CERTARA

AutoPilot Toolkit™ User's Guide

Applies to:
AutoPilot Toolkit™ 8.3 for Phoenix

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AutoPilot Toolkit

The AutoPilot Toolkit for Phoenix allows users to automatically create PK output such as graphs, tables, and text documents, from study data and NCA results. It provides the same functionality of the original AutoPilot Toolkit and it is integrated into the Phoenix framework. It is only available when running the 32 bit version of Phoenix.

The AutoPilot Toolkit consists of four main parts: the Administrator panel, the AP Automation object, the AP Comparison object, and Automation File Explorer. The AP Automation and the AP Comparison objects automate PK analyses and compare output from automation runs. They allow users to specify selections for input study data, analysis execution, and output on a run-by-run basis.

The Administrator panel allows users to select PK parameters, variables, and output types. Administrator selections are stored in XML (Extensible Markup Language) files and are applied to AutoPilot Toolkit runs.

Automation File Explorer helps users prepare reports that use AutoPilot Toolkit graph and worksheet output. Automation File Explorer loads the JPG, EMF, or WMF graphs and XLS worksheet from an AutoPilot Toolkit's project output files and exports them into Microsoft Word documents and PowerPoint presentations.

Information on the following topics is available:

Getting Started with AutoPilot Toolkit

This section contains the following topics:

Note: AutoPilot Toolkit users should run **Phoenix32** as opposed to **Phoenix** when running on 64-bit operating systems. The Phoenix desktop icon should be replace with one that references the Phoenix32 executable as well.

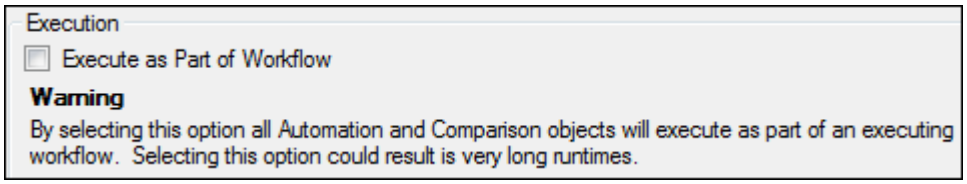
Note: This application is not intended to provide the technical controls required for a 21 CFR Part 11 compliant implementation.

Workflows and AutoPilot Toolkit objects

An AutoPilot Toolkit object can be incorporated into Phoenix workflows as with other Phoenix objects.

However, when a **Workflow** object is selected and ▶ is clicked, all operational objects in that workflow, except AutoPilot Toolkit objects, are run. This is done to avoid very long run times.

Users can change this default behavior through a preferences option available in the Phoenix *Preferences* dialog (**Edit > Preferences**, select **AutoPilot** in the list).



- Check the **Execute as Part of Workflow** checkbox to include AutoPilot Toolkit objects in workflow execution.

Note: This checkbox does not control an AutoPilot Toolkit object that is in a nested sub-workflow.

In the special situation where a custom XML settings file is used and saved with an AutoPilot Toolkit object as part of a template in a workflow, it is recommended that the AutoPilot object be disconnected, the custom settings file selected again, and the input reconnected. Save the project, close it, and load it again. This ensures that the template settings will refresh and the columns in the input source will be accessible through the template.

Language settings for non-unicode programs

In Chinese and Kanji (Japanese) versions of Windows, the language setting for non-Unicode programs must be set to English (United States). If English is not selected for non-Unicode programs, then the `PK_Stats.xls` and `Summary_PK_Text.doc` files are not created.

Configuration settings

AutoPilot Toolkit comes pre-configured and ready to use "out-of-the-box" with default settings. Designated AutoPilot Toolkit administrators (authenticated by user name and password) can modify these settings and adjust them to meet a company's or working group's SOPs. The administrator-defined settings, or configuration settings, define the default options available to users for automation and comparison projects.

The settings are stored in an XML file that can easily be transferred from one computer to another, or made part of an internal distribution for consistent implementation across an organization. The file content is altered using the Administrator Module. This file can be selected in AutoPilot Toolkit's General tab.

When a non-administrator user starts AutoPilot Toolkit for an Automation or Comparison run, the available settings are governed by the configuration settings and the default settings. Configuration settings take priority over the default settings. For many AutoPilot Toolkit features, the user can make selections for a specific run that override the administrator-defined configuration settings, allowing flexibility and control over specific analyses and output.

Conversely, there are also several cases in which the settings defined in the Administration Module cannot be modified in the User Module, where formats and business rules are considered to be part of SOPs. See "Administration Module" for a description of features that are user- or administrator-configurable.

Third-party application requirements

The following options must be set before using AutoPilot Toolkit.

SigmaPlot

The AutoPilot Toolkit supports SigmaPlot versions 11.1, 12.2, and 12.5. However, for the AutoPilot Toolkit to work properly, the SigmaPlot `spw.ini` file must be modified prior to running the application for the first time.

- Change the MaxNumberAutoLegends value in the `spw.ini` file to 600.

  By default, SigmaPlot installs this file in `C:\Users\<user name>\My Documents\SigmaPlot\SPW<version>`
- In SigmaPlot, select **Options** in the **Tools** menu and select the *Page* tab.
- Clear the **Graph objects resize with graph** checkbox.

Excel numerical values stored as text

The appearance of small green triangles in the cells of an AutoPilot Toolkit generated Excel spreadsheet indicates that numbers are stored as text in the spreadsheet. These triangles are only displayed on the screen and not when printed.

To disable the display of the small green triangles:

- Click **Office** and select **Excel Options**.
- Select the Formulas panel.
- In the Error check rules section, clear the **Numbers formatted as text or preceded by an apostrophe** checkbox and click **OK**.

If the SigmaPlot plug-in for Microsoft Excel is installed for Excel 2010, 2013 or 2016, then the following error may be encountered when opening an Excel worksheet created by AutoPilot Toolkit:

`The file you are trying to open 'excelint.exe' is in a different format than specified by the system.`

If this error message is displayed, users can either re-install SigmaPlot without Microsoft Excel integration or close Excel and move the integrated files to a new subfolder in the XLSTART folder.

- If Excel 2010 is installed. then go to `C:\Program Files\Microsoft Office\Office14\XLSTART`.
- If Excel 2013 is installed. then go to `C:\Program Files\Microsoft Office\Office15\XLSTART`.
- If Excel 2016 is installed, then go to `C:\Program Files\Microsoft Office\Office16\XLSTART`.

The XLSTART folder contains three files: `excelint.exe`, `sigmaplot.xla`, and `spRemove.xla`.

Word and appendix generation requests

When using Microsoft Word, the installed copy of Word needs to be personalized for AutoPilot Toolkit to correctly finish the creation of Word documents. Otherwise, when requesting the generation of Appendix documents, an error stating “Not all texts created” may appear at the end of the run.

To personalize the copy of Word:

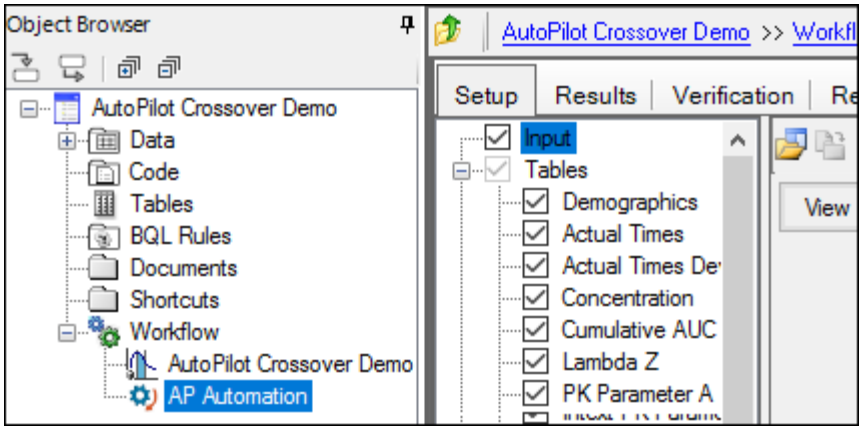
- Click on **Office** in the upper left corner of the *Word* window and click **Word Options** at the bottom of the dialog.
- In the *Word Options* dialog, enter a **User name** and **Initials** to personalize the copy of Word and click **OK**.

Installation test

To test that the AutoPilot Toolkit installation has been successful, users can create table, graph, and appendix output using sample AutoPilot Toolkit project files.

Note: This is not a full validation of the AutoPilot Toolkit.

- Start Phoenix by double-clicking the desktop icon  or selecting **Phoenix 32** from your computer’s Application list.
- Load the project …`\Examples\AutoPilot\AutoPilot Crossover Demo.phxproj`.



- Select **AutoPilot Crossover Demo _ Carterolol** in the Object Browser to review the NCA model.

The NCA model is a default plasma model with twelve subjects and oral drug administration. Select **AP Automation** in the Object Browser to review the automation project.

- Select individual tables and graphs, such as Demographics, PK Parameter A, Time Concentration, or Continuous Demographic in the Tables and Graphs nodes to view the selected variables and statistics.

  The General, Stratification/Normalization, Display, and Ordering tabs are used to choose study design, configuration settings, variable stratification, and output display options.

  Because an AutoPilot Toolkit run can take a long time, only two output types are going to be created.
- In the Setup tab, clear the **Tables** checkbox to remove all table selections.
- Check only the box for **Intext PK Parameter I**.
- Clear the **Graphs** checkbox to remove all graph selections.
- Check only the box for **Categorical Standard**.
- Clear the **Appendix** checkbox to remove all appendices.
- Click ▶ to run the automation project.

AutoPilot Toolkit output is listed in the Results tab.

Example comparison project

- Start the 32 bit version of Phoenix
- Load the project …`\Examples\AutoPilot\AutoPilot Comparison Demo - Stacked Data.phxproj`.

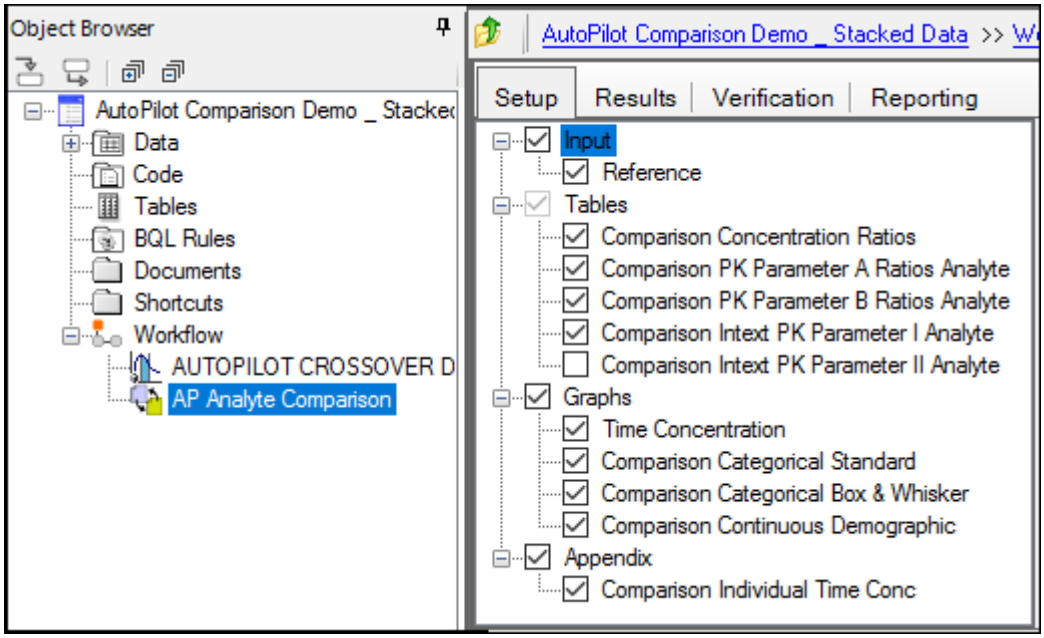


Figure 3-1. Comparison example project loaded into Phoenix

- Select **AUTOPILOT CROSSOVER DEMO _ CARTEROLOL Stacked** in the object browser to review the NCA model.

  The NCA model is a default plasma model with twelve subjects and oral drug administration. The input data contains two treatments and two analytes for use in the comparison.

- Select **AP Analyte Comparison** in the Object Browser to review the comparison project.
- Select individual tables and graphs, such as Comparison Concentration Ratios, Comparison PK Parameter A Ratios Analyte, Time Concentration, or Comparison Continuous Demographic in the Tables and Graphs nodes to view the selected variables and statistics.

  The General, Stratification, Display, and Ordering tabs are used to choose study design, configuration settings, variable stratification, and output display options.
- Execute the comparison project.

AutoPilot Toolkit output is listed in the Results tab.

Study Preparation

AutoPilot Toolkit PK Automation projects require an NCA model, which is created in Phoenix before running AutoPilot Toolkit. The model requirements vary depending on the study design selected in the AP Automation object and the NCA model used. Model requirements fall into the following categories:

- Model Variables: Sort, X (time), Y (concentration), and Carry. Any variables that are to be used for stratification or normalization must be mapped to the Carry context in the NCA model's Main Mappings panel.
- Dosing Regimen
- Regression or Lambda Z
- Partial Areas
- Model Options

The NCA model omits a column from the output worksheet if the column has all missing values. For example, if the Lambda Z value was not calculable for any profile in the project, there will be no Lambda Z column in the NCA output. Consequently, AutoPilot Toolkit output will not include any Lambda Z data.

Note: AutoPilot Toolkit cannot use input data that is derived from a sparse dataset.

Study data must be prepared according to the standards defined by Certara as part of the AutoPilot Toolkit description. AutoPilot Toolkit does not modify the original data worksheets.

The topics in this section include:

Study data variables

AutoPilot Toolkit analyses require that study data include specific variables for automation input. Once the study data variables are defined, the user must create a model that defines model settings and parameters for an AutoPilot Toolkit automation project. Specific model requirements are given in the previous section.

The variables fall into the following categories:

Subject
Dosing
Sample Collection Point (SCP)
Data Collection Point (DCP)
Demographic

The following tables list the default variables for an AutoPilot Toolkit-ready study, including required variables and additional variables that are often useful. See “Required data variables by study type” for a listing of required and optional variables for each study type.

Phoenix name: Required column name in Phoenix
Display name: Default column name used in final AutoPilot Toolkit output.

Note: AutoPilot Toolkit requires that the case of column names match the case in the user’s data. Otherwise, it can create differences in the output. For example, mapping the variable Gender to the user’s data column GENDER may place male data before female data in graphs stratified by gender.

Default subject and dosing variables

Phoenix Name	Display Name	Units	Precision	Restrictions	Comments
Subject	Subject	NA	No	Alphanumeric	Patient (subject) identifier
Dose	Dose	Yes	dec/0	Numeric	Dose administered

Default Sample Collection Point (SCP) variables

Phoenix Name	Display Name	Units	Precision	Restrictions	Comments
Relative_Nominal_Time	Nominal Time	Yes	dec/2	Numeric	Protocol/nominal time of sampling since last dose. Used for Time, Time-Conc, and Cumul AUC output and possibly X-var in model.
Relative_Actual_Time	Actual Time	Yes	dec/2	Numeric	Actual time of sampling since last dose. Used for Time, Time-Conc output. Often used for the X-var in model.
Relative_Nominal_End_Time	Nominal End Time	Yes	dec/2	Numeric	Two purposes: Observation sheet is nominal interval end time from last dose of sampling for urine (Upper Time in model) and Dosing sheet is nominal end time for infusion.
Relative_Actual_End_Time	Actual End Time	Yes	dec/2	Numeric	Two purposes: Observation sheet is actual interval end time from last dose of sampling for urine (Upper Time in model) and Dosing sheet is actual end time for infusion.
[Matrix]_[AnalyteID]_[Route]_[a]	[Matrix] (AnalyteID) Concentration[a]	Yes	sig/3	Numeric or identified as Missing	Concentration of sample collected. Every column name using this template is identified as a concentration column, e.g., [Matrix]_(AnalyteID)_RawCONC.
Volume	Volume	Yes	dec/0	Numeric	Sample collection volume (Required for Urine Models 210–212 only)
Midpoint	Midpoint Time	Yes	dec/2	Numeric	Calculated time point that is equidistant between the Lower and Upper collection times of a given urine collection interval.
Rate	Rate	Yes	sig/3	Numeric	Excretion rate for each interval (amount eliminated per unit of time) = (Concentration*Volume) / (Ending time – Starting time).
Amount_Urine	Amount Urine	Yes	sig/3	Volume	Concentration*Volume.

a. [Matrix] is replaced with the matrix value from the study data. (AnalyteID) is replaced with the Analyte ID from the study data. An administrator can configure the concentration columns regarding name, use, and order of Matrix and AnalyteID.

When running stacked data, Analyte is not to be included in the concentration template.

Default demographic variables

Phoenix Name	Display Name	Units	Precision	Restrictions	Comments
Discrete Demographic					
Sequence[a]	Sequence	NA	NA	Discrete, alphanumeric	Sequence of treatments received (randomized crossover studies only)
Gender	Gender	NA	NA	Discrete, values: male, female	Subject sex
Race	Race	NA	NA	Discrete, alpha. e.g., “Caucasian”	Subject ethnicity
Smoke	Smoke	NA	NA	Discrete, values: yes/no	Subject smoking status
Genotype	Genotype	NA	NA	Discrete, alphanumeric, e.g., “CYP2D6 Extensive”	Subject Baseline genotype status
Child_Pugh	Child Pugh	NA	NA	Discrete variable	Subject Child Pugh classification
Alcohol	Alcohol	NA	NA	Discrete, values: yes/no	Subject status: consumes alcohol or not
Continuous Demographic					
Age	Age	year	dec/0	Continuous, numeric	Subject age
Wgt	Weight	kg	dec/1	Continuous, numeric	Subject body weight at screening
Height	Height	cm	dec/0	Continuous, numeric	Subject height
BMI	BMI	kg/m2	dec/1	Continuous, numeric	Subject Body Mass Index
LBW	LBW	kg	dec/1	Continuous, numeric	Subject Lean Body Weight
BSA	BSA	m2	dec/2	Continuous, numeric	Subject Body Surface Area
CrCL	CrCL	mL/min	sig/3	Continuous, numeric	Subject Baseline Creatinine Clearance

a. Required for randomized crossover study designs to conduct inferential statistics.

An Administrator can add variables by providing the name, category, and data restrictions and map them to the AutoPilot Toolkit system variables. Associated units from these added variables is taken directly from the column headers in the study data.

Required data variables by study type

The following table identifies the required versus optional data variables, by study type and matrix (plasma or urine).

Req: Required

Opt: Optional

Variable	Study Design				
	*RCT	**NRCT	Replicated	Parallel	Trough (All)
Analyte [a]	Req	Req	Req	Req	Req
Subject	Req	Req	Req	Req	Req
Treatment_Description	Req	Req	Req	Req	Req
Period	Req	Opt	Req	Opt	Req for replicated, else Opt
Day	Req	Req	Req	Req	Req
RAT	Opt	Opt	Opt	Opt	Opt
RNT	Req	Req	Req	Req	Req
RAET	Opt	Opt	Opt	Opt	Opt
RNET	Opt (Plasma) Req (Urine)	Opt (Plasma) Req (Urine)	Opt (Plasma) Req (Urine)	Opt (Plasma) Req (Urine)	Opt (Plasma) Req (Urine)
XX_Dose	Req	Req	Req	Req	Req
Concentration variable[b]	Req	Req	Req	Req	Req
Volume	Req	Req	Req	Req	Req
Sequence	Req	Opt	Opt	Opt	Opt
Demogs (Categorical)	Opt	Opt	Opt	Opt	Opt
Demogs (Continuous)	Opt	Opt	Opt	Opt	Opt
Midpoint_Time	Opt	Opt	Opt	Opt	Opt

a. Analyte required for stacked data only.

b. Either XX_RawCONC or XX_PKCONC is required. What exactly is required depends on the base of the concentration template.

* RCT: Randomized Crossover Trial

** NRCT: Non-randomized Crossover Trial

Support of data stacked by analyte

Stacked data theory

The simplest datasets include data from a single concentration assayed from a single source, or matrix, and resulting from the drug being administered by a single route. Such data might have only time and concentration fields.

When clinical drug studies are run, researchers often gather a multitude of data from analyzing both blood and urine samples. The drug is often given in pill form during one part of the study, and it is given intravenously in another. The study may only analyze blood and urine samples for concentration amounts of the drug itself. Typically, however, concentrations of other chemical entities that exist in the body must be analyzed as well. Therefore, instead of a simple concentration being examined from one matrix as a result of a single route of administration, the data can consist of concentrations from a variety of analytes, found in multiple matrices, and resulting from a variety of administration routes.

The layout of such data varies. The data layout can be described as stacked, unstacked, or partially stacked. The levels of data stacking are listed under "Variable assignments". In AutoPilot Toolkit, there are three fields that determine how a dataset is stacked.

- Matrix: plasma or urine
- Analyte: drug given or other chemical entities
- Route: pill or intravenous

Using stacked data in AutoPilot Toolkit

In AutoPilot Toolkit, all of the analytes can be processed during a single run if the data is in a format such that all analyte concentration data is found in a single column. A new column, called Analyte, must contain the text names of the analytes themselves. These text values are similar to previous individual column headers in an unstacked dataset.

Refer to "Concentration Variable Template Selection tab" for additional details on how to setup the Administrator Tool to support stacked analyte data.

Variable assignments

The tables below detail the NCA model requirements for plasma and urine matrices, respectively, for different PK Automation study designs. The Sort Variables in the model must be ordered as they are presented in the table below. For example, Subject then Treatment_Description.

Note: Trough analyses do not require an NCA model.

NCA requirements for plasma data (Models 200–202) and urine data models (210–212) automation study design

Variable	Crossover RCT	Crossover Non-RCT	Crossover Replicated	Parallel
Sort Variables				
Analyte[a]	X	X		
Subject	X	X		

NCA requirements for plasma data (Models 200–202) and urine data models (210–212) automation study design

Variable	Crossover RCT	Crossover Non-RCT	Crossover Replicated	Parallel
Treatment_Description	X	X		
Period[b]				
Day[c]	X	X		
Lower Times				
Relative_Actual_Time or Relative_Nominal_Time	X	X	X	X
Upper Times				
Relative_Actual_End_Time or Relative_Nominal_End_Time	X	X	X	X
Volume				
Volume	X	X	X	X
Concentration				
Concentration variable	X	X	X	X
Carry-Alongs				
Sequence[d]	X			
Period[b]	X			
Treatment_Description			X	X

a. Required for stacked data only.

b. The variable Period is required as a Sort Variable for a Crossover-Replicated study design or as a Carry-Along variable for a Crossover-Randomized study that includes inferential statistics. Failure to include Period as a variable in your study data will result in the use of a parallel model for the calculation of the inferential statistics in the case of these Crossover-Randomized studies.

c. The variable Day is needed as a sort variable only when the study has multiple full-profile days. If Day is not selected as a Sort Variable or Carry-Along for single or multiple dose studies, then AutoPilot Toolkit automatically creates a Day column and sets all day values to "1". For this reason, if the study has Day values other than "1", Day must be included as a Carry-Along if it is not a Sort key.

d. The variable Sequence is needed as a Carry-Along variable only for a Randomized Crossover that includes inferential statistics.

Note: If there is a missing or blank Day value in a dataset, it is automatically set to “1”. This can result in discrepancies between the number of subjects in each sequence in InText PK Parameter and Lambda Z tables because the subject that has a missing or blank Day value, the subject will be counted in Day 1 of a study but not in the next Day of a study.

Other requirements and supported options

- ***Dosing Regimen***: AutoPilot Toolkit requires that, for stacked input data, dose data be specified in the NCA model.
- ***Lambda Z***: Turning off curve stripping is supported with stacked data. This option appears in the *Lambda Z Ranges* dialog (select **Lambda Z Ranges** in the NCA **Model** menu). When **Disable curve stripping** is selected, no Lambda Z selections are assigned. In this case, Phoenix does not calculate any PK Parameters that use the Lambda Z.
- ***Partial AUCs***: Partial AUC intervals can be defined in the NCA model for stacked data. AutoPilot Toolkit allows up to three partial AUC calculations per profile to be included in the output.

PK Automation

AutoPilot Toolkit supports automation of PK analyses through the use of the NCA model object's output. The PK Automation settings in the user interface can be saved as a Phoenix project or template file for re-use. The PK analyses supported by AutoPilot Toolkit can also be retrieved as scenarios from the PKS.

Use one of the following to add the object to a Workflow:

Right-click menu for a Workflow object: **New > AutoPilot > AP Automation**.
Or Main menu: **Insert > AutoPilot > AP Automation**.
Or right-click menu for a worksheet: **Send To > AutoPilot > AP Automation**.
Or select a workflow in the Object Browser and click  in the Object Toolbox on the left side of the Diagram tab.

An AP Automation object must have a source of input data assigned to it as a first step. When the input source is selected, AutoPilot Toolkit then creates the AP Automation user interface based on the input data.

Usually the Final Parameters table from an NCA model is mapped to the AP Automation object. In a trough automation project, on the other hand, the Observations dataset is used. Datasets from different operational objects can also be mapped to a trough automation project. For example, a worksheet that is created by the Column Transformation or Bioequivalence objects can be mapped to an AP Automation object as long as the worksheet contains valid data for trough automation.

When connected to an NCA object, the AP Automation object detects any changes to the NCA model and generates an alert. The AP Automation object does not correct the problem. It only alerts users that changes were detected in Sort Keys, Model Types, Dose Types, or Sparse settings. Users must revert their NCA changes or make the necessary changes to the AP Automation object. The Automation object will be marked as "out of date" if changes to the NCA model are detected or if the NCA model input data is changed. In the latter case, the NCA model will also be marked as "out of date."

Note: The reference treatment must exist in both the study worksheet and in the NCA model output in order for the PK Ratios and PK Statistics tables to be created. If the reference treatment does not exist in the NCA model output (due to less than two time points or invalid concentration values), then the two tables cannot be created and an error is displayed.

To change a source of input data

Once a source of input data is mapped to an Automation object, it can be changed by simply remapping the input to the new source. AutoPilot Toolkit will check the compatibility of the new source with the object.

- If the new source appears to be ***compatible*** with the object, a message to this effect is presented in a dialog along with a reminder to review the object's settings.
- If the new source is ***incompatible*** with the object (e.g., the object, initially connected to a plasma NCA model is remapped to a urine model), a warning is generated. Continuing with mapping of the incompatible data source to the object will result in all settings and/or previous results being cleared.

This section contains the following topics:

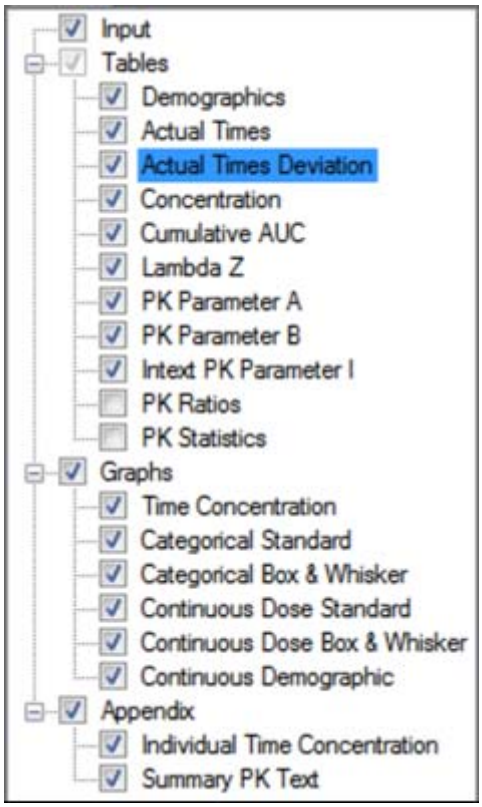
Stratification/Normalization tab
Display tabs
Ordering tab
Automation results

See also:

- "PK Automation tables" lists tables available for each combination of study design, dosing, regimen, and matrix.
- "PK Automation graphs" lists graphs available for each combination of study design, dosing, and matrix.
- "PK Automation appendix output" lists appendices available for each study design.

List of output types

The *Setup* tab consists of two areas, a hierarchical listing consisting primarily of output types available for the AP Automation object selected in the *Object Browser*, and a panel area for displaying options specific to an item selected in the hierarchical list.



- Check/clear the checkbox beside a table type to include/exclude the table in the output.
- Check/clear the checkbox beside the main **Tables**, **Graphs**, or **Appendix** items to add/remove all items under that heading from the output.
  Selecting **Tables** in the hierarchical list is only possible when stratifications or exclusions are set, or when the input data is stacked by analyte.
- To set options for an output type, click the name of the output type in the hierarchical list and make changes to the options displayed in the panel on the right.

Note: Be sure to uncheck the **Continuous Demographic** graph if the study does not contain continuous demographic variables.

Input panel

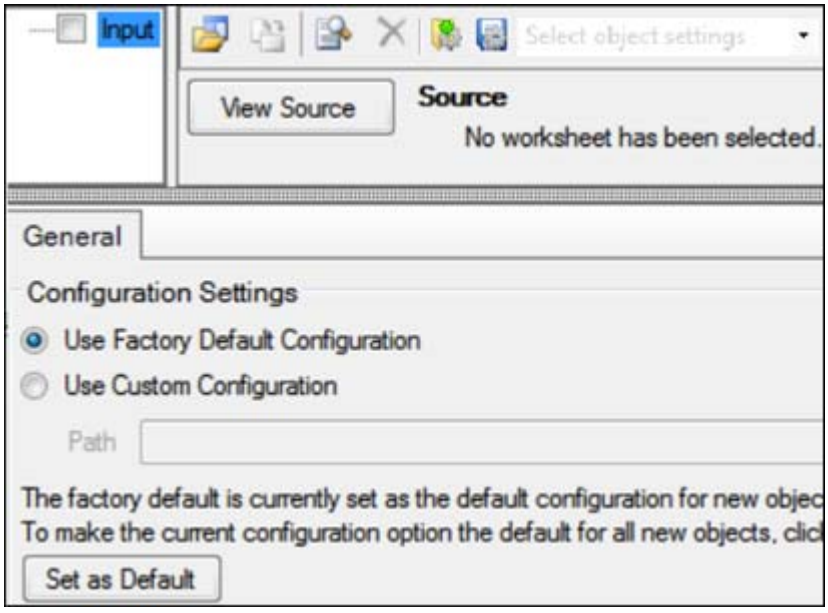
When an AP Automation object is inserted into a project, the input source must be assigned before the object can be used or modifications to object settings can be made. The input source can be mapped to an NCA Final Parameters worksheet or observations dataset.

Note: The units specified in a data set and in the NCA Model Options > Units tab must match in order for the output to make sense.

- In the *Setup* tab, select **Input** in the hierarchical list.

  Or

  In the *Diagram* tab, right-click an AP Automation object and select **View Setup**.



In the previous figure, no input source has been defined, so the options available are restricted to selecting the source and specifying an alternative source for configuration settings (refer to "General tab" for more information on configuration settings).

Table panels

Users can set the variables, statistics, or precision for each table type. The options available depend on the type of table selected.

The following sections describe the table options available:

Main Tables panel
Variables and Statistics tabs
Standard/Normalize tab
Precision tab
Statistical Analysis option

Main Tables panel

The main **Tables** panel is ***only available*** if the input source is stacked by analyte, or when stratifications or exclusions are set, and at least one individual table's checkbox must be checked. The panel shows options that can be applied when generating the tables. The options vary depending on whether the source is stacked or if stratifications and/or exclusions are defined.

