through the entire treatment period may have their samples collected as outpatients. Subject will return to the clinic for a follow-up visit 7 to 10 days following discharge from Treatment Period 2.

Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 to 4, and Group 5 (Treatment Period 1) who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

Subjects in Group 5 who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor if less than 6 subjects completed both treatment periods. Provided that at least 6 subjects completed Treatment Period 1, replacement subjects will only be enrolled to participate in Treatment Period 2 of the study.

Revised text:

Based on an interim review of the safety and pharmacokinetics data, subjects with severe renal impairment (previous Group 4) will not be recruited for this study and the study will be conducted in 2 parts.

Subjects will be enrolled into 1 of **4** groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate (eGFR), determined using the abbreviated, 4-variable Modification of Diet in Renal Disease formula as follows:

Group 1: control subjects with normal renal function: eGFR greater than 80 mL/min

Group 2: mild renal impairment: eGFR greater than or equal to 50 to 80 mL/min

Group 3: moderate renal impairment: eGFR greater than or equal to 30 to less than 50 mL/min

Group 5: end stage renal disease: eGFR less than 30 mL/min, currently receiving dialysis

Part 1, Groups 1 through 3:

Subjects in Groups 1 through **3** will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on

Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day **4**. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. **Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period. During Part 1, subjects in Groups 1 through 3 will have pharmacokinetic blood and urine samples collected through 72 hours postdose.**

Part 1, Group 5:

The first 4 subjects enrolled into Group 5 will participate in 2 treatment periods, and receive a single oral dose of TC-5214 on each occasion. For Treatment Period 1 subjects will be admitted into the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will receive a single dose of TC-5214 on Day 1 after completion of a dialysis session and will remain in the clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. Subjects who are unable to remain in the clinic during this time may have their samples collected as outpatients. Subjects will return to the clinic after a washout period of at least 2 weeks to start Treatment Period 2. Subjects will be admitted to the clinic the morning of Day -1 or on Day -2 at the discretion of the Investigator for Treatment Period 2. Time-matched vital signs will be collected on Day -1. Subjects in Treatment Period 2 will receive a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects will remain in the clinic until the start of their next dialysis session. Blood samples will be collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Safety assessments will be performed periodically throughout the treatment period. Dialysis fluid will be collected in 1-hour intervals. Subjects who are unable to remain in the clinic through the entire treatment period may have their samples collected as outpatients. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from Treatment Period 2. **Subjects who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor.**

Part 2, Groups 1 through 3:

Subjects in Groups 1 through **3** will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day **6**. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. **Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample**

collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

During Part 2, subjects in Groups 1 through 3 will have blood and urine samples collected through 120 hours postdose.

Part 2, Group 5:

The remainder of subjects enrolled into Group 5 will participate in 1 treatment period, and receive a single oral dose of TC-5214. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 after completion of their first inpatient dialysis session, and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 6.

Pharmacokinetic blood samples will be collected after a single oral dose (Day 1) for up to 120 hours postdose. Samples will be collected through 72 hours postdose (assessment between dialysis) and between 72 and 120 hours (assessment during dialysis). Pharmacokinetic urine samples will be collected for up to 120 hours postdose from subjects who are able to produce urine.

Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects who withdraw from the study prior to completion of all pharmacokinetic sample collections may be replaced at the discretion of the Sponsor.

Reason for Amendment:

To remove reference to the enrollment of subjects with severe renal impairment, clarify length of stay for Groups 1 to 3, outline single dose and single treatment period for remainder of Group 5 subjects, and clarify subject replacement.

Section of protocol affected:

Original Protocol Page 4, Protocol Synopsis, Target subject population

Amended Protocol Page 5

Previous text:

The target population will include male and female nonpregnant, nonlactating subjects with normal, and mild, moderate, and severe (on and off dialysis) renal impairment aged 18 to 80 years with a body mass index between 19 and 40 kg/m^2. The demographics of healthy subjects with normal renal function will be matched for age ± 10 years, and body mass index ± 3 kg/m^2, to the mean age and body mass index of subjects across the 4 renal impairment

groups. Sex will be matched to achieve similar distribution between male and female subjects.

Revised text:

The target population will include male and female nonpregnant, nonlactating subjects with normal, and mild, moderate, **and end stage renal impairment on dialysis**, aged 18 to 80 years with a body mass index between 19 and 40 kg/m^2. The demographics of healthy subjects with normal renal function will be matched for age ± 10 years, and body mass index ± 3 kg/m^2, to the mean age and body mass index of subjects across the **3** renal impairment groups. Sex will be matched to achieve similar distribution between male and female subjects.

Reason for Amendment:

To remove reference to the enrollment of subjects with severe renal impairment.

Section of protocol affected:

Original Protocol Page 4, Protocol Synopsis: Duration of treatment

Amended Protocol Page 5

Previous text:

For Groups 1 through 4 the duration of each subject's participation will be approximately 45 days, including a screening period of up to 30 days, a treatment period consisting of 4 to 5 nights (depending on the admission day) and a follow-up visit, 7 to 10 days after discharge from the treatment period. For subjects in Group 5 participating in the 2-period crossover portion of the study, duration of each subject's participation will be approximately 55 days.

Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator. Subjects in Group 5 will be given the option to remain at the clinic between samplings for the off dialysis assessment (post dialysis dosing) at the discretion of the Investigator.

Revised text:

For Groups 1 through **3** the duration of each subject's participation will be approximately **47** days, including a screening period of up to 30 days, a treatment period consisting of **6 to 7** nights (depending on the admission day) and a follow-up visit, 7 to 10 days after discharge from the treatment period.

For **the first 4 subjects** in Group 5 (Part 1) participating in the 2-period portion of the study, duration of each subject's participation will be approximately 55 days. **These subjects will be given the option to remain at the clinic between samplings for the off dialysis assessment (post dialysis dosing) at the discretion of the Investigator.**

For the remaining subjects in Group 5 (Part 2) participating in a single treatment period, duration of each subject's participation will be approximately 47 days.

Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.

Reason for Amendment:

Clarify length of stay given update in study design.

Section of protocol affected:

Page 16 and 17, Section 3.1, Overall study design and flow chart

Previous text:

This is a Phase I single dose, multi center, open-label study designed to evaluate the safety, tolerability and PK of TC-5214 in renally impaired subjects compared with subjects with normal renal function.

Subjects will be enrolled into 1 of 5 groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate (eGFR), determined using the abbreviated, 4-variable Modification of Diet in Renal Disease (MDRD) formula as follows:

Group 1: control subjects with normal renal function: eGFR greater than 80 mL/min

Group 2: mild renal impairment: eGFR greater than or equal to 50 to 80 mL/min

Group 3: moderate renal impairment: eGFR greater than or equal to 30 to less than 50 mL/min

Group 4: severe renal impairment: eGFR less than 30 mL/min

Group 5: end stage renal disease (ESRD): eGFR less than 30 mL/min, currently receiving dialysis

Subjects in Groups 1 through 4 will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 4. Study procedures in Group 4 may be extended by 24 hours (1 day) to Day 5 depending on a review of preliminary pharmacokinetic results obtained in Group 5 subjects. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic.

Subjects in Group 5 will be on dialysis. They participate in 2 treatment periods, and receive a single oral dose of TC-5214 on each occasion. For Treatment Period 1 subjects will be admitted into the clinic the morning of Day -1, or on Day -2 at the discretion of the

Investigator. Time-matched vital signs will be collected on Day -1. Subjects will receive a single dose of TC-5214 on Day 1 after completion of a dialysis session and will remain in the clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. Subjects who are unable to remain in the clinic during this time may have their samples collected as outpatients.

Subjects will return to the clinic after a washout period of at least 2 weeks to start Treatment Period 2. Subjects will be admitted to the clinic the morning of Day -1 or on Day -2 at the discretion of the Investigator for Treatment Period 2. Time-matched vital signs will be collected on Day -1. Subjects in Treatment Period 2 will receive a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects will remain in the clinic until the start of their next dialysis session. Blood samples will be collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Safety assessments will be performed periodically throughout the treatment period. Dialysis fluid will be collected in 1-hour intervals. Subjects who are unable to remain in the clinic through the entire treatment period may have their samples collected as outpatients. Subject will return to the clinic for a follow-up visit 7 to 10 days following discharge from Treatment Period 2.

Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 to 4, and Group 5 (Treatment Period 1) who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

Subjects in Group 5 who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor if less than 6 subjects completed both treatment periods. Provided that at least 6 subjects completed Treatment Period 1, replacement subjects will only be enrolled to participate in Treatment Period 2 of the study.

For details see the Study Flow Charts (Figure 1 and Figure 2) and the Study Plan Table 1 and Table 2 below.

Revised text:

This is a Phase I single dose, multi center, open-label study designed to evaluate the safety, tolerability and PK of TC-5214 in renally impaired subjects compared with subjects with normal renal function.

Based on an interim review of the safety and pharmacokinetics data, subjects with severe renal impairment (previous Group 4) will not be recruited for this study, and the study will be conducted in 2 parts.

Subjects will be enrolled into 1 of **4** groups in parallel, according to their degree of renal impairment based on their estimated glomerular filtration rate (eGFR), determined using the abbreviated, 4-variable Modification of Diet in Renal Disease (MDRD) formula as follows:

Group 1: control subjects with normal renal function: eGFR greater than 80 mL/min

Group 2: mild renal impairment: eGFR greater than or equal to 50 to 80 mL/min

Group 3: moderate renal impairment: eGFR greater than or equal to 30 to less than 50 mL/min

Group 5: end stage renal disease (ESRD): eGFR less than 30 mL/min, currently receiving dialysis

3.1.1 Part 1

Part 1, Groups 1 through 3:

Subjects in Groups 1 through **3** will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day **4**. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. **Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period. During Part 1, subjects in Groups 1 through 3 will have pharmacokinetic blood and urine samples collected through 72 hours postdose.**

Part 1, Group 5:

The first 4 subjects enrolled into Group 5 will participate in 2 treatment periods, and receive a single oral dose of TC-5214 on each occasion. For Treatment Period 1 subjects will be admitted into the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will receive a single dose of TC-5214 on Day 1 after completion of a dialysis session and will remain in the clinic for pharmacokinetic sample collections and safety assessments until the start of their next dialysis session. Subjects who are unable to remain in the clinic during this time may have their samples collected as outpatients. Subjects will return to the clinic after a washout period of at least 2 weeks to start Treatment Period 2. Subjects will be admitted to the clinic the morning of Day -1 or on Day -2 at the discretion of the Investigator for Treatment Period 2. Time-matched vital signs will be collected on Day -1. Subjects in Treatment Period 2 will receive a single dose of TC-5214 on Day 1, at 4 hours prior to the start of a dialysis session. Subjects will remain in the clinic until the start of their next dialysis session. Blood samples will be collected prior to dialysis, during the entire dialysis session, and until the start of their next dialysis session. Safety assessments will be performed periodically throughout the treatment period. Dialysis fluid will be collected in 1-hour intervals. Subjects who are unable to remain in the clinic through the entire treatment period may have their samples collected as outpatients. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from Treatment Period 2. **Subjects who withdraw from the study after**

completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor.

For details on Part 1, see the Study Flow Charts (Figure 1 and Figure 2) and the Study Plan Table 1 below.

3.1.2 Part 2

Part 2, Groups 1 through 3:

Subjects in Groups 1 through **3** will not be on dialysis. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day **6**. Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. **Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.**

During Part 2, subjects in Groups 1 through 3 will have blood and urine samples collected through 120 hours postdose.

Part 2, Group 5:

The remainder of subjects enrolled into Group 5 will participate in 1 treatment period, and receive a single oral dose of TC-5214. They will be admitted to the clinic the morning of Day -1, or on Day -2 at the discretion of the Investigator. Time-matched vital signs will be collected on Day -1. Subjects will then receive a single oral dose of TC-5214 on Day 1 after completion of their first inpatient dialysis session, and will remain in the clinic until the completion of the study assessments and procedures scheduled on Day 6.

Pharmacokinetic blood samples will be collected after a single oral dose (Day 1) for up to 120 hours postdose. Samples will be collected through 72 hours postdose (assessment between dialysis) and between 72 and 120 hours (assessment during dialysis). Pharmacokinetic urine samples will be collected for up to 120 hours postdose from subjects who are able to produce urine.

Subjects will return to the clinic for a follow-up visit 7 to 10 days following discharge from the clinic. Subjects who withdraw from the study prior to completion of all pharmacokinetic sample collections may be replaced at the discretion of the Sponsor.

For details on Part 2 see the Study Flow Charts (Figure 1 and Figure 3) and the Study Plan Table 2 below.

Reason for Amendment:

To remove reference to the enrollment of subjects with severe renal impairment, clarify length of stay for Groups 1 to 3, outline single dose and single treatment period for remainder of Group 5 subjects, and clarify subject replacement, akin to previous changes adopted for the protocol synopsis.

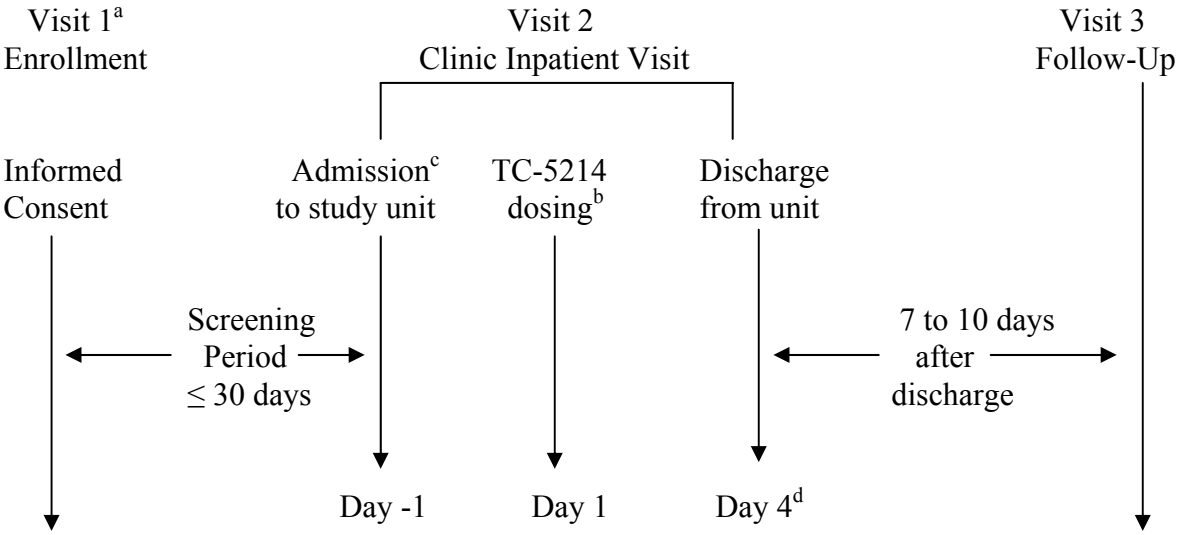
Section of protocol affected:

Original Protocol Pages 18 through 19, Section 3.1 Figures 1 and 2

Amended Protocol Pages 18 through 20

Previous text:

