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Parameter Estimation and Reporting in Noncompartmental Analysis of Clinical Pharmacokinetic Data

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Abstract

The noncompartmental analysis (NCA) of pharmacokinetic (PK) data is important throughout all phases of clinical drug development. Although there are numerous regulatory guidances and articles in the literature concerned with best practices for the modeling of PK data, there are relatively few sources of information on how to conduct a high-quality NCA. This article provides a systematic review of issues related to the estimation of plasma and urine PK parameters with the intent of encouraging rigor in the performance of NCAs so as to provide reliable and informative analysis results.

Keywords

best practices, noncompartmental analysis, parameter estimation, pharmacokinetics, summary statistics

The noncompartmental analysis (NCA) of pharmacokinetic (PK) data arising from intensive sampling schedules is invaluable in the clinical development of a drug. The insights that develop from thoughtful interpretation of a well-performed NCA critically inform the construction of the PK model that will be used to analyze the aggregate PK data collected in the course of the development of the drug. The NCA findings can also serve as a validation data set in the selection of the final PK model. In addition, NCA findings represent the preferred end points for many clinical pharmacology studies performed later in the development of a drug (eg, food effect, drug interaction, and bioequivalence studies).

Because of the importance that NCAs have in drug development, it is crucial that PK analysts perform such analyses competently and rigorously. This means judging if the data collected in the study and the quality of the data collection at the study site allow for the accurate estimation of the PK parameters of interest, given the PK behavior of the drug in the study population. A problem with NCAs is that PK parameters will be calculated by the NCA software even when there is reason to doubt the accuracy of the parameter estimates. It is the responsibility of the data analyst to recognize those situations (competence) and to avoid reporting unreliable or inaccurate parameter values (rigor).

This article has been written in the hopes that it will assist PK analysts in thinking critically about how they should conduct their NCAs so as to provide reliable and informative analysis results. It may also be useful to others involved in drug development who need to have an acquaintance with the fundamentals of PK data analysis. It is assumed that the reader has a general understanding of PK principles[1] and at least some familiarity with the PK parameters evaluated in an NCA[2,3] and with the objectives and design of drug development studies.[4,5]

Data Handling

Sampling Times

Actual sampling times should be used for the calculation of final PK parameters; they will always be available in the final PK data set. In conducting preliminary PK analyses, however, planned sampling times may be used because actual elapsed time data are often not yet available. This is done with the understanding that the actual sampling times can be expected to be reasonably close to the planned sampling times. If the trial circumstances call into question whether PK samples were collected at the planned times—as can sometimes happen

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when trial subjects are hospitalized patients—it must be decided whether the use of planned time points would make the NCA parameter estimates wholly unreliable. If so, the decision must be made to expedite the availability of actual sampling times and then perform the preliminary NCA.

Planned sampling times are used in summary tables and figures. Both planned and actual sampling times should be presented in listings.

Assay Quantitation Limits

When results are outside the limit of quantitation of the assay, the analytical laboratory will report the results as "below the LLOQ" or "above the ULOQ," where LLOQ stands for "lower limit of quantitation" and ULOQ stands for "upper limit of quantitation." The character codes used to indicate these situations may differ among laboratories. It is a good practice for the sponsor to adopt standard designations for out-of-range results. All samples initially found to have concentrations above the ULOQ should be reassayed (with appropriate dilution) and have numeric data reported in the final data set. Samples that are found to have concentrations below the LLOQ will be indicated as such using the designation agreed on (for example, BQL for "below quantitation limit"). The quantitation limits of the assay are included as variables in the data set. When the concentration data are analyzed, BQL results should be treated as concentrations of 0. BQL results are informative and should not be lost by designating them as missing.[6]

The target LLOQ for a drug concentration assay is the lowest concentration that will need to be measured in the course of the clinical development of the drug. As a rule, these are the concentrations seen at the lowest doses in the first-in-human clinical study. The target LLOQ should be 3- to 10-fold lower than the lowest concentration predicted to be needed to calculate the terminal disposition phase half-life of the drug at those low doses. There was a time when it was not technically feasible to achieve some target LLOQs. With modern bioanalytical methodology this situation is rare.

Missing Data

Planned concentration data may be missing because the analytical laboratory did not receive a sample for assay, because the sample volume was insufficient to perform the assay, because the sample had been lost or mishandled, or because the assay failed or the assay run was deemed out of control. The designations used to identify these situations should also be standardized by the sponsor and bioanalysis laboratory. The designations are documented in the study report and appear where appropriate in the report's concentration listings.

Data Exclusion

Data that are of questionable validity because of sample-handling errors or assay errors, or because they are biologically implausible, may be excluded from the analysis when the study is a "learning" study, such as single-ascending-dose and multiple-ascending-dose PK studies—one cannot learn from flawed data. If a data point is excluded, the exclusion should be documented in the clinical study report (CSR), and a scientific rationale for the exclusion should be provided.

Data are generally not excluded from the analysis of clinical pharmacology studies because the findings from these studies usually support label claims. This applies most especially to pivotal bioequivalence studies. If there are suspect data the NCA can be conducted twice, once with the complete data set and once with the suspect data excluded. If there is a meaningful difference in the analysis results, results from both analyses should be provided, and the issue should be discussed in the CSR.

Data Imputation

It is commom practice to impute a concentration of 0 for BQL results. This allows for the reporting of 0 values for PK measures of drug exposure, such as maximum concentration (C_{max}) and area under the concentration-time curve (AUC), if no measurable concentrations are observed at any time after administration of small doses of drug. This practice also allows for the estimation of the absorption lag time (T_{lag}) for drugs administered orally (BQL results early in the PK profile) and permits reporting a 0 value for end-of-dosing interval concentrations (C_{trough}) when concentrations are not measurable late in the dosing interval.

PK Parameters

Parameter Estimation: Single Dose, Multiple Dose, and Steady State

Drug concentrations may be obtained after a single dose of a drug or, if there is multiple dosing of the drug, during a dosing interval after the first dose but before the steady state has been attained, or during a dosing interval following the attainment of the steady state. Single-dose PK parameters of exposure and disposition can be calculated using drug concentrations collected after a single dose of drug. Steady-state parameters of exposure and disposition can be calculated using drug concentrations collected from a dosing interval after the steady state has been achieved (note that the formulas for the disposition parameters will be different from those used to calculate the same parameters following a single dose of drug). Parameters of exposure, but not parameters of disposition, can be estimated from concentration data arising from dosing intervals before

subjects attained the steady state. If, during multiple dosing, the steady state has not been attained at the time of sampling a dosing interval, only parameters of exposure should be reported for the interval; the parameters should be labeled according to the number of prior doses or days of dosing and should be distinguished from steady-state exposure parameters.

The attainment of the steady state should not simply be assumed based on half-life estimates; it should be demonstrated. It is a good practice to collect at least 3 consecutive predose plasma concentration specimens during multiple dosing; at a minimum these should be the predose specimen from the dosing interval before the interval of interest, the predose specimen from the interval of interest, and the predose specimen from the dosing interval following the interval of interest. Examination of the predose concentration pattern is usually considered adequate to determine if the steady state has been reached. If, for most study subjects, the concentration at each sampling time is larger than that at the preceding sampling time, the drug is likely still accumulating, which means that steady-state conditions have not been achieved. If, in general, the concentration at each sampling time is smaller than that at the preceding sampling time, it is possible that drug metabolism has been induced, and the steady state associated with the alteration in drug disposition has not been achieved. In most cases, if successive concentrations show an up-and-down or down-and-up pattern, the steady state can be considered to have been attained.

Parameter Estimation: Total Drug and Unbound Drug

For many drugs, unbound drug is the drug species that interacts with the drug's target.[7] For these drugs, it would ideally be best to characterize the PK of plasma unbound drug. However, the measurement of unbound drug concentrations is operationally difficult and adds to the expense of clinical trials. So the characterization of unbound drug PK is pursued only in the development of those drugs for which protein binding is expected to strongly impact the consistency of the relationship between unbound drug concentration and total drug concentration. As discussed in detail below, this can happen if a drug binds to a low-capacity plasma protein or if a drug is highly bound to a high-capacity plasma protein. For such drugs, efforts should be made to measure unbound drug concentrations at all stages in the development of the drug. Note that, for such drugs, the desirability of having and using unbound drug concentration extends into the clinic.[8]

For drugs that bind to plasma proteins, the parameter that characterizes the relationship between unbound and total drug concentration is the free drug fraction, the ratio of unbound drug concentration to total drug concentration. The free drug fraction is influenced by the affinity of the drug for its binding protein, the capacity of the binding protein relative to the drug concentrations anticipated in the clinic, and the variability in the plasma concentration of the binding protein in health and disease. Binding affinity and capacity are assessed in nonclinical studies, with the information usually being available in time for the planning of the first clinical study.

The quantitative influence of the variability in binding protein concentration is derived from the equilibrium relationship between unbound and total drug concentration,[9]

$$[\text{unbound drug}] = k_d \times \frac{[\text{bound drug}]}{[\text{total protein binding sites}]}$$

where k_d is the dissociation constant for binding and brackets indicate concentrations. For a high-capacity binding protein, substitution of [total drug] minus [unbound drug] for [bound drug] and rearrangement gives,

$$\text{free drug fraction} = \frac{1}{1 + [\text{total protein binding sites}]/k_d}$$

For a limited-capacity binding protein, substitution of [total protein binding sites] minus [bound protein binding sites] for [unbound protein binding sites] in the equilibrium relation, yields, on rearrangement,

$$\text{free drug fraction} = \frac{k_d + [\text{unbound drug}]}{[\text{total protein binding sites}] + k_d + [\text{unbound drug}]}$$

For high-capacity drug binding, the free drug fraction will be the same regardless of total drug concentration, given a constant concentration of binding protein. In that special case unbound drug concentration will be a constant proportion of total drug concentration, meaning that total drug concentrations will perfectly reflect unbound drug concentrations. There is, however, always variability in binding protein concentration, both within-individual variability over time (especially in disease states) and between-individual variability. That means that the free drug fraction will vary, blurring the relationship between total drug concentration and unbound drug concentration.

This is illustrated in Figure 1A for a hypothetical drug that binds to albumin, a high-capacity binding protein. The relationships depicted represent those for a drug with moderately high affinity for albumin, having a baseline free drug fraction of 0.10, where a baseline free drug fraction is the free fraction at the average

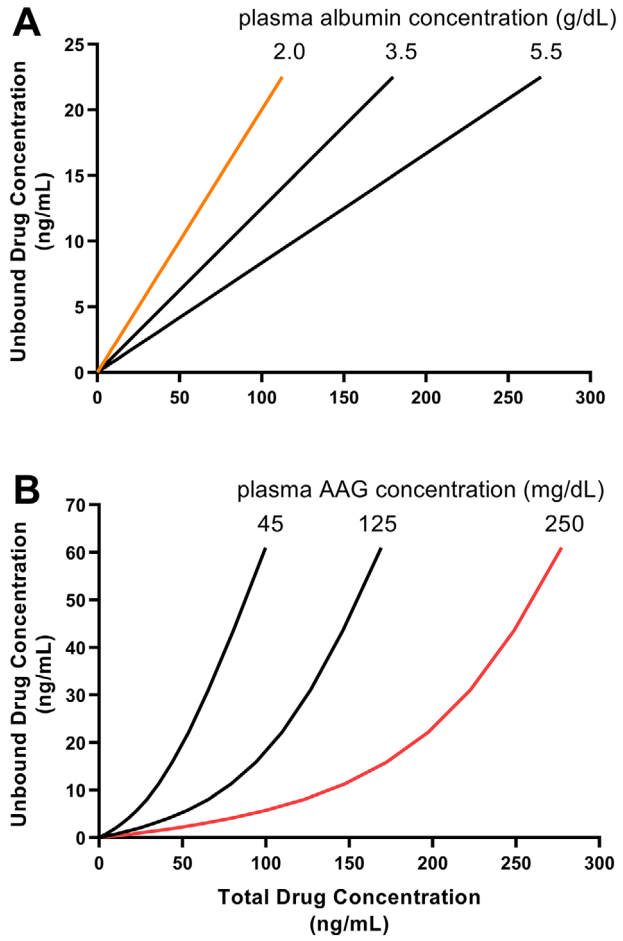

Figure 1. Theoretical effect of plasma binding protein concentration on the relationship between total drug concentration and unbound drug concentration for a drug with a free drug fraction of 0.10 at the average concentration of the binding protein in healthy individuals. A, Relationships for a drug that binds to albumin. Black lines, upper and lower limits of plasma albumin concentration in healthy individuals and most patients; orange line, low plasma albumin concentration in patients with marked hypoalbuminemia. B, Relationships for a drug that binds to α_1-acid glycoprotein (AAG). Black lines, upper and lower limits of plasma AAG concentration in healthy individuals and most patients; red line, high plasma AAG concentration in patients with active inflammation. Note the difference in the y-axis scale for the 2 panels.

albumin concentration of 4.5 g/dL. The total drug–unbound drug concentration relationships are shown for 3 values of albumin concentration: 5.5 and 3.5 g/dL (the range in albumin concentration seen in healthy individuals and most patients) and 2.0 g/dL (a reduced albumin concentration as might be seen in patients with significant hypoalbuminemia). For any given value of total drug concentration, the corresponding unbound drug concentration in most individuals can vary from that seen at an albumin concentration of 5.5 g/dL to that seen at an albumin concentration of 3.5 g/dL. In a patient population the unbound drug concentration can vary from that seen at an albumin concentration of 5.5 g/dL to that seen at a concentration of 2.0 g/dL. For a total drug concentration of 100 ng/mL, for example, unbound drug concentration can range from 8.3 ng/mL to 12.5 ng/mL in most individuals and from 8.3 ng/mL to 20.0 ng/mL in patients. These represent 1.5- and 2.4-fold ranges, respectively. Examining this behavior over a wide range of binding affinities reveals that, in most individuals, free drug fraction will vary from 1.5- to 1.6-fold for drugs that have a baseline free fraction of 0.1 or less. In a patient population, drugs that have a baseline free fraction between 0.2 and 0.5 will have their free fractions vary between 1.5- and 2.0-fold, drugs that have a baseline free fraction between 0.07 and 0.2 will have their free fractions vary between 2.0- and 2.5-fold, and drugs that have a baseline free fraction less than 0.07 will have their free fractions vary between 2.5- and 2.75-fold.