- In the *Setup* tab, select **Tables** in the hierarchical list.
- Check/Uncheck the **Standard** box to include/exclude a table in the output.

Table	Type	Grouping
	Standard	Group by Analyte
Demographics	☑	
Actual Times	☑	☐
Actual Times Deviation	☑	☐
Concentration	☑	☐

- Check the **Group by Analyte** box to group the data for each analyte as separate columns within the same table. Uncheck the box to create separate tables for each analyte.

  Grouping is not available for the Demographics table.

- When stratification schemes have been defined, they can be applied by checking the **Stratify by ___** box. Uncheck the box to generate only a standard table.

Note: At least one stratified table must be selected if stratifications are specified or the object will not pass verification.

Table	Type	Exclusion Criteria	
	Stratify by Gender	are not applied	are applied
Demographics	☐	☑	☐
Actual Times	☐	☑	☐
Actual Times Deviation	☐	☑	☐
Concentration	☐	☑	☐

- When **Exclusion Criteria** are defined, they can be applied when generating a table by checking the corresponding **are applied** box. Check the **are not applied** box to generate a table, ignoring the exclusion criteria.

See also:

Stratification/Normalization tab
Output Options tab for defining exclusions.

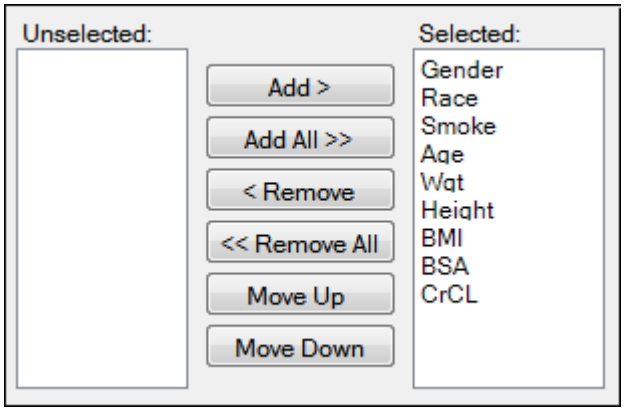
Variables and Statistics tabs

The *Variables* and *Statistics* tabs are formatted the same for most tables. See "PK Parameters" for a full list and descriptions of supported PK parameter study variables. See "Summary Statistics" for a full list and descriptions of supported statistics.

Note: The *Variables* tab may/may not be available, depending on the table type.

- In the *Setup* tab, select a table type in the hierarchical list.
- Select the **Variables** or the **Statistics** tab.

  Variables and statistics that are in the **Selected** column will be included in the output and will be reported in the order that they appear in the column.



  The following instructions apply to both the *Variables* tab and the *Statistics* tab.

- Select an item in one of the columns.
- Click **Add** or **Remove** to move the item from one column to another.
- Click **Add All** and **Remove All** to move all variables from one column to another.
- Click **Move Up** and **Move Down** to change the position of a selected item in the list.

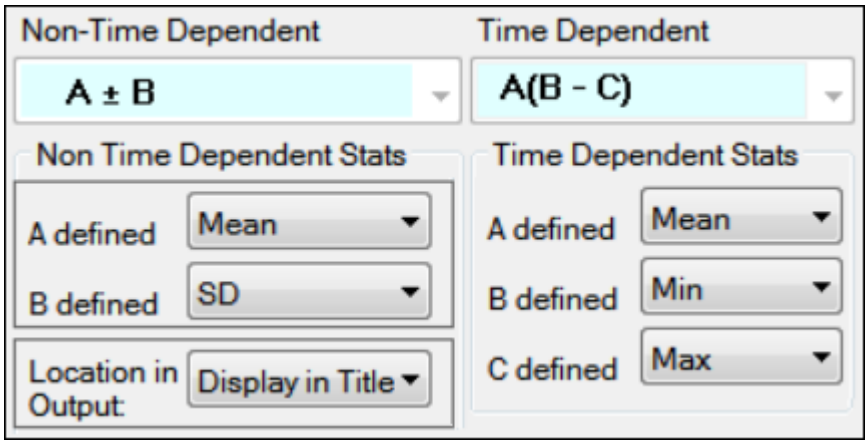
Note: Selecting a large number of PK Parameters for statistics can generate a table that will not fit on a single page and the table-splitting option does not currently work for the PK Stats table. Choose only 7 or 8 parameters for this table. If you require more parameters to be listed, perform additional Automation runs for the additional desired parameters and generate only the PK Stats table

Note: When PK Statistics are specified, the AutoPilot Toolkit object should be executed directly and not as part of the Phoenix workflow or the PK Stats table creation may fail.

Intext Table Statistics tab

The *Statistics* tab for Intext PK Parameter tables contains different options than *Statistics* tabs for other tables.

- In the *Setup* tab for an Intext PK Parameter type table, select the *Statistics* tab.



- In the **Non-Time Dependent** section, select the equation to be used (currently A +/- B is the only one available).
- Identify the statistics to use in the equations from the pull-down menus.
- Choose the location for displaying the information: **Display in Title**, **Display in Footnote**, **Do not display in output**.
- In the **Time Dependent** section, select the equation to be used (currently A(B – C) is the only one available).
- Identify the statistics to use in the equations from the pull-down menus.

Note: Changes made to the non-time dependent and time dependent statistics options in one Intext table are copied to the other Intext table. For example, if Comparison Intext PK Parameter II Analyte is selected in the Tables tab and the settings for A and B in the Non-Time Dependent Stats area are changed, the changes are automatically applied to the Comparison Intext PK Parameter I Analyte table.

Standard/Normalize tab

This tab becomes available for PK Parameter tables when normalization schemes are defined (see "Stratification/Normalization tab").

- In the *Setup* tab for a table of PK parameters, select the *Standard/Normalize* tab.
- Select the **Display** option **All standard, then all normalized by ____** to list all of the standard columns first, followed by normalized columns.
- To group the columns so that the standard and normalized version of the data are together, select the **Display** option **Group together standard and normalized by ____**.
- Toggle generation of tables with and/or without normalization for each parameter by selecting/unselecting the checkboxes in the **Normalize** and **Standard** columns.

Precision tab

For each variable and statistic, the precision can be set by the number of significant digits or decimal places. Selection of the type and value of numerical precision is also done through this tab.

- In the *Setup* tab, select a table type from the hierarchical list and select the *Precision* tab.

Precision Selection:

Variables	Statistics									
	Individual		N		Mean		SD		SE	
	Type	Valu	Type	Valu	Type	Valu	Type	Valu	Type	Valu
Tmax	Decimal	2	Decimal	0	Decimal	2	Decimal	2	Decimal	2
Cmax	Significant	3	Decimal	0	Significant	3	Significant	3	Significant	3
AUClast	Significant	3	Decimal	0	Significant	3	Significant	3	Significant	3
AUCINF_obs	Significant	3	Decimal	0	Significant	3	Significant	3	Significant	3
AUC_%Extrap_obs	Decimal	0	Decimal	0	Decimal	0	Decimal	0	Decimal	0

Min		Median		Max		CV%		Geometric Mean	
Type	Valu	Type	Valu	Type	Val	Type	Val	Type	Val
Decimal	2	Decimal	2	Decimal	2	Decimal	2	Decimal	0	Decimal	2
Significant	3	Significant	3	Significant	3	Significant	3	Decimal	0	Significant	3
Significant	3	Significant	3	Significant	3	Significant	3	Decimal	0	Significant	3
Significant	3	Significant	3	Significant	3	Significant	3	Decimal	0	Significant	3
Decimal	0	Decimal	0	Decimal	0	Decimal	0	Decimal	0	Decimal	0

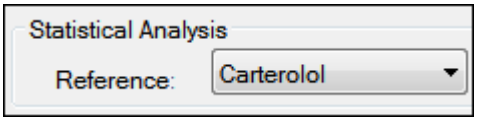
- In the **Type** menu for each statistic, select **Decimal** or **Significant**.
- Select a cell in the corresponding **Value** column to enter a new precision display value.

Statistical Analysis option

An option is available for PK Ratios and PK Statistics tables to include inferential statistics calculations and PK parameter ratios in order to produce additional output tables titled PK_Ratios and PK_Statistics. See “PK Automation tables” for descriptions of the tables.

- In the *Setup* tab, select **PK Ratios** or **PK Statistics** in the hierarchical list.
- In the **Reference** menu, select an analyte to include in the statistical analysis.

The **Reference** can be selected in the PK Ratios and PK Statistics panels. The specified reference treatment will be used as the denominator in the ratio and inferential statistics calculations.



Graph panels

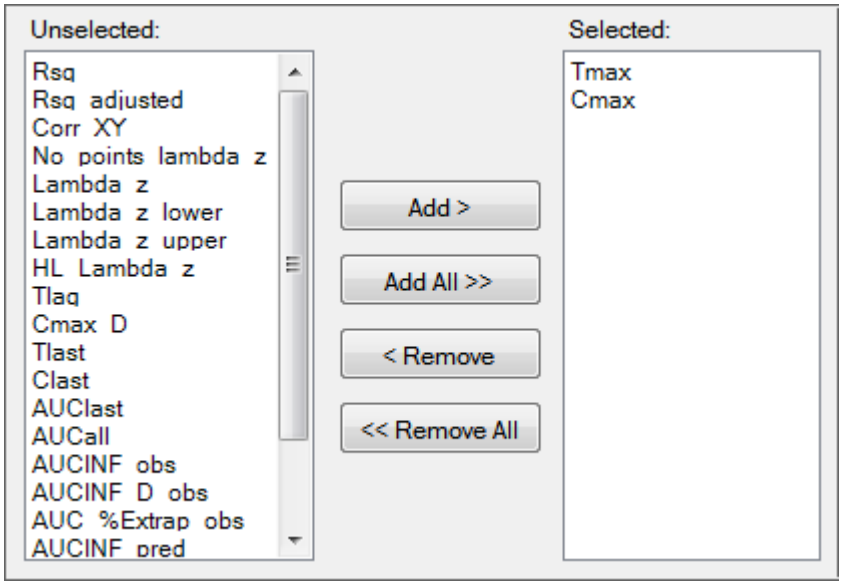
AutoPilot Toolkit allows the user to apply different attributes to each graph. These attributes include Y-axis scaling, summary value display, error bar display, and regression line options. Selection of PK parameters to include in the graphs is also available.

The following sections describe the graph options available for each graph type:

Main Graphs panel

- In the *Setup* tab, select **Graphs** in the hierarchical list.

  Parameters that are in the **Selected** column will be included in the output.

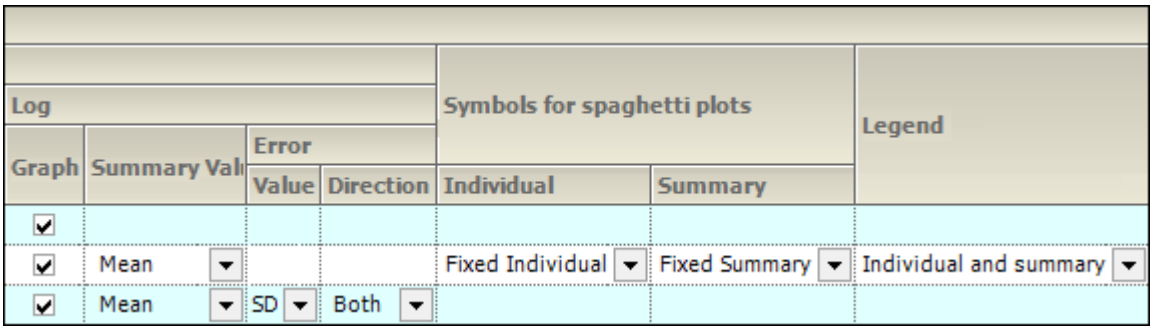


- Select an item in one of the columns.
- Click **Add** or **Remove** to move the item from one column to another.
- Click **Add All** and **Remove All** to move all variables from one column to another.

Time Concentration panel

- In the *Setup* tab, select **Time Concentration** in the hierarchical list.

Graph	Output	Display				
	Selected	Y-Axis Scaling				
		Linear				
		Graph	Summary Value	Error		
				Value	Direction	
Individual by Subject	☑	☑				
By Treatment	☑	☑	Mean			
Summary by Treatment	☑	☑	Mean	SD	Both	



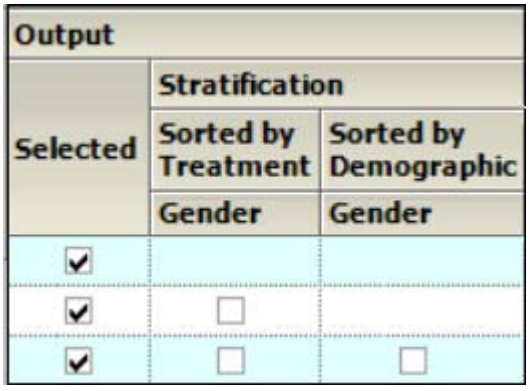
There are three types of Table Concentration graphs available:

- **Individual by Subject**: A separate graph is generated for each subject involved in the study. Each line on the graph represents a separate treatment.
- **By Treatment**: A separate graph is generated for each treatment performed during the study. Each line in the graph represents a separate subject. An additional **Summary Value** line may also be present.
- **Summary by Treatment**: A single graph is generated. Each line represents a separate treatment.

The panel displays a table of options for the Time Concentration graphs, grouped into categories and sub-categories:

Output

- Check/Uncheck the **Selected** box to include/exclude a type of Time Concentration graph in the output.



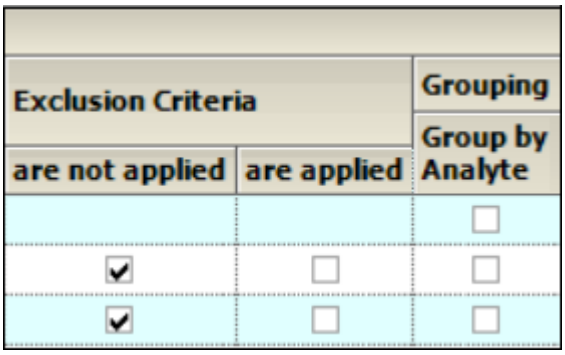
- When **Stratification** schemes are defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables in a **By Treatment** or **Summary by Treatment** graph type (**Sorted by Treatment**) or new sort variables in a **Summary by Treatment** graph type (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.

Display

- Graphs can be generated using a **Linear** or **Log Y-Axis Scaling**. The following options are available for both types of scaling:
  - Check/Uncheck the **Graph** box to use/not use the Y-axis scaling method. Checking boxes for both **Linear** and **Log** will generate two graphs, one using each method.
  - Available for **By Treatment** and **Summary by Treatment** types, select the statistic to use as the **Summary Value** when plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**, **None**.

    - Specify the **Value** (**SD**, **SE**, **Variance**, **Min and Max**, **None**, **68% Range**) and **Direction** (**Both**, **Down**, **Up**) of error bars to display on **Summary by Treatment** graphs.

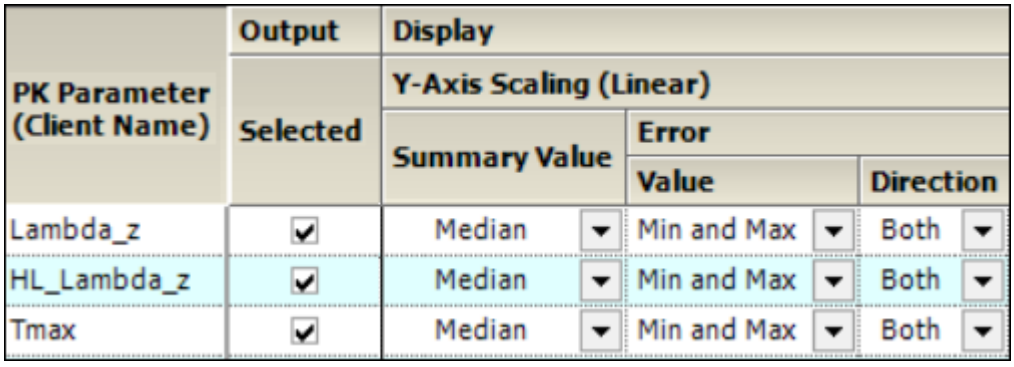
- When **Exclusion Criteria** are defined (see "Output Options tab") they can be applied when generating a graph by checking the corresponding **are applied** box. To ignore the exclusion criteria when generating the graph, check the **are not applied** box.



- When an input dataset is stacked by analyte, check the **Group by Analyte** box under **Grouping** to group the data by analyte within the same graph. Uncheck the box to generate separate graphs for each analyte.
- **Symbols for spaghetti plots**
    - **Individual**: Specify the symbol to use when plotting individual subject data points on a **By Treatment** graph. **Fixed Individual** uses the same symbol for all the individual subject data, **Variable Individual** uses a different symbol for each individual subject's data, **None** shows only the resulting line.
    - **Summary**: Specify the symbol to use when plotting the summarized data on a **By Treatment** graph. **Fixed Summary** displays the summary points on the graph using a symbol. **None** shows only the resulting line.
- Specify the information to display in a **Legend** for **By Treatment** graphs.
    - **None**: Do not display a legend.
    - **Individual and Summary**: Include the symbol for individual subject data points and the symbol for summary points.
    - **Summary Only**: Include only the symbol for summary points.

Categorical Standard panel

- In the *Setup* tab, select **Categorical Standard** in the hierarchical list.

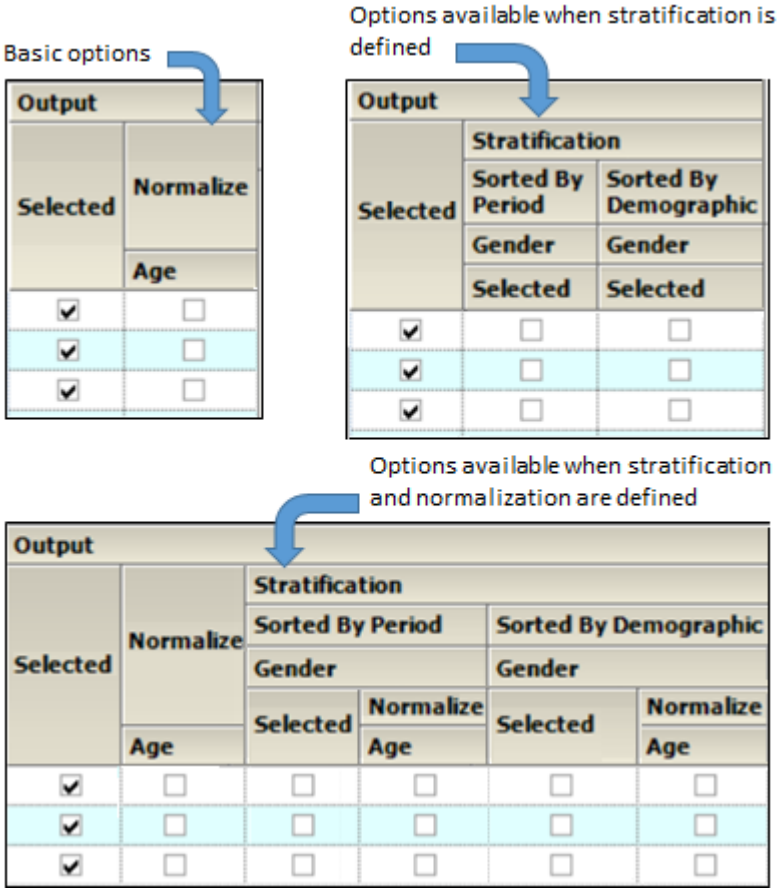


The PK Parameters available in the study are listed as rows in the table.

The panel displays a table of options for the Categorical Standard graphs, grouped into categories and sub-categories:

Output

- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

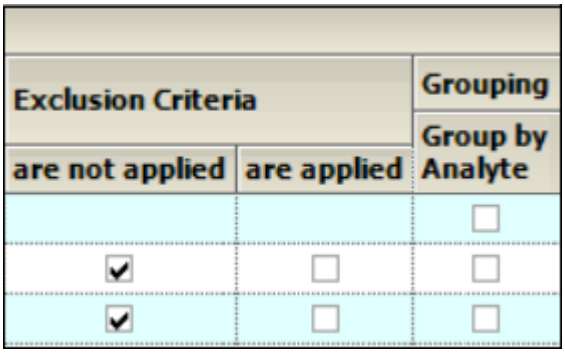


- When **Stratification** schemes are defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by Treatment** or **Sorted by Period** for replicated studies) or new sort variables (**Sorted by Demographic**). Check/Uncheck the **Selected** boxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes are also defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the stratified graphs.

Display

The graphs are generated with a **Linear** scaled Y-axis.

- Select the statistic to use as the **Summary Value** when plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**, **None**.
- Specify the **Value** (**Min and Max**, **Pseudo SD**, **SD**, **SE**, **Variance**, **68% Range**) of the **Error** bars. The only option available for **Direction** is **Both**.
- When **Exclusion Criteria** are defined (see "Output Options tab") they can be applied when generating a graph by checking the corresponding **are applied** box. To ignore the exclusion criteria when generating the graph, check the **are not applied** box.

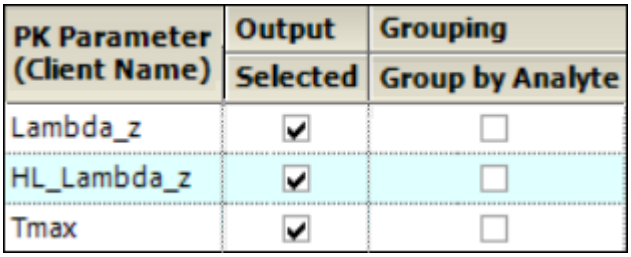


- When an input dataset is stacked by analyte, check the **Group by Analyte** box under **Grouping** to group the data by analyte within the same graph. Uncheck the box to generate separate graphs for each analyte.

Categorical Box and Whisker panel

Note: There must be at least three subjects in the study to create Box and Whisker graphs.

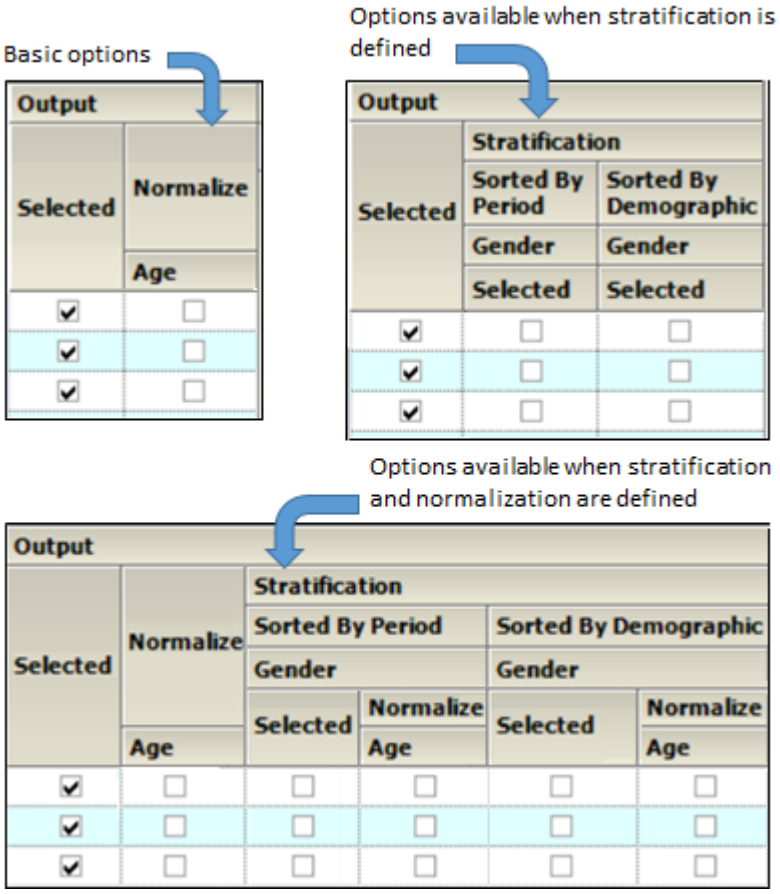
- In the *Setup* tab, select **Categorical Box & Whisker** in the hierarchical list.



The PK Parameters available in the study are listed as rows in the table.

Output

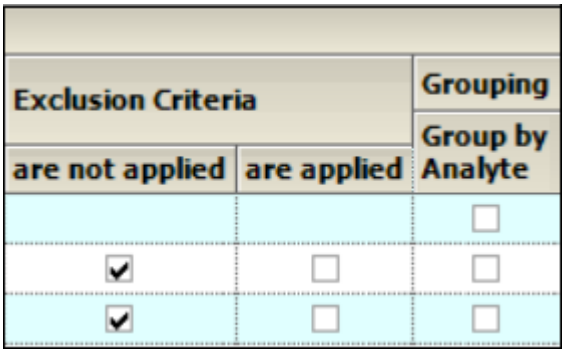
- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.



- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by Treatment** or **Sorted by Period** for replicated studies) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes are also defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Display

- When **Exclusion Criteria** have been defined (see "Output Options tab"), they can be applied when generating a graph by selecting the corresponding **are applied** checkbox. Select the **are not applied** checkbox to generate a graph, ignoring the exclusion criteria.



- When an input dataset is stacked by analyte, the data can be grouped by analyte within the same graph by checking the **Group by Analyte** box below **Grouping**. Unselect the checkbox to generate separate graphs for each analyte.

Continuous Dose Standard panel

- In the *Setup* tab, select **Continuous Dose Standard** in the hierarchical list.

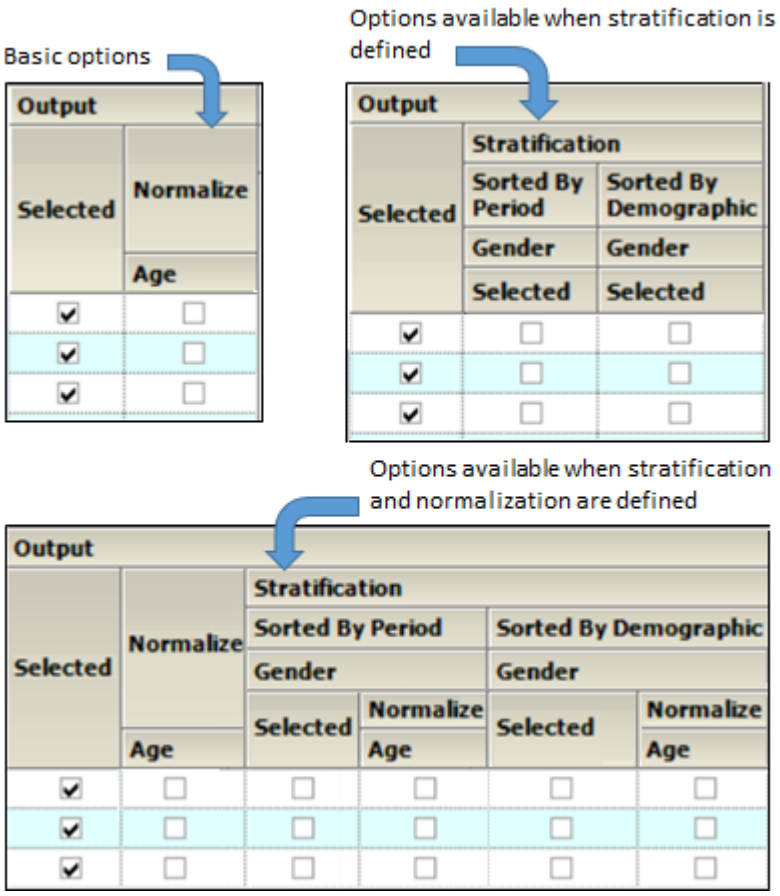
PK Parameter (Client Name)	Output	Display				
	Selected	Y-Axis Scaling (Linear)			Regression	
		Summary Value	Error			
			Value	Direction	Line	Equation
Lambda_z	☑	Median	Min and Max	Both	☐	☐
HL_Lambda_z	☑	Median	Min and Max	Both	☐	☐
Tmax	☑	Median	Min and Max	Both	☐	☐
Cmax	☑	Mean	SD	Both	☐	☐
Cavg	☑	Mean	SD	Both	☐	☐

The PK Parameters available in the study are listed as rows in the table.

The panel displays a table of options for the Continuous Dose Standard graphs, grouped into several categories and sub-categories:

Output

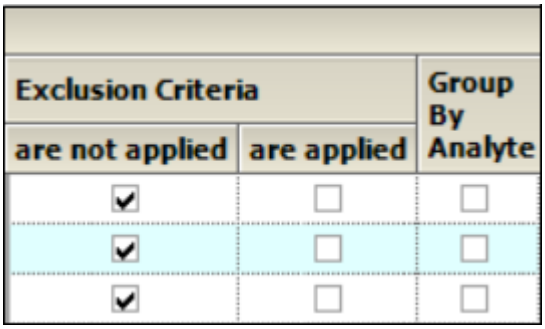
- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.



- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by Treatment**) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes are also defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Display

- Graphs are generated with a **Linear Y-Axis Scaling**.
  - Select the statistic to use as the **Summary Value** when plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**, **None**.
  - Specify the **Value** (**Min and Max**, **Pseudo SD**, **SD**, **SE**, **Variance**, **68% Range**) of the **Error** bars. The only option available for **Direction** is **Both**.
- For **Regression**, check the **Line** checkbox to include a regression line in the graph. Check the **Equation** box to display the regression equation in the graph.
- When **Exclusion Criteria** have been defined (see "Output Options tab"), they can be applied when generating a graph by selecting the corresponding **are applied** checkbox. Select the **are not applied** checkbox to generate a graph, ignoring the exclusion criteria.

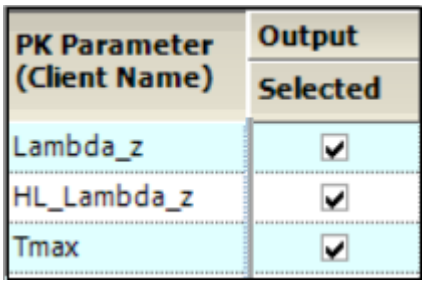


- The **Group by Analyte** category appears when an input dataset is stacked by analyte. Check the box to group the data by analyte within the same graph. Uncheck the box to generate separate graphs for each analyte.

Continuous Dose Box and Whisker panel

Note: There must be at least three subjects in the study to create Box and Whisker graphs.

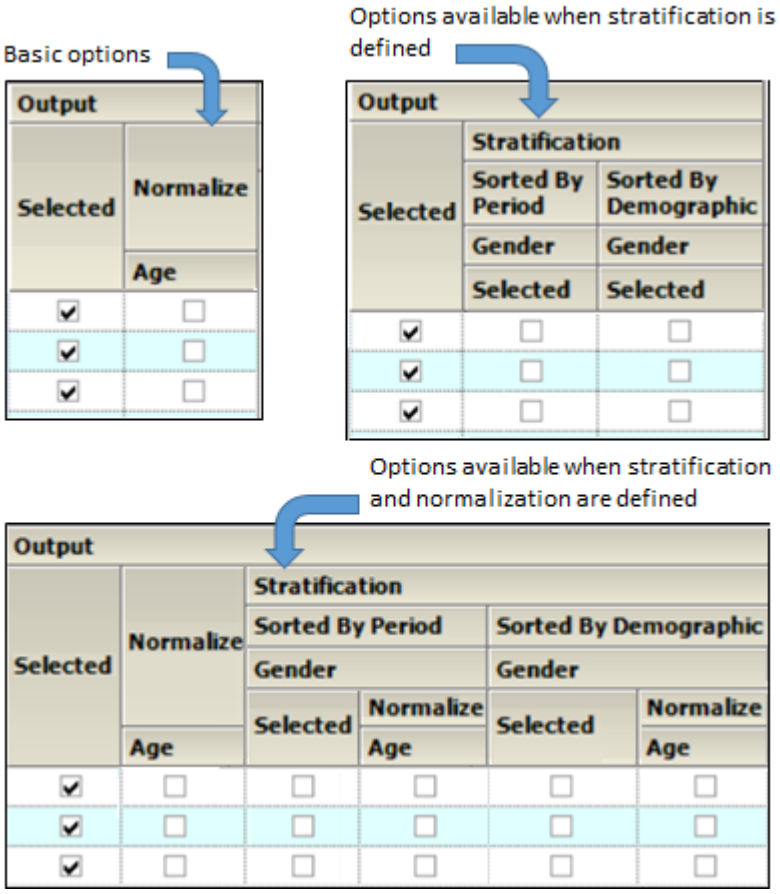
- In the *Setup* tab, select **Continuous Dose Box and Whisker** in the hierarchical list.