Figure 1: Study Flow Chart Groups 1 through 4



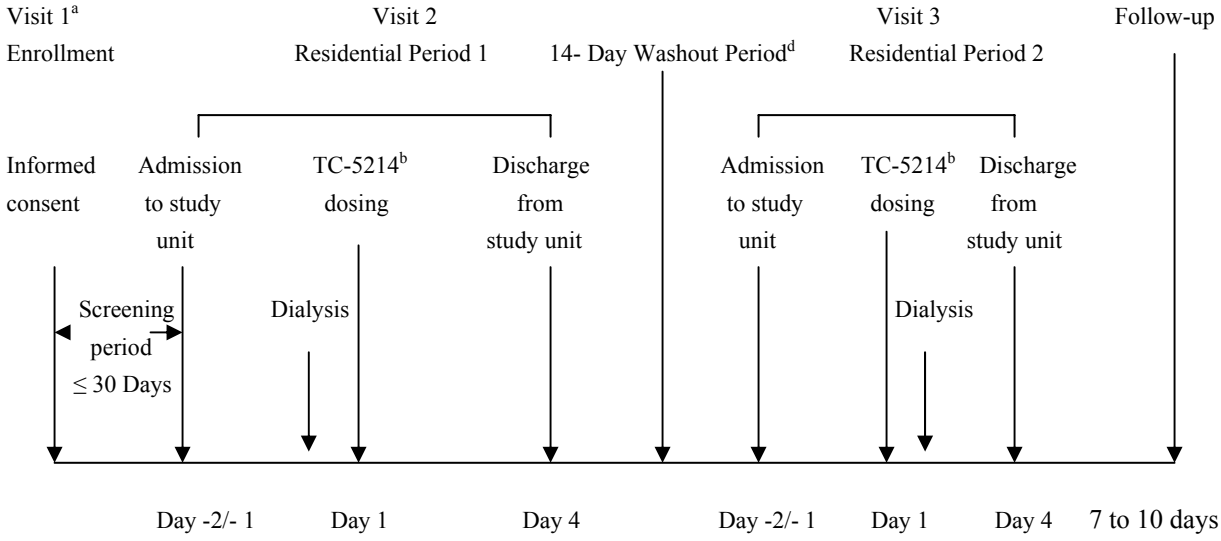
[a] Visit 1 may be conducted over 1 or more days during the screening period.

[b] A single dose of TC-5214 8 mg will be administered for Groups 1 and 2, 2 mg will be administered for Groups 3 and 4 on Day 1

[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.

[d] For Group 4, the clinic inpatient visit may be extended by 1 day with subjects discharged on Day 5 if warranted based on preliminary PK results from subjects in Group 5

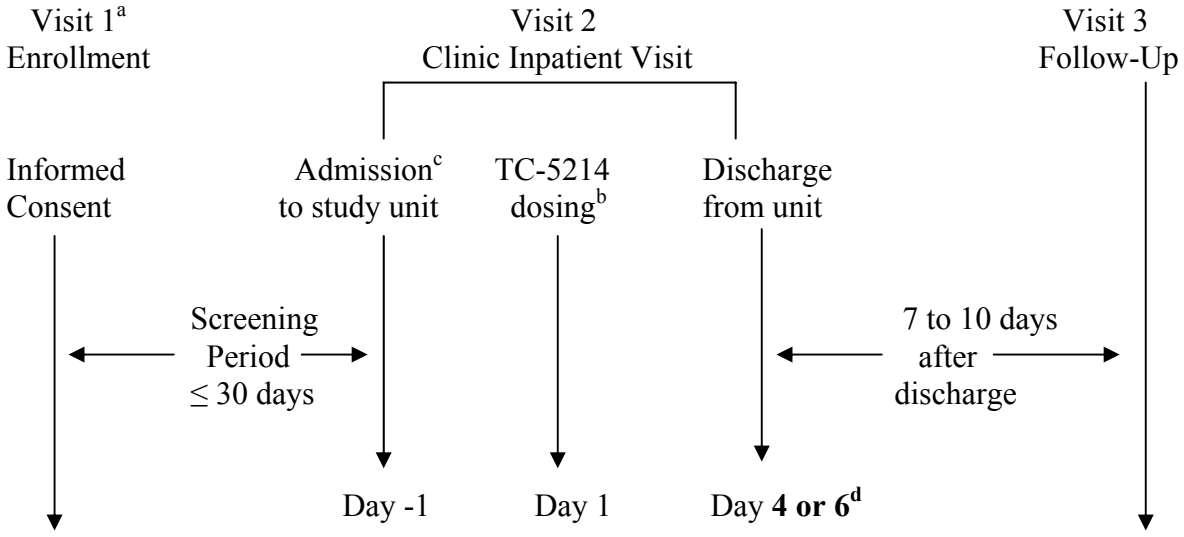
Figure 2: Study Flow Chart Group 5



[a] Visit 1 may be conducted over 1 or more days during the screening period.
[b] A single dose of TC-5214 2 mg will be administered to Group 5 on Day 1 of each residential period
[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.
[d] At least 14 days between TC-5214 administrations.

Revised text:

Figure 1: Study Flow Chart Groups 1 through **3**



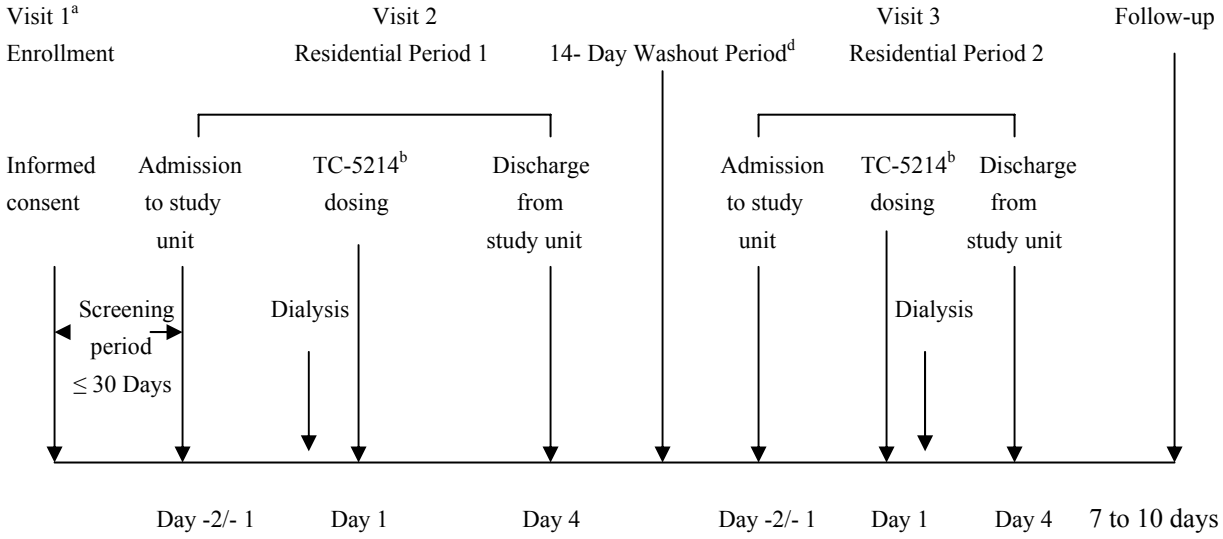
[a] Visit 1 may be conducted over 1 or more days during the screening period.

[b] A single dose of TC-5214 8 mg will be administered for Groups 1 and 2, 2 mg will be administered for **Group 3** on Day 1

[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.

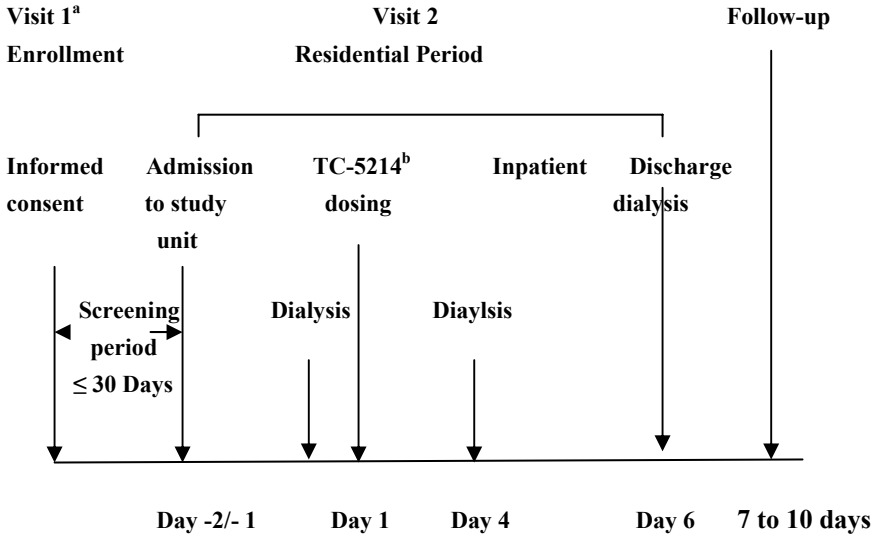
[d] **For subjects in Groups 1 through 3, during Part 1 blood and urine samples are collected through 72 hours postdose, and for Part 2, blood and urine samples are collected through 120 hours postdose.**

Figure 2: Study Flow Chart Group 5**, Part 1**



[a] Visit 1 may be conducted over 1 or more days during the screening period.
[b] A single dose of TC-5214 2 mg will be administered to Group 5 on Day 1 of each residential period**.**
[c] Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.
[d] At least 14 days between TC-5214 administrations.