Degrading the relationship between total drug concentration and unbound drug concentration by the addition of 2.0-fold or more variability is likely to be consequential for drugs that have a narrow therapeutic index. Because the use of total drug concentration will make it much more difficult to understand the relationships between drug exposure and efficacy and between drug exposure and toxicity, unbound drug concentration should probably be measured for narrow-therapeutic-range drugs that bind albumin with a baseline free fraction less than 0.2 and certainly for drugs with a baseline free fraction less than 0.07. Free drug fraction will also vary due to cotherapy with drugs competing for the binding site on albumin due to altered concentrations of endogenous plasma substances that compete for the binding site on albumin,[10] and due to drug binding to additional distinct binding sites on albumin or other plasma proteins. The presence of these sources of variability should further motivate the measurement of unbound drug concentration.

For limited-capacity drug binding, free drug fraction varies due to variability in the plasma concentration of the binding protein as for high-capacity binding, but it also varies depending on plasma drug concentration. This makes for a complex relationship between total and unbound drug concentration. This is shown in Figure 1B for a hypothetical drug binding to α_1-acid glycoprotein (AAG) with a baseline free drug fraction of 0.10, where baseline free drug fraction here is the free fraction at the average AAG concentration of 85 mg/dL. AAG is considered in this example because it is the most important limited-capacity drug-binding protein in plasma. The total drug–unbound drug concentration relationships are shown for AAG concentrations of 45 mg/dL (the lower limit of AAG

concentration in healthy individuals), 125 mg/dL (the upper limit of AAG concentration in healthy individuals and most patients), and 250 mg/dL (an elevated AAG concentration as might be seen in a patient with an inflammatory condition, because AAG is an acute-phase reactant). The relationships are markedly curvilinear for all 3 AAG concentrations. The drug concentration at which the curvature in each relationship becomes evident marks the transition from high-capacity drug binding (low concentration of drug relative to AAG binding capacity) to limited-capacity binding. At higher drug concentrations, the relationships become nearly linear, with each increment in total drug concentration producing an almost equal increment in unbound drug concentration. This occurs when the AAG binding sites are largely occupied. The curvilinearity in the relationships results in considerable uncertainty in unbound drug concentrations. For a total drug concentration of 25 ng/mL, for instance, unbound drug concentration can range from 6.6 ng/mL to 2.1 ng/mL in most individuals (3.1-fold range) and from 6.6 ng/mL to 1.0 ng/mL (6.5-fold range) in a patient population, whereas for a total drug concentration of 100 ng/mL, unbound drug concentration can range from 61 to 18 ng/mL (3.4-fold range) in most individuals and from 61 ng/mL to 5.7 ng/mL (10.6-fold range) in a patient population.

Because of the complexity of the relationship between total and unbound drug concentration when a drug binds to AAG, it is recommended that the measurement of unbound drug concentration be seriously considered for any drug with a narrow therapeutic index that binds to AAG with a baseline free drug fraction of 0.5 or less.

Parameter Terminology

The abbreviations for PK parameters used in this article are not standard; some are conventional, and all are meant to be easily interpreted. The logic used in devising the abbreviations is: the base entity is written in upper case (eg, C, concentration; CL, clearance; AUC, area under the curve), direct modifiers of the base entity are written as subscripts in lower case (eg, C_{max}, maximum concentration), and indirect modifiers are written as superscripts in upper case (eg, $C_{max}{}^{MET}$, C_{max} for a metabolite). A special consideration is the designation for steady state. For parameters that are determined or calculated in the same way following a single dose of a drug and following multiple dosing, the abbreviations are constant although, in some formulas, superscript SS (or SD, single dose) is added to clarifiy which parameter is meant. For those parameters that are calculated using a different formula under steady-state conditions, the lowercase subscript "ss" is used (eg, CL and CL_{ss} for single-dose and steady-state clearance, respectively).

CDISC Parameter Terminology

A comprehensive set of data standards for the electronic data exchange of nonclinical and clinical research information is being developed and maintained by the Clinical Data Interchange Standards Consortium (CDISC, www.cdisc.org). This important initiative has been undertaken in an effort to standardize research data sets so that they can be effectively and efficiently shared among all users and reviewers of the data.[11] The Study Data Tabulation Model (SDTM) is the set of standards concerned with clinical trial data tabulations, including PK data tabulations. The SDTM PK parameter and PK unit codes (referred to as controlled terminology submission values) are accepted, encouraged, and in some cases even required for PK data sets in regulatory submissions, including submissions to the FDA. Because it is essential for data analysts and clinical pharmacologists to be familiar with the SDTM controlled terminology submission values that will be used to specify the PK parameters in the data sets arising from NCAs, the values are included in the upper right corner of the text boxes that introduce each parameter description (where na indicates no CDISC term currently available). Note that these abbreviations generally differ from the abbreviations that are used in text, tables, and figures in scientific and regulatory reports and submissions. PK parameter SDTM controlled terminology submission values and the corresponding abbreviations and definitions used in this article are also presented in aggregate in an appendix. The most up-to-date, comprehensive list of SDTM controlled terminology submission values can be downloaded at www.cancer.gov/research/resources/terminology/cdisc.

Plasma PK Parameters of Exposure: Concentration Parameters

C_{max}	CMAX
The largest observed concentration.	

C_{max} is the noncompartmental estimate of the true maximum concentration following a single dose of drug or, for multiple dosing, the true maximum concentration during a dosing interval. This estimate is most accurate when C_{max} occurs during an intensely sampled period of the PK profile and is least accurate during periods of infrequent sampling, typically later in the PK profile. If it is found that C_{max} occurs in more than a few subjects at less-well-sampled times, the sampling scheme should be adjusted and the study cohort(s) rerun in order to obtain more accurate estimates of C_{max}. Improving the accuracy of C_{max} will also improve the

accuracy of all of the AUC parameters. This is a good reason to assay and examine PK data early in a study, so that necessary adjustments to the sampling scheme can be made with minimal impact on the study.

C_{min}	CMIN
The smallest observed concentration during a dosing interval.	

C_{min} is the noncompartmental estimate of the true minimum concentration during a dosing interval. It may or may not occur at the end of the dosing interval, so it may be different from C_{trough}. For example, C_{min} can occur before the end of the dosing interval if the PK profile is fairly flat during the late portion of the dosing interval and measurement variability results, by chance, in a concentration measured late in the dosing interval being lower than the concentration measured at the end of the dosing interval. C_{min} can also occur early in the dosing interval if there is enough delay in the absorption of an oral drug that the late decline in concentration in the PK profile from the preceding dosing interval continues on into the early portion of the current dosing interval. Similar to C_{max}, the accuracy of C_{min} depends on the frequency of sampling during that portion of the dosing interval during which the true minimum occurs.

C_{trough}	CTROUGH
The observed concentration at the end of a dosing interval.	

C_{trough} is the noncompartmental estimate of the true concentration at the end of the dosing interval, before administration of the next dose—it is the predose concentration of the following dosing interval. Because the sample for C_{trough} is almost always drawn very close to the actual end of the dosing interval, C_{trough} is a highly accurate estimator. In those cases in which the end-of-dose-interval PK sample is collected considerably before the actual end time of the dosing interval, C_{trough} can be estimated by extrapolation, using linear extrapolation if the area under the curve is being calculated with the linear trapezoidal rule or using exponential extrapolation if the area is being calculated with the logarithmic trapezoidal method (see below). If steady-state conditions exist, a missing end-of-dosing-interval concentration can be imputed using the predose concentration for the interval, and vice versa.

C_0	CO
The observed initial concentration following bolus IV dosing.	

C_{eoi}	na
The observed concentration at the end of an IV infusion.	

For drugs administered intravascularly, the true maximum concentration occurs immediately following bolus injection (C_0) or at the end of infusion (C_{eoi}). These 2 parameters are, therefore, the best estimators of the true maximum concentration, even if C_{max} is observed sometime later. An apparent "late" C_{max} can happen when the disposition kinetics of a drug are slow, so that the concentration of drug remains high for some time after drug administration, and measurement variability results in a concentration measured during this period being higher than the observed C_0 or C_{eoi}. It is good practice to include C_0 or C_{eoi} among the reported parameters, as well as observed C_{max}. If there is a meaningful difference in the average values of the parameters, this should be discussed in the study report.

Another cause of an apparent "late" C_{max} when drug is infused is continued administration of the drug present in the infusion tubing. If a prodrug is being administered, C_{max} for the drug will, of course, not be C_0 or C_{eoi} but a concentration some time after the administration of the prodrug.

Bolus dosing ideally means extremely rapid IV drug administration directly into the bloodstream. Extremely rapid should mean a timespan measured in seconds, but, in practice, drug administrations lasting up to 5 minutes are often thought of as bolus. If a drug is administered over a period longer than 1 minute, the administration should be considered a short infusion. The duration of the infusion should be accurately measured and accounted for in the calculation of the area under the disposition curve. For bolus dosing, if the sampling scheme can be designed so that the time of sampling of the first postdose specimen is very close to the time of drug administration, say within 1 or 2 minutes, that concentration can be used for C_0. Often the time of sampling of the first postdose specimen is not particularly close to the time of injection. In such cases C_0 is estimated as a derived parameter, the intercept of the linear regression fit of the log-transformed early concentration-time data.

For longer infusions the sampling scheme should be designed to include PK sampling during the infusion and a specimen immediately before the end of infusion. The concentration of such a specimen will, in almost all cases, be an accurate estimator of the true C_{eoi}. Because the time of infusion may vary from subject to subject, the Schedule of Events should stipulate "immediately before the actual end of infusion" rather than the planned stopping time of the infusion. Note that it is always advisable to include an instruction to

avoid early sampling from the arm being used for the infusion, even if a multilumen catheter is being used.

C_{avg}	CAVG
The average concentration during a dosing interval. Usually reserved for the steady state.	
$= \frac{AUC_{tau}}{tau}$	

C_{avg} is calculated as the area under the drug concentration-time curve over a dosing interval, AUC_{tau}, divided by the duration of the dosing interval, tau. Although the extreme values of concentration during a dosing interval are typically the more important characteristics of the multiple dose PK profile, C_{avg} is a useful measure of drug exposure for drugs whose effects are proportional to total drug exposure. This parameter is usually understood to represent the average concentration in the steady state.

Peak Trough Ratio	PTROUGHR
The ratio of highest concentration to lowest concentration during a dosing interval. Usually reserved for the steady state.	
$= \frac{C_{peak}}{C_{trough}}$ where $C_{peak} = C_{max}, C_0$, or C_{eoi}	

Peak Trough Fluctuation	FLUCP
The range in concentration during a dosing interval, expressed as a percentage of C_{avg}. Usually reserved for the steady state.	
$= 100\% \times \frac{C_{peak} - C_{trough}}{C_{avg}}$ where $C_{peak} = C_{max}, C_0$, or C_{eoi}	

Peak trough ratio and peak trough fluctuation are parameters that characterize the variation in concentration seen over a dosing interval in the steady state. They provide similar information, so only 1 of the parameters needs to be reported. The choice is made by the clinical pharmacologist or by standard department practice.

The parameter C_{trough} is used in the formula above for peak trough ratio and peak trough fluctuation so as to be consistent with the use of "trough" in the parameter names. However, most software packages use C_{min}, rather than C_{trough}, when calculating these parameters. The use of C_{min}, rather than C_{trough} gives a more accurate estimate of concentration variation. It would be helpful to have different names for these parameters to indicate whether C_{trough} or C_{min} is used in their calculation (for instance, peak trough and peak nadir), but for now it is the responsibility of the PK analyst to make clear whether C_{trough} or C_{min} is used.

Plasma PK Parameters of Exposure: Time Parameters

T_{max}	TMAX
The observed time of first occurrence of C_{max}.	

T_{max} is the noncompartmental estimate of the time at which the maximum concentration occurs. It is estimated as the time at which C_{max} occurs. In the event that C_{max} occurs at more than 1 time, the earliest such time is reported for T_{max}. The accuracy with which T_{max} identifies the true time of maximum concentration depends on the frequency of sampling around T_{max}. The accuracy is greatest if T_{max} occurs during a period of intense sampling and least during a period of infrequent sampling. It is desirable to have comparable accuracy across all reported T_{max} estimates so, as discussed above for C_{max}, if it is found that T_{max} occurs in more than a few subjects at less well-sampled times, the sampling scheme should be adjusted and the study cohort(s) rerun.

T_{min}	TMIN
The observed time of occurrence of C_{min} during a dosing interval.	

T_{min} is the noncompartmental estimate of the time at which the minimum concentration occurs during a dosing interval. It is estimated as the time at which C_{min} occurs. If C_{min} occurs at more than 1 time, the earliest such time is reported for T_{min}. As for T_{max}, the accuracy of T_{min} depends on the frequency of sampling around T_{min}.

T_{lag}	TLAG
The observed time lag after dosing before the occurrence of measurable concentrations.	