The PK Parameters available in the study are listed as rows in the table.

Output

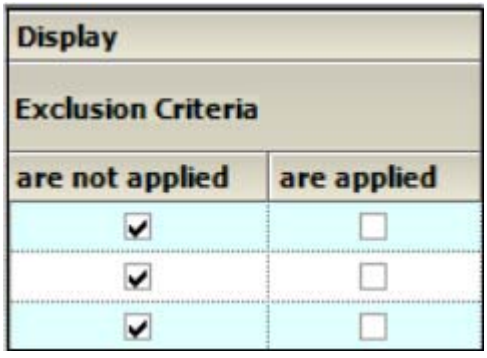
- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.



- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"). Select the checkbox to stratify the graph data.
  - If normalization schemes are also defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

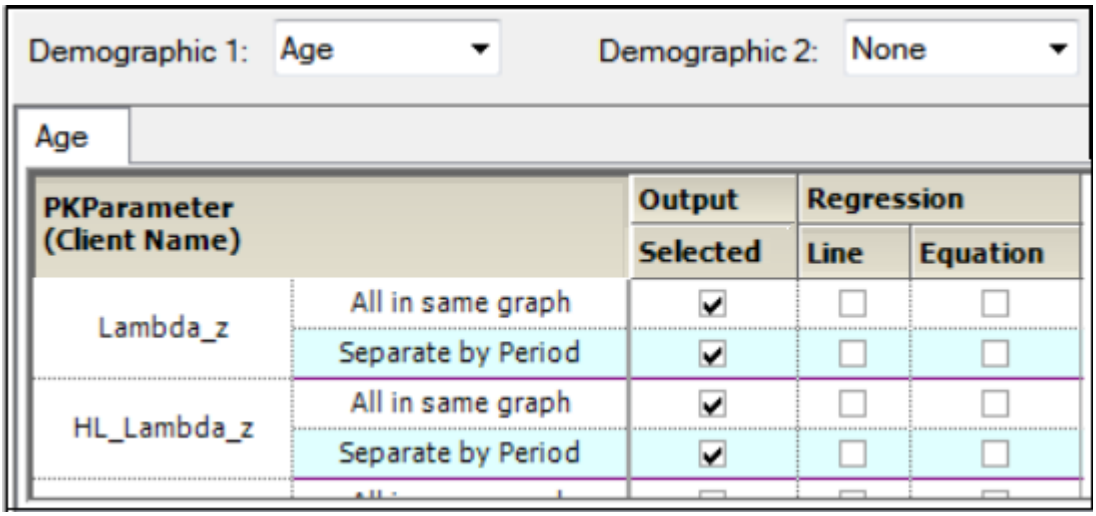
Display

- When **Exclusion Criteria** have been defined (see "Output Options tab"), they can be applied when generating a graph by selecting the corresponding **are applied** checkbox. Select the **are not applied** checkbox to generate a graph, ignoring the exclusion criteria.



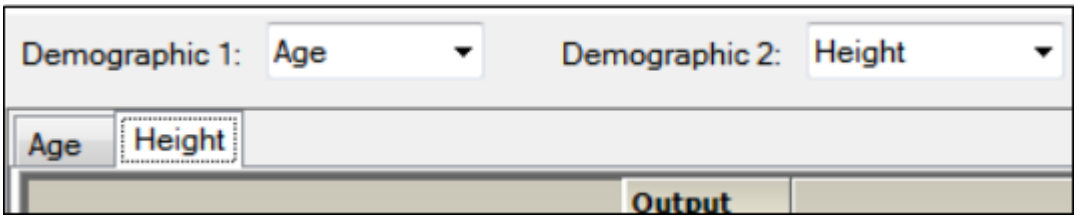
Continuous Demographic panel

- In the *Setup* tab, select **Continuous Demographic** in the hierarchical list.



The panel displays a section for selecting up to two demographic(s) to use for the X-axis (**Demographic 1** and **Demographic 2**).

When a second demographic type is selected, a second tab is created in the Continuous Demographic panel.



The PK Parameters available in the study are listed as rows in the table. For each parameter, there are two sub-rows:

- **All in Same Graph**: Include all treatments in the same graph.
- **Separate by Treatment**: Create a separate graph for each treatment.

The lower part of the panel contains a table of options for the Continuous Demographic graphs, grouped into several categories and sub-categories:

Output

- Check the **Selected** box to create a single graph for the parameter showing all the treatments or to create a separate graph for the parameter for each treatment performed. Uncheck the box to not generate the graph(s) for a parameter.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Basic options

Output		
Selected	Normalize	
	Age	
☑	☐	
☑	☐	
☑	☐	

Options available when stratification is defined

Output			
Selected	Stratification		
	Sorted By Period	Sorted By Demographic	
	Gender	Gender	
	Selected	Selected	
☑	☐	☐	
☑	☐	☐	
☑	☐	☐	

Options available when stratification and normalization are defined

Output					
Selected	Normalize	Stratification			
		Sorted By Period		Sorted By Demographic	
		Gender		Gender	
		Selected	Normalize	Selected	Normalize
	Age		Age		Age
☑	☐	☐	☐	☐	☐
☑	☐	☐	☐	☐	☐
☑	☐	☐	☐	☐	☐

- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by Treatment** or **Sorted by Period** for replicated studies) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes are also defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Display

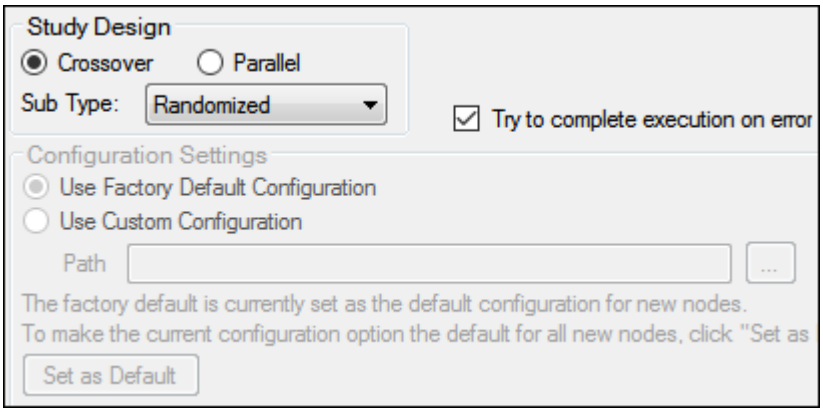
- Select the **Line** checkbox to include a **Regression** line in the graph. Select the **Equation** checkbox to display the regression equation in the graph.
- When **Exclusion Criteria** have been defined (see "Output Options tab"), they can be applied when generating a graph by selecting the corresponding **are applied** checkbox. Select the **are not applied** checkbox to generate a graph, ignoring the exclusion criteria.

Exclusion Criteria		Grouping
are not applied	are applied	Group by Analyte
☑	☐	☐
☑	☐	☐
☑	☐	☐

- When an input dataset is stacked by analyte check the **Group by Analyte** box to group the data by analyte within the same graph. Uncheck the box to generate separate graphs for each analyte.

General tab

The *General* tab allows users to select the study design type, configuration settings, and whether or not to try to complete an automation run if an error occurs.



The study design options in the *General* tab depend on the configuration settings. If the settings are changed, then the options could be different from the options listed below.

Note: The configuration settings must be specified before a dataset is mapped to the AP Automation object.

Study Design

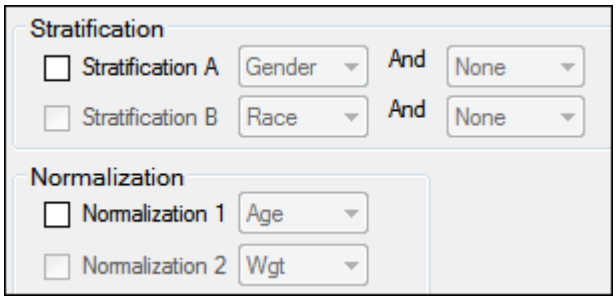
- Specify that the study design type is either **Crossover** or **Parallel**.
- For a **Crossover** study design, select the study **SubType** (**Randomized**, **Non-Randomized**, or **Replicated**).
- By default, AutoPilot Toolkit tries to complete an automation run even if errors are encountered and not all selected output can be created.
- Unselect the **Try to complete execution on error** checkbox to stop an automation run if any errors are encountered.

Configuration Settings

- Indicate the configuration settings to use. **Use Factory Default Configuration** is selected by default.
- To use customized settings, select **Use Custom Configuration** and click the **Change Directory [...]** button to select the directory where the custom configuration settings file is located.
- The customized settings can be defined as the default configuration settings to use for new projects by clicking **Set as Default**.

Stratification/Normalization tab

The **Stratification** and **Normalization** options allow users to create additional table and/or graph output.



Stratification

Results can be stratified (i.e., layered) using discrete demographic variables. Each stratification level can use one or two discrete demographic variables. If two variables are specified, they are associated using the logical operator AND.

Note: At least one stratified output type must be selected if stratification is enabled or the Automation project will not pass verification.

- To define the first level of stratification, select the **Stratification A** checkbox and choose the demographic variable(s) from the pull-down menu(s).
- To define a second level of stratification, select the **Stratification B** checkbox and choose the variable(s) from the pull-down menu(s).

If stratifications are selected, the automation run creates one table per stratum for the time and concentration, PK parameter, and intext PK parameter tables, using the stratification scheme as an additional group variable.

If graphs include stratification, the stratification schemes are used either as X-axis variables (sorted by treatment) or new sort variables (sorted by demographics), depending on the AutoPilot Toolkit Admin settings.

Normalization

Use the **Normalization** section to define normalization schemes to apply to the results. Each normalization scheme must use a different continuous demographic variable.

- To define the first level of normalization, select the **Normalization 1** checkbox and choose a demographic variable from the pull-down menu.
- To define a second level of normalization, select the **Normalization 2** checkbox and choose a variable from the pull-down menu.

AutoPilot Toolkit calculates the normalized PK parameters and includes them in the results. Users can select the **PK Parameter**, **Intext PK Parameter**, **PK Ratios**, and **PK Statistics** tables in the hierarchical list and choose which normalized parameters to display in each table. This allows PK Parameter automation tables to include both normalized and non-normalized values.

- Select the PK Parameter, Intext PK Parameter, PK Ratios, or PK Statistics table in the Tables node.
- Select the Standard/Normalize tab.
- In the **Display** menu, select how to display normalized PK parameters in the table output.

- Select the **Normalize** checkbox beside a PK parameter to include it in the table output.

For more on using the table panels, see "Table panels".

Column headers for the normalized variables include a normalization variable and its units. For example, oral clearance normalized by weight: CL/F/Weight (L/hr/kg). If graph output is selected that includes normalization, each normalized PK parameter is displayed in a separate graph. The Y-axis labels display the normalization in the same manner as tables.

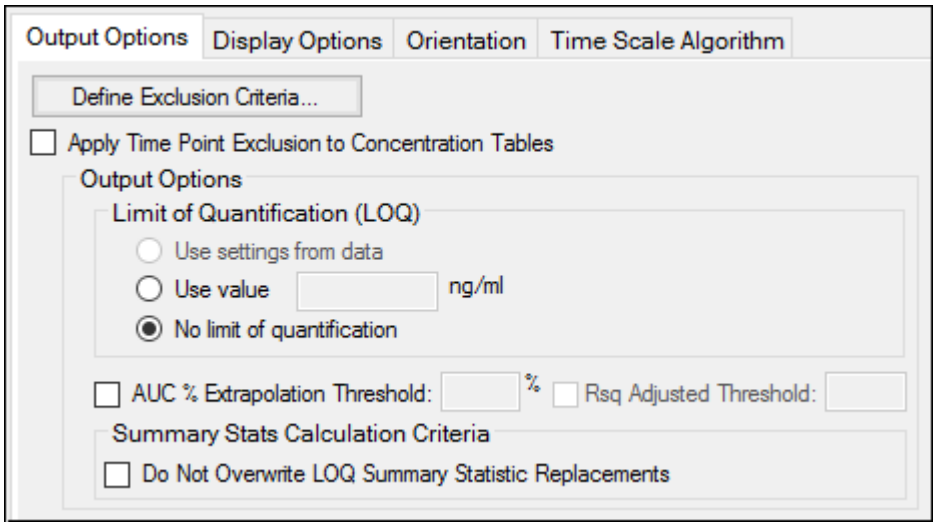
PK parameters that are excluded from normalization are listed in "PK automation parameters".

Display tabs

The *Display* tab contains four tabs that allow users to set output and display options, table and graph orientation, and the X- and Y-axes scaling for graphs.

Output Options tab

The *Output Options* tab allows users to define exclusions, the LOQ value, and the AUC percent extrapolation threshold value.



- Click **Define Exclusion Criteria** to open the *Excluded Profiles From Summary Statistics* dialog. (See "Excluded profiles from summary statistics".)

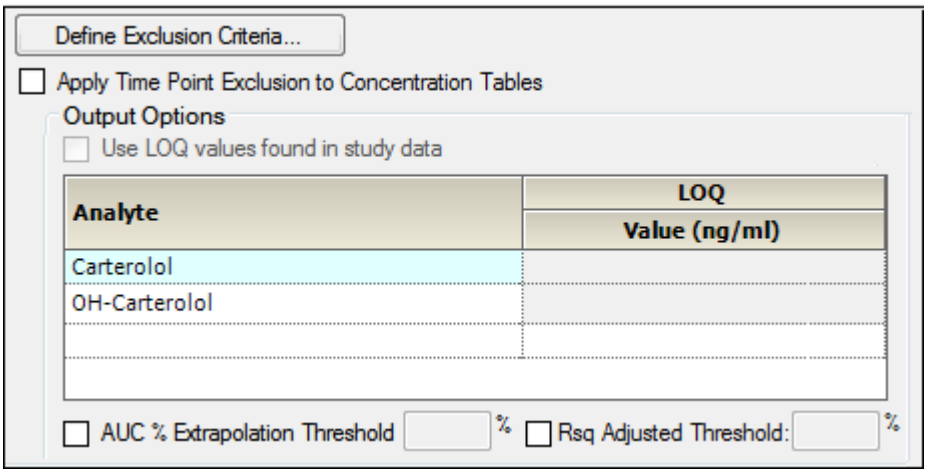
  The options for LOQ vary depending on the type of data used and the system configuration settings.

- Turn on the **Apply Time Point Exclusion to Concentration Tables** checkbox to exclude entire profiles based on the presence of values within the ExclusionFlag column in the input study data. The excluded profiles are still displayed in the results, but are excluded from calculation of summary statistics.

- For unstacked data, choose one of the following methods of defining the LOQ:
  - To set the LOQ value using the input data, click **Use setting from data**.
  - To enter a value, click **Use value** and type a value in the corresponding field.

- Click **No limit of quantification** to not set an LOQ limit.

If the input dataset contains stacked data, a different LOQ can be set for each analyte.



- For stacked input data, do one of the following to set the LOQ:
  - Turn on the **Use LOQ values found in study data** checkbox to set the values for LOQ using the input data.
  - Enter an LOQ value for each analyte in the Value column. (The concentration units are taken from the input dataset.)
  - To not use LOQ values, turn off the **Use LOQ values found in study data** checkbox and leave the Value column entries blank.

Note: If the LOQ is set to a value that exceeds all concentration values, no Concentration graphs will be created.

Note: Setting the LOQ value for all analyts can significantly extend the execution time.

For more information, see “LOQ replacement”.

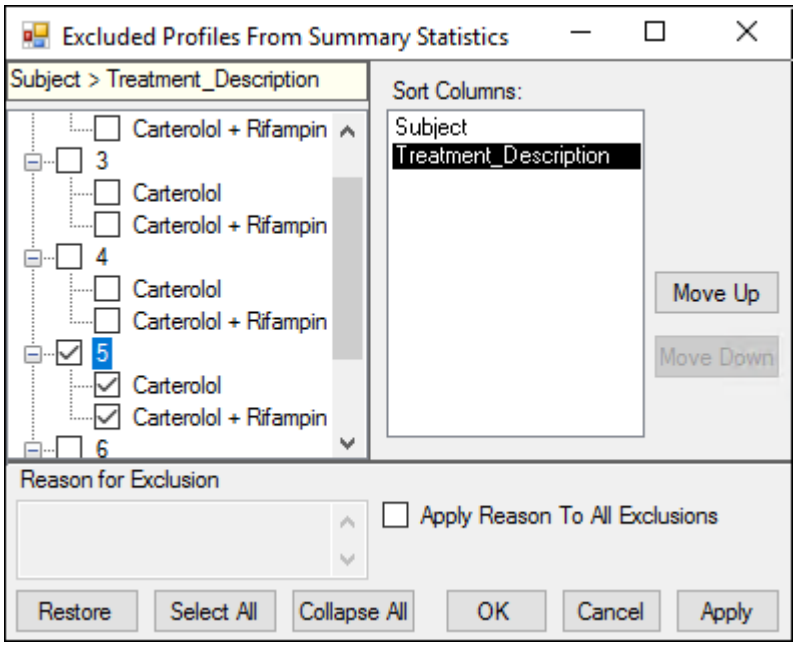
The following option is applicable to both stacked or unstacked input data:

- Turn on the **AUC% Extrapolated Threshold** checkbox to use the rules for handling AUC extrapolated values that exceed the specified percentage.

  See “PK parameter percent-extrapolated threshold” for details.
- Turn on the **Rsq Adjusted Threshold** checkbox to use the rules for handling Rsq Adjusted values that are lower than the specified value.
- Turn on the **Do Not Overwrite LOQ Summary Statistics Replacements** to retain the LOQ summary statistics values.

Excluded profiles from summary statistics

- Click **Define Exclusion Criteria** in the *Output Options* tab.



  Every profile in the study data is displayed in the Profile list on the left of the dialog. Users can exclude complete or partial profiles. The variables used to create each profile are displayed in the Sort Columns list. Each profile contains a subject ID and one or more treatments. By default, each profile is listed by subject ID, and the treatment or treatments are listed beneath each subject.

- Select the checkbox beside each subject ID to exclude the subject and any treatments given to the subject.
- Select the checkbox beside a treatment listed beneath a subject ID to exclude that treatment from the profile.
- To change the order of the profiles in the list, select a profile variable in the Sort Columns list and click **Move Up** or **Move Down**.

  For example, if the treatment is moved to the top of the Sort Columns list, then the Profile list displays the treatment first and lists the subject IDs underneath the treatment.

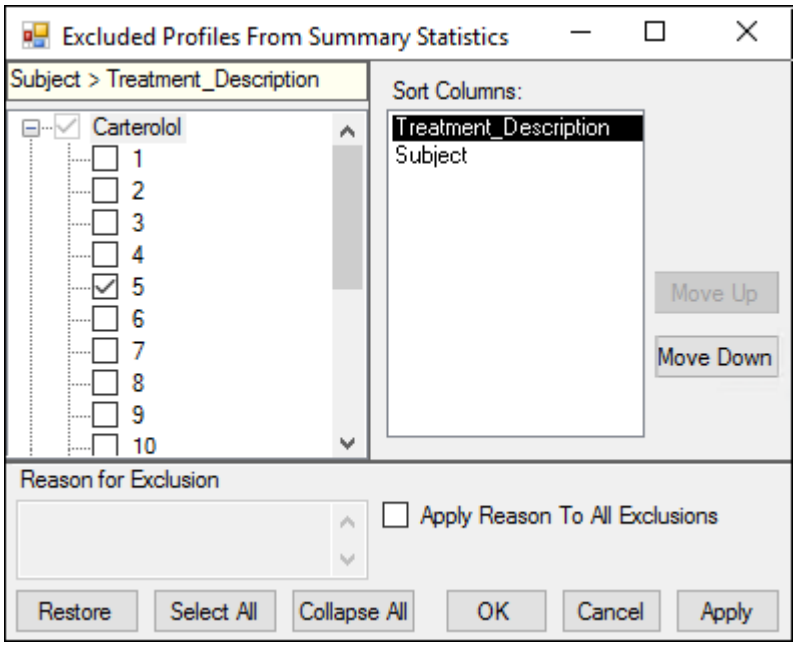
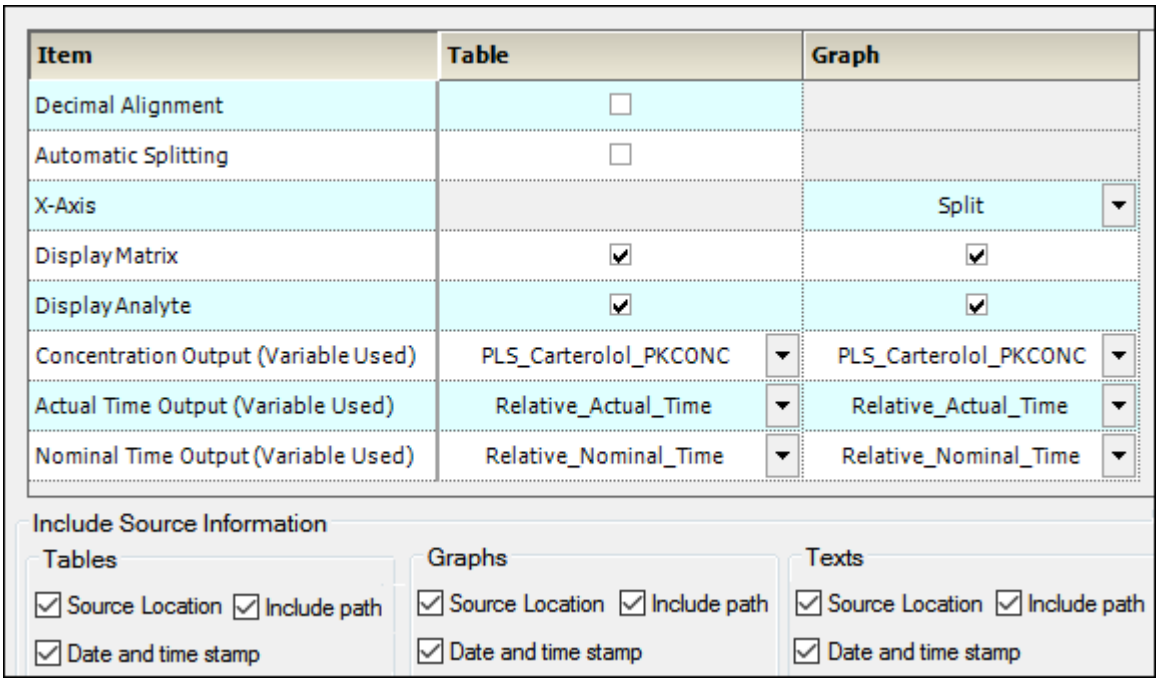


Figure 5-1. Sort Columns rearrange the order in which profiles are listed on the left

- To enter a reason for exclusion:
  - Select the item being excluded.
  - Enter the information in the **Reason for Exclusion** area below the profile list.
  - Turn on the **Apply Reason To All Exclusions** if the entered information is applicable to all items selected for exclusion in the profile list.
- Use the **Restore**, **Select All**, and **Collapse All** buttons to restore the profile list to its original status when the dialog was initially displayed, to select all items in the profile list, or to collapse all items in the list, respectively.

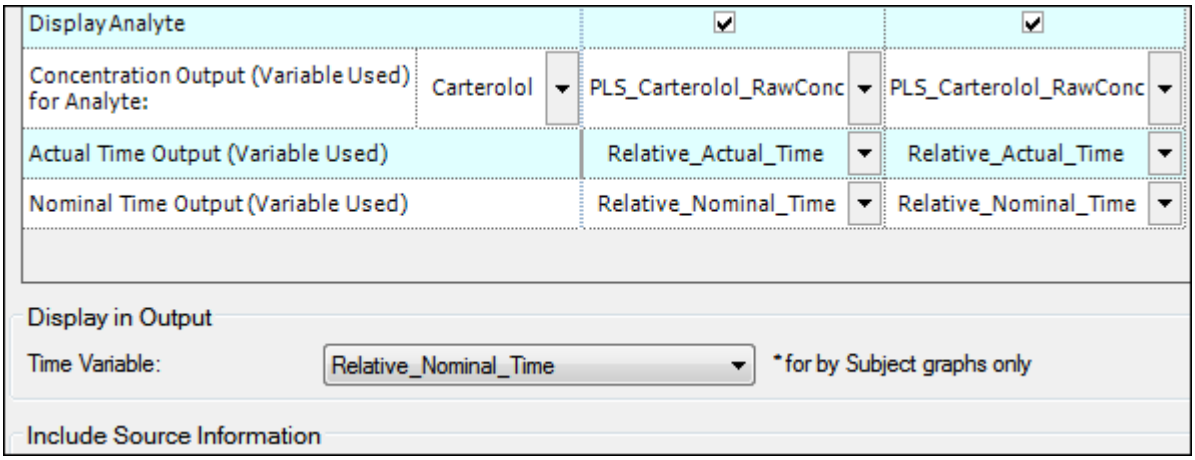
Display Options tab

The *Display Options* tab allows users to set table and graph output display options, select the time and concentration variables in the input dataset, and choose whether or not to include data source information.



- Turn on the **Decimal alignment** checkbox to align all values in a given column using their decimal points. See "Table data display using decimal alignment".
- Turn on the **Automatic splitting** checkbox to allow splitting large tables across multiple pages. See "Table business rules". (Splitting long tables can result in borders being improperly formatted.)
- Select from the **X axis** pull-down if the PK parameter graphs have a **Split** X-axis based on individual and summary values or **Offset**.
- Turn on the **Display Matrix** or **Display Analyte** checkbox to include the matrix or analyte information in the tables and/or graphs. See "Display analyte and matrix information" (tables) or "Display analyte and matrix information" (graphs).
- Select the concentration variable to use for creating time-concentration tables and graphs from the **Concentration Output (Variable Used)** pull-down menu.

  For trough projects with unstacked input data, this option changes to **Concentration Output (Variable Used) for Analyte**. Use the first pull-down to select the analyte whose concentrations are to be reported and then continue with specifying the concentration variables for the tables and graphs.
- Use the **Actual** and **Nominal Time Output (Variable Used)** pull-down menus to select which data column to use for the actual and nominal times. This is set using the Admin Module. See "Time Variables tab".
- The Display in Output section, available only for trough projects, contains a **Time Variable** pull-down menu. Select the actual or the nominal time variable to use in the Conc by Subject graphs, which display individual trough time and concentration for one subject per graph.



- In the **Include Source Information** section, select or clear the checkboxes to include or exclude the location of the input file, the path to that location, and a date and time stamp in the Table, Graph, and Text output.

Orientation tab

Through the *Orientation* tab, the orientation of each output item is set. A few additional settings regarding the appearance of graphs in a Word document are available for appendices involving individual time-concentration graphs.

Item	Orientation	Paper size	Presentation order	Graphs per page
Tables				
Demographic	Portrait			
Time Concentration	Portrait			
PK Parameter	Portrait			
Intext	Portrait			
PK Stats	Landscape			
Time Concentration Graphs				
Individual Subject	Portrait			
Individual Subject by Treatment	Portrait			
Summary	Portrait			
PK Parameter Graphs				
Categorical Standard	Portrait			
Categorical Box and Whisker	Portrait			
Continuous Dose	Portrait			
Continuous Demographic	Portrait			
Appendix (Word Documents)				
Individual Time Concentration	Portrait	Letter	All linear then all log	1 x 1
Summary PK Text	Landscape			

- In the Orientation column, select whether to position the output as a **Portrait** or in **Landscape** format from the pull-down menu for each table, graph, and appendix output.

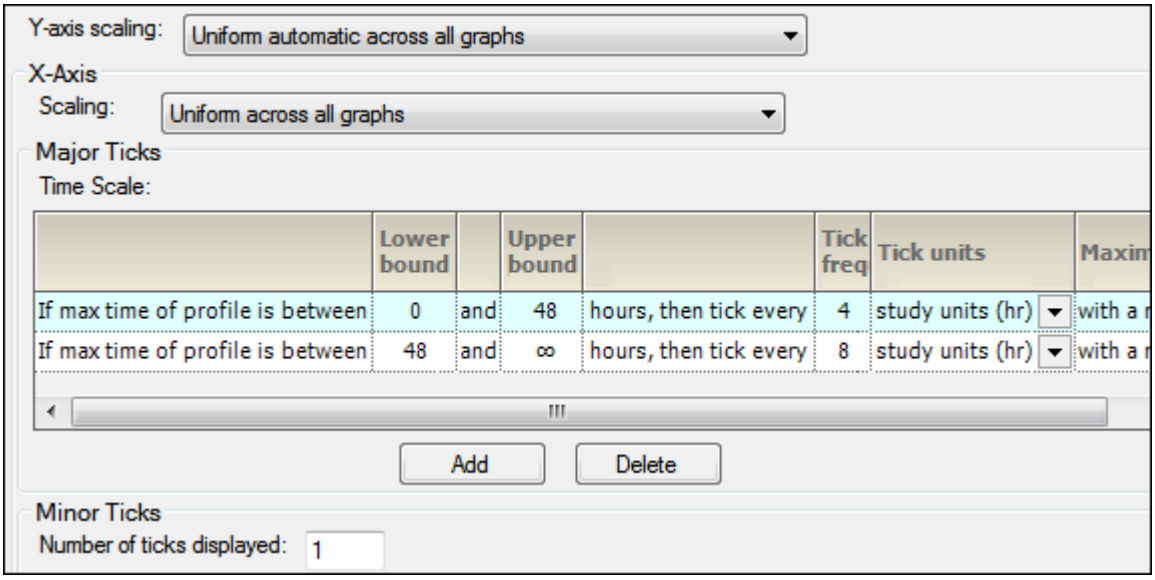
Note: Only certain tables and graphs can be changed to Landscape. If Landscape is not supported, the Orientation setting for that table or graph defaults to Portrait and the pull-down menu is disabled.

For the **Individual Time Concentration** appendix output type, the following specifications can also be made.

- Select the Paper Size as **Letter** or **A4** from the pull-down menu.
- Indicate the order in which the graphs are to appear using the Presentation Order column pull-down menu. Options include:
  - **All linear then all log**: Display the linear graphs (sorted by subject) before the log graphs (sorted by subject).
  - **All log then all linear**: Display the log graphs (sorted by subject) before the linear graphs (sorted by subject).
  - **Per profile, linear then log**: Graphs are grouped by subject and then by analyte, with the linear graph presented before the log graph. In the output, the graphs are displayed in subject order.
  - **Per profile, log then linear**: Graphs are grouped by subject and then by analyte, with the log graph presented before the linear graph. In the output, the graphs are displayed in subject order.
- Specify the number of graphs per page using the pull-down in the Graphs Per Page column. Options range from **1x1** up to **4x4**.