Figure 3: Study Flow Chart Group 5, Part 2



[a] **Visit 1 may be conducted over 1 or more days during the screening period.**
[b] **A single dose of TC-5214 2 mg will be administered to Group 5 on Day 1.**
[c] **Subjects may be admitted to the clinic on Day -2 to allow for the Day 1 time-matched safety assessments at the discretion of the Investigator.**

Reason for Amendment:

Figure 1 and figure 2 are updated to clarify subjects with severe renal impairment will not be enrolled, and the variable length of the residential period depending on the study part.
Figure 3 was added to reflect updated single dose design for Group 5, Part 2 subjects.

Section of protocol affected:

Original Protocol Pages 20 through 25, Tables 1 and 2

Amended Protocol Pages 21 through 26

See chart beginning on next page:

Previous text:

Table 1: Study Plan

Visit number	1	2 Residential Period (For Group 5 – 2 Residential Periods)					3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	Follow-Up 7 to 10 days following discharge	Details in Section
Informed consent	X							8.4
Demography	X							6.2
Inclusion/exclusion criteria	X	X						4
Physical Examination	X	X[i]				X[i]	X	6.3.6
Height and weight [a]	X	X				X		6.3.6
Medical and Surgical History	X							6.2
Columbia Suicide Severity Rating Scale	X	X				X	X	6.2
Clinical chemistry	X	X				X	X	6.3.5
Hematology	X	X				X	X	6.3.5
Urinalysis	X	X				X	X	6.3.5

Visit number	1	2 Residential Period (For Group 5 – 2 Residential Periods)					3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	Follow-Up 7 to 10 days following discharge	Details in Section
HIV and HBV Serology	X							6.3.5
Drugs of Abuse Screen	X	X						6.3.5
Alcohol Screen		X						6.3.5
Blood pregnancy test for female subjects of childbearing potential	X	X				X		6.3.5
Orthostatic blood pressure (supine, seated, and standing) and pulse[b]	X	X	X	X	X	X	X	6.3.7
Oral temperature and respiration rate	X	X	X	X	X	X	X	6.3.5
12-lead ECG [c]	X	X	X			X	X	6.3.6.1
Admission to the clinic		X						NA
Pharmacogenetic sampling (optional)[k]		X						6.5.1
TC-5214 administration [d]			X					5.5.2
Blood sample collection for PK [e]			X	X	X	X		6.4.1.1

Visit number	1	2 Residential Period (For Group 5 – 2 Residential Periods)					3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	Follow-Up 7 to 10 days following discharge	Details in Section
Urine sample collection for PK [f]			X	X	X	X		6.4.1.2
Dialysis Period / Dialysate Collection			X[j]					6.4.1.3
Discharge from clinic						X[g]		NA
Concomitant medications	X	X	X	X	X	X		5.6
Adverse Events	X	X	X	X	X	X	X	6.3

[a] Height will be measured during the screening visit only.
[b] Orthostatic blood pressure and pulse will be measured at the Screening Visit, on Day -1 (time to correspond with the planned predose and 4 hour postdose timings for Day 1), on Day 1 at predose and 4 hours post dose, each morning during the residential period and at the Follow-up Visit.
[c] Subjects must rest in the supine position for 10 minutes prior to the 12-lead ECG evaluation to be performed at screening, on admission on Day -1, on Day 1 at 4 hours postdose, before discharge on Day 4, and at the Follow-up Visit
[d] Study drug will be administered with 240 mL room temperature water
[e] For detailed timings of blood PK sampling times see Section 6.4.1.1.
[f] Urine collection times for Groups 1 to 4: Urine will be collected for 72 hours postdose in the following intervals: 0-12, 12-24, 24-48 and 48-72 hours.
[g] Subjects will be discharged from the unit after all study procedures have been completed.
[h] Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.
[i] Abbreviated physical examination.
[j] Applies only to Group 5, Treatment Period 2. Subjects will start their scheduled dialysis at 4 hours post TC-5214 administration. Dialysate will be collected over 1 hour intervals throughout the entire (approximately 4 hour) dialysis session (eg, 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours).
[k] Subjects must agree to sign a separate, optional informed consent for genetic research in order for this sample to be collected.

Table 2: Optional Study Plan for Group 4 to Accommodate a 24-hour Extension of Study Procedures

Visit number	1	2 Residential Period (For Group 5 – 2 Residential Periods)						3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	5	Follow-Up 7 to 10 days following discharge	Details in Section
Informed consent	X								8.4
Demography	X								6.2
Inclusion/exclusion criteria	X	X							4
Physical Examination	X	X[i]					X[i]	X	6.3.6
Height and weight [a]	X	X					X		6.3.6
Medical and Surgical History	X								6.2
Columbia Suicide Severity Rating Scale	X	X					X	X	6.2
Clinical chemistry	X	X					X	X	6.3.5
Hematology	X	X					X	X	6.3.5
Urinalysis	X	X					X	X	6.3.5
HIV and HBV Serology	X								6.3.5

Visit number	1	2 Residential Period (For Group 5 – 2 Residential Periods)						3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	5	Follow-Up 7 to 10 days following discharge	Details in Section
Drugs of Abuse Screen	X	X							6.3.5
Alcohol Screen		X							6.3.5
Blood pregnancy test for female subjects of childbearing potential	X	X					X		6.3.5
Orthostatic blood pressure (supine, seated, and standing) and pulse[b]	X	X	X	X	X	X	X	X	6.3.7
Oral temperature and respiration rate	X	X	X	X	X	X	X	X	6.3.5
12-lead ECG [c]	X	X	X				X	X	6.3.6.1
Admission to the clinic		X							NA
Pharmacogenetic sampling (optional)[j]		X							6.5.1
TC-5214 administration [d]			X						5.5.2
Blood sample collection for PK [e]			X	X	X	X	X		6.4.1.1
Urine sample collection for PK [f]			X	X	X	X	X		6.4.1.2

Visit number	1	2 Residential Period (For Group 5 – 2 Residential Periods)						3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	5	Follow-Up 7 to 10 days following discharge	Details in Section
Discharge from clinic							X[g]		NA
Concomitant medications	X	X	X	X	X	X	X		5.6
Adverse Events	X	X	X	X	X		X	X	6.3

Note: This optional Study Plan for Group 4 will only apply if PK data from Group 5 indicate that PK collections beyond 72 hours postdose are required to adequately characterize the PK of TC-5214 in this population. The decision to extent the study procedures to 5 days will be made after review of available preliminary PK data obtained in Group 5 subjects who complete Period 1.

[a] Height will be measured during the screening visit only.

[b] Orthostatic blood pressure and pulse will be measured at the Screening Visit, on Day -1 (time to correspond with the planned predose and 4 hour postdose timings for Day 1), on Day 1 at predose and 4 hours post dose, each morning during the residential period and at the Follow-up Visit.

[c] Subjects must rest in the supine position for 10 minutes prior to the 12-lead ECG evaluation to be performed at screening, on admission on Day -1, on Day 1 at 4 hours postdose, before discharge on Day 5, and at the Follow-up Visit

[d] Study drug will be administered with 240 mL room temperature water

[e] For detailed timings of blood PK sampling times see Section 6.4.1.1.

[f] Urine will be collected for 72 hours postdose in the following intervals: 0-12, 12-24, 24-48, 48-72, and 72-96 hours.

[g] Subjects will be discharged from the unit after all study procedures have been completed.

[h] Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.

[i] Abbreviated physical examination.