T_{lag} is the noncompartmental estimate of the time before systemic availability of the assayed species. T_{lag} is estimated as the last sampling time point before the occurrence of a measurable concentration. As such, its

accuracy depends on the frequency of sampling early in the PK profile.

λ_z	LAMZ
The exponential rate constant of the terminal disposition phase.	
= slope of linear regression fit of the log-transformed late concentration-time data.	

$T_{1/2Z}$	LAMZHL
The half-life of the terminal disposition phase.	
$= \frac{\ln(2)}{\lambda_z}$.	

It is usually assumed that, at some time point postadministration (T_z), and at all time points thereafter, the concentration of a drug in the plasma will decline in a monoexponential fashion. The portion of the plasma disposition profile that shows this behavior is referred to as the terminal disposition phase. The PK parameters that define this disposition phase are the terminal disposition rate constant, λ_z, and the terminal disposition half-life ($T_{1/2Z}$). It is not uncommon for λ_z to be referred to as the terminal elimination rate constant and $T_{1/2Z}$ as the terminal elimination phase half-life.[12] These are misnomers. The kinetics of the terminal disposition phase usually depends on concurrent drug elimination and drug distribution/redistribution. Indeed, a slow rate of drug redistribution can be the major determinant of terminal disposition phase kinetics. Additionally, for some drugs, terminal disposition phase kinetics largely reflects not elimination but a slow rate of uptake from an extravascular site of drug administration—so-called flip-flop kinetics.[13]

Estimation of λ_z and $T_{1/2Z}$ requires that the PK analyst determines which concentration data in a subject's PK profile, if any, are likely to be from the terminal disposition phase. In usual practice the start time of the terminal disposition data is determined by visual inspection of a subject's log-transformed concentration-time data and does not include T_{max} (extravascular administration) because it is assumed that the absorption disposition phase persists for at least a short period following the attainment of C_{max}. Alternatively, the data may be selected using an automated algorithm (most commonly, the adjusted-r^2 algorithm). The visual inspection approach is recommended for use in early drug development because visual assessment by an experienced analyst is invariably enriched and improved by the incorporation of across-subject information. Consider, for example, phase 1 study data for which limited assay sensitivity has resulted in truncation of the PK profiles of subjects given low doses of the study drug, resulting in little or none of the terminal disposition phase being present in the profiles. Examination of the profiles from subjects receiving higher doses will reveal that the terminal disposition phase has been missed, or largely missed, in the profiles from the low-dose cohort(s) and that λ_z and $T_{1/2Z}$ cannot be estimated for those profiles, even though estimates will be generated if an automated algorithm is employed. Later in drug development, when the PK of a drug is well understood, studies can be designed in such a way that the adjusted-r^2 algorithm can be used with confidence.[14]

It is common to apply 1 or more criteria of parameter estimate reliability to decide which λ_z and $T_{1/2Z}$ values can be reported and which should not be reported. Almost invariably, 3 measurable concentration measurements in the terminal disposition phase are considered as a minimum number for estimation of λ_z and $T_{1/2Z}$. This criterion is so deeply entrenched in usual practice and in regulatory thought that it should be employed. Two other frequently utilized criteria are the adjusted-r^2 value of the regression used to generate the estimate of λ_z and the time span of the data points used in the regression, where

$$\text{time span} = \frac{\text{time of the last data point} - \text{time of the first data point}}{T_{1/2Z}.}$$

A simulation study conducted by the author[15] showed that adjusted-r^2 does a poor job of identifying reliable parameter values. The same study found that the geometric mean of the time span values in a dosing cohort is a good discriminator of reliable parameter values. If the geometric mean terminal phase time span for a study cohort is 1.5 or greater (low level of measurement variability of the concentration data) or 2.5 or greater (high 2.5 low level of measurement variability), the overall accuracy of the λ_z and $T_{1/2Z}$ estimates for the subjects in the cohort will be high.

T_{ss}	na
The time required to achieve steady-state PK behavior with multiple dosing.	

T_{ss} is defined as the time to reach steady-state conditions. It is the time needed for a parameter characterizing multiple-dose PK to achieve a stipulated fraction of the value that parameter will have when steady-state conditions obtain. The most common parameter utilized is C_{trough}, given the ease of collecting predose PK specimens. Although a number of noncompartmental computational techniques have been proposed to

calculate T_{ss} as determined using C_{trough},[16] they are robust estimators of T_{ss} only if numerous C_{trough} values are available. This is an operational burden that is almost never undertaken. Instead, a practical number of predose PK specimens are collected and inspected graphically. Visual examination of a plot of aggregate dose-normalized C_{trough} data and a plot of median dose-normalized C_{trough} data usually allows the PK analyst to ascertain if the steady state has been achieved and to determine the time after which steady-state conditions obtain (T_{ss}).

To assure that the steady state will be reached in a multiple-dose PK study, it is recommended that T_{ss} be predicted from single-dose PK parameters and that multiple dosing be conducted for at least that length of time prior to the dosing interval that will be used to characterize the steady-state PK parameters. If the disposition of a drug does not change with multiple dosing and if the dosing interval is of sufficient duration that tau is greater than T_z, then the formula for T_{ss} for C_{trough}, expressed as multiples of $T_{1/2Z}$, is

$$T_{ss} \text{ for } C_{trough} = -\frac{\ln(1 - f_{ss})}{\ln(2)}$$

where f_{ss} is the stipulated fraction of the steady-state C_{trough} to be achieved. This simple formula indicates that 3.3 multiples of $T_{1/2Z}$ are needed to attain C_{trough} values equal to 90% of the steady-state C_{trough} ($C_{trough}{}^{SS}$) and that 4.3 multiples of $T_{1/2Z}$ are needed to attain C_{trough} values equal to 95% of $C_{trough}{}^{SS}$. Note that this formula can also be used to confirm the plausibility of T_{ss} as estimated empirically.

T_{ss} can also be defined in reference to steady-state AUC_{tau} ($AUC_{tau}{}^{SS}$). Because noncompartmental estimation of T_{ss} as defined by this parameter would require obtaining serial values of AUC_{tau}, it is not operationally feasible. However, this is the definition of T_{ss} that is most often used in compartmental and population modeling of multiple-dose PK. If a model-based treatment of multiple-dose data is planned, the multiple-dose study can be designed using the predicted value of T_{ss} for AUC_{tau}, which can differ considerably from T_{ss} for C_{trough}, especially if the terminal disposition phase makes only a small contribution to single-dose AUC_{inf} or if tau is long compared with $T_{1/2z}$. The formula for T_{ss} for AUC_{tau}, expressed as multiples of $T_{1/2Z}$, is

$$T_{ss} \text{ for } AUC_{tau} = \text{tau}/T_{1/2z} - \frac{\ln\left[1 - f_{ss} - (f_{ss} - 1) \times AUC_{tau}^{SD}/\left(C_{tau}^{SD}/\lambda_z\right)\right]}{\ln(2)}$$

where f_{ss} here is the stipulated fraction of $AUC_{tau}{}^{SS}$ to be achieved and $AUC_{tau}{}^{SD}$ and $C_{tau}{}^{SD}$ are AUC up to time tau and the concentration at time tau, respectively, as found in the single-dose PK study.[17]

Plasma PK Parameters of Exposure: AUC Parameters

Measuring AUC

All AUC parameters are derived parameters. They are calculated using the observed concentration-time data by assuming that between adjacent data points, (c1,t1) and (c2,t2), the concentration data have a linear form, in which case the area is calculated using the linear trapezoidal rule,

$$\text{interval AUC} = \frac{(t2 - t1) \times (c1 + c2)}{2}$$

or by assuming the concentration data have an exponential form, in which case the area is calculated using the logarithmic trapezoidal rule,

$$\text{interval AUC} = \frac{(t2 - t1) \times (c2 - c1)}{\ln(c2/c1)}$$

The analyst selects which data pairs in a PK profile are to be treated as linearly related and which are to be treated as exponentially related. The most common choices are the linear trapezoidal method, for which all data pairs are treated as linearly related, and the logarithmic trapezoidal method, for which data pairs after C_{max} are treated as exponentially related.

The linear trapezoidal rule overestimates the interval area when the concentration is declining exponentially, as in the terminal disposition phase, and it underestimates the interval area when the concentration is increasing in a concave fashion, as happens with many oral drugs as C_{max} is approached. The logarithmic trapezoidal rule underestimates the interval area when the concentration is declining in a concave fashion, as happens with oral drugs for a while following C_{max}, and when the concentration declines approximately linearly, as happens at the genu between postabsorption disposition phases. Excessive over- and underestimation of area is avoided by assuring an adequate density of PK sampling. This is perhaps most important to consider if the linear trapezoidal rule, rather than the logarithmic trapezoidal rule, is used to calculate area under the (log-linear) terminal disposition phase portion of the PK profile, when sampling time points are typically widely spaced. Overestimation of area will be modest (less than 4%) if the duration between samples is equal to or less than the half-life for the sampling interval

$$\text{interval half-life} = \frac{\ln(2) \times (t2 - t1)}{\ln(c1/c2)}$$

but will be large if the duration between samples is longer: 16% overestimation if the duration equals 2 times the half-life for the sampling interval and 34% overestimation if 3 times the half-life.[18]

AUC_{last}	AUCLST
The AUC from the time of dose administration to the time of the last measurable concentration (T_{last}), if T_{last} < last PK sampling time.	

AUC_{last_sample}	AUCINT
The AUC from the time of dose administration to the last PK sampling time (T_{last_sample}), if measurable concentrations are present at PK sampling times up to and including T_{last_sample}.	

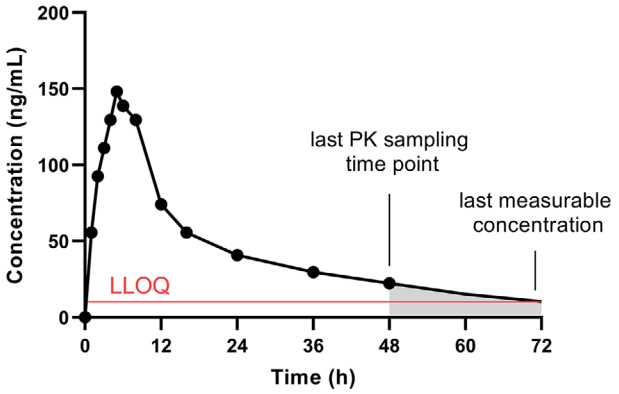

Figure 2. Hypothetical PK profile illustrating how AUC_{last_sample} potentially underestimates AUC_{last} by the amount of the AUC between the time of the last PK sample collection and what would have been the time of the last measurable concentration. AUC indicates area under the concentration-time curve; PK, pharmacokinetics.

Following a single dose of drug, the PK profile will have 1 of 3 patterns, depending on the PK of the drug and the PK sampling scheme.

First, the PK profile may consist of measurable drug concentrations up to a certain PK sampling time (T_{last}), after which all of the concentration results are below the LLOQ, that is, unmeasurable. Here the PK sampling scheme is long enough to capture all measurable concentration data at the doses studied. The AUC that is measured in this situation is AUC_{last}, the AUC from the time of dose administration to the time T_{last}.

AUC_{last} is not comparable across dose levels when different portions of the PK profile contribute to AUC_{last} at different dose levels. In that case, dose proportionality assessment using AUC_{last} is unreliable. Instead, one can use the AUC from the time of dose administration to a specified time (AUC_t), where the specified time is a postabsorption sampling time that yields measurable concentrations across all dose cohorts.

Second, the PK profile may consist of measurable drug concentrations at all PK sampling times. In this case there is a possibility that the PK sampling scheme does not cover the entire time span for which there are measurable drug concentrations at the doses studied. If, in fact, drug concentrations would be measurable at much later time points, the AUC to the last sampling time (AUC_{last_sample}) is not the same as AUC_{last}. In that case AUC_{last_sample} would underestimate AUC_{last} by the amount of the AUC between the time of the last sampling time and the later time point at which the concentration would be less than the LLOQ, as depicted in Figure 2. The unmeasured portion of AUC_{last} could be small if the concentration at the last PK sampling time is near the LLOQ, but it could also be large if the sampling scheme terminates well before the time that drug concentrations become unmeasurable, as can happen at high doses. If the researcher knows that the last PK sampling point is the last time point at which concentrations are measurable, AUC_{last} can be used to describe the area parameter, but if it is unknown if concentrations are measurable at later time points, AUC_{last_sample} (or some similarly informative abbreviation) should be used.

AUC_{last_sample} is a special case of AUC_t. As such, it shares with AUC_t the need to decide if the AUC will be calculated up to the actual time of the last PK sample (the AUC_{last} approach) or if the AUC will be calculated up to the planned time of the last PK sample (the partial area approach). For instance, the last PK sample may be planned for 24 hours, but the actual times of collection may vary from 23.5 to 24.5 hours; AUC_{last_sample} (equal to AUC_{24}) can be calculated using the actual times and observed concentrations, or it can be calculated using a time of 24 hours and interpolated/extrapolated concentration values for the 24-hour time point. In general, and certainly if the AUC_{last} approach is used, the data analyst needs to review the actual elapsed sampling times to see how greatly the actual end times differ from the specified end time. If the AUC_{last} approach is to be used, acceptability limits for sampling time deviations need to be established and documented in the noncompartmental analysis plan. The clinical protocol should stipulate PK sampling windows for every PK sampling time point.

Third, the PK profile may consist of measurable drug concentrations up to a certain PK sampling time, after which some of the concentration results are below the LLOQ and some are above the LLOQ. This can occur when the terminal disposition phase is shallow and the concentrations during the phase are close to the LLOQ. Measurement variability results in assay results

above and below the LLOQ. The best practice in this situation is to use AUC_{last} with T_{last} defined as the time of the measurable concentration immediately preceding the first concentration result below the LLOQ.