Time Scale Algorithm tab

The *Time Scale Algorithm* tab is used to specify the scaling options for the axes, the lower and upper bounds for time scale ticks, the tick frequency, the tick units, and the maximum time scale on the X-axis. See "Time scale algorithm" for more information.



- In the **Y-axis scaling** menu, choose whether to scale the Y-axis uniformly across all graphs or scale the Y-axis on a per graph basis.
- In the X-Axis area, select X-axis **Scaling** to be either uniformly across all graphs or on a graph by graph basis.

The Major Ticks area contains a table where each row represents a separate time scale.

- Enter new values for lower and upper bounds in the **Lower bound** and **Upper bound** fields.

  Use the Tick frequency and Tick units columns together to define the frequency with which tick marks are displayed along the X-axis.

- Enter the value directly in the **Tick frequency** field and then select the units from the **Tick units** pull-down menu. (The default is **study units**, indicating that the units are derived from the study data.)
- Set new values for the time scale multiple value in the **Maximum time scale** multiple value field.
- Click **Add** in the Major Ticks area to add another time scale.

  A new row is added to the table below the row that was selected or modified last.

- To remove an added time scale, click in that row and then click **Delete**.

  A minimum of two defined time scales is required.

- In the Minor Ticks area, change the number of minor ticks displayed between the major ticks by typing a new value in the **Number of ticks displayed** field.

Ordering tab

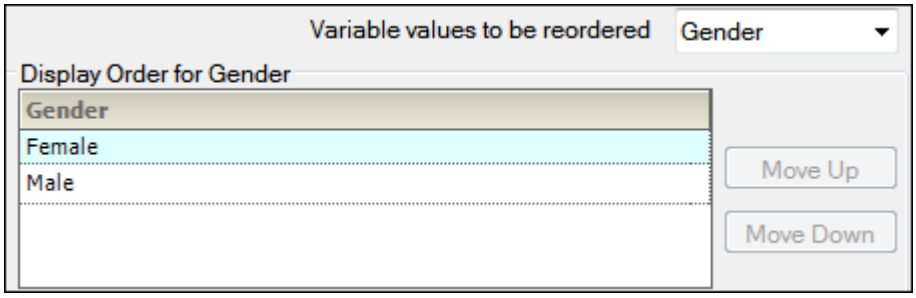
The *Ordering* tab is used to specify how the treatment descriptions and demographic study variables are ordered in the output.

Treatments sub-tab

- Select a treatment in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Discrete Variables sub-tab

The **Discrete Variables** tab contains the tools to reorder the attributes of any variables used for stratification.



- Use the **Variable values to be reordered** menu to select different discrete study variables.
- Select the variable in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Note: If the first treatment does not contain a stratification value then the order chosen in the Discrete Variables tab for the stratification is ignored in the graph output.

Analytes tab

This tab is present only if the input data is stacked and lists all of the analytes involved in the study.

- Select an analyte in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Note: Concentration table output will not maintain the order specified in this tab.

Automation results

Caution: Do not perform any operations on the computer while the automation run is in progress. Doing so could cause unpredictable results; keyboard and mouse input during an automation run might affect automated AutoPilot Toolkit operations.

After the project successfully completes, all output is arranged in groups in the *Results* tab.

Not all output can be viewed in Phoenix. In such cases, the right side of the *Results* tab will display a message with suggestions on how to view the results. One suggestion is to open an external program and load the results by clicking **View in External Viewer**.

The automation output can be individually exported to disk or copied to Phoenix's Data folder. All results can be exported using the File Explorer, which is located in the *Reporting* tab. For more using the File Explorer, see "AutoPilot File Explorer".

Analyte Comparison

AutoPilot Toolkit can run analyses to compare output from previously run NCA models. An AP Analyte Comparison object combines output from previously created NCA models to create additional report output. AutoPilot Toolkit supports plasma, urine, and trough analyte comparisons.

AutoPilot Toolkit can compare the output from up to six studies for wide data, and up to a 20 analyte study for stacked-by-analyte data. Comparison projects use NCA output or study data that is stored locally or in Certara PKS scenarios. The NCA projects can be imported into Phoenix from a disk or loaded from PKS. If PKS is used, then all NCA output must reside in the same PKS study.

Use one of the following to add the object to a Workflow:

Right-click menu for a Workflow object: **New > AutoPilot > AP Analyte Comparison**.
Or Main menu: **Insert > AutoPilot > AP Analyte Comparison**.
Or right-click menu for a worksheet: **Send To > AutoPilot > AP Analyte Comparison**.
Or select a workflow in the Object Browser and click  in the Object Toolbox on the left side of the Diagram tab.

An AP Analyte Comparison object must have an assigned source of input data for the Reference run and at least one other test run as a first step. If stacked data is being used, then only one input data source is needed. When the input sources are selected, AutoPilot Toolkit then creates the AP Analyte Comparison interface based on the input data.

Usually the Final Parameters table from an NCA model is mapped to the AP Analyte Comparison object. In a trough comparison project, on the other hand, the Observations dataset is used. Datasets from different operational objects can also be mapped to a trough comparison project. For example, a worksheet that is created by the Column Transformation or BioAvailability objects can be mapped to an AP Analyte Comparison object as long as the worksheet contains valid data for trough comparisons.

When connected to an NCA object, the AP Comparison object detects any changes to the NCA model and generates an alert. The AP Comparison object does not correct the problem. It only alerts users that changes were detected. Users must revert their NCA changes or make the necessary changes to the AP Comparison object.

The **Send To** command cannot be used to map data to the Test inputs. The **Select source** button or the *Diagram* tab must be used to map data to the Test inputs. The **Input** checkboxes in the *Setup* tab are also a quick way to map/unmap sources to the reference and various tests.

Note that up to five test input datasets can be mapped for comparison against the reference.

To change a source of input data

The source of the input data for a Comparison object can be changed by simply remapping the input to the new source. AutoPilot Toolkit will check the compatibility of the new source's study variables with the variables in the Comparison object's original dataset.

- If the new source appears to be ***compatible*** with the Comparison object, a message to this effect is presented in a dialog along with a reminder to review the object's settings.
- If the new source is ***incompatible*** with the Comparison object (e.g., the object, initially connected to a plasma NCA model is remapped to a urine model), a warning is generated. Continuing with mapping of the incompatible data source to the Comparison object will result in all settings and/or previous results being cleared.

This section contains the following topics:

Table panels
Graph panels
General tab
Display tabs
Stratification/Normalization tab
Ordering tab
Comparison results

See also:

"Comparison Output Examples" for a listing of tables and graphs available for each combination of study design, dosing, regimen, and matrix.
"PK Comparison appendix output" for a listing of appendices available for each study design.

Comparison types

The AP Analyte Comparison object handles three types of analyte comparisons: Plasma, Urine, and Trough.

For all three types, the AP Analyte Comparison object allows for up to six analytes (one parent and up to five metabolites) to be compared simultaneously per run for wide data, or up to 20 analytes for stacked data. When computing ratios of PK parameters (e.g., concentration ratios and/or metabolic ratios), the calculations are based on one parent (reference) and could include metabolite 1 vs. parent and metabolite 2 vs. parent, but not comparisons of metabolites directly (e.g., metabolite 1 vs. metabolite2).

Plasma

Input Data: Requires NCA Models 200–202[a] and runs must use same matrix, route, and regimen (SD or MD).

Output: Overlaid time-concentration graphs, concentration ratios, and calculation of metabolic ratios for PK parameters.

Urine

Input Data: Requires NCA Models 210–212[a] and runs must use same matrix, route, and regimen (SD or MD). If comparing two urine automation runs, either Day must be used as the Sort Variable in both projects or neither project (if only one uses Day, the comparison will fail).

Output: Overlaid percent dose remaining graphs, overlaid amount excreted over time graphs, and calculation of metabolic ratios for PK parameters.

Trough

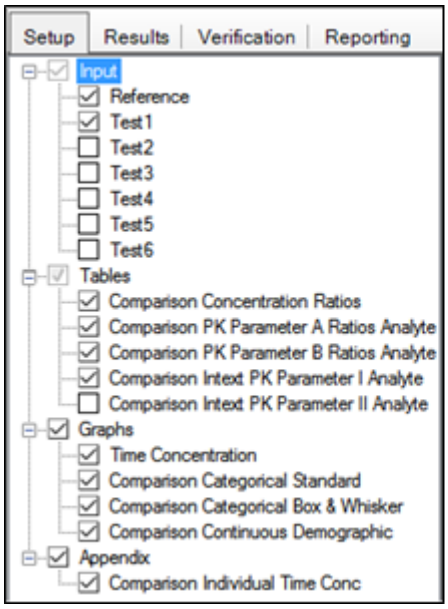
Input Data: No NCA Model is required. Data must be of a non-urine matrix (e.g., plasma).

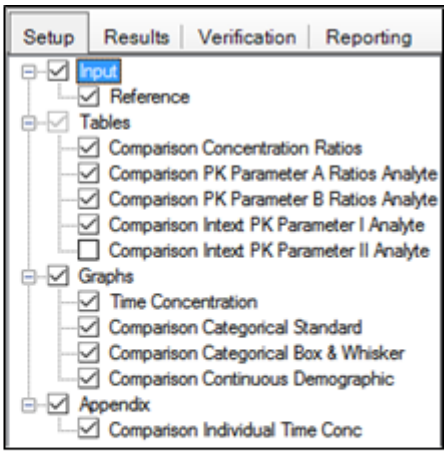
Output: Overlaid time-concentration graphs and concentration ratios.

[a]Each NCA model whose output is being compared must be of the same study design type. For PKS studies, all NCA output must reside in the same PKS study. Additionally, only one NCA model is required for any analyte comparison if stacked data is used. For non-stacked analyte comparisons, two NCA models are required.

List of output types

The *Setup* tab consists of two areas, a hierarchical listing consisting primarily of output types available for the AP Analyte Comparison object selected in the *Object Browser*, and a panel area for displaying options specific to an item selected in the hierarchical list.





The Input list will vary depending on whether an unstacked or a stacked data source was mapped to the **Reference** item. Test data inputs are not available if a stacked dataset is used as the reference.

To identify types of output:

- Check/clear the checkbox beside a table type to include/exclude the table in the output.
- Check/clear the checkbox beside the main **Tables**, **Graphs**, or **Appendix** items to add or remove all items under that heading from the output.
  Selecting **Tables** in the hierarchical list is only possible when stratifications or exclusions are set, or when the input data is stacked by analyte.
- To set options for an output type, click the name of the output type in the hierarchical list and make changes to the options displayed in the panel on the right.

Input panel

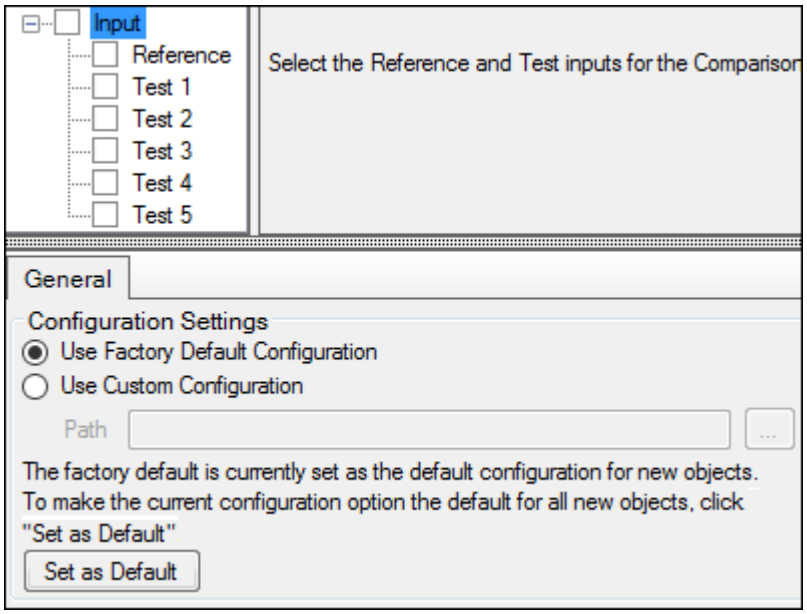
When an AP Analyte Comparison object is inserted into a project, the input source(s) must be assigned before the object can be used or modifications to object settings can be made. The input source can be mapped to NCA Final Parameters worksheets or observations datasets.

Note: The reference and test data sets used in a comparison must contain matching units for the variables being compared.

- In the *Setup* tab, select **Input** in the hierarchical list.

  OR

  In the *Diagram* tab, right-click an AP Analyte Comparison object and select **View Setup**.



If no input sources have been defined, the options available are restricted to selecting the source and specifying an alternative source for configuration settings (refer to "General tab" for more information on configuration settings).

Table panels

Users can set the variables, statistics, or precision for each table type. The options available depend on the type of table selected.

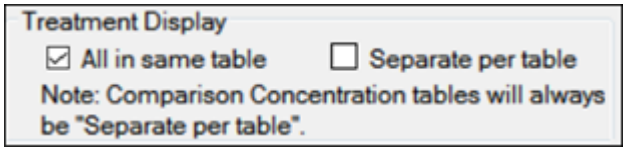
The following sections describe the table options available:

Main Tables panel
Variables and Statistics tabs
Standard/Normalize tab
Precision tab

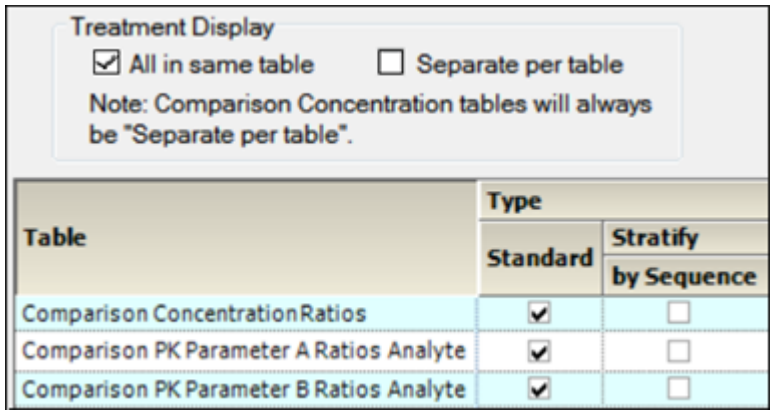
Main Tables panel

The main **Tables** panel shows options that can be applied when generating the tables. The options vary depending on whether stratifications are defined.

- In the *Setup* tab, select **Tables** in the hierarchical list.



- Check the **All in same table** box to generate a table that includes data from all treatments.
- Check the **Separate per table** box to generate a separate table for each treatment.
- When stratification schemes have been defined, (see "Stratification/Normalization tab") they can be applied by selecting the **Stratify by ___** checkbox. Unselect the checkbox to generate only a standard table.



Note: At least one stratified table must be selected if stratifications are specified or the Comparison object will not pass verification.

Variables and Statistics tabs

The *Variables* and *Statistics* tabs are formatted the same for most tables.

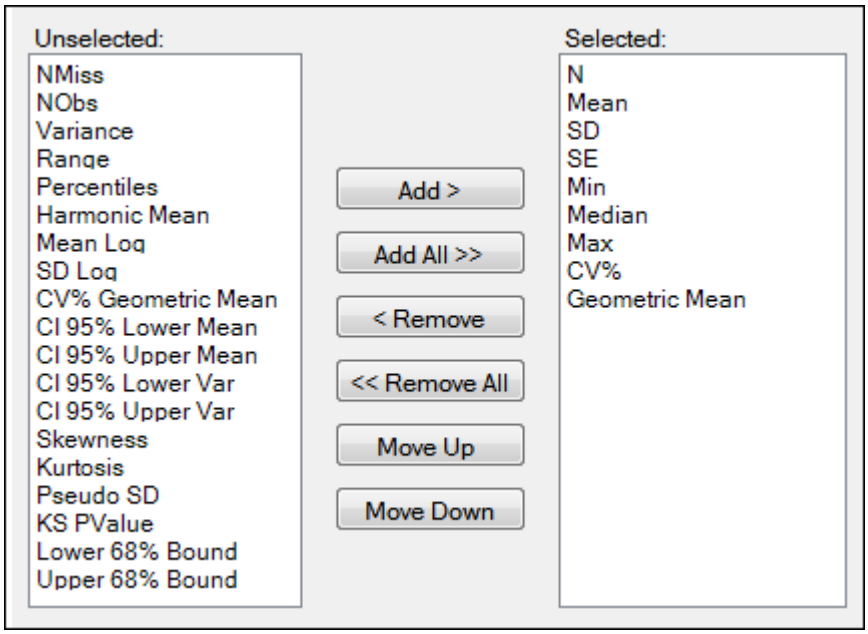
By default, AP Comparison output can include all PK parameters from the PK_Parameter (A–F) tables or the Intext tables and the additional parameters listed under "PK comparison parameters". For Plasma, Urine, and Trough Analyte comparisons, the PK Parameters that are available are the parameters common in all NCA models.

See "PK Parameters" for a full list and descriptions of supported PK parameter study variables. See "Summary Statistics" for a full list and descriptions of supported statistics.

Note: The *Variables* tab may/may not be available, depending on the table type.

- In the *Setup* tab, select a table type in the hierarchical list.
- Select the **Variables** or the **Statistics** tab.

  Variables and statistics that are in the **Selected** column will be included in the output and will be reported in the order that they appear in the column.



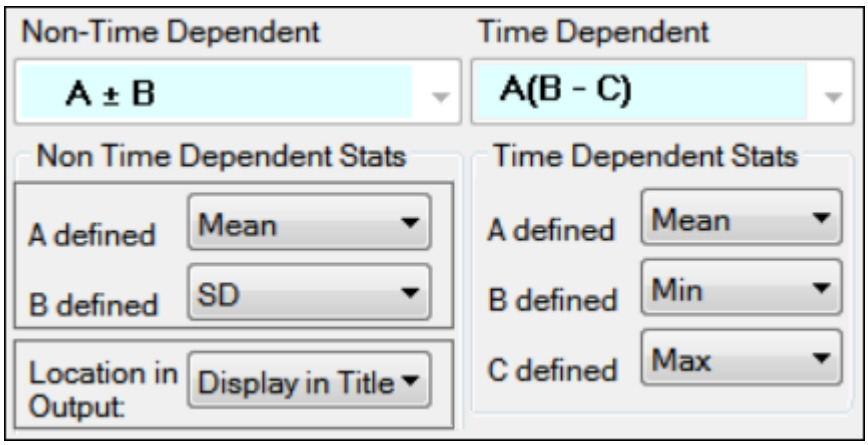
The following instructions apply to both the *Variables* tab and the *Statistics* tab.

- Select an item in one of the columns.
- Click **Add** or **Remove** to move the item from one column to another.
- Click **Add All** and **Remove All** to move all variables from one column to another.
- Click **Move Up** and **Move Down** to change the position of a selected item in the list.

Intext Table Statistics tab

The *Statistics* tab for Intext PK Parameter tables contains different options than *Statistics* tabs for other tables.

- In the *Setup* tab for an Intext PK Parameter type table, select the *Statistics* tab.



- In the **Non-Time Dependent** section, select the equation to be used (currently A +/- B is the only one available).
- Identify the statistics to use in the equations from the pull-down menus.
- Choose the location for displaying the information: **Display in Title**, **Display in Footnote**, **Do not display in output**.

- In the **Time Dependent** section, select the equation to be used (currently A(B – C) is the only one available).
- Identify the statistics to use in the equations from the pull-down menus.

Standard/Normalize tab

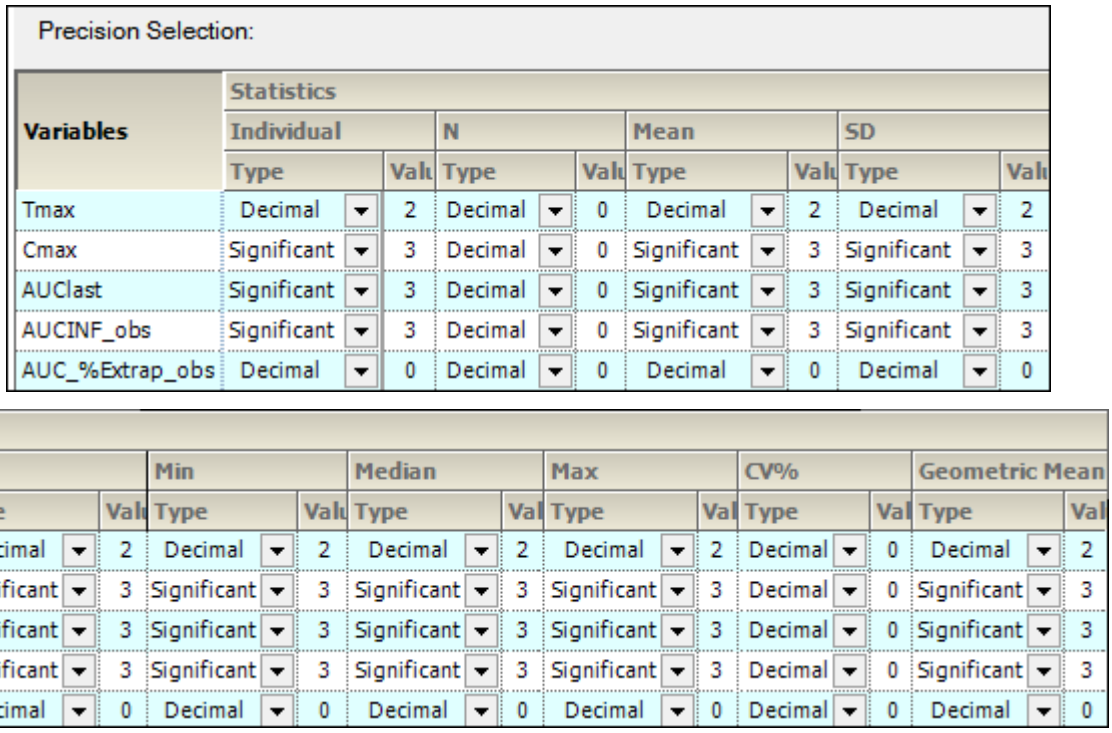
This tab becomes available for PK Parameter tables when normalization schemes are defined (see "Stratification/Normalization tab").

- In the *Setup* tab for a table of PK parameters, select the *Standard/Normalize* tab.
- Select the **Display** option **All standard, then all normalized by ____** to list all of the standard columns first, followed by normalized columns.
- To group the columns so that the standard and normalized version of the data are together, select the **Display** option **Group together standard and normalized by ____**.
- Toggle generation of tables with and/or without normalization for each parameter by selecting/unselecting the checkboxes in the **Standard** and **Normalize by ____** columns.

Precision tab

For each variable and statistic, the precision can be set by the number of significant digits or decimal places. Selection of the type and value of numerical precision is also done through this tab.

- In the *Setup* tab, select a table type and then click the *Precision* tab.



- In the **Type** menu for each statistic, select **Decimal** or **Significant**.
- Select a cell in the corresponding **Value** column to enter a new precision display value.

Graph panels

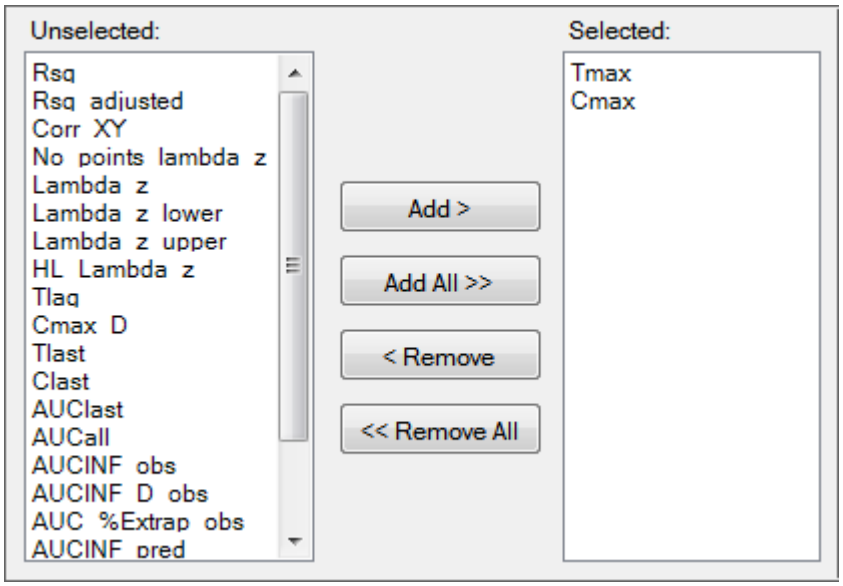
AutoPilot Toolkit allows the user to apply different attributes to each graph. These attributes include Y-axis scaling, summary value display, error bar display, and regression line options. Selection of PK parameters to include in the graphs is also available.

The following sections describe the graph options available for each graph type:

Main Graphs panel

- In the *Setup* tab, select **Graphs** in the hierarchical list.

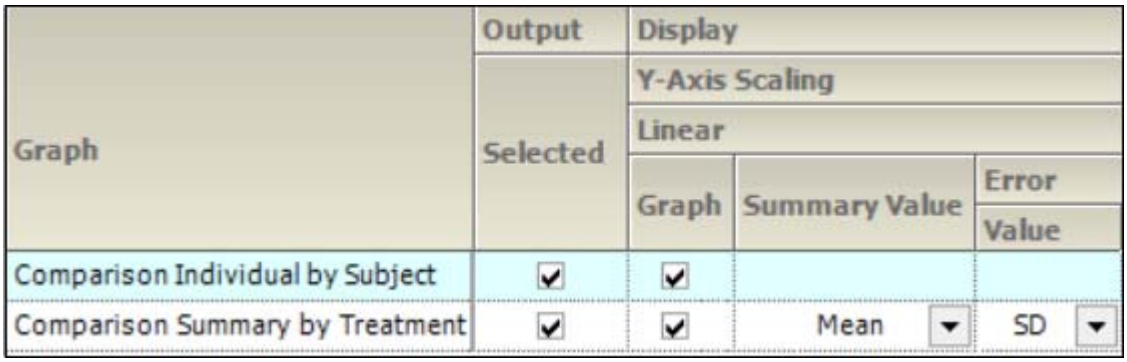
  Parameters that are in the **Selected** column will be included in the output.

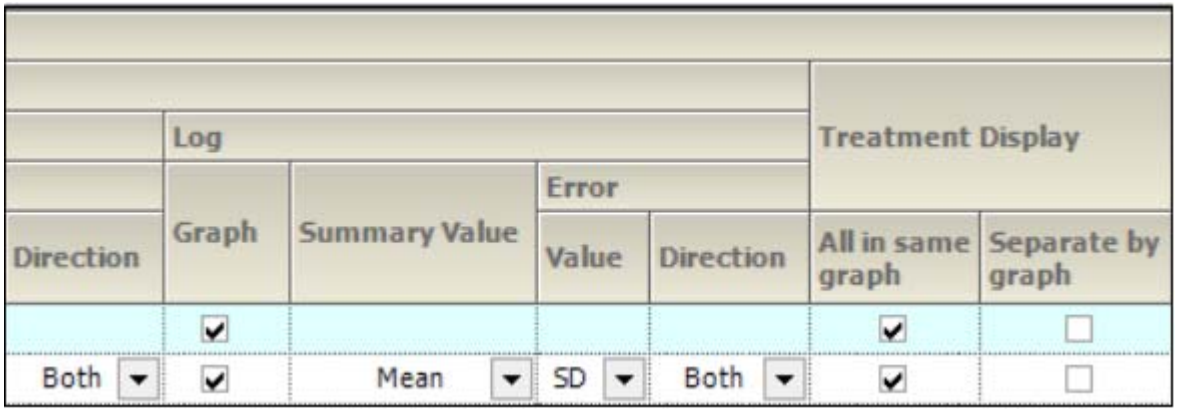


- Select an item in one of the columns.
- Click **Add** or **Remove** to move the item from one column to another.
- Click **Add All** and **Remove All** to move all variables from one column to another.
- Click **Move Up** and **Move Down** to change the position of a selected item in the list.

Time Concentration panel

- In the *Setup* tab, select **Time Concentration** in the hierarchical list.





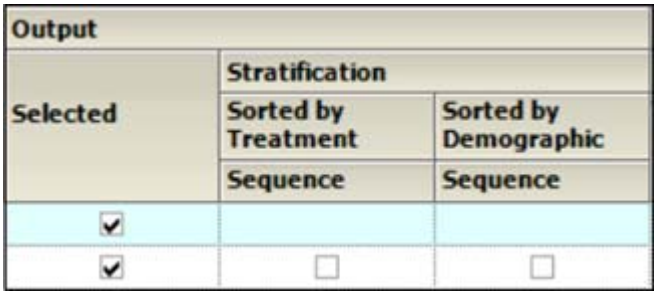
There are two types of Time Concentration graphs available:

- **Comparison Individual by Subject**: A separate graph is generated for each subject involved in the study. Each line on the graph represents a separate treatment.
- **Comparison Summary By Treatment**: A single graph is generated. Each line represents a separate treatment.

The panel displays a table of options for the Time Concentration graphs, grouped into several categories and sub-categories:

Output

- Check/Uncheck the **Selected** box to include/exclude a type of Time Concentration graph in the output.



- When **Stratification** schemes have been defined (see “Stratification/Normalization tab”), they can be used as X-axis variables in a **Summary by Treatment** graph type, **Sorted by Treatment** or **Sorted by Demographic**. Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.

Display

- Graphs can be generated with a **Linear** or **Log Y-Axis Scaling**. The following options are available for both types of Y-axis scaling:
  - In the **Graph** section, check the box to use the Y-axis scaling method. Unselect to not scale the Y-axis. Selecting this checkbox under both the **Linear** and **Log** sections will generate two graphs, one using each method.
  - For **Summary by Treatment** type, select the **Summary Value** to use for plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**.
  - Specify the **Value** (**SD**, **SE**, **Variance**, **Min and Max**, **None**, **68% Range**) and **Direction** (**Both**, **Down**, **Up**) of **Error** bars to display on **Summary by Treatment** graphs.
- Check the **All in same graph** box to generate a **Treatment Display** graph that includes data from all treatments. Select the **Separate per graph** checkbox to generate a separate graph for each treatment.

Comparison Categorical Standard panel

- In the *Setup* tab, select **Comparison Categorical Standard** in the hierarchical list.