Revised text:

Table 1: Study Plan, **Part 1**

Visit number	1	2 Residential Period (For Group 5**, Part 1** – 2 Residential Periods)					3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	Follow-Up 7 to 10 days following discharge	Details in Section
Informed consent	X							8.4
Demography	X							6.2
Inclusion/exclusion criteria	X	X						4
Physical Examination	X	X[i]				X[i]	X	6.3.6
Height and weight [a]	X	X				X		6.3.6
Medical and Surgical History	X							6.2
Columbia Suicide Severity Rating Scale	X	X				X	X	6.2
Clinical chemistry	X	X				X	X	6.3.5
Hematology	X	X				X	X	6.3.5
Urinalysis	X	X				X	X	6.3.5

Visit number	1	2 Residential Period (For Group 5**, Part 1** – 2 Residential Periods)					3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	Follow-Up 7 to 10 days following discharge	Details in Section
HIV and HBV Serology	X							6.3.5
Drugs of Abuse Screen	X	X						6.3.5
Alcohol Screen		X						6.3.5
Blood pregnancy test for female subjects of childbearing potential	X	X				X		6.3.5
Orthostatic blood pressure (supine, seated, and standing) and pulse[b]	X	X	X	X	X	X	X	6.3.7
Oral temperature and respiration rate	X	X	X	X	X	X	X	6.3.5
12-lead ECG [c]	X	X	X			X	X	6.3.6.1
Admission to the clinic		X						NA
Pharmacogenetic sampling (optional)[k]		X						6.5.1
TC-5214 administration [d]			X					5.5.2
Blood sample collection for PK [e]			X	X	X	X		6.4.1.1

Visit number	1	2 Residential Period (For Group 5**, Part 1** – 2 Residential Periods)					3	
Activity/ Day	-30 to -2 Screening	-1[h]	1	2	3	4	Follow-Up 7 to 10 days following discharge	Details in Section
Urine sample collection for PK [f]			X	X	X	X		6.4.1.2
Dialysis Period / Dialysate Collection			X[j]					6.4.1.3
Discharge from clinic						X[g]		NA
Concomitant medications	X	X	X	X	X	X		5.6
Adverse Events	X	X	X	X	X	X	X	6.3

[a] Height will be measured during the screening visit only.
[b] Orthostatic blood pressure and pulse will be measured at the Screening Visit, on Day -1 (time to correspond with the planned predose and 4 hour postdose timings for Day 1), on Day 1 at predose and 4 hours postdose, each morning during the residential period and at the Follow-up Visit.
[c] Subjects must rest in the supine position for 10 minutes prior to the 12-lead ECG evaluation to be performed at screening, on admission on Day -1, on Day 1 at 4 hours postdose, before discharge on Day 4, and at the Follow-up Visit.
[d] Study drug will be administered with 240 mL room temperature water.
[e] For detailed timings of blood PK sampling times see Section 6.4.1.1.
[f] Urine collection times for Groups 1 to **3**: Urine will be collected for 72 hours postdose in the following intervals: 0-12, 12-24, 24-48 and 48-72 hours.
[g] Subjects will be discharged from the unit after all study procedures have been completed.
[h] Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.
[i] Abbreviated physical examination.
[j] Applies only to Group 5, **Part 1,** Treatment Period 2. Subjects will start their scheduled dialysis at 4 hours post TC-5214 administration. Dialysate will be collected over 1 hour intervals throughout the entire (approximately 4 hour) dialysis session (eg, 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours).
[k] Subjects must agree to sign a separate, optional informed consent for genetic research in order for this sample to be collected.

Table 2: Study Plan, Part 2

Visit number	**1**	**2 Residential Period**							**3**	
Activity/ Day	**-30 to -2 Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**5**	**6**	**Follow-Up 7 to 10 days following discharge**	**Details in Section**
Informed consent	X									8.4
Demography	X									6.2
Inclusion/exclusion criteria	X	X								4
Physical Examination	X	X[i]						X[i]	X	6.3.6
Height and weight [a]	X	X						X		6.3.6
Medical and Surgical History	X									6.2
Columbia Suicide Severity Rating Scale	X	X						X	X	6.2
Clinical chemistry	X	X						X	X	6.3.5
Hematology	X	X						X	X	6.3.5
Urinalysis	X	X						X	X	6.3.5
HIV and HBV Serology	X									6.3.5

Visit number	**1**	**2 Residential Period**							**3**	
Activity/ Day	**-30 to -2 Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**5**	**6**	**Follow-Up 7 to 10 days following discharge**	**Details in Section**
Drugs of Abuse Screen	X	X								6.3.5
Alcohol Screen		X								6.3.5
Blood pregnancy test for female subjects of childbearing potential	X	X						X		6.3.5
Orthostatic blood pressure (supine, seated, and standing) and pulse[b]	X	X	X	X	X	X	X	X	X	6.3.7
Oral temperature and respiration rate	X	X	X	X	X	X	X	X	X	6.3.5
12-lead ECG [c]	X	X	X					X	X	6.3.6.1
Admission to the clinic		X								NA
Pharmacogenetic sampling (optional)[k]		X								6.5.1
TC-5214 administration [d]			X							5.5.2
Blood sample collection for PK [e]			X	X	X	X	X	X		6.4.1.1

Visit number	**1**	**2 Residential Period**						**3**	
Activity/ Day	**-30 to -2 Screening**	**-1[h]**	**1**	**2**	**3**	**4**	**5**	**6**	**Follow-Up 7 to 10 days following discharge**	**Details in Section**
Urine sample collection for PK [f]			X	X	X	X	X	X		6.4.1.2
Dialysis Period			X			X				6.4.1.3
Dialysate Collection						X[j]				6.4.1.3
Discharge from clinic								X[g]		NA
Concomitant medications	X	X	X	X	X	X	X	X		5.6
Adverse Events	X	X	X	X	X	X	X	X	X	6.3

[a] Height will be measured during the screening visit only.
[b] Orthostatic blood pressure and pulse will be measured at the Screening Visit, on Day -1 (time to correspond with the planned predose and 4 hour postdose timings for Day 1), on Day 1 at predose and 4 hours postdose, each morning during the residential period and at the Follow-up Visit.
[c] Subjects must rest in the supine position for 10 minutes prior to the 12-lead ECG evaluation to be performed at screening, on admission on Day -1, on Day 1 at 4 hours postdose, before discharge on Day **6**, and at the Follow-up Visit.
[d] Study drug will be administered with 240 mL room temperature water.
[e] For detailed timings of blood PK sampling times see Section 6.4.1.1.
[f] Urine collection times: Urine **samples for PK** will be collected for **120** hours postdose in the following intervals: 0-12, 12-24, 24-48, 48-72, **72-96, and 96-120** hours. **Urine will be collected for subjects in Part 2 for Groups 1 through 3, and for subjects in Group 5 who produce urine.**
[g] Subjects will be discharged from the unit after all study procedures have been completed.
[h] Subjects may be admitted to the clinic on Day -2 for the Day -1 assessments at the discretion of the Investigator.
[i] Abbreviated physical examination.
[j] **For Group 5 (Part 2),** dialysate will be collected over 1 hour intervals throughout the entire (approximately 4 hour) dialysis session (eg, **72 to 73, 73 to 74, 74 to 75, and 75 to 76** hours **postdose**).
[k] Subjects must agree to sign a separate, optional informed consent for genetic research in order for this sample to be collected.

Reason for Amendment:

To reflect updated study design.

Section of protocol affected:

Original Protocol Page 26, Section 3.2, Rationale for study design, doses and control groups, Paragraph 3 onward

Amended Protocol Page 27

Previous text:

In order to avoid bias due to demographic differences between the control subjects with normal renal function and subjects with renal impairment, the control group will be matched to the mean demographic characteristics of the 4 renal impairment groups with an allowable variability in age of +/- 10 years and in BMI of ± 3 kg/m^2. Sex will be matched to achieve similar distribution between male and female subjects. Only control subjects with stable chronic medical conditions will be included.

Based on available data to date, the mean terminal half-life ($t_{1/2,\lambda z}$) of TC-5214 in human plasma is approximately 8 to 9 hours. Renal impairment may increase the half-life of TC-5214, so the selected sampling period of up to 72 hours postdose is chosen to adequately determine the plasma PK of TC-5214.

For Group 4 (severely impaired renal patients not on dialysis), an optional extension of PK sampling for up to 96 hours postdose has been included as part of the study design, should preliminary PK results in ESRD subjects indicate that 72 hour PK sampling may be insufficient to characterize TC-5214 PK in this population due to reduced TC-5214 clearance caused by significant renal impairment.