AUC_t	AUCINT
The AUC from the time of dose administration to a specified time (t).	

The time specified for AUC_t can be any time of interest. Most commonly it is the last PK sampling time, in which case it is referred to as AUC_{last_sample}, as discussed above. It may also be a time before the last sampling time. An example of an AUC_t inside the PK sampling schedule would be the AUC measured up to the end time of the first urine collection interval in a study in which urine PK of a drug is being evaluated.

It is usual to include the specified time for AUC_t as 1 of the sampling times in the PK sampling scheme. If the actual elapsed time at that sampling time is equal to (or are very nearly equal to) the planned time, AUC_t can be estimated using the concentration measured at the specified time. If however, the actual elapsed time at the sampling time differs appreciably from the planned time, the PK analyst will need to decide if AUC_t will be measured to the actual elapsed sampling time (the AUC_{last} approach) or if AUC_t will be measured to the specified sampling time (the partial area approach). Use of the actual elapsed sampling time means accepting the measurement variability arising from imperfect sample timing in exchange for using empirical data only. Use of the specified sampling time means accepting the use of an interpolated concentration value at the specified time in exchange for decreased measurement variability due to imperfect sample timing. If the specified time is not a sampling time in the PK sampling scheme, or if the PK sample at the specified time is missing, it will, of course, be necessary to interpolate the concentration at the specified time in order to generate estimates of the parameter.

$AUC_{t1\text{-}t2}$	AUCINT
The AUC over the interval from a specified time (t1) to another specified time (t2).	

There are clinical studies in which a partial AUC of interest starts at some specified time after dosing, at time t1, and ends at a second specified time, t2. An example would be the AUC corresponding to the timing of an intermediate urine collection in a study in which the urine PK of a drug is being evaluated.

As for AUC_t, it is usual for the PK sampling scheme to include specimen collections at the time points stipulated for $AUC_{t1\text{-}t2}$ parameter estimation. The considerations involving the use of actual elapsed time versus planned time, as discussed for AUC_t, apply to $AUC_{t1\text{-}t2}$ at both the start and end times.

AUC_{inf}	AUCIFO AUCIFP
The AUC from the time of dose administration to infinite time. $= AUC_{last\_sample} + AUC_{extrap}$ or $= AUC_{last} + AUC_{extrap}$	

AUC_{inf} is the sum of the AUC calculated empirically, either AUC_{last_sample} or AUC_{last}, and the estimated AUC from the last measurable/measured concentration to infinity, AUC_{extrap}. Estimation of AUC_{extrap} depends on the same assumption concerning the terminal monoexponential decline in concentration used to justify the measurement of λ_z. Based on this assumption,

$$AUC_{extrap} = \frac{C_{last}}{\lambda_z}$$

where C_{last} is the last observed measurable concentration in the PK profile or, alternatively, it is the concentration predicted for that time point based on the regression fit of the terminal disposition phase. In theory, the predicted last concentration should yield a more accurate estimate of AUC_{inf} because it corrects for measurement error that is present in the last observed concentration. However, it introduces measurement error based on variability in the estimation of λ_z and, even more importantly, in the estimation of the value of the regression intercept. In practice, the estimates generated by the 2 approaches are highly correlated and very similar, so either approach can be used. CDISC Controlled Terminology distinguishes between AUC_{inf} estimated in the 2 different ways: AUCIFO is used for AUC_{inf} based on the observed concentration, and AUCIFP is used for AUC_{inf} based on the predicted concentration.

The simulation study referred to earlier[15] found that the estimates of AUC_{extrap}, and hence AUC_{inf}, in a study cohort are reliably identified if the variability in concentration measurement is low and the geometric mean terminal disposition time span for estimating λ_z is 2.5 or greater. Disappointingly, the study showed that estimation of AUC_{inf} is not very accurate if there is a high level of measurement variability.

Another rule that is often used to identify reliable estimates of AUC_{inf} is that AUC_{extrap} should not exceed 20% of AUC_{inf}.[2,3,12] This rule can be used to reject

AUC_{inf} estimates because this is the largest value of AUC_{extrap} possible for a PK profile allowing reliable estimation of AUC_{extrap}. However, the rule does not provide adequate justification for accepting an AUC_{inf} estimate. For multiphasic PK profiles where the area under the terminal disposition portion of the profile is less than 20% of AUC_{inf}, the estimated value of AUC_{extrap} will be much less than 20% of AUC_{inf} even in those cases in which the estimate of AUC_{extrap} is unreliable. Given the shortcomings of the 20% rule, a better rule, such as the rule discussed in the preceding paragraph, should be used to recognize and accept reliable AUC_{inf} estimates.

AUC_{tau}	AUCTAU
The AUC for a dosing interval.	

Because steady-state AUC_{tau} is used to calculate various PK parameters of disposition, such as CL_{ss}, it is often thought of as applying only to the steady state. However, AUC_{tau} is a useful measure of exposure following multiple dosing even when the steady state is not achieved by such dosing. For these reasons, the dosing interval evaluated—first dose or a later dose—and the PK character of the dosing interval—steady state or not—should be made explicit when AUC_{tau} is reported.

Calculation of AUC_{tau} in a non–steady-state dosing interval requires concentration measurements at the start and at the end of the dosing interval. PK specimens should be collected at both of these time points. For steady-state dosing intervals, if the PK sample at the start of the dosing interval is missing, its concentration can be imputed using the concentration measured at the end of the dosing interval, and vice versa. The validity of this practice depends on the steady state truly being present, in which case all end-of-dosing-interval concentrations will be equal, within the range of measurement variability.

For every-12-hours dosing, it is sometimes not possible to arrange for collection of a PK specimen 12 hours after the morning administration of drug. It is generally not appropriate to impute the morning-dose 12-hour concentration from the evening dose 12-hour concentration because the PK profiles for morning and evening dosing can be different. In those cases in which λ_z is estimable from the PK profile up to the last sampling time, the concentration at 12 hours can be imputed by extrapolation.

The considerations involving the use of actual elapsed time versus planned time, as discussed for AUC_t above, apply to the end-of-dosing-interval time of AUC_{tau}.

R_{ac}	ARAUC
A measure of increase in exposure with multiple dosing given dosing interval tau. Usually reserved for the steady state.	
$= \frac{AUC^{SS}_{tau}}{AUC^{SD}_{tau}}$	

Accumulation occurs with multiple dosing when drug reaching the systemic circulation has not been completely eliminated from the body by the time of the subsequent dose of the drug. The magnitude of drug accumulation depends on the dosing interval and, in a complex fashion, on the disposition kinetics of the drug.

Accumulation can also be quantified in terms of C_{max} (ARCMAX), C_{trough} (ARCTROUG), C_{min} (ARCMIN), or C_{avg}, depending on the nature of the parameter-effect relationships. If adverse events are related to C_{max}, for example, the increase in C_{max} with multiple dosing is a pertinent parameter. If maintaining a threshold C_{trough} (or C_{min}) is required for efficacy of the drug, the increase in C_{trough} with multiple dosing is a more informative parameter. Most often, what is of interest is the average drug concentration following multiple dosing. Because

$$C_{avg} = \frac{AUC_{tau}}{tau}$$

and tau is constant, it follows that

$$\frac{C^{SS}_{avg}}{C^{SD}_{avg}} = \frac{(AUC_{tau}/tau)^{SS}}{(AUC_{tau}/tau)^{SD}} = \frac{AUC^{SS}_{tau}}{AUC^{SD}_{tau}}$$

Notice that parameters of accumulation apply to steady-state accumulation unless otherwise stipulated and that the conventional symbol for accumulation ratio, R_{ac}, implies accumulation in terms of C_{avg}.

It is helpful to anticipate the values of C_{max} and C_{trough} that will be achieved in the steady state in a multiple-dose PK study. There is no simple way to do this for C_{max} (although simulation by noncompartmental superposition can be used), but there is a simple formula for predicting steady-state C_{trough}. If the disposition of a drug does not change with multiple dosing, and if the dosing interval is of sufficient duration that tau is greater than T_z, then

$$C^{SS}_{trough} = \frac{C^{SD}_{trough}}{1 - e^{-\lambda_z tau}}$$

Plasma PK Parameters of Disposition: Elimination

The noncompartmental PK parameters of drug elimination are systemic drug clearance and renal drug clearance. Systemic drug clearance is considered here, and renal drug clearance is discussed later, with other parameters of urine PK.

Systemic clearance only has pharmacologic meaning if the elimination of drug from the body is first order in its kinetics, meaning that the rate of removal of drug is proportional to the concentration of drug at the site of elimination. Satisfaction of this requisite condition can be demonstrated by the finding of dose proportionality of systemic drug exposure. This is done by analyzing the data from an ascending-dose clinical study and by performance of a dose proportionality clinical pharmacology study. When data from an ascending-dose clinical study are used, the dose range should include the entirety of eventual clinical dosage, and, ideally, there should be many subjects at each dose level, and the number of subjects at each dose level should be roughly equal. Visual examination of such dose-exposure data will reveal if there is obvious curvilinearity. This is very important because the standard statistical test of dose proportionality, the power model (linear regression of log-transformed parameter values versus log-transformed dose), is not an appropriate model for 2 common causes of nonproportionality: convex nonproportionality due to saturable drug elimination and concave nonproportionality due to saturable drug uptake (for drugs administered extravascularly). When the power model is used to evaluate dose proportionality, slopes greater than 1.2 and less than 0.8 indicate a marked departure from proportionality and should, therefore, be considered provisional evidence of dose nonproportionality, regardless of the *P* value for the difference between 1.0 and the slope estimate. A subsequent, well-powered, study of dose proportionality is needed to confirm nonproportionality.

If systemic exposure is found to be non–dose proportional, systemic clearance does not have a pharmacologic meaning. Specifically, it is not the average or effective systemic clearance associated with a particular dose level. If systemic exposure is not dose proportional, systemic clearance estimates should not be reported. In addition, the terminal disposition-phase volume of distribution (V_z, as discussed below) should not be reported because calculation of that PK parameter depends on a valid estimate of systemic clearance.

Note that drugs that have non–dose-proportional PK behavior will generally show nearly dose-proportional behavior at low doses. It is often of interest in the development of a drug to identify this dose range. For convex non–dose proportionality (disproportionately large increases in exposure with increasing dose), the drug may turn out to be clinically effective even when dosing is restricted to the lower dose range. For concave dose proportionality (disproportionately small increases in exposure with increasing dose), which is often due to capacity limitation of drug uptake, the need to develop an alternative formulation may be signaled by the flattening of the dose-exposure relationship at higher doses. As a rule of thumb, the nearly linear portion of a convex dose-exposure relationship is that dose range for which the exposures at the lower doses in the range allow fairly accurate prediction of the exposures at the 2 highest dose levels in the range, with the definition of fairly accurate depending on the exposure-safety profile of the drug. For saturable drug uptake, the nearly linear portion of the concave dose-exposure relationship is that dose range that precedes obvious flattening of the relationship, with flattening confirmed by similar exposures at 3 higher dose levels.

CL	CLO CLP
Single-dose systemic clearance following IV drug administration. CLO is CL based on AUC_{inf} calculated using observed C_{last}; CLP is CL based on AUC_{inf} calculated using predicted C_{last}.	
$= \frac{dose}{AUC_{inf}}$	

CL/F	CLFO CLFP
Single-dose apparent clearance following extravascular drug administration. CLFO is CL/F based on AUC_{inf} calculated using observed C_{last}; CLFP is CL/F based on AUC_{inf} calculated using predicted C_{last}.	
$= \frac{dose}{AUC_{inf}}$	

Measurement of CL depends on knowing the actual amount of drug entering the systemic circulation. Because there is unavoidable uncertainty regarding the fraction of an extravascular dose that ends up entering the systemic circulation, CL can be estimated only when there is intravascular administration of drug.

Apparent clearance (CL/F) is the parameter that is quantified following extravascular drug administration. CL/F is simply the ratio that results from algebraic rearrangement of the equation that describes systemic

clearance when only a portion of the administered dose enters the systemic circulation,

$$CL = \frac{F \times dose}{AUC_{inf}}$$

giving

$$CL/F = \frac{dose}{AUC_{inf}}$$

Because CL/F depends on F as well as systemic drug elimination, it is possible for CL/F to change as a result of a change in F when there is no change in systemic drug elimination. This can happen when there is a change in drug formulation leading to a change in the fraction absorbed or when dose levels exceed the uptake capacity at the site of drug absorption. Furthermore, F can change for oral drugs when changes in diet, the coadministration of absorption-interfering agents, or gastrointestinal disease alter the fraction of drug absorbed. Clearly, in these settings, CL/F must be interpreted carefully.

For drugs that are partially or completely eliminated by the intestines and/or liver, changes in systemic drug elimination are accompanied by changes in F. Because F will increase when hepatic/intestinal CL decreases and F will decrease when hepatic/intestinal CL increases, their ratio, CL/F, will exaggerate the underlying change in CL. This makes the physiologic basis of a change in CL/F more difficult to assess; however, the change in CL/F will accurately reflect the change in drug exposure (measured as AUC) that the change in CL has brought about.

An important consideration when reporting CL and CL/F is the reliability of the estimated AUC_{inf}. If AUC_{inf} cannot be estimated with acceptable reliability, then neither can CL or CL/F. In such circumstances it is far preferable to wait to measure and report CL_{ss} or CL/F_{ss} because AUC_{tau} can almost always be very accurately estimated.