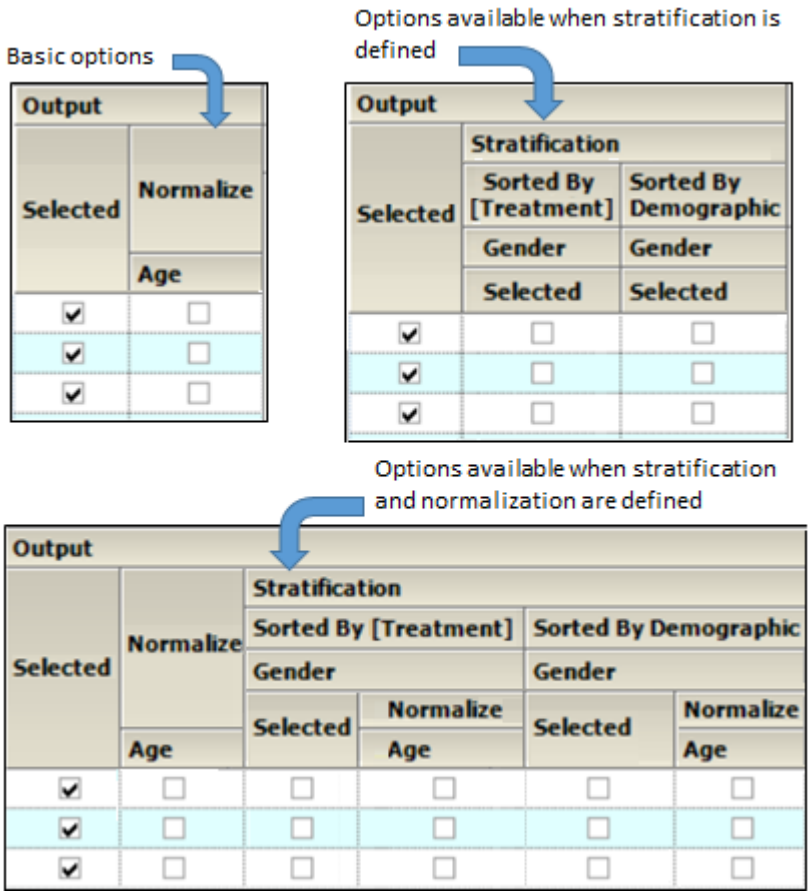
PK Parameter (Client Name)	Output	Display				
	Selecte	Y-Axis Scaling (Linear)			Treatment Display	
		Summary Val	Error			
			Value	Direction	All in same	Separate
Lambda_z	☑	Median	Min and Max	Both	☑	☐
HL_Lambda_z	☑	Median	Min and Max	Both	☑	☐
Tmax	☑	Median	Min and Max	Both	☑	☐

The PK Parameters available in the study are listed as rows in the table.

The panel displays a table of options for the Comparison Categorical Standard graphs, grouped into several categories and sub-categories:

Output

- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes have also been defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.



- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by [Treatment]**) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes have also been defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the stratified graphs

Display

- Graphs can be generated using a **Linear Y-Axis Scaling**. The following options are available:
  - Select the statistic to use as the **Summary Value** when plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**.
  - Specify the **Value** (**Min and Max**, **Pseudo SD**, **SD**, **SE**, **Variance**, **68% Range**) of the **Error** bars. The only option available for **Direction** is **Both**.
  - For **Treatment Display**, check the **All in same graph** box to generate a graph that includes data from all treatments. Select the **Separate per graph** checkbox to generate a separate graph for each treatment.

Comparison Categorical Box & Whisker panel

Note: There must be at least three subjects in the study to create Box & Whisker graphs.

- In the *Setup* tab, select **Comparison Categorical Box & Whisker** in the hierarchical list.

PK Parameter (Client Name)	Output	Treatment Display	
	Selected	All in same graph	Separate by graph
Lambda_z	☑	☑	☐
HL_Lambda_z	☑	☑	☐
Tmax	☑	☑	☐

The PK Parameters available in the study are listed as rows in the table.

Output

- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Basic options

Output		
Selected	Normalize	
	Age	
☑	☐	
☑	☐	
☑	☐	

Options available when stratification is defined

Output			
Selected	Stratification		
	Sorted By [Treatment]	Sorted By Demographic	
	Gender	Gender	
	Selected	Selected	
☑	☐	☐	
☑	☐	☐	
☑	☐	☐	

Options available when stratification and normalization are defined

Output					
Selected	Normalize	Stratification			
		Sorted By [Treatment]		Sorted By Demographic	
		Gender		Gender	
		Selected	Normalize	Selected	Normalize
	Age		Age		Age
☑	☐	☐	☐	☐	☐
☑	☐	☐	☐	☐	☐
☑	☐	☐	☐	☐	☐

- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by [Treatment]**) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes are also defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

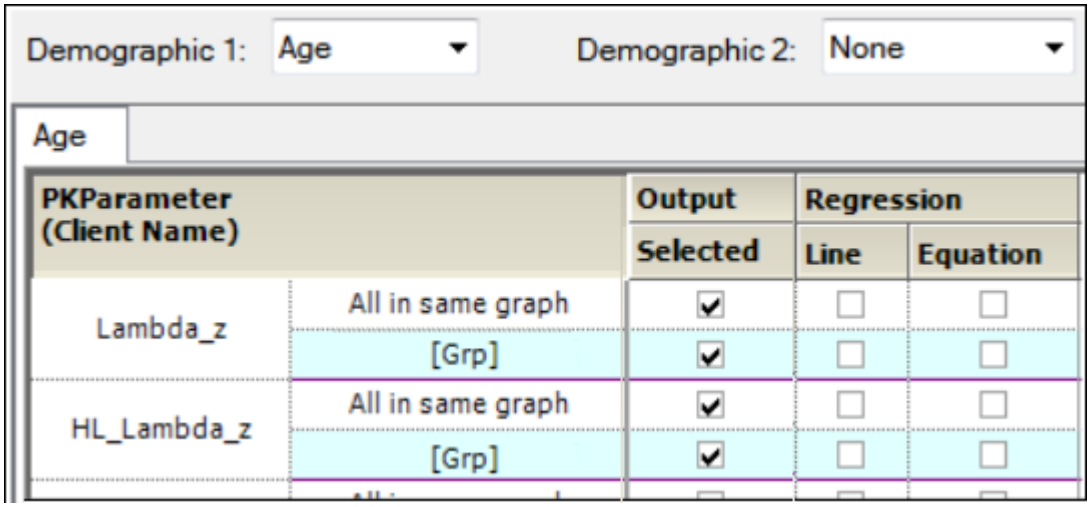
Treatment Display

- Check the **All in same graph** checkbox to generate a graph that includes data from all treatments.

- Check the **Separate per graph** checkbox to generate a separate graph for each treatment.

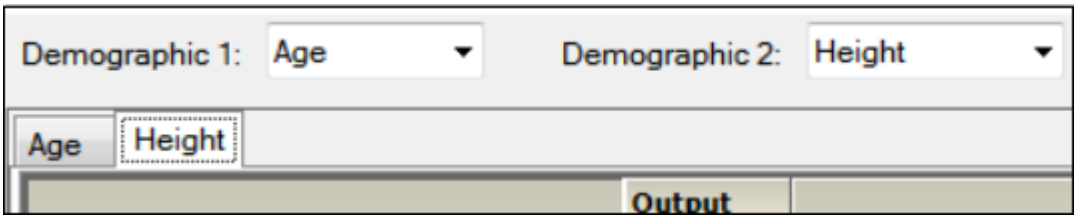
Continuous Demographic panel

- In the *Setup* tab, select **Comparison Continuous Demographic** in the hierarchical list.



The panel displays a section for selecting up to two demographic(s) to use for the X-axis (**Demographic 1** and **Demographic 2**).

When a second demographic type is selected, a second tab is created in the Comparison Continuous Demographic panel.



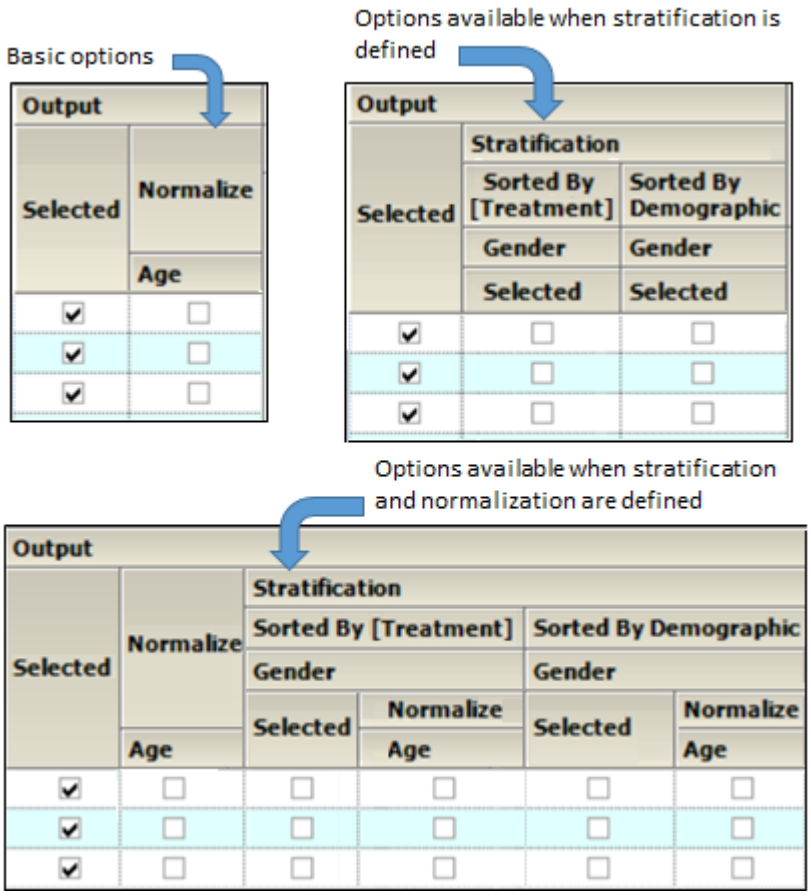
The PK Parameters available in the study are listed as rows in the table. Each parameter will have two sub-rows:

- **All in Same Graph**: Sort all graphs by analyte.
- **[Grp]**: Group all graphs by analyte.

The lower part of the panel contains a table of options for the Comparison Continuous Demographic graphs, grouped into several categories and sub-categories:

Output

- Check the **Selected** box to create graphs for the parameter that are sorted by analyte and/or to create graphs for the parameter that are grouped by analyte. Unselect a checkbox to not generate the graph(s) for a parameter.
  - If normalization schemes are also defined (see “Stratification/Normalization tab”), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.



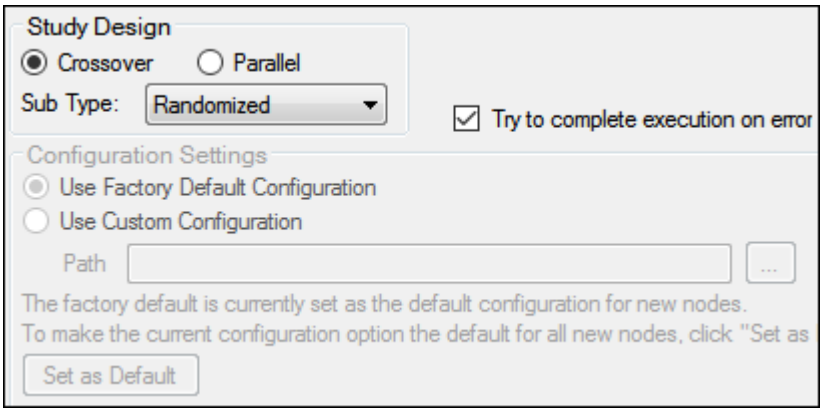
- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by [Treatment]** or **Sorted by Period** for replicated studies) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes have also been defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Regression

- Check the **Line** checkbox to include a regression line in the graph.
- Check the **Equation** checkbox to display the regression equation in the graph.

General tab

The *General* tab allows users to select the study design type, configuration settings, and whether or not to try to complete a comparison run if an error occurs.



The study design options in the *General* tab depend on the configuration settings. If the settings are changed, then the options could be different from the options listed below.

Note: The configuration settings must be specified before a dataset is mapped to the AP Comparison object.

Study Design

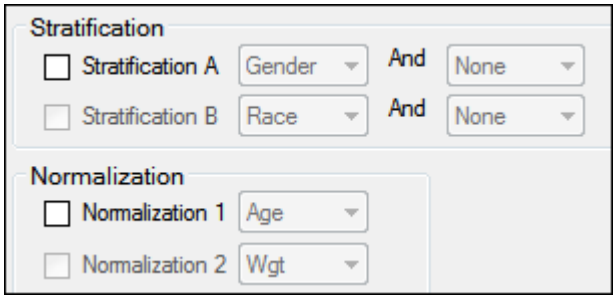
- Specify that the study design type is either **Crossover** or **Parallel**.
- For a **Crossover** study design, select the study **SubType** (**Randomized**, **Non-Randomized**, or **Replicated**).
- By default, AutoPilot Toolkit tries to complete a comparison run even if errors are encountered and not all selected output can be created.
- Unselect the **Try to complete execution on error** checkbox to stop a comparison run if any errors are encountered.

Configuration Settings

- Indicate the configuration settings to use. **Use Factory Default Configuration** is selected by default.
- To use customized settings, select **Use Custom Configuration** and click the **Change Directory […]** button to select the directory where the custom configuration settings file is located.
- The customized settings can be defined as the default configuration settings to use for new projects by clicking **Set as Default**.

Stratification/Normalization tab

The **Stratification** and **Normalization** options allow users to create additional table and/or graph output.



Stratification

Results can be stratified (i.e., layered) using discrete demographic variables. Each stratification level can use one or two discrete demographic variables. If two variables are specified, they are associated using the logical operator AND.

Note: At least one stratified output type must be selected if stratification is enabled or the Comparison project will not pass verification.

- To define the first level of stratification, select the **Stratification A** checkbox and choose the demographic variable(s) from the pull-down menu(s).
- To define a second level of stratification, select the **Stratification B** checkbox and choose the variable(s) from the pull-down menu(s).

If stratifications are selected, the comparison run creates one table per stratum for the time and concentration, PK parameter, and intext PK parameter tables, using the stratification scheme as an additional group variable.

If graphs include stratification, the stratification schemes are used either as X-axis variables (sorted by treatment) or new sort variables (sorted by demographics), depending on the AutoPilot Toolkit Admin settings.

Normalization

Use the **Normalization** section to define normalization schemes to apply to the results. Each normalization scheme must use a different continuous demographic variable.

- To define the first level of normalization, select the **Normalization 1** checkbox and choose a demographic variable from the pull-down menu.
- To define a second level of normalization, select the **Normalization 2** checkbox and choose a variable from the pull-down menu.

  AutoPilot Toolkit calculates the normalized PK parameters and includes them in the results. Users can select the **PK Parameter** and **Intext PK Parameter** tables in the hierarchical list and choose which normalized parameters to display in each table. This allows PK Parameter automation tables to include both normalized and non-normalized values.
- Select the PK Parameter, Intext PK Parameter, PK Ratios, or PK Statistics table in the Tables node.
- Select the Standard/Normalize tab.
- In the **Display** menu, select how to display normalized PK parameters in the table output.
- Select the **Normalize** checkbox beside a PK parameter to include it in the table output.

For more on using the table panels, see "Table panels".

Column headers for the normalized variables include a normalization variable and its units. For example, oral clearance normalized by weight: CL/F/Weight (L/hr/kg). If graph output is selected that includes normalization, each normalized PK parameter is displayed in a separate graph. The Y-axis labels display the normalization in the same manner as tables.

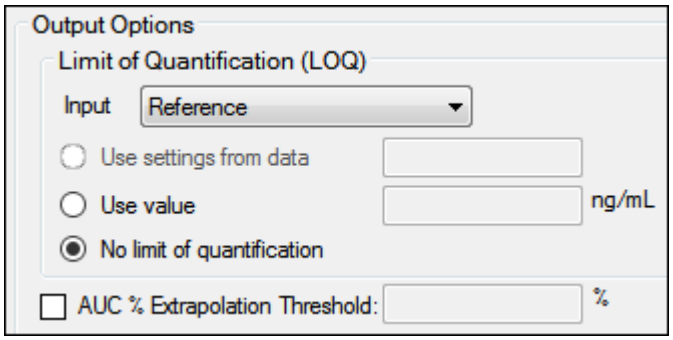
PK parameters that are excluded from normalization are listed in "PK automation parameters".

Display tabs

The *Display* tab contains four tabs that allow users to set output and display options, table and graph orientation, and the X- and Y-axes scaling for graphs.

Output Options tab

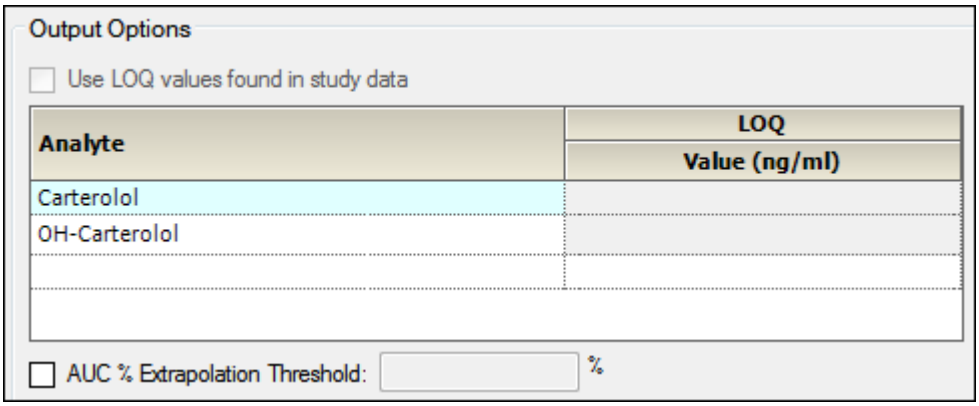
The *Output Options* tab allows users to define the LOQ value and the AUC percent extrapolation threshold value.



The options for LOQ vary depending on the type of data used and the system configuration settings.

- For unstacked data, choose one of the following methods of defining the LOQ:
  - To set the LOQ value using the input data, click **Use setting from data**.
  - To enter a value, click **Use value** and type a value in the corresponding field.
  - Click **No limit of quantification** to not set an LOQ limit.

  If the input dataset contains stacked data, a different LOQ can be set for each analyte.



- For stacked input data, do one of the following to set the LOQ:
  - Turn on the **Use LOQ values found in study data** checkbox to set the values for LOQ using the input data.
  - Enter an LOQ value for each analyte in the Value column. (The concentration units are taken from the input dataset.)
  - To not use LOQ values, turn off the **Use LOQ values found in study data** checkbox and leave the Value column entries blank.

Note: Setting the LOQ value for all analyts can significantly extend the execution time.

For more information, see "LOQ replacement".

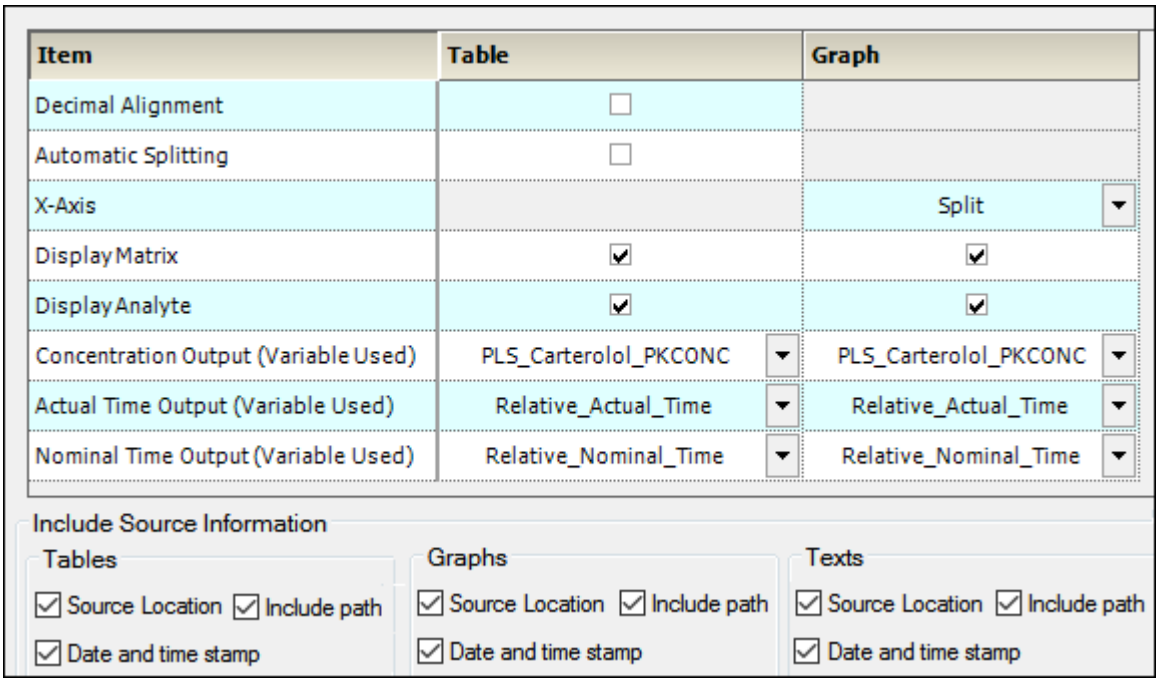
The following option is applicable to both stacked or unstacked input data:

- Turn on the **AUC% Extrapolated Threshold** checkbox to use the rules for handling AUC extrapolated values that exceed the specified percentage.

See "PK parameter percent-extrapolated threshold" for details.

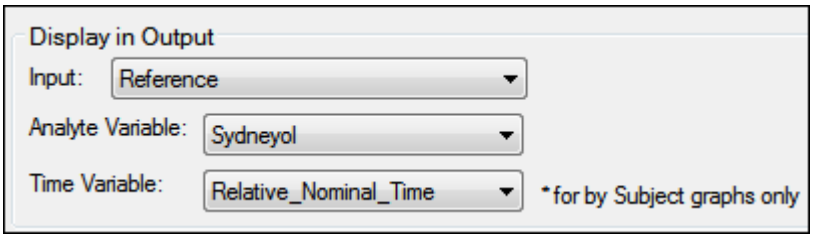
Display Options tab

The *Display Options* tab allows users to set table and graph output display options, select the time and concentration variables in the input dataset, and choose whether or not to include data source information.



- Turn on the **Decimal alignment** checkbox to align all values in a given column using their decimal points. See "Table data display using decimal alignment".
- Turn on the **Automatic splitting** checkbox to allow splitting large tables across multiple pages. See "Table business rules".
- Select from the **X axis** pull-down if the PK parameter graphs have a **Split** X-axis based on individual and summary values or **Offset**.
- Turn on the **Display Matrix** or **Display Analyte** checkbox to include the matrix or analyte information in the tables and/or graphs. See "Display analyte and matrix information" (tables) or "Display analyte and matrix information" (graphs).
- Select the concentration variable to use for creating time-concentration tables and graphs from the **Concentration Output (Variable Used)** pull-down menu.
- Use the **Actual** and **Nominal Time Output (Variable Used)** pull-down menus to select which data column to use for the actual and nominal times. This is set using the Time Variables tab in the Admin Module.

- The Display in Output section, available only for trough projects, contains an **Input** pull-down menu. Select whether to use the reference or a test input in the AutoPilot Toolkit output.



- In the **Analyte Variable** menu, select the analyte to display in the AutoPilot Toolkit output.

Note: If the trough input dataset is stacked by analyte, then users cannot select the analyte to be used in the output.

- In the **Time Variable** menu, users can select the actual or the nominal time variable to be used in the Concentration by Subject graphs, which display individual trough time and concentration for one subject per graph.
- In the **Include Source Information** section, select or clear the checkboxes to include or exclude the location of the input file, the path to that location, and a date and time stamp in the Table, Graph, and Text output.

Orientation tab

Through the *Orientation* tab, the orientation of each output item is set. A few additional settings regarding the appearance of graphs in a Word document are available for appendices involving individual time-concentration graphs.

Item	Orientation	Paper size	Presentation order	Graphs per page
Tables				
Comparison Time Concentration	Portrait			
Comparison PK Parameter	Portrait			
Comparison Intext	Portrait			
Time Concentration Graphs				
Comparison Individual Subject	Portrait			
Comparison Summary	Portrait			
PK Parameter Graphs				
Comparison Categorical Standard	Portrait			
Comparison Categorical Box and Whisker	Portrait			
Comparison Continous Demographic	Portrait			
Appendix (Word Documents)				
Comparison Inidividual Time Concentration	Portrait	Letter	All linear then all log	1 x 1

- In the Orientation column, select whether to position the output as a **Portrait** or in **Landscape** format from the pull-down menu for each table, graph, and appendix output.

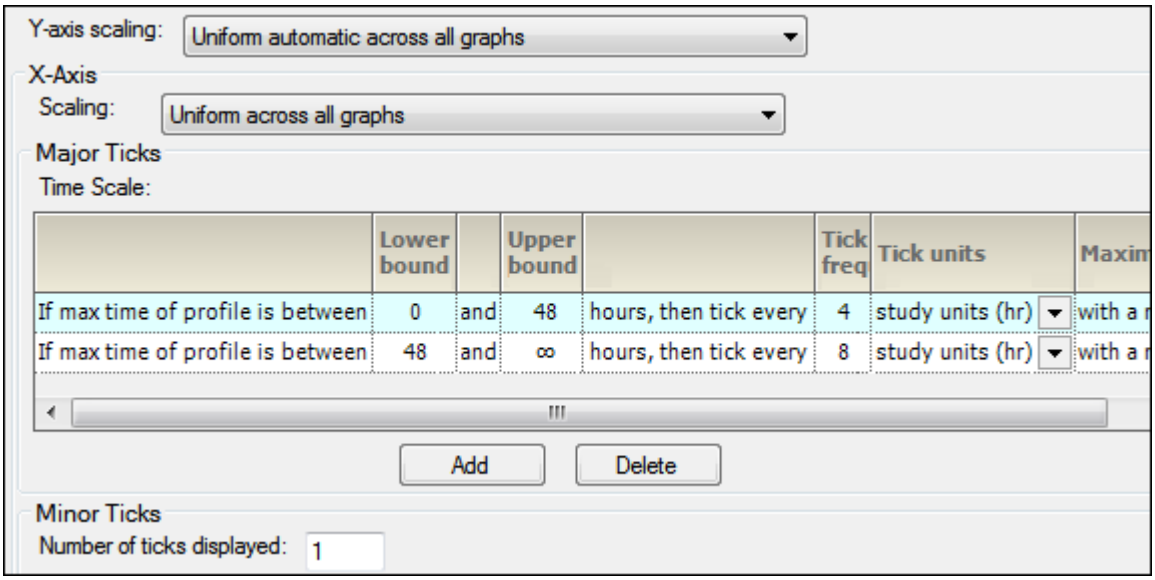
Note: Only certain tables and graphs can be changed to Landscape. If Landscape is not supported, the Orientation setting for that table or graph defaults to Portrait and the pull-down menu is disabled.

For the **Individual Time Concentration** appendix output type, the following specifications can also be made:

- Select the Paper Size as **Letter** or **A4** from the pull-down menu.
- Indicate the order in which the graphs are to appear using the Presentation Order column pull-down menu. Options include:
  - **All linear then all log**: Display the linear graphs (sorted by subject) before the log graphs (sorted by subject).
  - **All log then all linear**: Display the log graphs (sorted by subject) before the linear graphs (sorted by subject).
  - **Per profile, linear then log**: Graphs are grouped by subject and then by analyte, with the linear graph presented before the log graph. In the output, the graphs are displayed in subject order.
  - **Per profile, log then linear**: Graphs are grouped by subject and then by analyte, with the log graph presented before the linear graph. In the output, the graphs are displayed in subject order.
- Specify the number of graphs per page using the pull-down in the Graphs Per Page column. Options range from **1x1** up to **4x4**.

Time Scale Algorithm tab

The *Time Scale Algorithm* tab is used to specify the scaling options for the axes, the lower and upper bounds for time scale ticks, the tick frequency, the tick units, and the maximum time scale on the X-axis. See "Time scale algorithm" for more information.



- In the **Y-axis scaling** menu, choose whether to scale the Y-axis uniformly across all graphs or scale the Y-axis on a per graph basis.
- In the X-Axis area, select X-axis **Scaling** to be either uniformly across all graphs or on a graph by graph basis.

  The Major Ticks area contains a table where each row represents a separate time scale.
- Enter new values for lower and upper bounds in the **Lower bound** and **Upper bound** fields.

Use the Tick frequency and Tick units columns together to define the frequency with which tick marks are displayed along the X-axis.

- Enter the value directly in the **Tick frequency** field and then select the units from the **Tick units** pull-down menu. (The default is **study units**, indicating that the units are derived from the study data.)
- Set new values for the time scale multiple value in the **Maximum time scale** multiple value field.
- Click **Add** in the Major Ticks area to add another time scale.

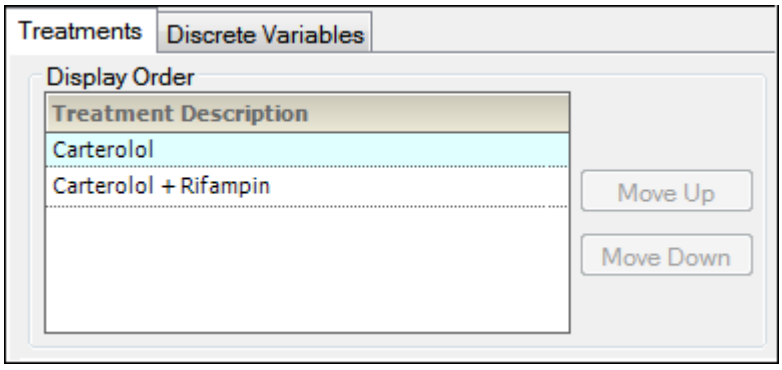
  A new row is added to the table below the row that was selected or modified last.
- To remove an added time scale, click in that row and then click **Delete**.

  A minimum of two defined time scales is required.
- In the Minor Ticks area, change the number of minor ticks displayed between the major ticks by typing a new value in the **Number of ticks displayed** field.

Ordering tab

The *Ordering* tab is used to specify how the treatment descriptions are ordered in the output.

- In the Treatment tab, select a treatment in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.



- In the Discrete Variables tab, use the **Variable values to be reordered** menu to select different discrete study variables.
- Select the variable in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Analyte tab

This tab is present only if the input data is stacked and lists all of the analytes involved in the study.

Select an analyte in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Comparison results

Caution: Do not perform any operations on the computer while the comparison run is in progress. Doing so could cause unpredictable results; keyboard and mouse input during a comparison run might affect automated AutoPilot Toolkit operations.

After the project is run, all output is arranged in groups in the *Results* tab.

Not all output can be viewed in Phoenix. In such cases, the right side of the *Results* tab will display a message with suggestions on how to view the results. One suggestion is to open an external program and load the results by clicking **View in External Viewer**.

AutoPilot Toolkit output can be individually exported to disk or copied to Phoenix's Data folder. All results can be exported using AutoPilot File Explorer, which is located in the *Reporting* tab. For more using AutoPilot File Explorer, see "AutoPilot File Explorer".

Accumulation and Other Comparisons

AutoPilot Toolkit can run analyses to compare output from previously run NCA models. The Accumulation, Absolute Bioavailability, and Renal Clearance Comparison objects combine output from previously created NCA models to create additional report output.

The AP Accumulation, Absolute Bioavailability, and Renal Clearance Comparison objects compare output from two studies. Comparison projects use NCA output or study data that is stored locally or in Certara PKS scenarios. The NCA projects can be imported into Phoenix from a disk or loaded from PKS. If PKS is used, then all NCA output must reside in the same PKS study.

Note: There are a number of situations where comparing treatment values of differing levels between two studies can create output that may not be useful. There are also cases where such comparisons may prove valuable. The AutoPilot Toolkit does not make any assessment of when such comparisons should be done or not. For this reason, the user should be careful in the selection of the study data to be processed by the AutoPilot Toolkit's Comparison tool, particularly when there are treatments in one study that do not appear in the other.

Use one of the following to add the object to a Workflow:

Right-click menu for a Workflow object: **New > AutoPilot > AP Accumulation/Absolute Bioavailability/Renal Clearance Comparison**.
Or Main menu: **Insert > AutoPilot > AP Accumulation/Absolute Bioavailability/Renal Clearance Comparison**.
Or right-click menu for a worksheet: **Send To > AutoPilot > AP Accumulation/Absolute Bioavailability/Renal Clearance Comparison**.
Or select a workflow in the Object Browser and click  for accumulation or  for absolute bioavailability or  i for renal clearance in the Object Toolbox on the left side of the Diagram tab.