Revised text:

In order to avoid bias due to demographic differences between the control subjects with normal renal function and subjects with renal impairment, the control group will be matched to the mean demographic characteristics of the **3** renal impairment groups with an allowable variability in age of +/- 10 years and in BMI of ± 3 kg/m^2. Sex will be matched to achieve similar distribution between male and female subjects. Only control subjects with stable chronic medical conditions will be included.

Based on available data to date, the mean terminal half-life ($t_{1/2,\lambda z}$) of TC-5214 in human plasma is approximately 8 to 9 hours. **Based on limited interim PK data in 2 subjects with moderate impairment, and 2 subjects with ESRD, renal impairment has been shown to increase the half-life of TC-5214 by approximately 3 and 10 fold, respectively.**

For Groups 1 to 3, the study design has been updated to extend the sampling period to 120 hours postdose to adequately characterize the elimination phase of TC-5214 and more accurately determine TC-5214 PK parameters (eg $t_{1/2,\lambda z}$, AUC, and CL/F). For Group 5 it was determined that a single dose of TC-5214 administered after the completion of a dialysis session, with the collection of blood samples for PK through 120 hours postdose (including a 4 hour dialysis session beginning approximately 72 hours postdose) would enhance patient safety.

The PK profile in patients with severe renal failure will be extrapolated from the data in subjects on dialysis obtained between their dialysis sessions, thus subjects with severe renal impairment (eGFR <30 mL/min) will not be recruited for this study.

Reason for Amendment:

To add additional rationale for study design changes.

Section of protocol affected:

Original Protocol Page 32, Section 5.2, Subject enrollment and initiation of investigational product

Amended Protocol Page 33

Previous text:

The Investigator will ensure:

1. Signed informed consent is obtained from each potential subject before any study specific procedures are performed

2. The eligibility of each subject is determined. See Sections 4.1 and 4.2.

3. Each screened subject is assigned a unique enrollment number or Ecode (eg E0001001) at screening (before any procedures are completed)

4. Subjects who pass all screening procedures will return to the clinic on Day -1

Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 to 4, and Group 5 (Treatment Period 1) who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

Subjects in Group 5 who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor (Section 5.9) if less than 6 subjects completed both treatment periods. Provided that at least 6 subjects completed Treatment Period 1, replacement subjects will only be enrolled to participate in Treatment Period 2 of the study.

All replacements must be approved by AstraZeneca. If a subject withdraws his/her participation in the study, then his/her enrollment code cannot be reused. Enrollment codes for replacement subjects will be assigned as follows: the original subject's number plus 1000 (eg, if the original subject being replaced had a subject number of 504, the replacement subject's number will be 1504).

Revised text:

The Investigator will ensure:

1. Signed informed consent is obtained from each potential subject before any study specific procedures are performed

2. The eligibility of each subject is determined. See Sections 4.1 and 4.2.

3. Each screened subject is assigned a unique enrollment number or Ecode (eg E0001001) at screening (before any procedures are completed)

4. Subjects who pass all screening procedures will return to the clinic on Day -1

Subjects in Group 1 who withdraw from the study prior to completion of all PK sample collections may be replaced; subjects in Groups 2 and 3 who withdraw from the study prior to completion of all PK sample collections may be replaced to ensure a minimum of 6 subjects complete the treatment period.

Subjects in Group 5, **Part 1**, who withdraw from the study after completion of Treatment Period 1 (assessments between dialysis) and before entering Treatment Period 2 (assessments during dialysis) may be replaced at the discretion of the Sponsor (see Section 5.9). **Subjects in Group 5, Part 2 may be replaced.**

All replacements must be approved by AstraZeneca. If a subject withdraws his/her participation in the study, then his/her enrollment code cannot be reused. Enrollment codes for replacement subjects will be assigned as follows: the original subject's number plus 1000 (eg, if the original subject being replaced had a subject number of 504, the replacement subject's number will be 1504).

Reason for Amendment:

Subjects in group 4 will not be enrolled.

Section of protocol affected:

Original Protocol Page 33, Section 5.5.2: Doses and treatment regimens

Amended Protocol Page 34 and 35

Previous text:

Investigational product will be administered with 240 mL of water. For details on food and fluid intake surrounding drug administration refer to Section 5.1.

Subjects in Groups 1 and 2 will receive a single dose of TC-5214 8 mg (2 x 4 mg tablets).

Subjects in Groups 3 and 4 will receive a single dose of TC-5214 2 mg.

Subjects in Groups 5 will receive a single dose of TC-5214 2 mg, on 2 occasions, once during each treatment period. These doses will be separated by a washout period of at least 14 days.

Revised text:

Investigational product will be administered with 240 mL of water. For details on food and fluid intake surrounding drug administration refer to Section 5.1.

Subjects in Groups 1 and 2 will receive a single dose of TC-5214 8 mg (2 x 4 mg tablets).

Subjects in Groups 3 will receive a single dose of TC-5214 2 mg.

Subjects in **Groups 5, Part 1** will receive a single dose of TC-5214 2 mg, on 2 occasions, once during each treatment period. These doses will be separated by a washout period of at least 14 days.

Subjects in Groups 5, Part 2 will receive a single dose of TC-5214 2 mg.

Reason for Amendment:

Clarify doses to be administered.

Section of protocol affected:

Original Protocol Page 37, Section 6.2.1, Follow-up procedures, Sentence 1

Amended Protocol Page 39

Previous text:

A poststudy medical examination will be performed 7 to 10 days after discharge (for Group 5, after Treatment Period 2) from the study site.

Revised text:

A poststudy medical examination will be performed 7 to 10 days after the **final** discharge from the study site.

Reason for Amendment:

Clarify instructions.

Section of protocol affected:

Original Protocol Page 42, Section 6.3.5, Laboratory safety assessment, Paragraph 2

Amended Protocol Page 43

Previous text:

If a urine sample is positive for protein or blood, a microscopic examination of the urine sediment will be performed. Urine samples will not be required for anuric subjects.

Revised text:

If a urine sample is positive for protein or blood, a microscopic examination of the urine sediment will be performed. Urine **safety** samples will not be required for anuric subjects.

Reason for Amendment:

To clarify that urine will be collected for subjects in Group 5, Part 2 to determine TC-5214 if available.

Section of protocol affected:

Original Protocol Page 44 to 45, Section 6.4, Pharmacokinetics

Amended Protocol Pages 45 through 47

Previous text:

6.4.1 Collection of samples

All samples will be collected, labelled stored and shipped as detailed in Laboratory Manual. It must be ensured that samples collected for subjects in Group 5 will be clearly labeled with the treatment period information.

6.4.1.1 Blood Samples

Blood samples (approximately 6 mL, split into 2 tubes, collected in K2 EDTA tubes) for determination of TC-5214 in plasma will be taken on the days presented in the study plans Table 1 and Table 2.

For Group 1, Group 2, and Group 3 blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose.

For Group 4 blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose. If study procedures for any subjects in Group 4 are extended by 24 hours to Day 5, PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose.

For Group 5 blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose. For Treatment Period 2, the timing of sample collections is the same as for Treatment Period 1, however, the sample scheduled for collection at 4 hours must be collected immediately before dialysis start, and the sample scheduled at 8 hours must be collected immediately after dialysis completion rather than strictly adhering to the scheduled

sampling times at 4 and 8 hours. For Treatment Period 2, the blood samples during and surrounding the hemodialysis session will be collected from predialyzer lines.

For Groups 1 to 4, and Group 5 for Treatment Period 1, 2 plasma samples (2.5 and 12 hour postdose) will be initially analyzed for unbound concentrations of TC-5214. After review of these data, if plasma protein binding of TC-5214 appears to be concentration or time-dependent, some or all of the remaining samples from each subject may be analyzed. Plasma samples from Group 5, Treatment Period 2 will not be analyzed for unbound concentrations of TC-5214.

The date and time of collection of each sample will be recorded on the pCRF. For blood volume, see Section 7.1.

6.4.1.2 Urine Samples

Urine samples (approximately 10 mL in total, split into 2 tubes) from subjects in Groups 1 through 4 for determination of concentrations of TC-5214 in urine will be taken from the total urine sample provided during each collection period presented in the study plans. The weight, volume, specific gravity, and start/stop time for each interval of each urine collection will be recorded.