Because CL and CL/F have meaning as elimination parameters only when the drug under study shows dose proportionality within the clinical range of drug dosages, if the drug does not behave in a dose proportional fashion, CL and CL/F should not be reported. What should be reported is the extremely consequential finding of dose nonproportionality. The curvilinear relationships between C_{max} and dose and between AUC_{inf} and dose should be presented graphically, and, if an appropriate model of the dose-exposure relationship is found, the parameter values for the model should be provided and the fits of the data shown. The clinical meaningfulness of the nonproportionality should be evaluated as it relates to the observed and expected safety and efficacy exposure margins of the drug.

CL_{ss}	CLTAU
Steady-state systemic clearance following multiple IV drug administrations.	
$= \frac{dose}{AUC_{tau}^{SS}}$	

CL/F_{ss}	CLFTAU
Steady-state apparent clearance following multiple extravascular drug administrations.	
$= \frac{dose}{AUC_{tau}^{SS}}$	

CL_{ss} and CL/F_{ss} are calculated based on the notion that the amount of drug eliminated over a dosing interval is equal to the bioavailable dose of drug. This is only so in the steady state because, until the steady state is achieved, drug is still accumulating in the body; hence, drug elimination over the dosing interval is less than drug input. Thus, it is essential that these parameters be calculated and reported only if the steady state has been achieved. In usual practice this means collecting predose PK specimens for a number of the dosing intervals preceding the intensively sampled dosing interval and visually inspecting a plot of the C_{trough} values to confirm that the values are approximately constant.

$AUC_{tau}{}^{SS}$ is estimated with high reliability as long as predose and end-of-dosing-interval PK specimens are collected and the concentrations are measurable. This makes for high reliability in the quantitation of systemic clearance. For this reason, CL_{ss} and CL/F_{ss} should be preferred over CL and CL/F as the parameters for characterizing systemic clearance. This is especially true for drugs that will be administered chronically because the magnitude of systemic clearance following multiple dosing is the most relevant clearance measure for long-term drug therapy.

CL_{ss} and CL/F_{ss} should be reported only when steady-state PK data show dose proportionality within the clinical range of drug dosages.

R_s	SRAUC
The stationarity ratio.	
$= \frac{AUC_{tau}^{SS}}{AUC_{inf}^{SD}}$	

Because drug disposition, in particular drug elimination, may change with multiple dosing, it is of interest

to determine if such a change has occurred. The parameter used to explore this is R_s. Because

$$AUC_{tau}^{SS} = AUC_{inf}^{SD}$$

if the disposition of drug stays constant, their ratio (R_s) should be 1 if multiple dosing has not changed drug disposition. The finding of an appreciable difference of the ratio from 1 indicates that drug disposition has changed, usually due to altered systemic elimination.

Plasma PK Parameters of Disposition: Metabolism

Study of the PK of primary drug metabolites, and even downstream metabolites, may be of interest because of nonclinical study findings, because of the intended pharmacology of the parent drug (eg, it is a prodrug), or because of findings in the human mass balance study of the parent drug.[19] If a metabolite (or metabolites) is pharmacologically active, it will be important to account for it when defining the exposure-efficacy relationship. It is also important to ascertain if a metabolite (or metabolites) contributes to the exposure-toxicity relationship; indeed, it sometimes happens that a metabolite is far more toxic than the parent drug such that the exposure-toxicity relationship depends primarily or solely on metabolite exposure.

Plasma metabolite concentrations are assayed to ascertain if measurable concentrations are present when the parent drug is dosed at clinically relevant levels and, if so, C_{max}, AUC, and $T_{1/2Z}$ of the metabolites ($C_{max}{}^{MET}$, AUC^{MET}, and $T_{1/2Z}{}^{MET}$) should be characterized following a single dose of parent drug and, importantly, in the steady state. Metabolite exposure parameter values are usually expressed in absolute terms and also relative to the value of the corresponding parameter value for the parent drug ($C_{max}{}^{MET}/C_{max}{}^{PARENT}$ and AUC^{MET}/AUC^{PARENT}).

CL^{MET}/F^{MET}	na
Apparent clearance of metabolite.	
$= \frac{\text{dose equivalent}}{AUC_{inf}^{MET}}$	

Directly interpretable disposition parameters for metabolites cannot be obtained solely by the analysis of PK data following parent drug administration because F^{MET} is unknown. For an example of a clinical study designed to estimate F^{MET} and CL^{MET}, see Greenblatt et al.[20]

Because the $T_{1/2Z}$ of a metabolite can be longer than that of the parent drug, the reliability of the estimation of $AUC_{inf}{}^{MET}$ must be considered separate from the determination of the reliability of estimating $AUC_{inf}{}^{PARENT}$. This is especially important if steady-state exposures of the metabolite will be predicted using the single-dose data.

$CL^{MET}/F^{MET}{}_{ss}$	na
Steady-state apparent clearance of metabolite following multiple drug administrations.	
$= \frac{\text{dose equivalent}}{AUC_{tau}^{MET}}$	

In the steady-state, changes in CL^{MET} and F^{MET} resulting from multiple dosing are accounted for, making it a superior descriptive parameter for drugs administered chronically. In addition, the use of $AUC_{tau}{}^{MET}$ rather than $AUC_{inf}{}^{MET}$ assures reliability of the AUC estimate used in the calculation.

$\lambda_z{}^{MET}$	LAMZ
Exponential rate constant of the metabolite terminal disposition phase.	
= slope of linear regression fit of the log-transformed late metabolite concentration-time data.	

$T_{1/2Z}{}^{MET}$	LAMZHL
The half-life of the metabolite terminal disposition phase.	
$= \frac{\ln(2)}{\lambda_z^{MET}}$	

When the concentrations of a metabolite are measured, $\lambda_z{}^{MET}$ and $T_{1/2Z}{}^{MET}$ of the metabolite should be estimated using the same approach and reliability criteria as for the parent drug. Note that the terminal disposition phase of a metabolite following parent drug administration may differ from that seen when the metabolite itself is administered. This is because, following parent drug administration, the disposition of a metabolite depends on the kinetics of formation of the metabolite as well as on the postformation dispositional behavior of the metabolite. When the kinetics of metabolite formation is similar to or slower than the kinetics of its systemic disposition, a situation that is not uncommon, the terminal disposition phase of the metabolite will predominantly reflect the kinetics of formation of the metabolite. Hence, $\lambda_z{}^{MET}$ and $T_{1/2Z}{}^{MET}$ will be the same as $\lambda_z{}^{PARENT}$ and $T_{1/2Z}{}^{PARENT}$. The influence of formation kinetics on metabolite disposition should be discussed in the study report.

Plasma PK Parameters of Disposition: Distribution

V_0	VO
The volume of distribution immediately following bolus IV drug administration.	
for a single dose $= \frac{\text{dose}}{C_0}$ for multiple dosing $= \frac{\text{dose}}{C_0 - C_{\text{trough, previous dose}}}$	

For a single dose of drug, V_0 is the noncompartmental estimate of the ratio of the amount of drug in the body and the concentration of drug in the plasma immediately after bolus IV administration of drug. For multiple dosing, when the plasma concentration is often non-0 predose, V_0 is the noncompartmental estimate of the ratio of the amount of drug in the body introduced by bolus IV administration of drug and the difference between the predose and immediate postdrug concentrations. In both cases the assumption is that the change in plasma concentration of drug (C_0 or C_0 minus C_{trough}) is measured before any elimination or extravascular distribution of the newly administered dose of drug. The accuracy of V_0 estimates depends on the accuracy of the estimate of C_0, as discussed previously.

V_z	VZO VZP
Single-dose terminal disposition–phase volume of distribution following IV drug administration. VZO is V_z based on CL estimated using AUC_{inf} calculated using observed C_{last}. VZP is V_z based on CL estimated using AUC_{inf} calculated using predicted C_{last}.	
$= \frac{CL}{\lambda_z}$	

V_z/F	VZFO VZFP
Single-dose apparent terminal disposition–phase volume of distribution following extravascular drug administration. VZFO is V_z/F based on CL/F estimated using AUC_{inf} calculated using observed C_{last}. VZFP is V_z/F based on CL/F estimated using AUC_{inf} calculated using predicted C_{last}.	
$= \frac{CL/F}{\lambda_z}$	

V_z is the noncompartmental estimate of the ratio of the amount of drug in the body and the concentration of drug in the plasma during the terminal disposition phase following IV drug administration. During the terminal disposition phase, the amount of drug in every kinetic compartment in the body declines exponentially with the same rate constant, λ_z. Hence, the total amount of drug in the body decreases exponentially with rate constant λ_z, the plasma drug concentration declines with rate constant λ_z, and their ratio, V_z, remains constant. This makes V_z a meaningful parameter of drug distribution throughout the terminal distribution phase.[21]

Because V_z is calculated using the elimination parameter CL, V_z only has meaning when it is valid to estimate CL, that is, when the study drug has dose-proportional PK. If the PK is not dose proportional, neither CL nor V_z should be reported.

Objections to the use of V_z have been raised because the parameter depends on CL, which is an elimination parameter, not a distribution parameter.[22] If V_z were an anatomic compartment, the volume should not be influenced by CL, but V_z does not represent an anatomic compartment volume: it is a proportionality constant of the amount of drug in the body and the concentration of drug in the plasma. Any circumstance that alters that proportionality must lead to different values of V_z. That is exactly what happens when CL varies. As CL increases, a disproportionately larger fraction of the drug in the body is present in peripheral distribution sites. So, for any given concentration of drug in the plasma, when the amount of drug in the plasma (ie, the central distribution site) is the same, there will be more drug in the peripheral distribution sites and hence more total drug in the body. Thus, the ratio of drug in the body to the concurrent plasma drug concentration will be greater; V_z will be larger. The opposite occurs when CL decreases. In this way V_z accurately reflects the changed distribution of body drug caused by changes in CL.[23] It is critical to recognize that the magnitude of the change in V_z for a given change in CL depends very much on the original disposition of a drug such that the change in V_z caused by a change in CL may be relatively large for some drugs and yet too small to be detected for other drugs.

Following extravascular drug administration, dividing clearance by λ_z yields the apparent terminal disposition-phase volume of distribution (V_z/F). V_z has a straightforward physiologic interpretation. V_z/F has no physiological meaning, even if the magnitude of F is known. It is purely a mathematical construct. For this reason, even though NCA software packages provide estimates of V_z/F, this parameter should not be reported. If a highly reliable prediction of F has been derived from in silico modeling

and/or nonclinical PK studies, *provisional* estimates of V_z can be calculated and reported. The logic and results of this exercise should be discussed in the study report.

$V_{z,ss}$	VZTAU
Steady-state terminal disposition-phase volume of distribution following multiple IV drug administrations.	
$= \frac{CL_{ss}}{\lambda_z}$	

V_z/F_{ss}	VZFTAU
Steady-state apparent terminal disposition–phase volume of distribution following multiple extravascular drug administrations.	
$= \frac{CL/F_{ss}}{\lambda_z}$	

Because drug disposition can change with multiple dosing, the ratio of the amount of drug in the body and the concentration of drug in the plasma during the terminal disposition phase following a single dose may be different from that following multiple dosing; thus, $V_{z,ss}$ may be different from V_z. Just as CL and CL_{ss} should not be reported as a single parameter unless it has been decided that drug disposition is unchanged with multiple dosing, V_z and $V_{z,ss}$ should not be reported as a single parameter without evidence that multiple dosing has not resulted in a change in the disposition of the drug. Although it is provided by NCA software, V_z/F_{ss} should not be reported. Similar to the single-dose setting, this parameter can be used to calculate *provisional* estimates of $V_{z,ss}$ if a highly reliable prediction of F is available.

In order to estimate λ_z in the steady state, it is usually necessary to obtain concentration data after the end of the steady-state dosing interval used to estimate CL_{ss} or CL/F_{ss}. So it is a good practice to collect PK specimens during a washout period immediately following the dosing interval; if the washout period is long enough, it will be possible to estimate λ_z reliably.

Steady-State Volume of Distribution

Most NCA software packages calculate a parameter called the steady-state volume of distribution (V_{ss}). This volume is the noncompartmental estimate of the ratio of the amount of drug in the body and the concentration of drug in the plasma at steady state following prolonged IV drug infusion. It is also the ratio of the average steady-state total drug body content and the average steady-state plasma concentration following repetitive IV bolus or short infusion dosing. Interestingly, although the parameter characterizes drug distribution in the steady state, it can be calculated using the concentration-time data obtained following a single IV drug dose, although the value estimated using actual steady-state data can vary from that derived from single-dose data if the disposition of the drug has changed with multiple dosing.

There is disagreement in the literature concerning the theoretical merits of V_{ss} and V_z as measures of drug distribution (see, for example, Greenblatt et al[21] and Gobburu and Holford[22]). Preference for V_{ss} as a distribution parameter is due primarily to the fiction that it is more volume-like than V_z, forgetting that neither parameter is a physiologic volume—both are simply proportionality constants. V_z describes distribution in the terminal disposition phase, be it following a single dose of drug or in the steady state, whereas V_{ss} applies only in the steady state. Also, valid estimation of V_{ss} requires that all drug elimination occur solely from the kinetic compartment that includes the plasma,[24] a restrictive assumption. For these reasons, it seems reasonable to recommend the use of V_z and to discourage the use of V_{ss}.

Plasma PK Parameters of Disposition: Absorption

Characterizing Drug Absorption

The PK of drug absorption is characterized by measures of "how much" and "how fast." Noncompartmental parameters of bioavailability are used to quantify "how much." "How fast" and elaborations of that question are much more difficult to answer, even with sophisticated mechanistic PK modeling approaches. The noncompartmental method relies on T_{max} as the measure of "how fast." This is not particularly satisfying because T_{max} is affected by the kinetics of drug distribution and elimination, as well as drug absorption, but T_{max} has nevertheless proven to be a useful, if rough, guide to the rapidity of drug absorption.

F	na
Absolute bioavailability.	