An AP Comparison object must have an assigned source of input data for the Reference run and at least one other Test run as a first step. If stacked data is being used, then only one input data source is needed. When the input sources are selected, AutoPilot Toolkit then creates the AP Comparison interface based on the input data.

When connected to an NCA object, the AP Comparison object detects any changes to the NCA model and generates an alert. The AP Comparison object does not correct the problem. It only alerts users that changes were detected. Users must revert their NCA changes or make the necessary changes to the AP Comparison object.

The **Send To** command cannot be used to map data to the Test inputs. The **Select source** button or the *Diagram* tab must be used to map data to the Test inputs. The **Input** checkboxes in the *Setup* tab are also a quick way to map/unmap sources to the reference and various tests.

To change a source of input data

The source of the input data for an Comparison object can be changed by simply remapping the input to the new source. AutoPilot Toolkit will check the compatibility of the new source's study variables with the variables in the Comparison object's original dataset.

- If the new source appears to be ***compatible*** with the Comparison object, a message to this effect is presented in a dialog along with a reminder to review the object's settings.
- If the new source is ***incompatible*** with the Comparison object (e.g., the object, initially connected to a plasma NCA model is remapped to a urine model), a warning is generated. Continuing with mapping of the incompatible data source to the Comparison object will result in all settings and/or previous results being cleared.

This section contains the following topics:

See also:

"PK Comparison tables" for a listing of tables available for each combination of study design, dosing, regimen, and matrix.
"PK Comparison graphs" for a listing of graphs available for each combination of study design, dosing, and matrix.
"PK Comparison appendix output" for a listing of appendices available for each study design.

Comparison types

The differences between the three Accumulation, Absolute Bioavailability, and Renal Clearance comparison types are outlined below.

Accumulation

Input Data: Requires both datasets to be either stacked or unstacked, the same analyte to be compared between the two datasets, NCA Models 200–202[a], runs to use same matrix and route, reference input data to be from a single-dose NCA model and test input data to be from a multiple-dose NCA model.

Output: Overlaid percent dose remaining graphs, overlaid amount excreted over time graphs, and calculation of additional parameters such as Accumulation (RA) and Linearity (LI). Comparisons are between the single-dose day and a multi-dose day, but not between two multi-dose days.

Absolute Bioavailability

Input Data: Requires both datasets to be either stacked or unstacked, the same analyte to be compared between the two datasets, NCA Models 200–202[a], study design type to be Crossover, runs to use same matrix and regimen, reference input data to be from a non-extravascular route containing one Treatment, which is either IV Bolus (model 201) or IV Infusion (model 202), test input data to be from an extravascular route (model 200) and can have multiple Treatments.

Output: Overlaid time-concentration graphs, calculation of additional parameters such as Absolute Bioavailability (F), and calculation of ratios for PK parameters. If route information is unavailable from the reference and test studies, the text strings "IV" and "Ext" will be used in legends or X-axis levels as appropriate.

Renal Clearance

Input Data: Requires both datasets must be either stacked or unstacked, the same analyte to be compared between the two datasets, NCA Models 200–212[a], runs to use the same route and regimen, reference input data to be from a non-urine-based matrix (model 200–202), test input data to be from a urine-based matrix (model 210–212), and the urine and blood draw collection intervals to be the same.

Output: Calculation of additional parameters such as Renal Clearance (CLr=Ae/AUClast) and concentration ratios for PK parameters.

[a]Each NCA model whose output is being compared must be of the same study design type. For PKS studies, all NCA output must reside in the same PKS study. Additionally, only one NCA model is required for any analyte comparison if stacked data is used. For non-stacked analyte comparisons, two NCA models are required.

Note: Phoenix does not allow users to select steady state dosing for urine models. AutoPilot Toolkit uses the steady state flag to distinguish between SD (single dose) and MD (multiple dose) regimens. Therefore, AutoPilot Toolkit considers a urine study to be MD or steady state if Day is used as a Sort Variable and SD if Day is not used as a Sort Variable.

List of output types

The *Setup* tab consists of two areas, a hierarchical listing consisting primarily of output types available for the AP Analyte Comparison object selected in the *Object Browser*, and a panel area for displaying options specific to an item selected in the hierarchical list.

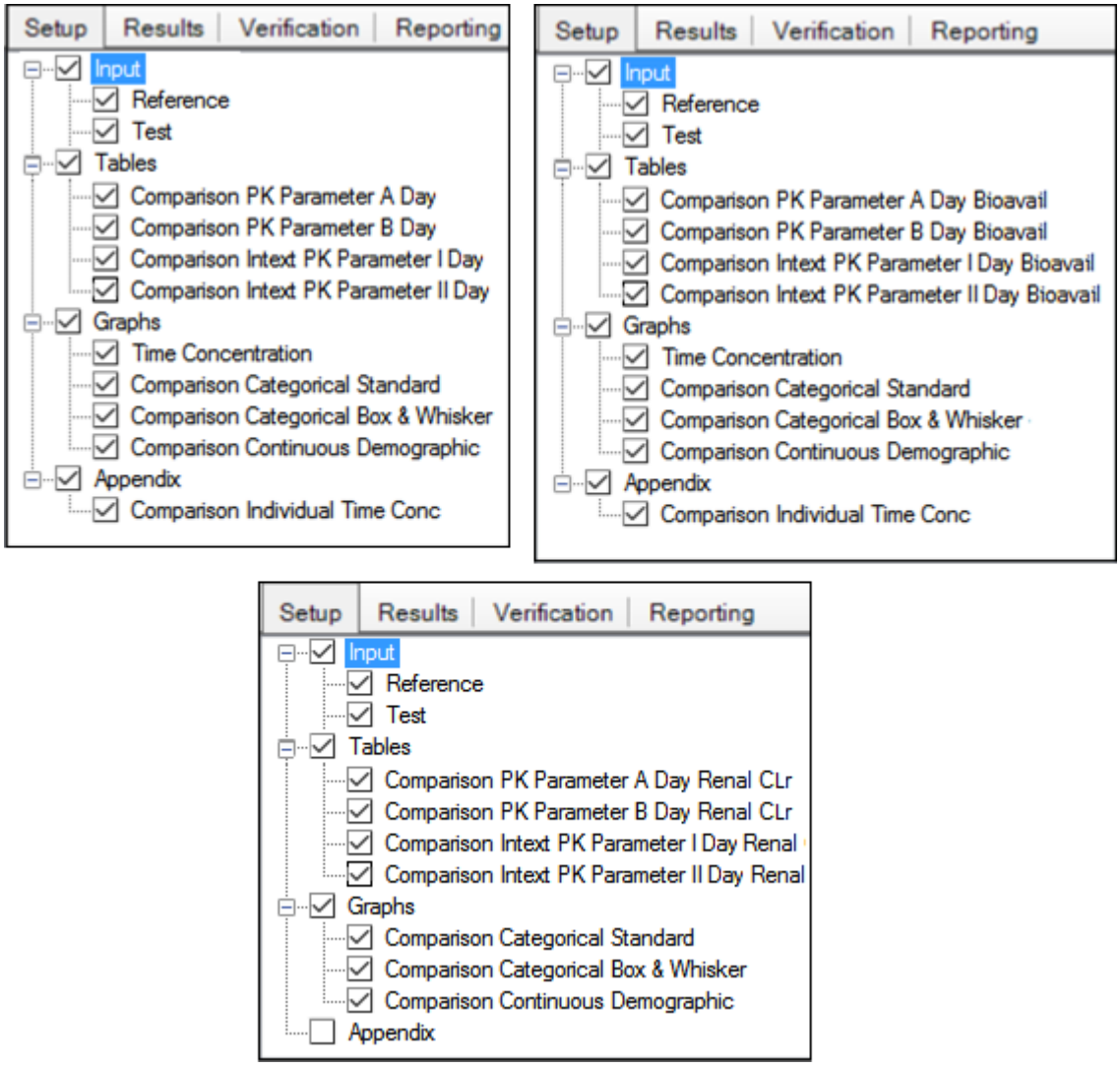


Figure 7-1. Setup tab for Accumulation, Absolute Bioavailability, and Renal Clearance Comparison objects

The Input list will vary depending on whether a stacked or unstacked data source was mapped to the **Reference** item. Test data inputs are not available if a stacked dataset is used as the reference.

To identify types of output:

- Check/clear the checkbox beside a table type to include/exclude the table in the output.
- Check/clear the checkbox beside the main **Tables**, **Graphs**, or **Appendix** items to add or remove all items under that heading from the output.
  Selecting **Tables** in the hierarchical list is only possible when stratifications or exclusions are set, or when the input data is stacked by analyte.
- To set options for an output type, click the name of the output type in the hierarchical list and make changes to the options displayed in the panel on the right.

Input panel

When an AP Comparison object is inserted into a project, the input source(s) must be assigned before the object can be used or modifications to object settings can be made. The input source can be mapped to NCA Final Parameters worksheets or observations datasets.

Note: The reference and test data sets used in a comparison must contain matching units for the variables being compared.

- In the *Setup* tab, select **Input** in the hierarchical list.

  OR

  In the *Diagram* tab, right-click an AP Comparison object and select **View Setup**.

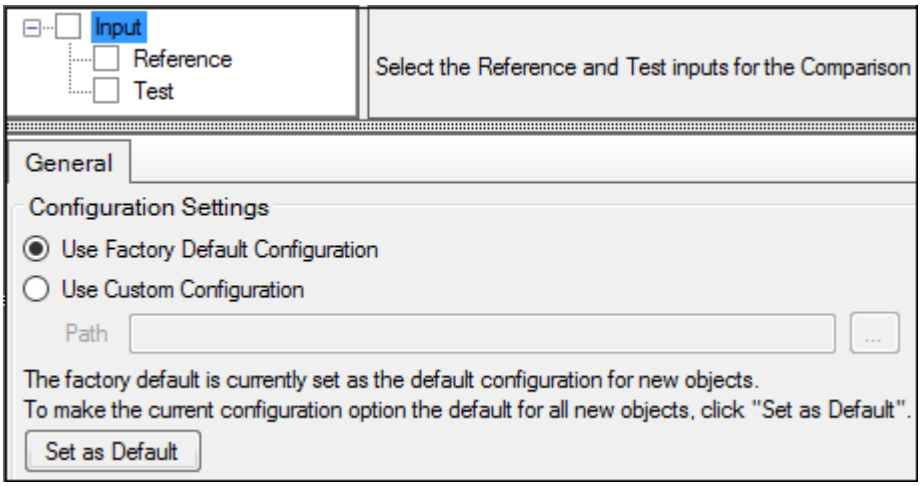


Figure 7-2. Setup tab with no input source defined

If no input sources have been defined, the options available are restricted to selecting the source and specifying an alternative source for configuration settings (refer to "General tab" for more information on configuration settings).

Table panels

Users can set the variables, statistics, or precision for each table type. The options available depend on the type of table selected.

The following sections describe the table options available:

"Main Tables panel"
"Variables and Statistics tabs"

"Standard/Normalize tab"
"Precision tab"

Main Tables panel

The main **Tables** panel shows options that can be applied when generating the tables. The options vary depending on whether stratifications are defined.

- In the *Setup* tab, select **Tables** in the hierarchical list.

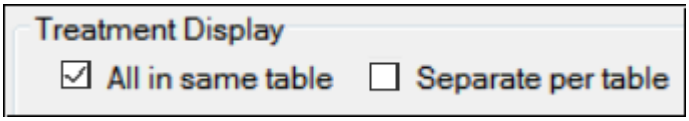


Figure 7-3. Tables panel for unstacked data

- Check the **All in Same Table** box to generate a table that includes data from all treatments.
- Check the **Separate per Table** box to generate a separate table for each treatment.
- When stratification schemes have been defined, (see "Stratification/Normalization tab") they can be applied by selecting the **Stratify by ___** checkbox. Unselect the checkbox to generate only a standard table.

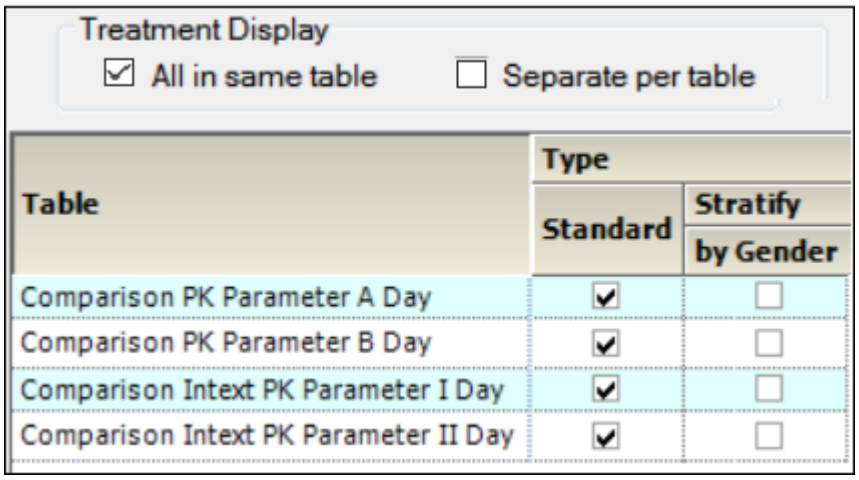


Figure 7-4. Tables panel for stacked data

Note: At least one stratified table must be selected if stratifications are specified or the Comparison object will not pass verification.

Variables and Statistics tabs

The *Variables* and *Statistics* tabs are formatted the same for most tables.

By default, AP Comparison output can include all PK parameters from the PK_Parameter (A – F) tables or the Intext tables and the additional parameters listed under "PK comparison parameters".

For Absolute Bioavailability and Accumulation comparisons, the PK Parameters that are common in all NCA models are listed in the **Selected** list and all other parameters are listed in the **Unselected** list.

For Renal Clearance comparisons, since there are no common Plasma and Urine parameters, all parameters from either run are available in the comparison **Unselected** list.

See "PK Parameters" for a full list and descriptions of supported PK parameter study variables. See "Summary Statistics" for a full list and descriptions of supported statistics.

Note: The *Variables* tab may/may not be available, depending on the table type.

- In the *Setup* tab, select a table type in the hierarchical list.
- Select the **Variables** or the **Statistics** tab.

  Variables and statistics that are in the **Selected** column will be included in the output and will be reported in the order that they appear in the column.

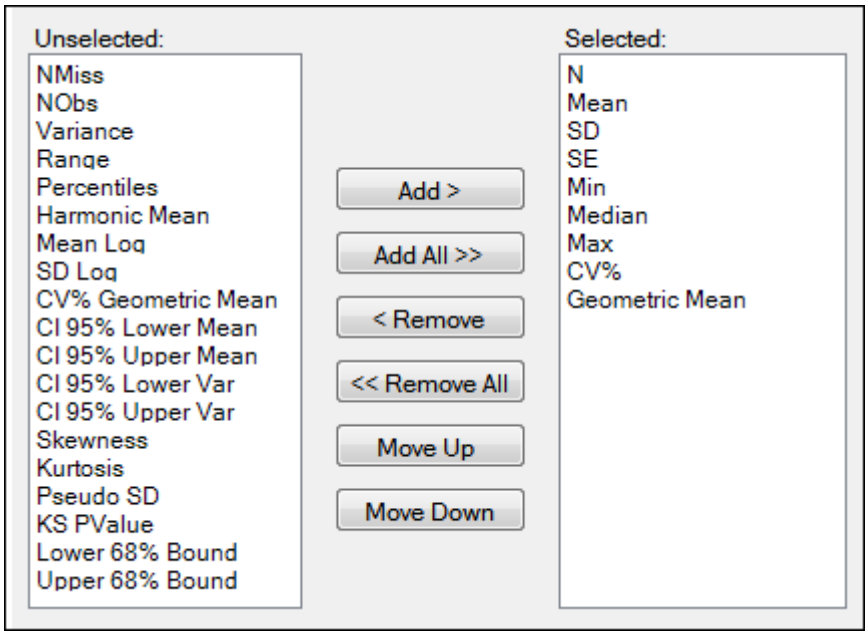


Figure 7-5. Statistics tab

The following instructions apply to both the *Variables* tab and the *Statistics* tab.

- Select an item in one of the columns.
- Click **Add** or **Remove** to move the item from one column to another.
- Click **Add All** and **Remove All** to move all variables from one column to another.
- Click **Move Up** and **Move Down** to change the position of a selected item in the list.

Intext Table Statistics tab

The *Statistics* tab for Intext PK Parameter tables contains different options than *Statistics* tabs for other tables.

- In the *Setup* tab for an Intext PK Parameter type table, select the *Statistics* tab.

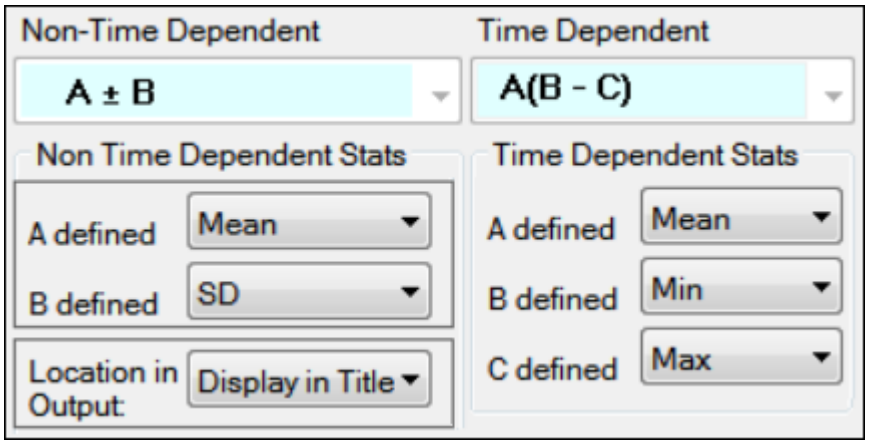


Figure 7-6. Statistics tab for intext PK parameters

- In the **Non-Time Dependent** section, select the equation to be used (currently A +/- B is the only one available).
- Identify the statistics to use in the equations from the pull-down menus.
- Choose the location for displaying the information: **Display in Title**, **Display in Footnote**, **Do not display in output**.
- In the **Time Dependent** section, select the equation to be used (currently A(B – C) is the only one available).
- Identify the statistics to use in the equations from the pull-down menus.

Standard/Normalize tab

This tab becomes available for PK Parameter tables when normalization schemes are defined (see "Stratification/Normalization tab").

- Select the **Display** option **All standard, then all normalized by ____** to list all of the standard columns first, followed by normalized columns.
- To group the columns so that the standard and normalized version of the data are together, select the **Display** option **Group together standard and normalized by ____**.
- Toggle generation of tables with and/or without normalization for each parameter by selecting/unselecting the checkboxes in the **Normalize** and **Standard** columns.

Precision tab

For each variable and statistic, the precision can be set by the number of significant digits or decimal places. Selection of the type and value of numerical precision is also done through this tab.

- In the *Setup* tab, select the *Precision* tab.

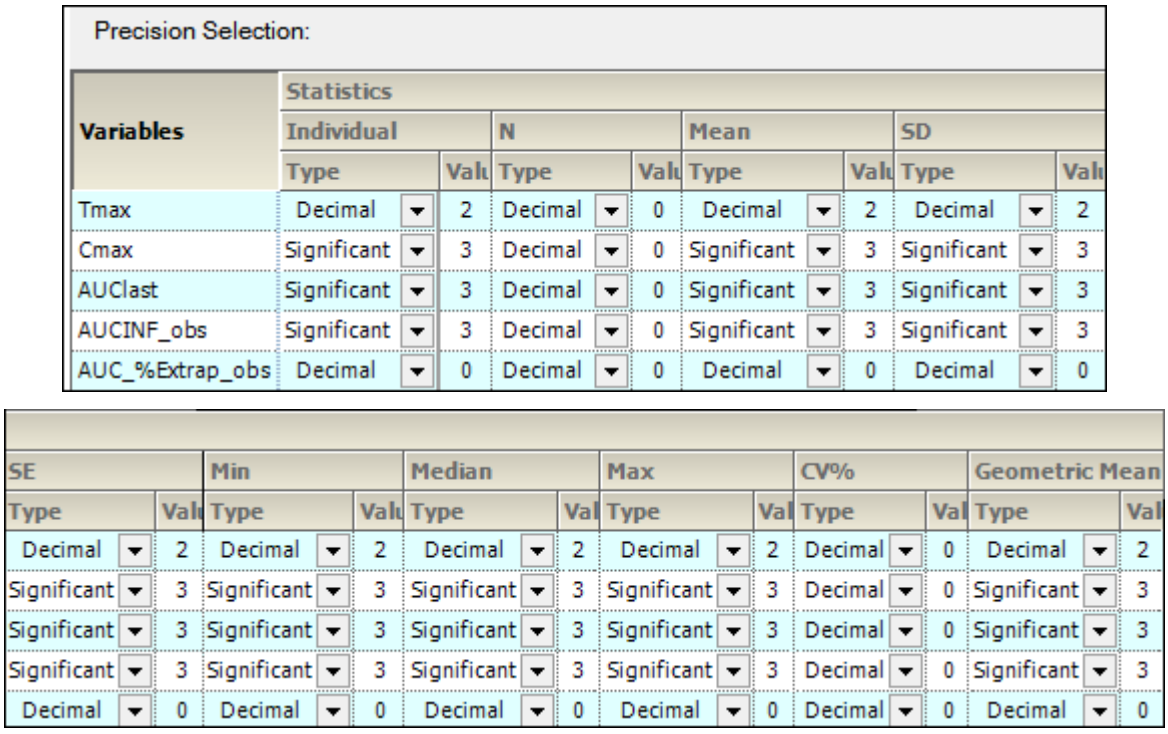


Figure 7-7. Precision tab

- In the **Type** menu for each statistic, select **Decimal** or **Significant**.
- Select a cell in the corresponding **Value** column to enter a new precision display value.

Graph panels

AutoPilot Toolkit allows the user to apply different attributes to each graph. These attributes include Y-axis scaling, summary value display, error bar display, and regression line options. Selection of PK parameters to include in the graphs is also available.

The following sections describe the graph options available for each graph type:

"Main Graphs panel"
"Time Concentration panel"
"Comparison Categorical Standard panel"
"Comparison Categorical Box & Whisker panel"
"Continuous Demographic panel"

Main Graphs panel

- In the *Setup* tab, select **Graphs** in the hierarchical list.

  Parameters that are in the **Selected** column will be included in the output.

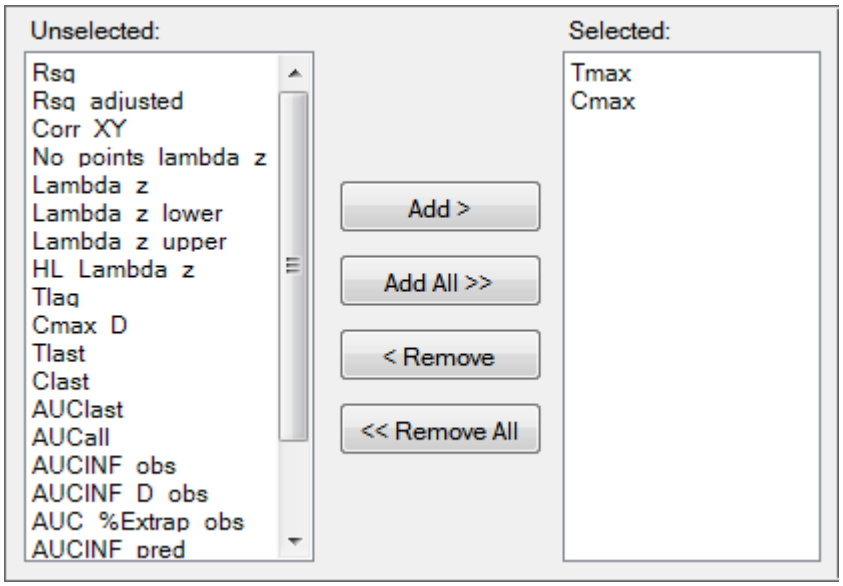


Figure 7-8. Graphs panel

- Select an item in one of the columns.
- Click **Add** or **Remove** to move the item from one column to another.
- Click **Add All** and **Remove All** to move all variables from one column to another.

Time Concentration panel

Time Concentration graphs are available for Absolute Bioavailability and Accumulation Comparisons, but not for Renal Clearance Comparisons.

- In the *Setup* tab, select **Time Concentration** in the hierarchical list.

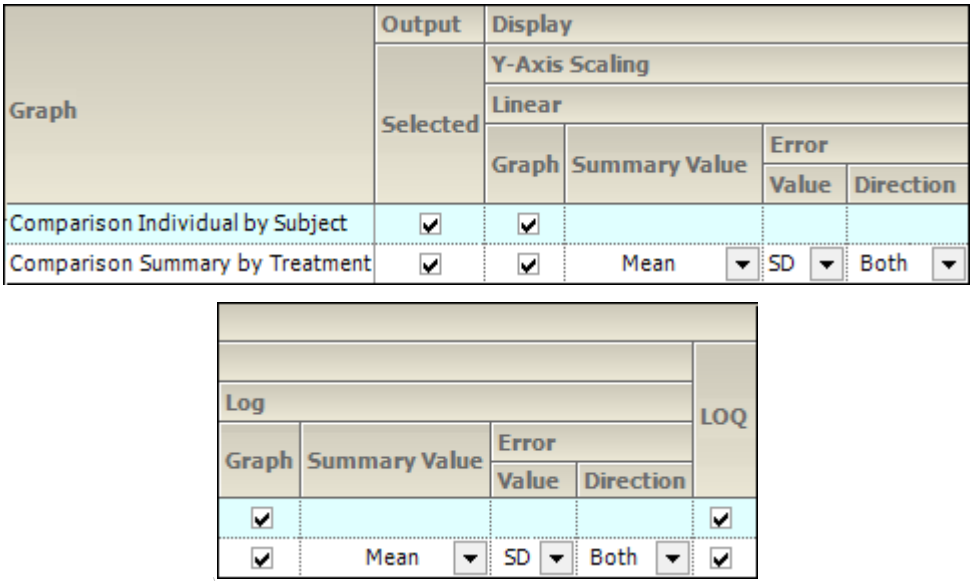


Figure 7-9. Time Concentration panel

There are two types of Table Concentration graphs available:

- **Comparison Individual by Subject**: A separate graph is generated for each subject involved in the study. Each line on the graph represents a separate treatment.
- **Comparison Summary By Treatment**: A single graph is generated. Each line represents a separate treatment.

The panel displays a table of options for the Time Concentration graphs, grouped into several categories and sub-categories:

Output

- Check/Uncheck the **Selected** box to include/exclude a type of Time Concentration graph in the output.

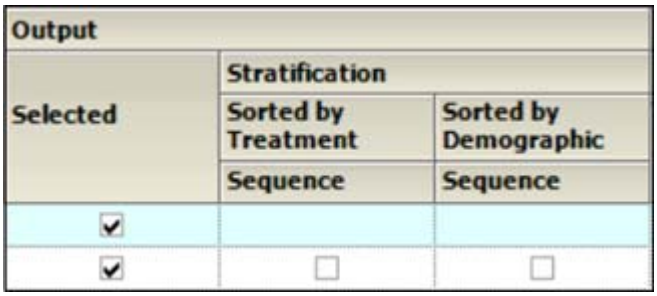


Figure 7-10. Output section of Time Concentration panel

- When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables in a **Summary by Treatment** graph type, **Sorted by Treatment** or **Sorted by Demographic**. Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.

Display

- Graphs can be generated with a **Linear** or **Log Y-Axis Scaling**. The following options are available for both types of Y-axis scaling:
  - In the **Graph** section, check the box to use the Y-axis scaling method. Unselect to not scale the Y-axis. Selecting this checkbox under both the **Linear** and **Log** sections will generate two graphs, one using each method.
  - For **Summary by Treatment** type, select the **Summary Value** to use for plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**.
  - Specify the **Value** (**SD**, **SE**, **Variance**, **Min and Max**, **None**, **68% Range**) and **Direction** (**Both**, **Down**, **Up**) of error bars to display on **Summary by Treatment** graphs.
- **LOQ**: Select the checkbox to include a regression line in the graph.

Comparison Categorical Standard panel

- In the *Setup* tab, select **Comparison Categorical Standard** in the hierarchical list.

PK Parameter (Client Name)	Output	Display				
	Selecte	Y-Axis Scaling (Linear)			Treatment Display	
		Summary Val	Error			
			Value	Direction	All in same	Separate
Lambda_z	☑	Median	Min and Max	Both	☑	☐
HL_Lambda_z	☑	Median	Min and Max	Both	☑	☐
Tmax	☑	Median	Min and Max	Both	☑	☐

Figure 7-11. Categorical Standard panel

The PK Parameters available in the study are listed as rows in the table.

The panel displays a table of options for the Comparison Categorical Standard graphs, grouped into several categories and sub-categories:

Output

- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes have also been defined (see “Stratification/Normalization tab”), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

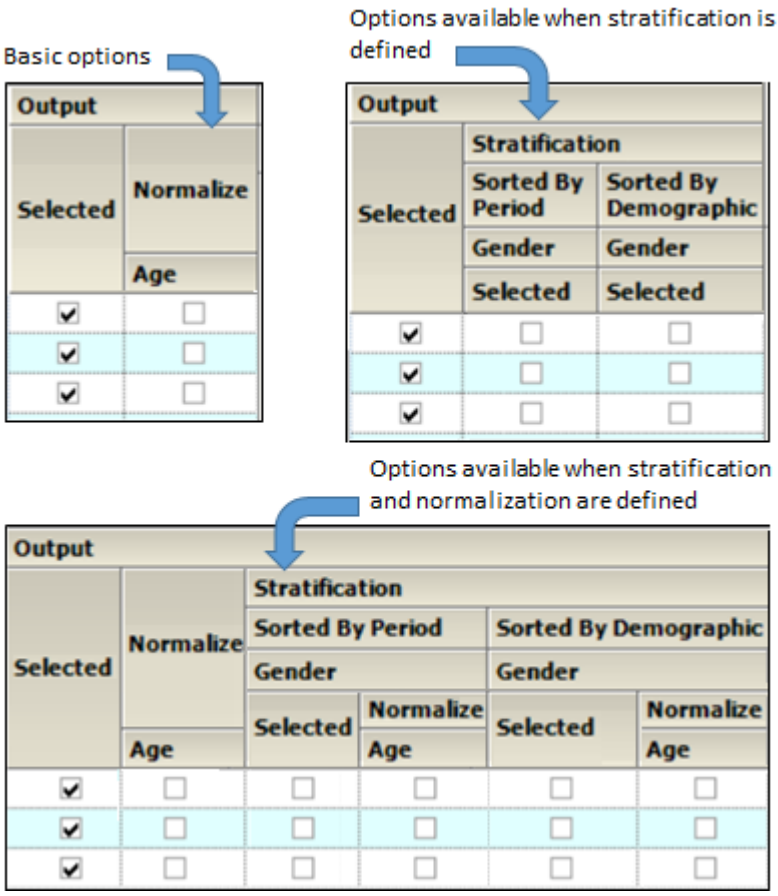


Figure 7-12. Output section of Categorical Standard panel

- **Stratification**: When **Stratification** schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by [Treatment]**) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes have also been defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Display

- Graphs can be generated using a **Linear Y-Axis Scaling**. The following options are available:
  - Select the statistic to use as the **Summary Value** when plotting the summary line: **Mean**, **Median**, **Geometric Mean**, **Harmonic Mean**.
  - Specify the **Value** (**Min and Max**, **Pseudo SD**, **SD**, **SE**, **Variance**, **68% Range**) of the **Error** bars. The only option available for **Direction** is **Both**.
  - For **Treatment Display**, check the **All in same graph** box to generate a graph that includes data from all treatments. Select the **Separate per graph** checkbox to generate a separate graph for each treatment.