Urine will be collected for the determination of TC-5214 from predose to 72 hours post dose over the intervals presented in Table 1 and Table 2.

6.4.1.3 Dialysate Samples

For Group 5, Treatment Period 2, the dialysate will be collected in custom buckets over 1 hour intervals throughout the entire (approximately 4 hours) dialysis period (eg, 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours). The blood flow, dialysate flow rate, dialysate volume, and the make and model of the dialyzer will be recorded. The entire dialysate will be collected, its volume recorded, and a sample retained for the analysis of TC-5214 concentrations.

Revised text:

6.4.1 Collection of samples

All samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual. It must be ensured that samples collected for subjects in **Group 5, Part 1** will be clearly labeled with the treatment period information.

6.4.1.1 Blood Samples

Blood samples (approximately 6 mL, split into 2 tubes, collected in K2 EDTA tubes) for determination of TC-5214 in plasma will be taken on the days presented in the study plans.

Part 1:

For Group 1, Group 2, and Group 3 blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose.

For Group 5, Part 1, blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose. For Treatment Period 2, the timing of sample collections is the same as for Treatment Period 1, however, the sample scheduled for collection at 4 hours must be collected immediately before dialysis start, and the sample scheduled at 8 hours must be collected immediately after dialysis completion rather than strictly adhering to the scheduled sampling times at 4 and 8 hours. For Treatment Period 2, the blood samples during and surrounding the hemodialysis session will be collected from predialyzer lines.

Part 2:

For Part 2, Group 1, Group 2, and Group 3, blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours postdose.

For Group 5, Part 2, blood PK samples will be collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 74, 76, 96, and 120 hours postdose. The sample scheduled for collection at 72 hours must be collected immediately before dialysis start, and the sample scheduled at 76 hours must be collected immediately after dialysis completion rather than strictly adhering to the scheduled sampling times. Blood samples during and surrounding the hemodialysis session will be collected from predialyzer lines.

The date and time of collection of each sample will be recorded on the pCRF. For blood volume, see Section 7.1.

6.4.1.2 Protein binding

For Groups 1 to **3**, Group 5**, Part 1** for Treatment Period 1**, and Group 5, Part 2,** 2 plasma samples (2.5 and 12 hour postdose) will be initially analyzed for unbound concentrations of TC-5214. After review of these data, if plasma protein binding of TC-5214 appears to be concentration or time-dependent, some or all of the remaining samples from each subject may be analyzed.

Plasma samples from Group 5, **Part 1,** Treatment Period 2, will not be analyzed for unbound concentrations of TC-5214.

The date and time of collection of each sample will be recorded on the pCRF. For blood volume, see Section 7.1.

6.4.1.3 Urine Samples

Urine samples (approximately 10 mL in total, split into 2 tubes) for determination of concentrations of TC-5214 in urine will be taken from the total urine sample provided during each collection period presented in the study plans. The weight, volume, specific gravity, and start/stop time for each interval of each urine collection will be recorded.

For Part 1, urine will be collected in Groups 1 through 3 from predose to 72 hours postdose (see Table 1).

For Part 2, urine will be collected in Groups 1 through 3 and in Group 5 subjects who are able to produce urine from predose to 120 hours postdose (see Table 2).

6.4.1.4 Dialysate Samples

For Group 5, the dialysate will be collected in custom buckets over 1 hour intervals throughout the entire (approximately 4 hours) dialysis period (eg, Part 1, Residential Period 2: 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours; Part 2, Residential Period; 72 to 73, 73 to 74, 74 to 75, and 75 to 76 hours).

The blood flow, dialysate flow rate, dialysate volume, and the make and model of the **dialyser** will be recorded. The entire dialysate will be collected, its volume recorded, and a sample retained for the analysis of TC-5214 concentrations.

Reason for Amendment:

Clarify PK sampling details to reflect updated study design.

Section of protocol affected:

Original Protocol Page 48 to 49, Section 7.1, Volume of blood

Amended Protocol Pages 49 and 50

Previous text:

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 4: Volume of blood to be drawn from each subject in Groups 1 through 4

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8	4	32
	Hematology	4	4	16
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics[b]		6	14 (15)	84 (90)
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	14 (15)	28 (30)
Pharmacogenetics		10	1	10
Total			38 (40)	178 (186)

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.
[b] One additional PK sample may be collected for Group 4. The total number of samples and associated blood volumes are indicated in parentheses.

Table 5: Volume of blood to be drawn from each subject in Group 5

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8	7	56
	Hematology	4	7	28
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics		6	28	168
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	28	56
Pharmacogenetics		10	1	10
Total			72	326

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data become available. However, the maximum volume to be drawn from each subject will not exceed 450 mL (ie, the same volume as would be drawn during a regular blood donation), unless additional tests are mandated by the Investigator for safety laboratories or repeat testing.

Revised text:

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 4: Volume of blood to be drawn from each subject in Groups 1 through **3**

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8	4	32
	Hematology	4	4	16
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics[b]		6	**14 (16)**	**84 (96)**
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	**14 (16)**	**28 (32)**
Pharmacogenetics		10	1	10
Total			**38(42)**	**178(194)**

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.
[b] **The total number of samples and associated blood volumes for Part 2 are indicated in parentheses.**

Table 5: Volume of blood to be drawn from each subject in Group 5**, Part 1**

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a]	8	7	56
	Hematology	4	7	28
	HIV, Hepatitis B and C	8	1	8
Pharmacokinetics		6	28	168
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		2	28	56
Pharmacogenetics		10	1	10
Total			72	326

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.

Table 6: Volume of blood to be drawn from each subject in Group 5, Part 2

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	**Clinical chemistry[a]**	**8**	**7**	**56**
	Hematology	**4**	**7**	**28**
	HIV, Hepatitis B and C	**8**	**1**	**8**
Pharmacokinetics		**6**	**18**	**108**
If using an indwelling catheter 2.0 mL of blood will be removed prior to PK sample collection		**2**	**18**	**36**
Pharmacogenetics		**10**	**1**	**10**
Total			**48**	**246**

[a] Sample volume sufficient to include lipid panel and pregnancy (female subjects) test.

The maximum volume to be drawn from each subject will not exceed 450 mL (ie, the same volume as would be drawn during a regular blood donation), unless additional tests are mandated by the Investigator for safety laboratories or repeat testing.

Reason for Amendment:

To characterize changes in PK sampling and associated blood volumes.

Section of protocol affected:

Original Protocol Page 57, Section 11.2, Calculation or derivation of pharmacokinetic variables, Start of paragraph 2

Amended Protocol Pages 58 through 60

Previous text:

Where possible, the following plasma PK parameters will be determined for TC-5214:

- Maximum plasma concentration (C_{max}, ng/mL), obtained directly from the observed concentration versus time data
- Time to maximum plasma concentration (t_{max}, h), obtained directly from the observed concentration versus time data
- Terminal rate constant (λ_z). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points, with an Rsq of greater than or equal to 0.8 will be used for determination.
- Terminal half-life ($_{t1/2\lambda z}$, h)
- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration [$AUC_{(0-t)}$]
- Area under the plasma concentration-time curve from 4 to 8 hours [$AUC_{(4-8)}$] to match the dialysis period, Group 5, Treatment Period 2 only
- Area under the plasma concentration-time curve from zero to infinity (AUC) calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-t)} + C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 30% of AUC, then AUC will not be reported
- Apparent plasma clearance (CL/F, L/h)
- Apparent volume of distribution (V_z/F, L)

The following plasma PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression used to determine $t_{½\lambda z}$
- Number of data points included in the log-linear regression analysis
- Goodness of fit statistic for calculation of λ_z (Regression coefficient)
- Percentage of AUC obtained by extrapolation (%AUC_{ex}).