F_{rel}	na
Relative bioavailability.	

Bioavailability is the fraction or percentage of an administered dose of a drug that reaches the systemic circulation intact (ie, as the administered drug or as

the active drug when a prodrug is administered) when compared with a reference administration of the drug. For absolute bioavailability, F the reference, is an IV administration of drug. For relative bioavailability, F_{rel}, the reference is administration of a different formulation of the drug using the same extravascular route or the same formulation of the drug administered via a different route.

The systemically available dose of a drug equals

$$CL \times AUC_{inf}$$

where CL is the systemic clearance of drug (discussed below).

So

$$F = \frac{(CL \times AUC_{inf})^{EV}}{(CL \times AUC_{inf})^{IV}}$$

and

$$F_{rel} = \frac{(CL \times AUC_{inf})^{EV2}}{(CL \times AUC_{inf})^{EV1}}$$

if equal doses of drug are given for the test and reference drug administrations.

Assuming that the systemic elimination of drug is the same regardless of the route of administration,

$$F = \frac{AUC_{inf}{}^{EV}}{AUC_{inf}{}^{IV}}$$

and

$$F_{rel} = \frac{AUC_{inf}{}^{EV2}}{AUC_{inf}{}^{EV1}}$$

If unequal doses of drug are given in the test and reference periods, dose-normalized AUC_{inf} is used in the formulas. For reasons of practicality, if a drug has a long $T_{1/2Z}$ (longer than 24 h), a limited duration of PK sampling is usually used, and AUC_{last_sample} is used in place of AUC_{inf} when calculating F or F_{rel}. The duration of sampling should be at least as long as T_z plus $T_{1/2Z}$ for the test formulation/route and, if possible, should yield an AUC_t that is a reasonably large fraction of AUC_{inf} for that formulation/route. FDA Guidance is that "the sponsor should consult the appropriate review division to seek agreement on the duration of sampling."[25]

Although F and F_{rel} can be estimated for individual subjects and summarized using geometric statistics, in modern practice these parameters are estimated as population parameters by mixed-effects ANOVA of the log-transformed study AUC data.

Urine PK Parameters: Urinary Excretion Parameters

AE_t	RCAMINT
The amount excreted from the time of dose administration to a specified time (t).	
= volume of urine collected × concentration of drug in urine	

$AE_{t1\text{-}t2}$	RCAMINT
The amount excreted over the interval from 1 specified time (t1) to another specified time (t2).	
= volume of urine collected × concentration of drug in urine	

Initial evaluation of the extent of urinary excretion of drug should be conducted early in the development of the drug so that data-based exclusion criteria for renal impairment can be established for the initial phase 2 studies of the drug. Ideally, a validated urine assay should be in place to support the first-in-human study.

Measurement of the urinary excretion of drug is best accomplished using a series of urine collections. If the drug is expected to be rapidly cleared from the body, the initial urine collection should be brief, with the duration selected based on the expected rapidity of drug clearance. Even for slowly cleared drugs, the initial urine collection should last no longer than 8 hours. This allows for a supervised, complete urine collection, and for drugs with little elimination in the urine, maximizes the chances of having a measurable drug concentration in the urine specimen. Subsequent urine collections should be short but also practical given the clinical circumstances. For rapidly cleared drugs, a few 4-hour collections are desirable, followed by an overnight collection. For more slowly cleared drugs, an 8-hour collection followed by an overnight collection is recommended. Thereafter, the length of the urine collections can be extended to 8 to 12 hours.

Total amount of excreted drug for the entire period of urine sampling is the sum of the amounts in each of the short collections. If the urine concentration for a collection is BQL, AE_t (or $AE_{t1\text{-}t2}$) for that interval is usually imputed as 0.

Accurate measurement of AE requires complete collection of all urine voided over the specified time interval, including a forced voiding at the end of the collection. This is difficult for unconfined subjects to do, given the extreme change in daily voiding habit required. If subjects are going to be sent home on the day of dosing, it is usually better to plan a supervised

Table 1. Approximate Daily Urine Output in Healthy Individuals

Age Range, y	Urine Output, L/d	References
8–9	0.25–1.0	26
12–14	0.5–1.5	26
20–30	0.75–2.5	27
30–80	0.75–3	28, 29

in-clinic urine collection before releasing the subject rather than attempting an extended home urine collection. This provides for a high-quality urine collection that will allow for accurate estimation of CL_{renal} (see below).

If urine must be collected outside of clinic, it is advisable to compare the collection volumes with the approximate daily urine output (L/day) as measured in healthy individuals, as shown in Table 1. Deviations from the expected volume of urine may represent instances of under- or overcollection of urine, or other methodologic issues (eg, transcription errors).

AE_{tau}	RCAMTAU
The amount excreted over a dosing interval. Usually reserved for the steady state.	
= volume of urine collected × concentration of drug in urine	

If the steady state has been achieved with multiple dosing, AE_{tau} is the most reliable means for assessing total urinary excretion of drug if all urine collections over the dosing interval have measurable drug concentrations, thus assuring that the totality of excreted drug is accounted for. If, even after multiple dosing, there are urine collections with BQL concentration results, or if it is not practical to collect urine throughout the entirety of the dosing interval, AE_{tau} can be calculated using the formula

$$AE_{tau} = CL_{tau} \times AUC_{tau}$$

where CL_{renal} has been determined using the collected urine excretion data (see the section that directly follows).

FE_t	RCPCINT
The fraction of the administered dose excreted from the time of dose administration to a specified time (t).	
$= \frac{AE_t}{\text{administered dose}}$	

$FE_{t1\text{-}t2}$	RCPCINT
The fraction of the administered dose excreted over the interval from a specified time (t1) to another specified time (t2).	
$= \frac{AE_{t1-t2}}{\text{administered dose}}$	

FE_{tau}	RCPCTAU
The fraction of the administered dose excreted over a dosing interval. Usually reserved for the steady state.	
$= \frac{AE_{tau}}{\text{administered dose}}$	

The proportion of a dose of drug excreted in the urine quantifies the contribution of urinary elimination to the disposition of the drug. The proportion can only be accurately determined for drugs administered intravascularly, in which case it is the amount excreted divided by the dose. For drugs administered extravascularly,

$$FE = \text{proportion of dose eliminated in the urine} \times F$$

where F is the systemic bioavailability of the drug formulation via the particular route of administration. Hence, FE is an underestimate of the true proportion of dose eliminated in the urine, and, for drugs with low absolute bioavailability, a substantial underestimate. For this reason, FE should not be reported for drugs administered extravascularly. If it is reported, it must be made very clear that it refers to the proportion of "administered dose" rather than "systemically available dose."

Note that when calculating FE for a drug metabolite, it is critical to account for the difference in molecular weight between the parent drug and the metabolite by expressing metabolite AE in terms of parent drug weight equivalents.

Urine PK Parameters: Urinary Clearance Parameters

CL_{renal}	RENALCL RNCLINT
The renal clearance of drug based on urinary excretion of the drug. RENALCL is CLrenal based on AE_t; RNCLINT is CLrenal based on $AE_{t1\text{-}t2}$	
$= \frac{AE_t}{AUC_t}$ or $= \frac{AE_{t1-t2}}{AUC_{t1-t2}}$	

When renal clearance of drug into the urine behaves as a first-order process,

$$\text{urine excretion rate} = CL_{renal} \times \text{plasma drug concentration}$$

Integrating this equation over time gives

$$AE_{t1-t2} = CL_{renal} \times AUC_{t1-t2}$$

which on rearrangement gives the formula for CL_{renal},

$$CL_{renal} = \frac{AE_{t1-t2}}{AUC_{t1-t2}} \text{ or } \frac{AE_t}{AUC_t} \text{ if } t1 = 0.$$

When the urinary excretion of drug is measured using a series of urine collections, it is possible to calculate CL_{renal} using $AE_{t1\text{-}t2}$ from any of the individual collections or AE_t as found by combining $AE_{t1\text{-}t2}$ interval data from a number of successive, or all, urine collections. It is good practice to use AE_t with the end time being the end of the last urine collection with a measurable drug concentration. If plasma concentration data are BQL while drug concentration can still be measured in the urine collections, AUC_t will need to be derived by extrapolation. This should be done only when the extrapolation is based on a reliable estimate of the slope of the late portion of the plasma concentration curve. If the slope cannot be estimated reliably, CL_{renal} should be calculated using AE_t and AUC_t, with the end time here being the end of the last urine specimen collected while drug concentrations were still measurable in plasma.

The prolonged collection of urine is sometimes operationally difficult in the clinical setting. In such a case, CL_{renal} can be calculated using AE_t as determined over a time interval for urine collection that is operationally convenient, such as the interval from the time of drug administration to the time of the final PK blood specimen collection during a clinic visit (eg, 8 hours postdose).

$CL_{renal,ss}$	RENCLTAU
The renal clearance of drug based on urinary excretion of the drug over a dosing interval (AE_{tau}). Usually reserved for the steady state.	
$= \frac{AE_{tau}}{AUC_{tau}}$	

$CL_{renal,ss}$ is the estimate of renal clearance obtained using AE and plasma AUC data obtained over a dosing interval following multiple dosing of a drug and attainment of the steady state. $CL_{renal,ss}$ is the most reliable measure of renal clearance of drug if all urine collections over the dosing interval have measurable drug concentrations because all excreted drug from the dose administered at the start of the dosing interval has been accounted for, given that the steady state has actually been achieved.

Summary Statistics

Summarizing Data

Concentration data and pharmacokinetic parameter data are summarized using descriptive statistics, with grouping by treatment regimen and day of treatment. Data may also be grouped according to clearly defined subpopulations (eg, gender).

A combination of nonparametric, arithmetic, and geometric summary statistics is typically reported in the study report's appendix tables. Because these tables are not constrained by space considerations, there is no reason not to be expansive, providing statistics calculated using each of the 3 statistical approaches. Table 2 provides a compilation of useful summary statistics, and Table 3 lists a coherent subset of sample size, location, and dispersion statistics.

When summarizing concentration data in the body of a report, arithmetic statistics (mean and SD or coefficient of variation [CV]) are usually presented. Even though it is widely accepted that concentration data distributions tend to be log-normal, arithmetic statistics are used because geometric statistics cannot be calculated if any of the concentration data are set to 0 because they are BQL, which is not an uncommon situation. Arithmetic statistics are also often used to summarize PK parameter data for both practical and theoretical reasons.[6,30] Because the data distributions for PK parameters tend to be more accurately described using geometric statistics,[31,32] it is recommended to also present geometric summary statistics (geomean and geoSD or geoCV), if the data permit calculation of the statistics. This practice is consistent with the assumption of log-normality imposed in the statistical analysis of parameter data from clinical pharmacology studies and the assumption of parameter log-normality in population PK modeling. T_{lag} and T_{max} are interval-censored parameters, the values of which are discrete (ie, noncontinuous), and, as a result, neither arithmetic nor geometric summary statistics are appropriate; nonparametric statistics are recommended for these parameters.

Harmonic Mean

Many NCA software packages include harmonic mean among the statistics calculated when summarizing PK parameter values,

$$\textit{harmonic mean} = \frac{N}{\sum \frac{1}{x_i}}$$

Table 2. Common Summary Statistics

Statistic	Arithmetic	Geometric	Nonparametric
Sample Size	N	N	N
Location	Mean	geomean = exp(mean$_{log}$)	median
Dispersion index	SD	geoSD = exp(SD$_{log}$)	P_{25}, P_{75} interquartile range (IQR)
Scaled dispersion index	CV	geoCV = sqrt(exp[SD$_{log}^2$] − 1)	not applicable
Extrema	…	…	maximum, minimum

Table 3. Recommended Summary Statistics of Sample Size, Location, and Dispersion to Include in CSR Appendix Tables

Data	Statistics
All	N
PK concentrations and parameters except T_{lag} and T_{max}	mean, SD, CV geomean, geoSD, geoCV median, IQR, minimum, maximum
T_{lag}, T_{max}	median, IQR, minimum, maximum

In particular, this statistic is often used when summarizing $T_{1/2Z}$ data, in which case

$$\text{harmonic mean of } T_{1/2z} = \frac{N}{\sum \frac{1}{\lambda_{z,i}}}$$

This practice is supported by a number of articles in the literature that demonstrate the superior accuracy of the harmonic mean as a summary statistic for PK parameters, such as $T_{1/2Z}$, that are derived as reciprocals of other PK parameters.[33,34] However, the conclusions are based on the assumption that the parameter used in the derivation (eg, λ_z for $T_{1/2Z}$) is normally distributed. If the parameter is not normally distributed, there is no reason to expect the harmonic mean to outperform other averaging statistics. Indeed, when experimental PK parameter data have been examined, the harmonic mean has not been found to be more accurate than the arithmetic mean as a descriptor of the central tendency of $T_{1/2Z}$.[35] Other reciprocal PK parameters, such as CL, tend to be well described by geometric statistics because the base parameters (AUC_{inf} for CL) tend to be log-normally distributed, and reciprocal parameters of log-normally distributed parameters are log-normally distributed.

Quantitation of Variability

Almost all of the clinical studies that have PK data that are analyzed by noncompartmental methods enroll a small number of subjects into each study arm or each dose cohort. The number of enrollees usually allows for acceptable precision in the estimation of central tendency (average value) of concentration data and PK parameter values but not of their variability.[30] This fact should be kept in mind when presenting measures of variability from a clinical study and even more so when powering subsequent clinical trials based on estimates of PK variability.

When describing the variability of a parameter in a group of subjects, there is a strong temptation to rely on descriptive terms rather than numerical expressions. Thus, one finds the estimates of a parameter being described as being slightly, or moderately, or markedly variable without knowing the criteria that have been used to define the terms.