Comparison Categorical Box & Whisker panel

Note: There must be at least three subjects in the study to create Box & Whisker graphs.

- In the *Setup* tab, select **Comparison Categorical Box & Whisker** in the hierarchical list.

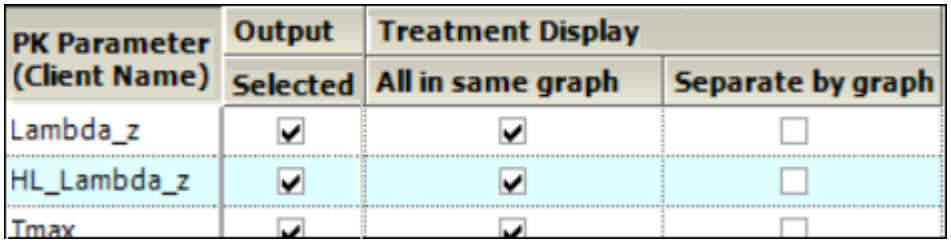


Figure 7-13. Categorical Box and Whisker panel

The PK Parameters available in the study are listed as rows in the table.

Output

- Check/Uncheck the **Selected** box to include/exclude a parameter when generating graphs.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

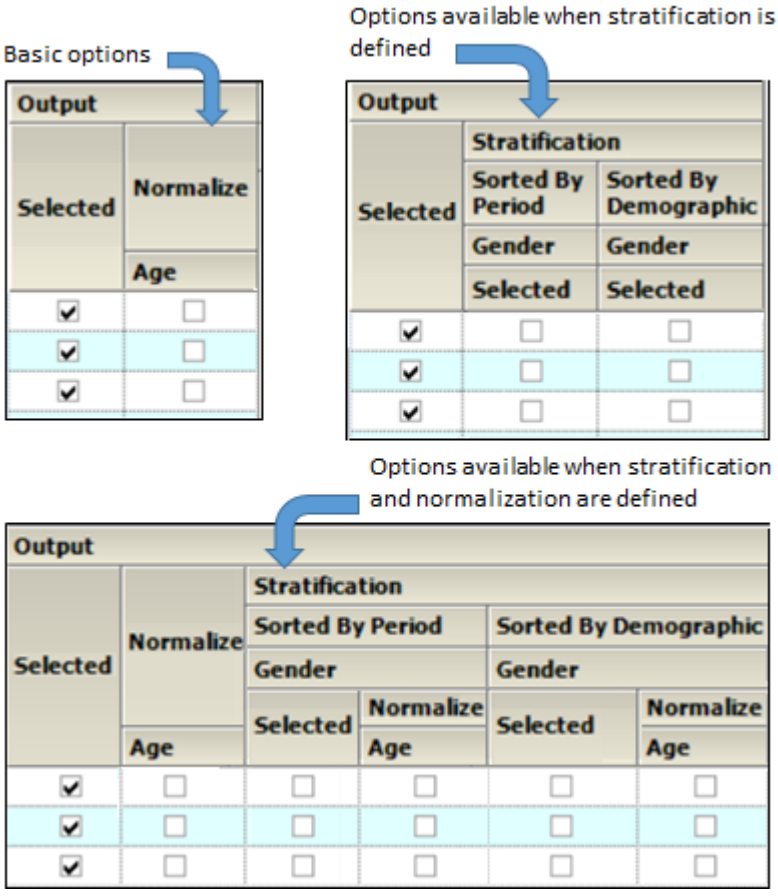


Figure 7-14. Output section of Categorical Box and Whisker panel

- **Stratification**: When stratification schemes have been defined (see "Stratification/Normalization tab"), they can be used either as X-axis variables (**Sorted by [Treatment]**) or new sort variables

(**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.

- If normalization schemes have also been defined, the stratified graphs can be normalized using the **Normalize** subcategory checkboxes.
- Use the **Selected** checkboxes to produce stratified graphs that are not normalized.

Treatment Display

- Check the **All in same graph** checkbox to generate a graph that includes data from all treatments.
- Check the **Separate per graph** checkbox to generate a separate graph for each treatment.

Continuous Demographic panel

- In the *Setup* tab, select **Comparison Continuous Demographic** in the hierarchical list.

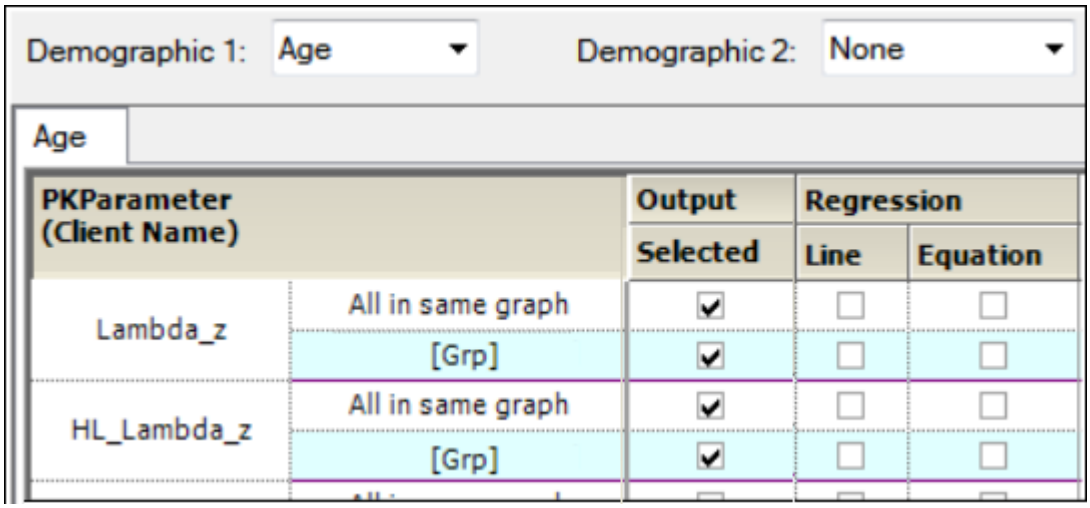


Figure 7-15. Setup tab for Continuous Demographic graphs

The panel displays a section for selecting up to two demographic(s) to use for the X-axis (**Demographic 1** and **Demographic 2**).

When a second demographic type is selected, a second tab is created in the Comparison Continuous Demographic panel.

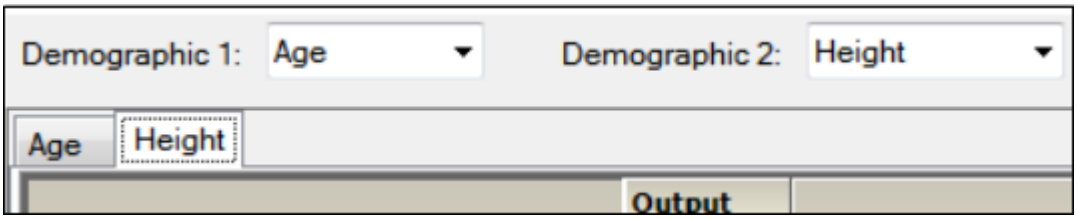


Figure 7-16. Each demographic type has its own tab in the Continuous Demographic panel

The PK Parameters available in the study are listed as rows in the table. Each parameter will have two sub-rows:

- **All in Same Graph**: Sort all graphs by analyte.
- **[Grp]**: Group all graphs by analyte.

The lower part of the panel contains a table of options for the Comparison Continuous Demographic graphs, grouped into several categories and sub-categories:

Output

- Check the **Selected** box to create graphs for the parameter that are sorted by analyte and/or to create graphs for the parameter that are grouped by analyte. Unselect a checkbox to not generate the graph(s) for a parameter.
  - If normalization schemes are also defined (see "Stratification/Normalization tab"), check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

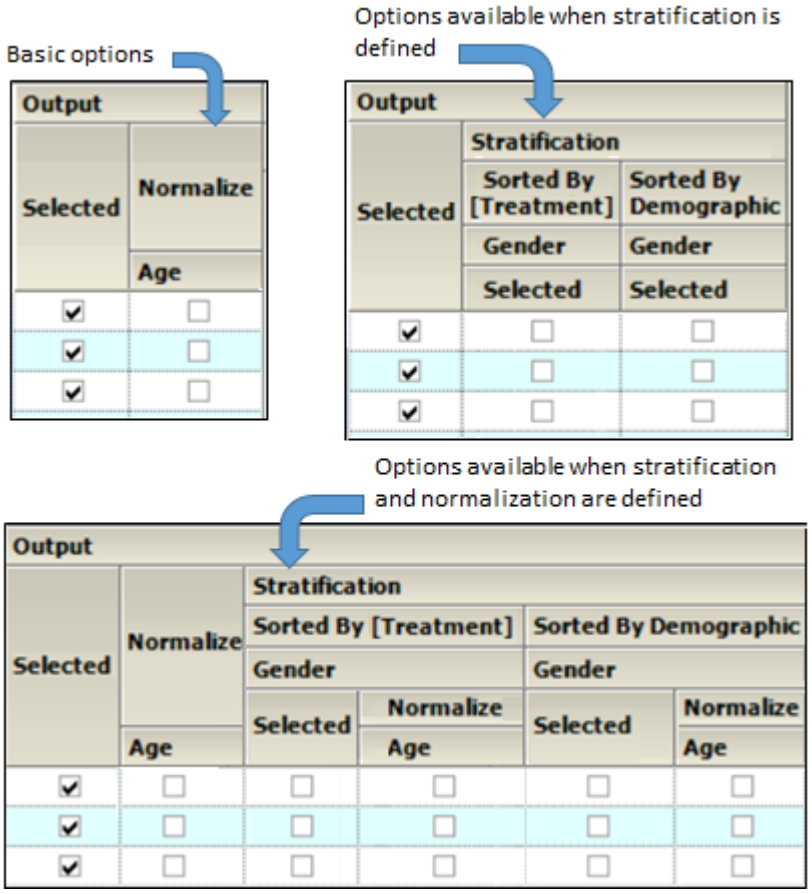


Figure 7-17. Output section of Continuous Demographic panel

- When **Stratification** schemes have been defined (see Time Scale Algorithm tab), they can be used either as X-axis variables (**Sorted by [Treatment]**) or new sort variables (**Sorted by Demographic**). Use the checkboxes to indicate the sorting mechanism(s) for each stratification scheme.
  - If normalization schemes have also been defined, check/uncheck the **Normalize** subcategory boxes to normalize/not normalize the graphs.

Regression

- Check the **Line** checkbox to include a regression line in the graph.
- Check the **Equation** checkbox to display the regression equation in the graph.

General tab

The *General* tab allows users to select the study design type, configuration settings, and whether or not to try to complete a comparison run if an error occurs.

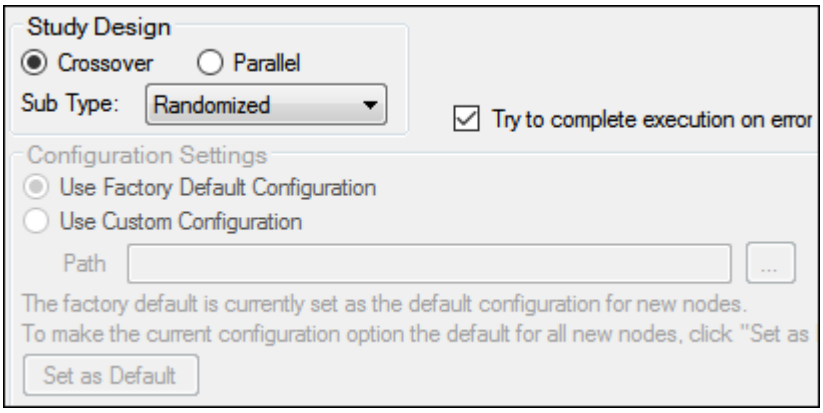


Figure 7-18. General tab in the Properties panel

The study design options in the *General* tab depend on the configuration settings. If the settings are changed, then the options could be different from the options listed below.

Note: The configuration settings must be specified before a dataset is mapped to the AP Comparison object.

Study Design

- Specify that the study design type is either **Crossover** or **Parallel**.
- For a **Crossover** study design, select the study **SubType** (**Randomized**, **Non-Randomized**, or **Replicated**).
- By default, AutoPilot Toolkit tries to complete a comparison run even if errors are encountered and not all selected output can be created.
- Unselect the **Try to complete execution on error** checkbox to stop a comparison run if any errors are encountered.

Configuration Settings

- Indicate the configuration settings to use. **Use Factory Default Configuration** is selected by default.
- To use customized settings, select **Use Custom Configuration** and click the **Change Directory [...]** button to select the directory where the custom configuration settings file is located.
- The customized settings can be defined as the default configuration settings to use for new projects by clicking **Set as Default**.

Stratification/Normalization tab

The **Stratification** and **Normalization** options allow users to create additional table and/or graph output.

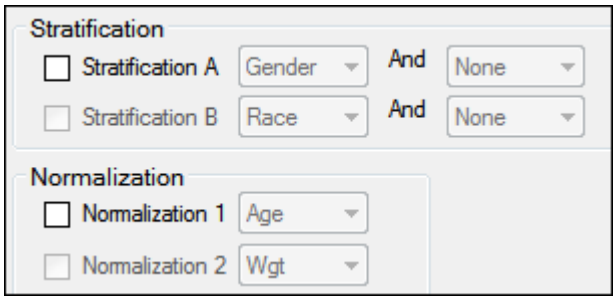


Figure 7-19. Stratification/Normalization tab in the Properties panel

Stratification

Results can be stratified (i.e., layered) using discrete demographic variables. Each stratification level can use one or two discrete demographic variables. If two variables are specified, they are associated using the logical operator AND.

Note: At least one stratified output type must be selected if stratification is enabled or the Comparison project will not pass verification.

- To define the first level of stratification, select the **Stratification A** checkbox and choose the demographic variable(s) from the pull-down menu(s).
- To define a second level of stratification, select the **Stratification B** checkbox and choose the variable(s) from the pull-down menu(s).

If stratifications are selected, the comparison run creates one table per stratum for the time and concentration, PK parameter, and intext PK parameter tables, using the stratification scheme as an additional group variable.

If graphs include stratification, the stratification schemes are used either as X-axis variables (sorted by treatment) or new sort variables (sorted by demographics), depending on the AutoPilot Toolkit Admin settings.

Normalization

Use the **Normalization** section to define normalization schemes to apply to the results. Each normalization scheme must use a different continuous demographic variable.

- To define the first level of normalization, select the **Normalization 1** checkbox and choose a demographic variable from the pull-down menu.
- To define a second level of normalization, select the **Normalization 2** checkbox and choose a variable from the pull-down menu.

AutoPilot Toolkit calculates the normalized PK parameters and includes them in the results. Users can select the **PK Parameter** and **Intext PK Parameter** tables in the hierarchical list and choose which normalized parameters to display in each table. This allows PK Parameter automation tables to include both normalized and non-normalized values.

- Select the PK Parameter, Intext PK Parameter, PK Ratios, or PK Statistics table in the Tables node.
- Select the Standard/Normalize tab.
- In the **Display** menu, select how to display normalized PK parameters in the table output.
- Select the **Normalize** checkbox beside a PK parameter to include it in the table output.

For more on using the table panels, see “Table panels”.

Column headers for the normalized variables include a normalization variable and its units. For example, oral clearance normalized by weight: CL/F/Weight (L/hr/kg). If graph output is selected that includes normalization, each normalized PK parameter is displayed in a separate graph. The Y-axis labels display the normalization in the same manner as tables.

PK parameters that are excluded from normalization are listed in "PK automation parameters".

Display tabs

The *Display* tab contains four tabs that allow users to set output and display options, table and graph orientation, and the X- and Y-axes scaling for graphs.

Output Options tab
Display Options tab
Orientation tab
Time Scale Algorithm tab

Output Options tab

The *Output Options* tab allows users to define exclusions, the LOQ value, and the AUC percent extrapolation threshold value.

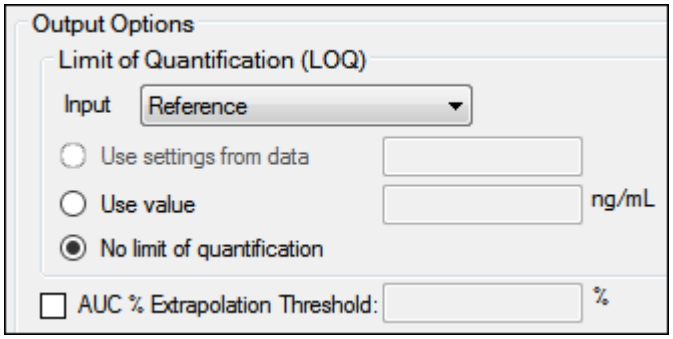


Figure 7-20. Output Options — Display tab in the Properties panel

The options for LOQ vary depending on the type of data used and the system configuration settings.

- For unstacked data, choose one of the following methods of defining the LOQ:
  - To set the LOQ value using the input data, click **Use setting from data**.
  - To enter a value, click **Use value** and type a value in the corresponding field.
  - Click **No limit of quantification** to not set an LOQ limit.

  If the input dataset contains stacked data, a different LOQ can be set for each analyte.

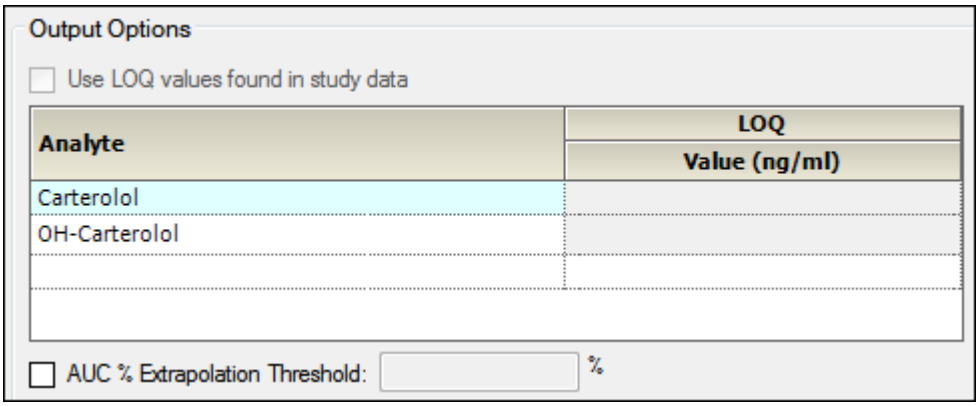


Figure 7-21. Output options for stacked data

- For stacked input data, choose one of the following to define the LOQ value:
  - Turn on the **Use LOQ values found in study data** checkbox to set the values for LOQ using the input data.
  - Enter an LOQ value for each analyte in the Value column. (The concentration units are taken from the input dataset.)
  - To not use LOQ values, turn off the **Use LOQ values found in study data** checkbox and leave the Value column entries blank.

Note: Setting the LOQ value for all analyts can significantly extend the execution time.

For more information, see “LOQ replacement”.

The following option is applicable to both stacked or unstacked input data:

- Turn on the **AUC% Extrapolated Threshold** checkbox to use the rules for handling AUC extrapolated values that exceed the specified percentage.

See “PK parameter percent-extrapolated threshold” for details.

Display Options tab

The *Display Options* tab allows users to set table and graph output display options, select the time and concentration variables in the input dataset, and choose whether or not to include data source information.

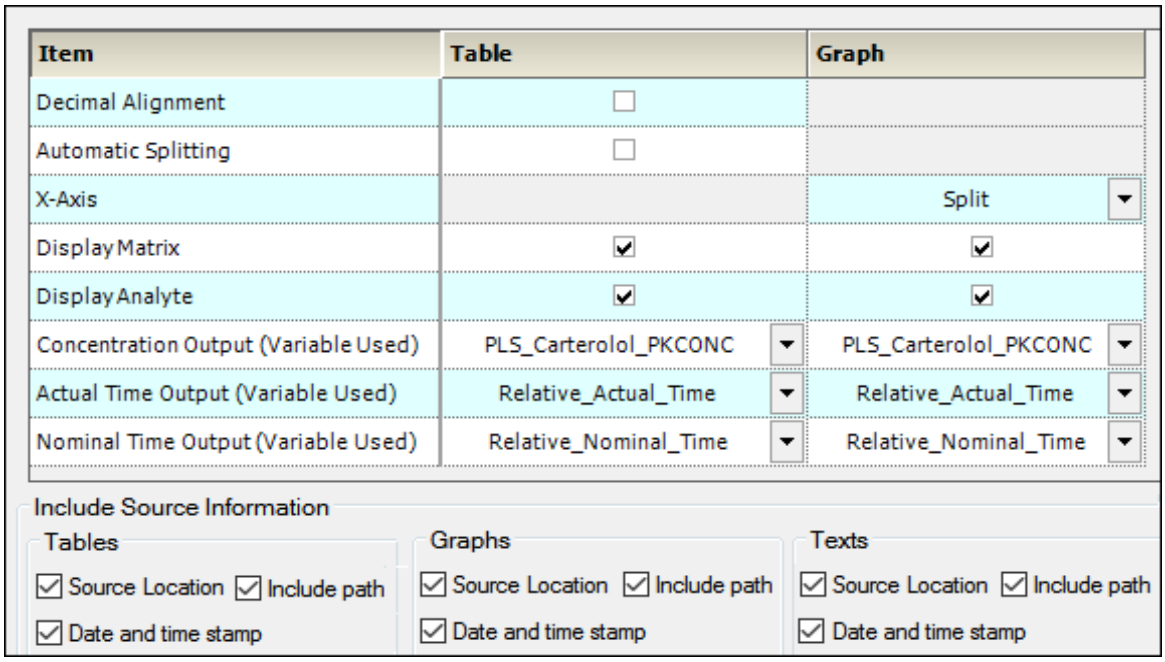


Figure 7-22. Display Options — Display tab in the Properties panel

- Turn on the **Decimal Alignment** checkbox to align all values in a given column using their decimal points. See "Table data display using decimal alignment".
- Turn on the **Automatic Splitting** checkbox to allow splitting large tables across multiple pages. See "Table business rules".
- Select from the **X-Axis** pull-down if the PK parameter graphs have a **Split** X-axis based on individual and summary values or **Offset**.
- Turn on the **Display Matrix** or **Display Analyte** checkbox to include the matrix or analyte information in the tables and/or graphs. See "Display analyte and matrix information" (tables) or "Display analyte and matrix information" (graphs).
- Select the concentration variable to use for creating time-concentration tables and graphs from the **Concentration Output (Variable Used)** pull-down menu.
- Use the **Actual** and **Nominal Time Output (Variable Used)** pull-down menus to select which data column to use for the actual and nominal times. This is set using the Admin Module. "Time Variables tab"

Orientation tab

Through the *Orientation* tab, the orientation of each output item is set. A few additional settings regarding the appearance of graphs in a Word document are available for appendices involving individual time-concentration graphs.

Item	Orientation	Paper size	Presentation order	Graphs per page
Tables				
Comparison Time Concentration	Portrait			
Comparison PK Parameter	Portrait			
Comparison Intext	Portrait			
Time Concentration Graphs				
Comparison Individual Subject	Portrait			
Comparison Summary	Portrait			
PK Parameter Graphs				
Comparison Categorical Standard	Portrait			
Comparison Categorical Box and Whisker	Portrait			
Comparison Continous Demographic	Portrait			
Appendix (Word Documents)				
Comparison Inidividual Time Concentration	Portrait	Letter	All linear then all log	1 x 1

Figure 7-23. Orientation — Display tab in the Properties panel

- In the Orientation column, select whether to position the output as a **Portrait** or in **Landscape** format from the pull-down menu for each table, graph, and appendix output.

Note: Only certain tables and graphs can be changed to Landscape. If Landscape is not supported, the Orientation setting for that table or graph defaults to Portrait and the pull-down menu is disabled.

For the **Individual Time Concentration** appendix output type, the following specifications can also be made:

- Select the Paper Size as **Letter** or **A4** from the pull-down menu.
- Indicate the order in which the graphs are to appear using the Presentation Order column pull-down menu. Options include:
  - **All linear then all log**: Display the linear graphs (sorted by subject) before the log graphs (sorted by subject).
  - **All log then all linear**: Display the log graphs (sorted by subject) before the linear graphs (sorted by subject).
  - **Per profile, linear then log**: Graphs are grouped by subject and then by analyte, with the linear graph presented before the log graph. In the output, the graphs are displayed in subject order.
  - **Per profile, log then linear**: Graphs are grouped by subject and then by analyte, with the log graph presented before the linear graph. In the output, the graphs are displayed in subject order.
- Specify the number of graphs per page using the pull-down in the Graphs Per Page column. Options range from **1x1** up to **4x4**.

Time Scale Algorithm tab

The *Time Scale Algorithm* tab is used to specify the scaling options for the axes, the lower and upper bounds for time scale ticks, the tick frequency, the tick units, and the maximum time scale on the X-axis. See “Time scale algorithm” for more information.

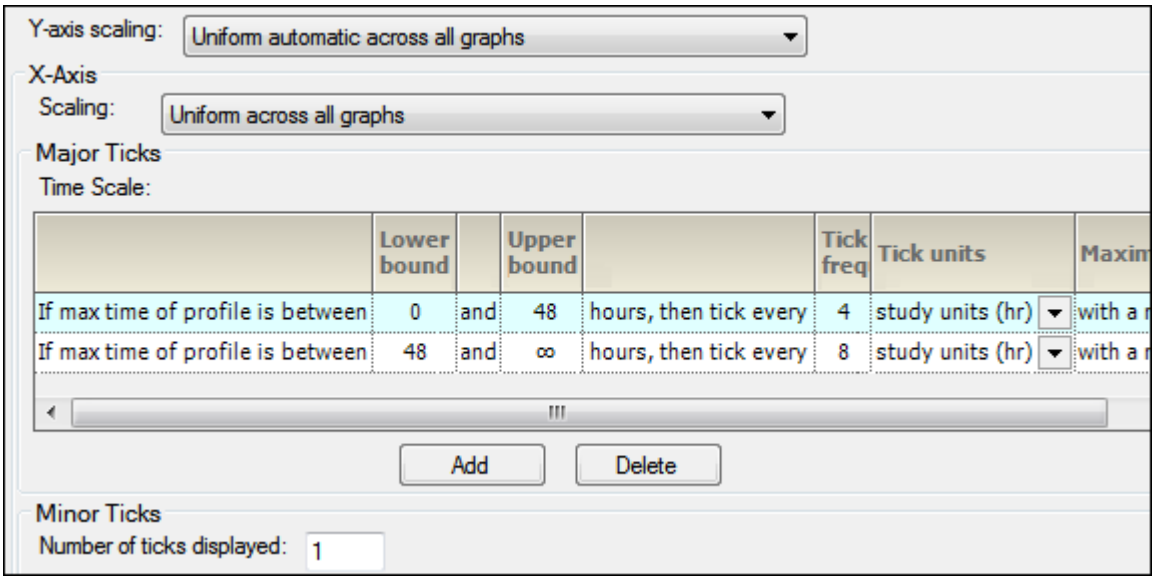


Figure 7-24. Time Scale Algorithm-Display tab in the Properties panel

- In the **Y-axis scaling** menu, choose whether to scale the Y-axis uniformly across all graphs or scale the Y-axis on a per graph basis.
- In the X-Axis area, select X-axis **Scaling** to be either uniformly across all graphs or on a graph by graph basis.

  The Major Ticks area contains a table where each row represents a separate time scale.
- Enter new values for lower and upper bounds in the **Lower bound** and **Upper bound** fields.

  Use the Tick frequency and Tick units columns together to define the frequency with which tick marks are displayed along the X-axis.
- Enter the value directly in the **Tick frequency** field and then select the units from the **Tick units** pull-down menu. (The default is **study units**, indicating that the units are derived from the study data.)
- Set new values for the time scale multiple value in the **Maximum time scale** multiple value field.
- Click **Add** in the Major Ticks area to add another time scale.

  A new row is added to the table below the row that was selected or modified last.
- To remove an added time scale, click in that row and then click **Delete**.

  A minimum of two defined time scales is required.
- In the Minor Ticks area, change the number of minor ticks displayed between the major ticks by typing a new value in the **Number of ticks displayed** field.

Ordering tab

The *Ordering* tab is used to specify how the treatment descriptions and demographic study variables are ordered in the output.

- In the Treatments tab, select a treatment in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

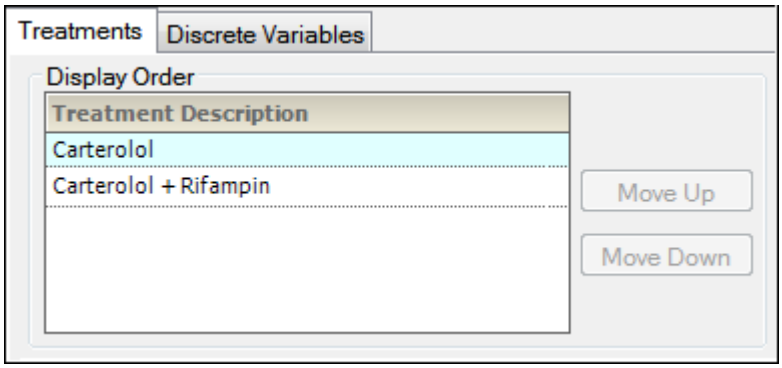


Figure 7-25. Treatments — Ordering tab in the Properties panel

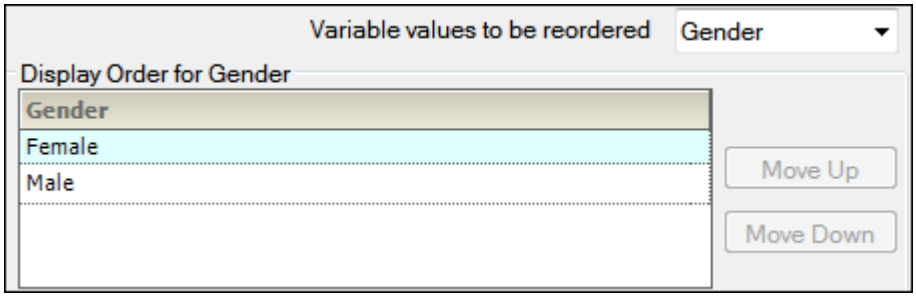


Figure 7-26. Discrete Variables — Ordering tab in the Properties panel

- In the Discrete variables tab (available for Accumulation Comparisons), use the **Variable values to be reordered** menu to select different discrete study variables.
- Select the variable in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Analytes tab

This tab is present only if an Accumulation, Absolute Bioavailability, or Renal Comparison project uses stacked datasets for reference and test inputs.

- In the **Analyte** menu, select the analyte to use in the output.

  When a stacked data PK Automation project is chosen for comparison, and an analyte comparison type is selected, users can select the analyte to be used as reference, as well as change the display order of the remaining test analytes.
- Select an analyte in the list and use the **Move Up** and **Move Down** buttons to rearrange its position in the display order.

Comparison results

Caution: Do not perform any operations on the computer while the comparison run is in progress. Doing so could cause unpredictable results; keyboard and mouse input during a comparison run might affect automated AutoPilot Toolkit operations.

After the project is run, all output is arranged in groups in the *Results* tab.

Not all output can be viewed in Phoenix. In such cases, the right side of the *Results* tab will display a message with suggestions on how to view the results. One suggestion is to open an external program and load the results by clicking **View in External Viewer**.

AutoPilot Toolkit output can be individually exported to disk or copied to Phoenix's Data folder. All results can be exported using AutoPilot File Explorer, which is located in the *Reporting* tab. For more using AutoPilot File Explorer, see "AutoPilot File Explorer".