Where possible, the following urine PK parameters will be determined for TC-5214:

- Cumulative amount of drug excreted unchanged into urine from zero to time t hours ($A_{e(0-t)}$, mg). The amount will be calculated and reported for each collection interval and cumulatively
- Fraction of dose excreted as unchanged drug into urine (f_e; % dose). The fraction will be calculated and reported for each collection interval and cumulatively
- Renal clearance (CL_R, L/h), calculated as $A_{e(0-t)}$ divided by $AUC_{(0-t)}$

For Group 5, Treatment Period 2, the following PK parameters for TC-5214 will be derived using the dialysate concentrations:

- Cumulative amount of drug extracted unchanged into the dialysate over the dialysis period (time: 4 hours postdose to 8 hours postdose) ($Ad_{(4-8)}$, mg). The amount will be calculated and reported for each 1-hour dialysate collection interval, and cumulatively
- Fraction of dose extracted unchanged into the dialysate over the dialysis period ($fd_{(4-8)}$; % dose). The fraction will be calculated and reported for each collection interval and cumulatively.
- Dialysate clearance (CL_D, L/h), calculated as $Ad_{(4-8)}$ divided by $AUC_{(4-8)}$

Revised text:

Where possible, the following plasma PK parameters will be determined for TC-5214:

- Maximum plasma concentration (C_{max}, ng/mL), obtained directly from the observed concentration versus time data
- Time to maximum plasma concentration (t_{max}, h), obtained directly from the observed concentration versus time data

- Terminal rate constant (λ_z). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points, with an Rsq of greater than or equal to 0.8 will be used for determination.

- Terminal half-life ($t_{1/2\lambda z}$, h)

- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration [$AUC_{(0-t)}$]

- Area under the plasma concentration-time curve from 4 to 8 hours [$AUC_{(4-8)}$] to match the dialysis period, Group 5, Treatment Period 2, **Part 1,** only

- **Area under the plasma concentration-time curve from 72 to 76 hours [$AUC_{(72-76)}$] to match the dialysis period, Group 5, Part 2, only**

- Area under the plasma concentration-time curve from zero to infinity (AUC) calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-t)} + C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 30% of AUC, then AUC will not be reported

- Apparent plasma clearance (CL/F, L/h)

- Apparent volume of distribution (V_z/F, L)

The following plasma PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression used to determine $t_{½\lambda z}$

- Number of data points included in the log-linear regression analysis

- Goodness of fit statistic for calculation of λ_z (Regression coefficient)

- Percentage of AUC obtained by extrapolation (%AUC_{ex}).

Where possible, the following urine PK parameters will be determined for TC-5214:

- Cumulative amount of drug excreted unchanged into urine from zero to time t hours ($A_{e(0-t)}$, mg). The amount will be calculated and reported for each collection interval and cumulatively

- Fraction of dose excreted as unchanged drug into urine (f_e; % dose). The fraction will be calculated and reported for each collection interval and cumulatively

- Renal clearance (CL_R, L/h), calculated as $A_{e(0-t)}$ divided by $AUC_{(0-t)}$

For Group 5, **Part 1,** Treatment Period 2, the following PK parameters for TC-5214 will be derived using the dialysate concentrations:

- Cumulative amount of drug extracted unchanged into the dialysate over the dialysis period (time: 4 hours postdose to 8 hours postdose) ($Ad_{(4-8)}$, mg). The amount will be calculated and reported for each 1-hour dialysate collection interval, and cumulatively

- Fraction of dose extracted unchanged into the dialysate over the dialysis period ($fd_{(4-8)}$; % dose). The fraction will be calculated and reported for each collection interval and cumulatively.

- Dialysate clearance (CL_D, L/h), calculated as $Ad_{(4-8)}$ divided by $AUC_{(4-8)}$

For Group 5, Part 2, the following PK parameters for TC-5214 will be derived using the dialysate concentrations:

- **Cumulative amount of drug extracted unchanged into the dialysate over the dialysis period (time: 72 hours postdose to 76 hours postdose) ($Ad_{(72-76)}$, mg). The amount will be calculated and reported for each 1-hour dialysate collection interval, and cumulatively**

- **Fraction of dose extracted unchanged into the dialysate over the dialysis period ($fd_{(72-76)}$; % dose). The fraction will be calculated and reported for each collection interval and cumulatively.**

- **Dialysate clearance (CL_D, L/h), calculated as $Ad_{(72-76)}$ divided by $AUC_{(72-76)}$**

Reason for Amendment:

To clarify the additional parameters to be determined based on updated single dose study design for Group 5.

Section of protocol affected:

Original Protocol Page 62, Section 12.2.3, Pharmacokinetics

Amended Protocol Page 64

Previous text:

For Groups 1 through 4 and Group 5, Treatment Period 1, regression models will be used to assess and quantify the relationship between renal function, as measured by eGFR, and TC-5214 dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The initial model will specify a linear relationship between primary pharmacokinetic parameters and eGFR and will be estimated using ordinary least squares. Log-transformations may be used to

improve model fit. Non-linear models will be used if there is statistical evidence of departure from linearity at the 0.10 significance level. Further, models which are non-linear in the model parameters may be used if simpler models do not provide adequate fit. Model parameters, 90% CI and p-values will be reported. From the linear and final models, estimates of the mean pharmacokinetic parameters and 90% CI will be made at the median eGFR of each of the renal function groups, as will the differences (or ratios) and 90% CI relative to the normal renal group (at the group median eGFR).

As an exploratory analysis, the renal function groups will be compared using a one-way analysis of variance model on the log-transformed dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The renal impairment groups will be compared to the control subjects with normal renal function (Group 1), with the latter as reference. Geometric least-squares means with corresponding 95% CI and ratios of geometric least squares with corresponding 90% CI will be presented.

Comparisons of PK parameters for subjects in Group 5 with ESRD between the two treatment periods (ie on a non dialysis day with those on a dialysis day) will be performed using a paired t-test (C_{max} and AUC).

Revised text:

For Groups 1 through **3** and Group 5, (**Part 1,Treatment Period 1 and Part 2**), regression models will be used to assess and quantify the relationship between renal function, as measured by eGFR, and TC-5214 dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The initial model will specify a linear relationship between primary pharmacokinetic parameters and eGFR and will be estimated using ordinary least squares. Log-transformations may be used to improve model fit. Non-linear models will be used if there is statistical evidence of departure from linearity at the 0.10 significance level. Further, models which are non-linear in the model parameters may be used if simpler models do not provide adequate fit. Model parameters, 90% CI and p-values will be reported. From the linear and final models, estimates of the mean pharmacokinetic parameters and 90% CI will be made at the median eGFR of each of the renal function groups, as will the differences (or ratios) and 90% CI relative to the normal renal group (at the group median eGFR).

As an exploratory analysis, the renal function groups will be compared using a one-way analysis of variance model on the log-transformed dose-normalized primary pharmacokinetic parameters (C_{max} and AUC). The renal impairment groups will be compared to the control subjects with normal renal function (Group 1), with the latter as reference. Geometric least-squares means with corresponding 95% CI and ratios of geometric least squares with corresponding 90% CI will be presented.

Comparisons of PK parameters for subjects in Group 5, **Part 1,** with ESRD between the two treatment periods (ie on a non dialysis day with those on a dialysis day) will be performed using a paired t-test (C_{max} and AUC).

Reason for Amendment:

To update analysis language to reflect removal of Group 4, and the removal of a second dose period for Group 5.

Persons who initiated the Amendment:

This amendment was initiated by AstraZeneca in order to update the study design.

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	TC-5214
Study Code	D4130C00008
Edition Number	1
Date	[redacted]
Protocol Dated	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

This Clinical Study Protocol and Amendment 1 to the CSP has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

Date
Day Month Year)

Work: [redacted]

ASTRAZENECA SIGNATURE(S)

An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

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AstraZeneca Research and Development site representative

[redacted]

Date
(Day Month Year)

Work: [redacted]

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SIGNATURE OF CO-ORDINATING PRINCIPAL INVESTIGATOR

An Open-Label, Multi-Center, Phase I Study To Compare the Pharmacokinetics of a Single Oral Dose of TC-5214 (S-Mecamylamine) in Subjects with Renal Impairment with Subjects with Normal Renal Function

This Clinical Study Protocol and Amendment 1 to the CSP has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this Protocol and Amendments Number 1, dated [redacted]. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Centre No.: [redacted]

Signature: [redacted]

[redacted]

Date
(Day Month Year)

Work: [redacted]

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[redacted]