It is a good practice to be disciplined when using quantifying adverbs. To assist in this, the following are suggested: slightly variable should be used if the CV (arithmetic or geometric) is less than 20%, moderately variable should be used if the CV is between 20% and 35%, and markedly variable should be used if the CV is greater than 35%.

Incomplete Data Sets

There are times when values are missing from a data set, for example, an uncollected blood specimen resulting in a missing concentration value. The impact of missing data on the accuracy of central location statistics depends on the proportion of data that are missing and on the reason that the data are missing. Data missing at random do not introduce bias in the estimation of central location. If, however, the data are truncated, estimates of central location will be biased. If the missing data are those with the lowest values, central location will be overestimated, and if the missing data are those with the highest values, central location will be underestimated.

For concentration data sets, BQL results should never be treated as missing PK. If such data were considered as missing, there would be selective truncation of low data values, leading to overestimation of the average concentration at those time points for which BQL values are present. The greater the number of

BQL values, the greater would be the overestimation of the average concentration. When BQL values are assigned a value of 0, the practice recommended here, the arithmetic mean will be underestimated, but only very slightly, because modern assay LLOQs are so small. The median will be accurately estimated, just as long as the number of BQL values is less than N/2. The geomean, of course, cannot be estimated when there are any concentration values equal to 0.

Unlike the practice recommended in this article—to report either all or none of the subject values for a parameter in a treatment cohort—it is common practice to classify individual subject parameter values according to some reliability criterion or criteria and to report only those individual values that are deemed reliable. This practice can result in the exclusion of the lowest values of λ_z and CL and the highest values of $T_{1/2Z}$ and AUC_{inf} within a treatment cohort. This will, of course, lead to overestimation of average λ_z and CL and underestimation of average $T_{1/2Z}$ and AUC_{inf}, with greater over- and underestimation the larger the proportion of values that are unreported. The presence of selective data truncation for these parameters and the potential for bias in the summary statistics need to be discussed in the study report. Also, the potential for bias needs to be recognized and accounted for when the statistics are used to assist in the design of subsequent clinical studies.

Noncompartmental Analysis Plan

The noncompartmental analysis plan is an essential component of the overall Data Analysis Plan for any clinical study for which PK data are collected and analyzed by noncompartmental methods. The plan should be comprehensive and detailed. It is recommended that the plan include text and, where helpful, tables, for the following items:

1. PK experience with chemically related drugs or in silico, nonclinical or clinical PK data that support the proposed PK sampling scheme.
2. Description of the general study design (eg, single dose, multiple dose, crossover, route and method of drug administration).
3. Protocol study objectives justifying the collection of PK data.
4. Definition of PK-evaluable population.
5. Detailed description of PK sampling scheme for all biofluids sampled.
6. Description of data-handling issues (eg, handling of BQL concentration data).
7. Listing of and definitions of PK parameters to be estimated based on the PK sampling schedule.
8. Instructions concerning listing, tabulation, and graphical presentation of concentration data and PK parameter data.
9. Instructions concerning any statistical tests to be performed.

The noncompartmental analysis plan will reflect the clinical pharmacology goals and PK data needs for the clinical trial being undertaken. For ascending-dose studies, where characterization of the PK of a drug in humans is the goal, extensive plasma and urine concentration data should be collected, and a comprehensive set of plasma and urine PK parameters should be reported. Appendix 1 provides a sample noncompartmental analysis plan for an ascending dose study in which single-dose and multiple-dose (steady-state) plasma and urine PK are to be characterized for an oral drug.

Clinical pharmacology studies are focused clinical studies that are used to extend the investigation of the fundamental PK properties of a drug or drug formulation (bioavailability study, bioequivalence study, mass balance study) or to contrast the PK of a drug under different study conditions (food effect study, drug-drug interaction study) or in different clinical subpopulations (hepatic impairment study, renal impairment study, age effect study, gender effect study). NCA-derived PK parameters are the primary end points for these studies. In order to provide high-quality parameter estimates, concentration data collection is extensive, with intensive sampling for extended periods following dosing. The appropriate regulatory guidances[5] should be consulted for designing these studies and for preparing the noncompartmental analysis plan.

Reporting NCA Results in the Clinical Study Report

If the NCA is performed to support a healthy-subject ascending-dose study or a clinical pharmacology study, the clinical pharmacologist will typically be responsible for writing most or all of the CSR. If the NCA is conducted on PK data from a patient-subject ascending-dose study, from a phase 2 clinical trial, or from data arising from a PK substudy within a phase 2 or phase 3 clinical trial, the clinical pharmacologist will contribute material to a jointly authored CSR. In all cases the authoring responsibilities should be clearly delineated at the time the study is being designed.

The CSR should present all of the information needed to judge the scientific quality of the design, performance, and interpretation of the NCA[36,37] and should present the information in an orderly fashion. The usual order of presentation for a scientific report

describing a healthy-subject ascending-dose study or a clinical pharmacology study is this:

1. Study background and rationale
2. Study methods
   2.1. General trial design
   2.2. Planned number of subjects and planned makeup of the study population; informed consent procedures
   2.3. Non-PK study procedures, including all procedures for monitoring subject safety
   2.4. PK sampling schedule, the specimen collection procedure(s), and sample handling and storage procedures.
   2.5. Drug concentration assay methodology
   2.6. NCA methodology and software
   2.7. Statistical methodology and software
3. Results
   3.1. Actual number of study subjects and makeup of the study population
   3.2. PK concentration data
   3.3. PK parameter data
   3.4. Statistical test results and derived summary measures
   3.5. Safety findings in study subjects
4. Discussion

Much of the information relating to the NCA design and methods can be copied from the noncompartmental analysis plan. Not infrequently, the circumstances encountered in the performance of the study necessitate some changes in study design; those changes that are relevant to the PK objectives of the study should be discussed. Similarly, any changes from the noncompartmental analysis plan in the conduct of the NCA, due to unexpected PK findings, should be discussed. The text concerned with the methodology of the drug assay(s) should describe the critical considerations in specimen collection, handling, and storage in addition to providing a detailed description of the analytic methodology employed, and pertinent operational characteristics of the method, such as the LLOQ. The clinical pharmacologist should confirm that all specimens were actually collected according to protocol, that specimens were processed within stipulated preparation times and under proper conditions (for example, using a centrifuge kept at -20°C), and that samples were stored promptly at the specified storage temperature, and were assayed within the analyte stability time frame established during assay development.

The data analyst, clinical pharmacologist, and biostatistician should discuss and agree on the details of the presentation of the NCA data and findings,[12] documenting the details in the noncompartmental analysis plan. The drug concentration and PK parameter tables and figures stipulated in the plan are realized in the CSR. They represent the primary means of communicating the study's PK results. The purpose of the accompanying text is to point out especially informative entries in the tables and figures and to summarize the data presented in the form of "findings," such as "oral absorption was rapid with T_{max} less than 2 hours in all subjects." The text should not simply be a reiteration of the summary statistics.

The interpretation of the PK findings is usually limited to addressing the PK objectives of the study. If the objective is "to characterize" the PK of a drug in early development, little or no interpretation of the findings is generally required. In particular, the clinical pharmacologist must avoid the temptation to state conclusions that are not justified because of the limited statistical power of early development studies.[38] If there are unexpected or anomalous PK findings, these should be discussed. The lessons learned concerning the PK design requirements for future clinical studies should be documented, if not explicitly in the CSR, then elsewhere for later reference. For clinical pharmacology studies, the PK objective is typically to quantify the nature and magnitude of the effect that some clinical variable (eg, food intake, concomitant drug administration, or demographic category) has on the PK of the investigational drug. In this case, the extent of the effect can be interpreted using established scientific or regulatory criteria, but because the therapeutic context in which a drug will be used is rarely fully captured by such criteria, it is important for the PK findings to be interpreted by the clinical pharmacologist with due consideration for the PK, pharmacodynamic, and clinical context.[36]

Conflicts of Interest

Dennis Noe has no conflicting interests. The work in this article was unsponsored and unfunded.

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Appendix 1

Sample Noncompartmental Analysis Plan

Background. PK studies in dogs found that study drug YYYYY was rapidly absorbed (median T_{max} of 2 hours) and had a geometric mean terminal disposition phase half-life of 12 hours. Based on these observations, the PK sampling scheme in this first-in-human clinical trial is intensive for the first 4 hours following dosing and has samples collected up to 72 hours postdose (more than 5 times the half-life in the dog).

Study Design. Study XXXX is a multiple-dose, parallel-group, dose-escalation clinical trial of study drug YYYYY administered orally. The study drug is administered on study day 1, followed by drug washout on study days 2 and 3, followed by daily morning dosing on study days 4-15, and finally, drug washout on study days 16 and 17. Each dose cohort will consist of 8 subjects taking the study drug and 2 subjects taking placebo.

PK data collection and analysis are listed as objectives in the study protocol: Secondary objective 2 is to characterize the single-dose and multiple-dose plasma and urine PK of study drug YYYYY.

Blood specimens for plasma concentration measurement are collected using the following schedule:

Study Day	Dosing	Time of Specimen Collection Postdose (h)	Notes
1	Dose	Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	
2		24, 36	
3		48	
4	Dose	72	Pre–day 4 dose
5	Dose	Predose	
6	Dose		
7	Dose		
8	Dose	Predose	
9	Dose		
10	Dose		
11	Dose		
12	Dose	Predose	
13	Dose		
14	Dose		
15	Dose	Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	
16		24, 36	
17		48	
18		72	

Urine specimens for urine concentration measurement are collected using the following schedule:

Study Day	Time of Specimen Collection Postdose (h)	Notes
1	Predose	Spot urine collection
15	0-8, 8-16, 16-24	Timed urine collections

Plasma and urine study drug concentrations will be measured using validated bioanalytical methods. Both the plasma and urine methods use high-performance liquid chromatography with column switching and tandem mass spectrometry detection using negative ion electrospray. The LLOQ of the plasma assay is xx ng/mL, and that of the urine assay is yy ng/mL. The assays will be performed at ZZ Laboratories (Somewhere, USA). Internal assay quality control will be conducted in accordance with the laboratory's quality-control standard operating procedures.

PK-Evaluable Population

The PK-evaluable population of study subjects will consist of those subjects who are PK-evaluable for either study day 1 or study day 15 or both. Subjects will be PK-evaluable for study day 1 if they have received a dose of study drug on that day and if they have concentration-time data that permit the estimation of at least C_{max}. Subjects will be PK-evaluable for study day 15 if they have been dosed daily before study day 15 (the required length of daily

dosing to be determined by the PK analyst after examination of the study data), if they have received a dose of study drug on study day 15 and if they have concentration-time data that permit the estimation of at least C_{max}.

Data Handling

Concentration data will be summarized according to the planned sampling time. PK parameters will be calculated using the actual time of specimen collection. If the actual time of collection is missing, the PK analyst will determine if the actual collection time can be imputed from the planned collection time or if, instead, the data point will be excluded from the analysis. Data that have been collected outside of the protocol-stipulated collection window will be excluded from calculation of the concentration summary statistics but may be included in the estimation of PK parameters.

Concentration data with a BQL result will be imputed as having a value of 0. Missing data will not be imputed, with 1 exception: if the steady-state has been reached by study day 15, the concentration at time 0 on study day 15 may be used to impute the concentration at 24 hours if the 24-hour time point is missing, and vice versa.

Anomalous concentration data will be excluded from the analysis. Anomalous data include non-0 predose concentrations on study day 1, a predose concentration during multiple dosing that is much higher than concentrations in predose samples that precede and follow the data point, and low/BQL concentrations bracketed by concentrations well above the LLOQ. Excluded data will be documented in the CSR and the concentration listings and a rationale for the exclusion provided.

Plasma PK Profiles

All concentration data will be listed with planned time of specimen collection and actual date, time, and elapsed time of the specimen collection. If applicable, a notation will be included indicating that the concentration has been excluded from the analysis.

Concentration data will be summarized and tabulated according to dose cohort, dosing day, and planned collection time. The following summary statistics will be calculated, as data permit: mean, SD, CV; geomean, geoSD, geoCV; and median, interquartile range (IQR), minimum, and maximum.

Figures will be generated to show day 1 (0-72 hours), day 15 (0-72 hours), and C_{trough} (72 hours postdose day 4; predose days 5, 8, 12, 15; 24 hours postdose day 16) median/IQR concentrations by dose cohort and aggregate individual subject concentrations for each dose cohort.

Plasma PK Parameters

The following single-dose plasma PK parameters will be estimated, as data permit, using WinNonlin Phoenix v 7.0 (Certara, Princeton, New Jersey). These parameters will be estimated using concentration-time data collected on study days 1-4, collection times 0-72 hours postdosing. AUC_{tau} will be estimated using concentration-time data collected on study days 1-2, collection times 0-24 hours postdosing. T_z, the time to the start of the terminal disposition phase, will be estimated by visual inspection of the aggregate concentration-time data for each dose cohort.

Single-Dose PK Parameters		
Parameter, Unit	CDISC Code	Description
T_{lag}, h	TLAG	Time from dose administration to first observed measurable concentration.
C_{max}, ng/mL	CMAX	The largest observed concentration.
T_{max}, h	TMAX	Time of first occurrence of C_{max}.
AUC_{last}, h*ng/mL	AUCLST	AUC from the time of dose administration to the time of the last measurable concentration. Calculated using the linear up–logarithmic down trapezoidal method.
AUC_{last_sample}, h*ng/mL	AUCINT	AUC from the time of dose administration to the last PK sampling time. Calculated using the linear up–logarithmic down trapezoidal method.
AUC_{tau}, h*ng/mL	AUCTAU	AUC from the time of dose administration to time tau (24 h). Calculated using the linear up–logarithmic down trapezoidal method.
λ_z, 1/hr	LAMZ	Exponential rate constant of the terminal disposition phase. Terminal disposition phase data points selected by PK analyst.

Single-Dose PK Parameters		
Parameter, Unit	CDISC Code	Description
$T_{1/2Z}$, h	LAMZHL	Half-life of the terminal disposition phase.
AUC_{inf}, h*ng/mL	AUCIFO	AUC from the time of dose administration to infinite time, measured using the observed value of the last concentration value (C_{last}). Calculated as $AUC_{last} + C_{last}/\lambda_z$.
CL/F, L/h	CLFO	Apparent systemic clearance after a single dose. Calculated as Dose/AUC_{inf}.

AUC_{last} will be reported for PK profiles for which 1 or more concentrations in the late part of the PK profile are unmeasurable. AUC_{last_sample} will be reported for PK profiles with measurable concentrations up to and including the last sampling time point (T_{last}). For PK profiles for which 1 or more concentrations in the late portion of the PK profile are unmeasurable, AUC_{last_sample} may be estimated as

$$AUC_{last} + (C_{last}/\lambda_z) \times \{1 - \exp(-\lambda_z \times [\text{last sample time} - T_{last}])\}$$

if λ_z can be reliably estimated from the measurable concentrations.

The following multiple-dose plasma PK parameters will be estimated, as data permit, using WinNonlin Phoenix v 7.0. These parameters will be estimated using concentration-time data collected on study day 15, collection times 0-24 hours postdosing. λ_z and $T_{1/2Z}$ will be estimated using concentration-time data collected on study days 15-18, collection times 0-72 hours postdosing. T_{ss}, the time required to achieve steady-state PK behavior, will be estimated by visual inspection of the aggregate C_{trough}-time data for each dose cohort.

Multiple-Dose PK Parameters		
Parameter, Unit	CDISC Code	Description
T_{lag}, h	TLAG	Time from dose administration to first observed measurable concentration during the dosing interval.
C_{max}, ng/mL	CMAX	The largest observed concentration during the dosing interval.
T_{max}, h	TMAX	Time of first occurrence of C_{max} during the dosing interval.
C_{min}, ng/mL	CMIN	The smallest observed concentration during the dosing interval.
C_{trough}, ng/mL	CTROUGH	The observed concentration at the end of the dosing interval.
Peak/trough ratio	PTROUGHR	Ratio of C_{max} to C_{trough}.
AUC_{last}, h*ng/mL	AUCLST	AUC from the time of dose administration to the time of the last measurable concentration. Calculated using the linear up–logarithmic down trapezoidal method.
AUC_{tau}, h*ng/mL	AUCTAU	AUC from the time of dose administration to time tau (24 h). Calculated using the linear up–logarithmic down trapezoidal method.
CL/F, L/h	CLFTAU	Apparent systemic clearance after multiple dosing. Calculated as Dose/AUC_{tau}^{SS}. Estimated only if steady state is achieved.
R_{ac} ratio	ARAUC	Accumulation ratio based on AUC_{tau}. Calculated as $AUC_{tau}^{SS}/AUC_{tau}^{SD}$. Estimated only if steady state is achieved.
R_s ratio	SRAUC	Stationarity ratio. Calculated as AUC_{tau}^{SS} / AUC_{inf}^{SD}. Estimated only if steady-state achieved.

Multiple-Dose PK Parameters		
Parameter, Unit	CDISC Code	Description
λ_z, 1/hr	LAMZ	Exponential rate constant of the terminal disposition phase. Terminal disposition phase data points selected by PK analyst.
$T_{1/2Z}$, h	LAMZHL	Half-life of the terminal disposition phase.

AUC_{last} will be reported for PK profiles for which 1 or more concentrations before and including the 24-hour time point are unmeasurable. AUC_{tau} will be reported for PK profiles with measurable concentrations up to and including the 24-hour time point. For PK profiles for which 1 or more concentrations in the late portion of the dosing interval are unmeasurable, AUC_{tau} may be estimated as

$$AUC_{last} + (C_{last}/\lambda_z) \times \{1 - \exp[-\lambda_z \times (24\ h - T_{last})]$$

if λ_z can be estimated from the measurable concentrations.

λ_z will be estimated only if a PK profile has 3 or more data points in the terminal disposition phase. For the purpose of qualifying the reliability of individual λ_z estimates, the regression data time span will be estimated for all PK profiles for which λ_z is estimated, where

time span = (time postdose of last data point – time postdose of first data point)/$T_{1/2Z}$.

The geometric mean values of the time span estimates will be calculated for each dose cohort. In addition, the level of measurement variability in the data will be assessed based on the range of adjusted- r^2 values of the regressions used to derive estimates of λ_z.

If it is ascertained that measurement variability is low, the λ_z and $T_{1/2Z}$ estimates will be reported for dose cohorts with geometric mean time spans of 1.5 or greater. If measurement variability is not low, λ_z and $T_{1/2Z}$ estimates will be reported only for dose cohorts with geometric mean time spans of 2.5 or greater.

If measurement variability is low, AUC_{inf} will be reported for dose cohorts with geometric mean time spans of 2.5 or greater. If measurement variability is not low, AUC_{inf} will not be reported for any cohort. Day 1 CL/F will be reported if AUC_{inf} is reportable. Day 15 CL/F will be reported if day 15 AUC_{tau} is estimable. Day 1 V_z /F will be reported if day 1 CL/F is reportable, and day 15 V_z/F will be reported if day 15 λ_z is reportable and AUC_{tau} is estimable.

All plasma PK parameter data will be listed. PK parameters that cannot be calculated or reported will be indicated as NOT DONE, and the reason for not being listed will be provided.

Plasma PK parameter data will be summarized and tabulated according to matrix, dose cohort, and dosing day. The following summary statistics will be calculated for all parameters, as data permit, except T_{max} and T_{lag}: mean, SD, CV; geomean, geoSD, geoCV; and median, IQR, minimum, and maximum. For T_{max} and T_{lag} the following summary statistics will be calculated: median, IQR, minimum, maximum. Figures will be generated to show day 1 median C_{max}, AUC_{tau}, and AUC_{inf} and day 15 median C_{max} and AUC_{tau} versus dose.

Urine PK Parameters

The following multiple-dose urine PK parameters will be estimated, as data permit, using WinNonlin Phoenix v 7.0 (Certara, Princeton, New Jersey). These parameters will be estimated using urine concentration and timed urine collection volume data collected on study day 15, collection times 0-24 hours postdosing.

Parameter Unit	CDISC Code	Description
AE_{tau}, ng, μg, or mg depending on the amount excreted	RCAMTAU	AE over the dosing interval. Calculated as Σ $AE_{t1\text{-}t2}$ of timed urine collections within the dosing interval.
$CL_{renal,ss}$, L/h	RENCLTAU	Renal clearance of drug based on urinary excretion of the drug over the dosing interval. Calculated as AE_{tau}/AUC_{tau}.

If $AE_{t1\text{-}t2}$ equals 0 for later urine collection periods because the urine concentration of study drug is not measurable, $CL_{renal,ss}$ will be calculated using AUC_t where t equals the end-of-collection time for the last urine collection with a measurable concentration of study drug.

All urine concentration and (for study day 15) collection volume data will be listed with planned time of specimen collection and actual date, time, and elapsed time of specimen collection.

Urine PK parameter data will be summarized and tabulated according to dose cohort, and dosing day. The following summary statistics will be calculated, as data permit: mean, SD, CV; geomean, geoSD, geoCV; and median, IQR, minimum, and maximum.

Exploratory Dose Proportionality

Dose proportionality will be assessed in an exploratory fashion. LOESS plots of day 1 C_{max} and AUC_{inf} and day 15 C_{max} and AUC_{tau} versus dose will be examined for visual evidence of nonproportionality. These data will also each be fitted by linear regression to the following form of the power model:

$$\ln\{\text{dose-normalized PK parameter}\} = \text{intercept} + \text{slope} \times \ln\{\text{dose}\}$$

The point estimates and 90% confidence intervals for slope will be tabulated.

Dose levels for which day 1 AUC_{inf} is not reportable for more than 2 subjects will be excluded from the regression modeling. If this leads to the exclusion of dose levels within the clinically relevant dose range, day 1 AUC_{tau} data, rather than day 1 AUC_{inf} data, will be used in the dose proportionality assessment.

Dose proportionality analysis output will be tabulated according to dosing day and PK parameter. Figures will be generated to show dose-normalized PK parameter values versus dose and ln{dose-normalized PK parameter values} versus ln{dose} for each of the PK parameters analyzed. The plots of the untransformed data will show the LOESS fit of the data, and the plots of the transformed data will show the linear regression fit of the data.

Appendix 2

SDTM controlled terminology submission values for PK parameters discussed in this article.

SDTM Submission Value	Text Name	Parameter Definition
ARAUC	R_{ac}	Measure of increase in exposure with multiple dosing given dosing interval tau.
AUCIFO	AUC_{inf}	AUC from the time of dose administration to infinite time calculated using observed C_{last}.
AUCIFP	AUC_{inf}	AUC from the time of dose administration to infinite time calculated using predicted C_{last}.
AUCINT	AUC_t	AUC from the time of dose administration to a specified time (t).
AUCINT	$AUC_{t1\text{-}t2}$	AUC over the interval from a specified time (t1) to another specified time (t2).
AUCINT	AUC_{last_sample}	AUC from the time of dose administration to the last PK sampling time (T_{last_sample}) if measurable concentrations are present at PK sampling times up to and including T_{last_sample}.
AUCLST	AUC_{last}	AUC from the time of dose administration to the time of the last measurable concentration (T_{last}) if T_{last} < last PK sampling time.
AUCTAU	AUC_{tau}	AUC for a dosing interval.
CAVG	C_{avg}	Average concentration during a dosing interval.
na	C_{eoi}	Observed concentration at the end of an IV infusion.
na	CL^{MET}/F^{MET}	Apparent clearance of metabolite.
na	$CL^{MET}/F^{MET}{}_{ss}$	Steady-state apparent clearance of metabolite following multiple drug administrations.

SDTM Submission Value	Text Name	Parameter Definition
CLFO	CL/F	Single-dose apparent clearance following extravascular drug administration based on AUC_{inf} calculated using observed C_{last}.
CLFP	CL/F	Single-dose apparent clearance following extravascular drug administration based on AUC_{inf} calculated using predicted C_{last}.
CLFTAU	CL/F_{ss}	Steady-state apparent clearance following multiple extravascular drug administrations.
CLO	CL	Single-dose systemic clearance following IV drug administration based on AUC_{inf} calculated using observed C_{last}.
CLP	CL	Single-dose systemic clearance following IV drug administration based on AUC_{inf} calculated using predicted C_{last}.
CLTAU	CL_{ss}	Steady-state systemic clearance following multiple IV drug administrations.
CMAX	C_{max}	Largest observed concentration.
CMIN	C_{min}	Smallest observed concentration during a dosing interval.
CO	C_0	Observed initial concentration following bolus IV dosing.
CTROUGH	C_{trough}	Observed concentration at the end of a dosing interval.
na	F	Absolute bioavailability.
na	F_{rel}	Relative bioavailability.
FLUCP	Peak trough fluctuation	Range in concentration during a dosing interval, expressed as a percentage of C_{avg}.
LAMZ	λ_z	Exponential rate constant of the terminal disposition phase.
LAMZ	λ_z^{MET}	Exponential rate constant of the metabolite terminal disposition phase.
LAMZHL	$T_{1/2z}$	Half-life of the terminal disposition phase.
LAMZHL	$T_{1/2z}^{MET}$	Half-life of the metabolite terminal disposition phase.
PTROUGHR	Peak trough ratio	Ratio of highest concentration to lowest concentration during a dosing interval.
RCAMINT	AE_t	Amount excreted from the time of dose administration to a specified time (t).
RCAMINT	AE_{t1-t2}	Amount excreted over the interval from a specified time (t1) to another specified time (t2).
RCAMTAU	AE_{tau}	Amount excreted over a dosing interval.
RCPCINT	FE_t	Fraction of the administered dose excreted from the time of dose administration to a specified time (t).
RCPCINT	FE_{t1-t2}	Fraction of the administered dose excreted over the interval from a specified time (t1) to another specified time (t2).
RCPCTAU	FE_{tau}	Fraction of the administered dose excreted over a dosing interval.
RENALCL	CL_{renal}	Renal clearance of drug based on AE_t.
RENCLTAU	$CL_{renal,ss}$	Renal clearance of drug based AE_{tau}.
RNCLINT	CL_{renal}	Renal clearance of drug based on AE_{t1-t2}.
SRAUC	R_s	Stationarity ratio.
TLAG	T_{lag}	Observed time lag after dosing before the occurrence of measurable plasma concentrations.
TMAX	T_{max}	Observed time of first occurrence of C_{max}.
TMIN	T_{min}	Observed time of occurrence of C_{min} during a dosing interval.
na	T_{ss}	Time required to achieve steady-state PK behavior with multiple dosing.
VO	V_0	Volume of distribution immediately following bolus IV drug administration.
VZFTAU	V_z/F_{ss}	Steady-state apparent terminal disposition phase volume of distribution following multiple extravascular drug administrations.
VZO	V_z	Single-dose terminal disposition phase volume of distribution following IV drug administration based on CL/F estimated using AUC_{inf} calculated using observed C_{last}.
VZP	V_z	Single-dose terminal disposition phase volume of distribution following IV drug administration based on CL/F estimated using AUC_{inf} calculated using predicted C_{last}.
VZTAU	$V_{z,ss}$	Steady-state terminal disposition phase volume of distribution following multiple IV drug administrations.

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