Output File Naming Conventions

Filenames consist of a series of name parts, which are typically determined by “attributes”. Each attribute in the filename is separated by a “_” and all values within an attribute are separated by a “-”. This naming convention makes it easier to identify attribute values within a filename.

This section contains the following topics:

Filename components

Automation output are named according to the following schema:

```
[Ex_]<BaseFilename>
[_Norm-<Var>]
[_Trt#]
[_Analyte]
[_Per#]
[_Day#]
[{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<varA>[-<VarB>]}]
```

The following lists the components of a filename.

[Ex_]<BaseFilename>: The base filename is the main part of the filename that indicates the type of table or graph being created. [Ex_] indicate that exclusions were defined and used in the creation of the table/graph in the file.

Trt: Treatment

Per: Period

Day: Day

Analyte: Client name of analyte

Strat-<Var>: Stratification by the values indicated by client names for VarA and VarB.

Demog: Demographic

Norm-: Normalization

Lin/Log: Linear or Logarithmic

_by-Dose: Continuous dose

_vs-Cont: Continuous demographics

Comp_: Comparison

[]: Denotes optional values based on GUI choice, data in study, or output object type

#: Sequence number generated internally by AutoPilot Toolkit and will be the same for tables and graphs

{}: Indicates that the contained values are a part of the filename based on a choice made in the GUI of study type. Values within the brackets are separated by “,”.

< >: Indicates that the indicated value will be replaced with the variable names created by the client.

Several output options are not associated with attributes but do affect the filename. These options are described below.

Split tables: Users have an option to create multiple tables from one single table in order to create a better fit on the page. Split tables will have an additional _1_1 or _1_2 appended to the filename to denote which part of the table the file contains.

Profile exclusions: These files are created in addition to the regular tables and graphs only if profiles have been excluded. The filenames for both graphs and tables will begin with "EX_"

Box and whisker plots: Box and whisker plot file names all begin with "Box_".

PK table files

Demographic

Format: [Ex_]Demographics[_Trt#][_Analyte#]
Example: Demographics_Trt1.xls

Actual Times

Format: [Ex_]Actual_Times_Trt#[_Analyte#][_Per#][_Day#][_Strat-<VarA>#[-<VarB>#]]
Example: Actual_Times_Trt1_Per1_Day1_Strat-Gender1-Race2_1.xls

Actual Times Deviation

Format: [Ex_]Actual_Times_Deviation_Trt#[_Analyte#][_Per#][_Day#][_Strat-<VarA>#[-<VarB>#]]
Example: Actual_Times_Deviation_Trt1_Per1_Day1_Strat-Gender1-Race2_1.xls

Concentration

Format: [Ex_]Concentration_Trt#[_Analyte#][_Per#][_Day#][_Strat-<VarA>#[-<VarB>#]]
Example: Concentration_Trt1_Per1_Day1_Strat-Gender1-Race2_1.xls

Cumulative AUC

Format: [Ex_]Cumulative_AUC_Trt#[_Analyte#][_Per#][_Day#][_Strat-<VarA>#[-<VarB>#]]
Example: Cumulative_Trt1_Per1_Day1_Strat-Gender1-Race2.xls

PK Parameter

Format: [Ex_]PK_Parameter_{A-F}_Trt#[_Analyte#][_Per#][_Day#][_Strat-<VarA>#[-<VarB>#]]
Example: PK_Parameter_A_Trt1_Per1_Day1_Strat-Gender1-Race2.xls

Intext

Format: [Ex_]Intext_PK_Parameter_{I-II}_[Analyte#].xls
Example: Intext_PK_Parameter_I_Analyte1.xls

PK graph files

Concentration by Subject

Format:
[Ex_]{Conc_by_Subject,Amount_Excreted_by_Subject,Cumulative_Amount_Excreted_by_Subject,Percent_Dose_Remaining_by_Subject}#[_Analyte#][_Per#][_Day#]_{Lin,Log}
Example: Conc_by_Subject1_Analyte1_Lin.jnb

Concentration by Treatment

Format: [Ex_]{Conc,Amount_Excreted,Cumulative_Amount_Excreted,Percent_Dose_Remaining}[_Trt#][_Analyte#][_Per#][_Day#][_GroupBy-Strat-<VarA>[-<VarB>]]_{Lin,Log}
Example: Conc_Trt1_GroupBy-Strat-Gender-Smoke_Lin.jnb

Summary Concentration

Format: [Ex_]{Summary_Conc,Summary_Amount_Excreted,Summary_Cumulative_Amount_Excreted,Summary_Excretion_Rate,Summary_Percent_Dose_Remaining}[_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]_{Lin,Log}
Example: Summary_Conc_GroupBy-Strat-Gender-Smoke_Lin.jnb

Categorical Standard

Format: [Ex_][PKParam][_Norm-<Var>][_Trt#][_Analyte#][_Per#][_Day#][{_Strat<VarA>#[-<VarB>#], _GroupBy-Strat<VarA>[-<VarB>]}]
Example: Cmax_Trt1_GroupBy-Strat-Gender-Smoke.jnb

Categorical Box and Whisker

Format: [Ex_]Box_[PKParam][_Norm-<Var>][_Trt#][_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]
Example: Box_Cmax_Trt1_GroupBy-Strat-Gender-Smoke.jnb

Continuous Dose Standard

Format: [Ex_][PKParam][_Norm-<Var>][_Analyte#][_Per#][_Day#]_by-Dose
Example: Cmax_Analyte1_by-Dose.jnb

Continuous Dose Box and Whisker[a]

Format: [Ex_]Box_[PKParam][_Norm-<Var>][_Analyte#][_Per#][_Day#]_by-Dose
Example: Box_Cmax_Analyte1_by-Dose.jnb

Continuous Demographic

Format: [Ex_][PKParam][_Norm-<Var>][_Trt#][_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]_vs-Cont-<IndependentVar>
Example: Cmax_Trt1_GroupBy-Strat-Gender-Smoke_vs-Cont-Age.jnb

[a]Grouped by Analyte and sorted by Gender graphs and Grouped by Analyte and Gender graphs are not possible because SigmaPlot does not allow multiple boxes for one x value in box and whisker plots.

PK Comparison graph and table files

Comparison tables and graphs follow a similar format to that previously described. All comparison tables and graphs begin with “Comp_”.

PK comparison tables

Concentration

Format: Comp_<BaseFileName>[_Trt#][_Per#][_Day#][_Strat<VarA>#[-<VarB>#]]
Example: Comparison_Concentration_Ratios_Trt1.xls

Intext

Format: Comp_<BaseFileName>[_Trt#][_Strat<VarA>#[-<VarB>#]]
Example: Comparison_Intext_PK_ParameterI_Analyte.xls

PK Parameter

Format: Comp_<BaseFileName>[_Trt#][_Per#][_Day#][_Strat<VarA>#[-<VarB>#]]
Example: Comparison_PK_ParameterA_Ratios_Analyte.xls

PK comparison graphs

Concentration by Subject

Format:
Comp_{Conc_by_Subject,Amount_Excreted_by_Subject,Cumulative_Amount_Excreted_by_Subject,Percent_Dose_Remaining_by_Subject}#[_Analyte#][_Per#][_Day#]_{Lin,Log}
Example: Comp_Conc_by_Subject1_Analyte1_Lin.jnb

Summary Concentration

Format: Comp_{Summary_Conc,Summary_Amount_Excreted,Summary_Cumulative_Amount_-Excreted, Summary_Excretion_Rate,Summary_Percent_Dose_Remaining}[_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]_{Lin,Log}
Example: Comp_Summary_Conc_GroupBy-Strat-Gender-Smoke_Lin.jnb

Categorical Standard

Format: Comp[PKParam][_Norm-<Var>][_Trt#][_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]
Example: Comp_Cmax_Trt1_GroupBy-Strat-Gender-Smoke.jnb

Categorical Box and Whisker

Format: Comp_Box_[PKParam][_Norm-<Var>][_Trt#][_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]
Example: Comp_Box_Cmax_Trt1_GroupBy-Strat-Gender-Smoke.jnb

Continuous Demographic

Format: Comp_[PKParam][_Norm-<Var>][_Trt#][_Analyte#][_Per#][_Day#][{_Strat-<VarA>#[-<VarB>#], _GroupBy-Strat-<VarA>[-<VarB>]}]_vs-Cont-<IndependentVar>
Example: Comp_Cmax_Trt1_GroupBy-Strat-Gender-Smoke_vs-Cont-Age.jnb

Output

AutoPilot Toolkit produces four types of output:

Phoenix WinNonlin files

Tables as Microsoft Excel files

Graphs as SigmaPlot files and Windows Metafile graphics

Text, which is displayed in Microsoft Word documents.

Additionally, the Phoenix output includes the files produced by an NCA model during model fitting. Refer to the "Administration Module" section to learn how to configure which of the available files are produced.

The available output for both automation and comparison are described in the following sections:

Table output

- PK Automation tables
- PK Comparison tables

Graph output

- PK Automation graphs
- PK Comparison graphs

Appendix output

- PK Automation appendix output
- PK Comparison appendix output

Note: Subject IDs with many digits (e.g., 100010901) are displayed in exponential format in the output tables.

Note: On Chinese and Japanese (Kanji) operating systems, the multiplication symbol is displayed as an question mark in all output generated from automation and comparison objects

Note: When "mu" or "u" is used for variable units or in treatment descriptions, it is not replaced by the Greek symbol (μ) in the generated tables.

Table output

Table output can sometimes be truncated when displayed in Excel. If this happens, drag the right border of the column to resize it.

- PK Automation tables
- PK Comparison tables

PK Automation tables

Depending on the settings in the Admin Module, AutoPilot Toolkit automation projects can create combinations of the tables listed below. The table following the list summarizes the tables available for each combination of study design and dosing.

Note that for all tables containing summary statistics, the values shown in the output table are not used to calculate summary statistics. Instead, the raw values from the NCA model are used for these calculations.

Table/file names marked with an asterisk have example output tables located in "Automation Output Examples" and the associated Phoenix Table Template for each is shown in square brackets.

*__Demographics__ [Table 3]

Subject baseline demographics (age, weight) values for individuals with summary statistics sorted by treatment. Crossover study designs create one table with all subjects included. Parallel study designs create a unique table per treatment.

*__Actual_Times__ [Table 6]

Actual sample times for individuals with summary statistics sorted by treatment.

*__Trough_Actual_Times_Trt__ [Table 6]

Actual sample times (Trough only) for individuals with summary statistics sorted by treatment.

*__Actual_Times_Dev__ [Table 6]

Actual sample time deviations (difference of actual time and nominal time) for individuals sorted by treatment.

*__Concentration__ [Table 6]

Concentration values for individuals with summary statistics sorted by treatment.

*__Concentration_Strat-<Var>__ [Table 6]

Concentration values for individuals with summary statistics sorted by treatment along with user-specified stratification variable.

*__Trough_Concentration_Trt__ [Table 3]

Concentration (Trough only) values for individuals with summary statistics sorted by treatment.

*__Trough_Concentration_Strat-<Var>_Trt__ [Table 3]

Concentration (Trough only) values for individuals with summary statistics sorted by treatment along with user-specified stratification variable.

*__Urine_ Amount__[a] [Table 6]

Urine amount excreted over discrete collection intervals, or over the midpoints of discrete collection intervals, for individuals with summary statistics sorted by treatment.

__Urine_Amount_Strat-<Var>__[a] [Table 6]

Urine amount excreted over discrete collection intervals of summary statistics sorted by treatment along with stratification variable selected in the interface.

*__Urine_Cumul_Amount__[a] [Table 6]

Urine amount excreted over cumulative collection intervals for individuals with summary statistics sorted by treatment.

*__Urine_Cumul_Amount_Strat-<Var>__[a] [Table 6]

Urine amount excreted over cumulative collection intervals for summary statistics sorted by treatment along with user-specified stratification variable.

*__Urine_Actual_Times__ [Table 6]

Actual time intervals for urine collection. Derived from actual time/nominal time.

*__Lambda_Z__ [Table 3]

Individual values for selected regression fits by treatment with summary statistics. If Phoenix cannot create a regression line (for instance, when concentration increases over time), AutoPilot Toolkit cannot generate any table based on regression values like Lambda_Z. To force a regression line, set the start and stop times in Phoenix larger than t_{last}.

*__Cumul_AUC__ [Table 6]

Individual AUC values by RNT by treatment with summary statistics.

*__PK_Parameter_{a-z}__[b] [Table 3]

PK parameters values for individuals with summary statistics sorted by treatment. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications).

*__PK_Parameter_{a-z}_Strat-<Var>__[b] [Table 3]

PK parameters summary statistics sorted by treatment along with stratification variable selected in the interface. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications).

__Urine_PK_Parameter__[b] [Table 3]

Urine PK parameters values for individuals with summary statistics sorted by treatment. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications).

__Urine_PK_Parameter_Strat-<Var>__[b] [Table 3]

Urine PK parameters summary statistics sorted by treatment along with user-specified stratification variable. The PK parameters displayed depend upon interface selections (NCA Model selected and output specifications).

*__Intext_PK__Parameter_{a-z}__[b] [Special template]

PK parameter summary statistics values are displayed by treatment. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications). The summary term (e.g., Mean, Median, Harmonic Mean, and Geometric Mean) and error term (e.g., SD, SE, and Variance) can be selected.

*__Intext_PK_Parameter_{a-z}_Strat-<Var>__[b] [Special template]

PK parameter summary statistics values are displayed by treatment along with user-specified stratification variable. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications). The summary term (e.g., Mean, Median, Harmonic Mean, and Geometric Mean) and error term (e.g., SD, SE, and Variance) can be selected.

__Urine_Intext_PK_Parameter_Analyte__[b] [Special template]

Urine PK parameter summary statistics values are displayed by treatment. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications). The summary term (e.g., Mean, Median, Harmonic Mean, and Geometric Mean) and error term (e.g., SD, SE, and Variance) can be selected.

__Urine_Intext_PK_Parameter_Strat-<Var>__[b] [Special template]

Urine PK parameter summary statistics values are displayed by treatment along with user-specified stratification variable. The PK parameters displayed depend upon interface selections (NCA model selected and output specifications). The summary term (e.g., Mean, Median, Harmonic Mean, and Geometric Mean) and error term (e.g., SD, SE, and Variance) can be selected.

***PK_Ratios** [Table 3]

PK parameter ratio values for individuals with summary statistics sorted by a pair-wise treatment comparison. The table is only produced for a Crossover study type and with interface selections for PK Ratios and Reference.

Urine_PK_Ratios [Table 3]

Urine PK parameter ratio values for individuals with summary statistics sorted by a pair-wise treatment comparison. The table is only produced for a Crossover study type and with interface selections for PK Ratios and Reference.

***PK_Stats** (Randomized Crossover, Non-Randomized Crossover, Parallel) [Special template]

Inferential statistics on user-specified subset of PK parameters. Tables are only produced when selecting Calculate Inferential Statistics and a Reference.

Urine_PK_Stats (Randomized Crossover, Non-Randomized Crossover, Parallel) [Special template]

Inferential statistics on a subset of Urine PK parameters are displayed in PK parameter tables. Provides p-value information for all tables. For a Crossover study design, additional values for Statistical Power, GLSM, and Confidence intervals are displayed. Only one table is created for all study designs. Tables are only produced when selecting Calculate Inferential Statistics and a Reference.

Profile_Exclusions [Special template]

Listing of subjects with their profile data collection variables that were excluded using the Automation Exclusion feature. No summary statistics.

[a]If a cumulative amount excreted dataset includes negative time values, then both midpoint and rate are calculated using nominal times instead of the NCA Summary worksheet. This can possibly result in values being different between the tables and the NCA Summary worksheet, and the cumulative value per profile could be different compared to the amount excreted PK Parameter value in the Final Parameters worksheet.

[b]A replicated Crossover design creates two sets of table outputs consisting of set one = sorted by Treatment, 'Trt', where the values are the ratio of Period 2/Period 1 for all variables except time parameters (e.g., tmax is subtracted [Period 2 - Period 1]) and set two = sorted by period, 'Per'. By Period tables are created for all table types; tables with a footnote '1' are also created by Trt method above.

PK Automation Tables by Study Design, Dosing, and Matrix

The following table details which tables are available for each study type, dosing, and matrix. Abbreviations in the table include:

SD: Single-Dose applies to Plasma
MD: Multiple-Dose applies to Plasma
TR:Trough
UR: Urine

Filename (.xls)	**Study Design and Dosing/Matrix**							
	Crossover[a]				**Parallel**			
	SD	**MD**	**TE**	**UR**	**SD**	**MD**	**TR**	**UR**
Demographics Table								
Demographics	X	X		X	X	X		X
Time-Concentration Tables								

Filename (.xls)	Study Design and Dosing/Matrix							
	Crossover[a]				Parallel			
	SD	MD	TE	UR	SD	MD	TR	UR
Actual_Times	X	X			X	X		
Trough_Actual_Times_Trt			X				X	
Actual_Times_Dev	X	X			X	X		
Concentration	X	X			X	X		
Concentration_Strat_-<Var>[b]	X	X			X	X		
Trough_Concentration_Trt			X				X	
Trough_Concentration_Strat-<Var>_Trt[b]			X				X	
Urine_Amount				X				X
Urine_Amount_Strat-<Var>[b]				X				X
Urine_Cumul_Amount				X				X
Urine_Cumul_Amount_-<Var>[b]				X				X
PK Parameter Tables								
Cumul_AUC	X	X			X	X		
Lambda_Z	X	X			X	X		
PK_Parameter_A (applies to all six tables, A–F)	X	X			X	X		
PK_Parameter_A_Strat_-<Var>[b](applies to all six tables, A–F)	X	X			X	X		
Urine_PK_Parameter				X				X
Urine_PK_Parameter_Strat-<Var>[b]				X				X
Intext Table								
Intext_PK_Parameter_I (applies to both tables, I–II)	X	X			X	X		
Intext_PK_Parameter_I_Strat-<Var>[b] (applies to both tables, I–II)	X	X			X	X		
Urine_Intext_PK_Parameter				X				X
Urine_Intext_PK_Parameter_Strat-<Var>[b]				X				X
PK_Stats Tables[c]								
PK_Ratios[d]	X	X						
Urine_PK_Ratios[c]				X				X
PK_Stats[e] specific to study design type, e.g., PK Stats (Randomized Crossover)	X	X			X	X		
Urine_PK_Stats[d] specific to study design type, e.g., PK Stats (Randomized Crossover)				X				X
Other Tables								

Filename (.xls)	Study Design and Dosing/Matrix							
	Crossover[a]				Parallel			
	SD	MD	TE	UR	SD	MD	TR	UR
Profile Exclusions[f]	X	X	X	X	X	X	X	X

a. A randomized and non-randomized Crossover design creates output sorted by Treatment (e.g., Trt) only. A replicated Crossover design results in two sets of table output, with the first set sorted by Treatment, where the values are the ratio of Period 2/Period 1, and the second set sorted by period.

b. [strat] is replaced by the name of the stratification variable, if any.

c. When a large number of PK parameters are selected, the output can be incorrect and include the text string "CF ("convergence failure")" in the table.

d. User must select the option: Calculate PK Parameter Ratios.

e. User must select the option: Calculate Inferential Statistics.

f. Created only if using the Automation Exclusion functionality.

PK Comparison tables

For all comparison types that include PK parameters (excluding the Analyte types of Plasma and Urine), the PK parameters that were used in the automation runs in PK Parameter A–F tables and the Intext table become the master list of available PK parameters that can be used in a Comparison project.

For the Analyte comparison types, the list of available PK parameters for the comparison run also come from the PK Parameter A–F and Intext tables, but are only the intersection of common parameters used in the automation runs.

Depending on the AutoPilot Toolkit Admin settings, PK Comparison projects can output combinations of the tables listed in the following table. The second table lists tables available for each comparison type.

Table/file names marked with an asterisk (*) have example output tables located in "Comparison Output Examples" and the associated Phoenix Table Template for each is shown in square brackets.

***Comparison_Concentration_Ratios** [Table 6]

Concentration ratio values for individuals with summary statistics. One table per treatment or period and day (if multiple dose) with the ratios based on analyte (parent vs. metabolite). Limited to Analyte-Plasma comparisons of automation runs using NCA models 200–202.

Comparison_Trough_Concentration_Ratios [Table6]

Trough concentration ratio values for individuals with summary statistics. One table per treatment or period and day (if multiple dose) with the ratios based on analyte (parent vs. metabolite). Limited to Analyte-Plasma comparisons for Trough (no NCA model) automations.

***Comparison_PK_Parameter_{a-z}_Ratios**, for Analyte, Day, Abs Bioavail, and CLr[a] [Table3]

PK parameter ratio values for individuals with summary statistics. Analyte Comp (Plasma): ratios based on analyte (parent vs. metabolite). Accumulation Comp: ratios based on day (multiple dose (test) vs. ref (SD)). Abs Bioavail Comp: ratios based on treatment (100 mg PO vs. 100 mg IV). Renal CLr Comp: ratios based on matrix (Plasma (test) vs. Ref (Ext)).
Note: In some instances, the table does not display the entire treatment description if table splitting is applied.

***Comparison_Intext_PK_Parameter** for Analyte, Day, Abs Bioavail, and CLr[a] [Special template]

PK parameter summary statistic values. Analyte Comp (Plasma): separate columns for each analyte. Accumulation Comp: separate columns for each day. Abs Bioavail Comp: separate columns for each treatment. Renal CLr Comp: separate columns for plasma matrix data.

[a]These tables can have all treatments displayed within the same type or one table per treatment depending on the selection made in the Comparison interface (all in same table or separate by table).

Comparison Tables by Type and Matrix

The following table describes which output tables can be generated by each PK Comparison type, depending on Admin settings and interface selections.

(In the following table “Pl” = Plasma, “Ur” = Urine, “Tr” = Trough, “Acc” = Accumulation, “AbBio” = Absolute Bioavailability, “RenCl” = Renal Clearance.)

Filenames (*.xls)	Analyte			Acc	AbBio	RenCl
	Pl	Ur	Tr			
Time-Concentration Tables						
Comparison_Concentration_Ratios	X					
Comparison_Trough_Concentration_Ratios			X			
Comparison_Urine_Amount_Ratios		X				
Comparison_Urine_Cumul_Amount_Ratios		X				
PK Parameter Tables						
Comparison_PK_Parameter_{a-z}_Ratios_Analyte (applies to both tables, A and B)	X					
Comparison_Urine_PK_Parameter_Ratios_Analyte		X		X		
Comparison_PK_Parameter_{a-z}_Ratios_Day (applies to both tables, A and B)				X		
Comparison_PK_Parameter_{a-z}_Ratios_Abs_Bioavail					X	
Comparison_PK_Parameter_{a-z}_Ratios_Renal_CLr						X
Intext Tables						
Comparison_Intext_PK_Parameter_{a-z}_Analyte (applies to both tables, I–II)	X					
Comparison_Urine_Intext_PK_Parameter_{a-z}_Analyte		X				
Comparison_Intext_PK_Parameter_{a-z}_Day (applies to both tables, I–II)				X		
Comparison_Intext_PK_Parameter_{a-z}_Abs_Bioavail (applies to both tables, I–II)					X	
Comparison_Intext_PK_Parameter_{a-z}_Renal_CLr (applies to both tables, I–II)						X

Graph output

PK Automation graphs
PK Comparison graphs

Each graph is created as an originating SigmaPlot file (`*.jnb`), followed by one of the following, depending on the version of SigmaPlot being used:

JPG using SigmaPlot 12.x (`*.jpg`)
EMF using SigmaPlot 11.x (`*.emf`)
WMF using SigmaPlot 10.x (`*.wmf`)

For some graphs (Concentration by Subject, Excretion Rate by Subject, Percent Dose Remaining by Subject, Trough Concentration by Subject, Individual Cumulative Amount Excreted, and Individual Amount Excreted), the individual `*.jpg`,`*.wmf`, or `*.EMF` files are gathered into MS Word documents. Each of these types also generates a single `*.jnb` file containing all subjects.

For all PK parameter graphs the [PK_Param] part of the filename can be changed by the administrator. The resulting filename can only include allowed characters for the Windows operating system.

With SigmaPlot box/whisker graphs, at least three data points are necessary to show a box graph and at least nine data points are needed for a whisker graph. Also, if none of the x values have more than two data points associated with them, then the graph itself is not created. SigmaPlot automatically calculates the mean, median and confidence interval values. Therefore, these plot types ***do not*** make use of the small sample size business rules.

Note: If X-axis tick-mark labels are too long, they may overlap. This problem can also occur when there are time values that are closely grouped together.

Note: If the first tick mark on X-axes is clipped, edit the.jnb file and set the Start value of the Range for the X-axis to a smaller value. As a result, the first tick mark and the label will move to the left and the whole text will be displayed.

A note about graph legends: On occasion, the text in a graph legend can become misaligned. For example, when a graph involves LOQ lines, the LOQ text displayed in graph legends (LOQ=X ug/mL) is not aligned with the rest of the legend text. The width of the symbols in the legend can be manually adjusted in order to correctly align the text with the following steps:

1. Right-click on any text in the legend and select **Edit**.
2. In the *Edit Text* dialog, click **Symbol** to open the *Symbols* dialog.
3. Adjust the width of all symbols and/or lines to an equal width, for example 0.25".
4. Click **OK**, then close the *Edit Text* dialog.

PK Automation graphs

Depending on the settings in the Admin Module, AutoPilot Toolkit automation projects can create combinations of the graphs listed below. The table following the list summarizes the graphs available for each combination of study design and dosing. PK_Parameter graphs are available with normalized or stratified data. Graph file names marked with an asterisk (*) have example output graphs located in "Automation Output Examples".

Time Concentration Graphs — Plasma

***Conc_by_Subject**

Individual time-concentration plot, one subject per graph. Activate **Individual Time Concentration** checkbox in the Appendix list to incorporate these graphs into a Word file called Individual_Time_Concentration.doc.

***Conc_Trt**[a]

Spaghetti individual time-concentration plot, one graph per unique treatment or period. Can have variability data (e.g., mean, median, etc.).

***Conc_Trt_GroupBy-Strat-[Demog]**[b]

Spaghetti individual time-concentration plot, one graph per unique treatment or period. Can contain variability data, separated by All or demographic variables (e.g., All Mean, Male Mean, Female Mean).

***Summary_Conc_Trt**[a]

Time-concentration summary, all treatments or periods on one graph.

***Summary_Conc_Trt_GroupBy-Strat-[Demog]**[a]

Time-concentration summary, all treatments or periods on one graph with demographic variables in the legend (e.g., Treatment 1 Male, Treatment 1 Female).

Summary_Conc_Strat-[Demog][Value]

Time-concentration summary, one graph per demographic variable value (e.g., Male) with all treatments or periods in the legend (e.g., Treatment 1, Treatment 2).

Time Concentration Graphs — Urine

***Excretion_Rate_by_Subject_Lin/Log**

Individual urine excretion rate, one subject per graph. Activate **Individual Excretion Rate** checkbox in the Appendix list to incorporate these graphs into a Word file called Individual_Excretion_Rate.doc.

***Excretion_Rate_Trt_Lin/Log**[a]

Spaghetti urine individual excretion rate plot, one graph per unique treatment or period, can have variability data (e.g., mean, median).

Excretion_Rate_Trt_GrouBy-Strat-[Demog]_Lin/Log[a]

Spaghetti individual urine excretion rate plot, one graph per unique treatment or period. Can contain variability data, separated by All or demographic variables (e.g., All Mean, Male Mean, Female Mean).

***Summary_Excretion_Rate_Lin/Log**[a]

Excretion rate summary, all treatments or periods on one graph.

Note: If one or more subjects in a data set have a negative relative actual time value, the mean values are not displayed in the plots when the relative actual end time is used as the X-axis variable. If the default X-axis variable Midpoint Time is used, then the mean values in the table are plotted.

Summary_Excretion_Rate_Trt_GroupBy-Strat-[Demog]_Lin/Log[a]

Excretion rate summary, all treatments or periods on one graph with demographic variables in the legend (e.g., Treatment 1 Male, Treatment 1 Female).

Summary_Excretion_Rate_Strat-[Demog][Value]_Lin/Log[a]

Excretion rate summary, one graph per demographic variable value (e.g., Male) with all treatments or periods in the legend (e.g., Treatment 1, Treatment 2).

Percent_Dose_Remaining_by_Subject_Lin/Log[a]

Percent dose remaining to be excreted (%) one subject per graph. Activate **Individual Percent Excreted** checkbox in the Appendix list to incorporate these graphs into a Word file called Individual_Percent_Excreted.doc.

Percent_Dose_Remaining_Trt_Lin/Log[a]

Spaghetti percent dose remaining to be excreted individual (%) plot, one graph per unique treatment or period. Can have variability data (e.g., mean, median).

Percent_Dose_Remaining_Trt_GroupBy-Strat_[Demog]_Lin/Log[a]

Spaghetti individual percent dose remaining plot, one graph per unique treatment or period. Can contain variability data, separated by All or demographic variables (e.g., All Mean, Male Mean, Female Mean).

Summary_Percent_Dose_Remaining_Lin/Log[a]

Percent dose remaining to be excreted summary, all treatments or periods on one graph.

Summary_Percent_Dose_Remaining_Trt_GroupBy-Strat-[Demog]_Lin/Log[a]

Percent dose remaining summary, all treatments or periods on one graph with demographic variables in the legend (e.g. Treatment 1 Male, Treatment 1 Female).

Summary_Percent_Dose_Remaining_Strat-[Demog][Value]_Lin/Log

Percent dose remaining summary, one graph per demographic variable value (e.g. Male) with all treatments or periods in the legend (e.g. Treatment 1, Treatment 2).

***Cumulative_Amount_Excreted_by_Subject_Lin/Log**

Individual line plot of the cumulative amount excreted by subject vs. midpoint or end time; linear and logarithmic scaling available. Activate **Individual Cumulative Amount Excreted** checkbox in the Appendix list to incorporate these graphs into a Word file called Individual_Cumulative_Amount_Excreted.doc.

***Cumulative_Amount_Excreted_Trt_Lin/Log**

Spaghetti plot of the cumulative amount excreted by treatment vs. midpoint or end time; linear and logarithmic scaling available.

Note: If one or more subjects in a data set have a negative relative actual time value, the mean values are not displayed in the plots when the relative actual end time is used as the X-axis variable. If the default X-axis variable Midpoint Time is used, then the mean values in the table are plotted.

Cumulative_Amount_Excreted_Trt_GroupBy-Strat_[Demog]_Lin/Log[a]

Spaghetti individual cumulative amount excreted plot, one graph per unique treatment or period. Can contain variability data, separated by All or demographic variables (e.g., All Mean, Male Mean, Female Mean).

Summary_Cumulative_Amount_Excreted_Lin/Log[a]

Cumulative amount excreted summary, all treatments or periods on one graph.

Summary_Cumulative_Amount_Excreted_Trt_GroupBy-Strat-[Demog]_Lin/Log[a]

Cumulative amount excreted summary, all treatments or periods on one graph with demographic variables in the legend (e.g. Treatment 1 Male, Treatment 1 Female).

Summary_Cumulative_Amount_Excreted_Strat-[Demog][Value]_Lin/Log

Cumulative amount excreted summary, one graph per demographic variable value (e.g. Male) with all treatments or periods in the legend (e.g. Treatment 1, Treatment 2).

***Amount_Excreted_by_Subject_Lin/Log**

Individual line plot of amount excreted by subject vs. midpoint or end time; linear and logarithmic scaling available. Activate **Individual Amount Excreted** checkbox in the Appendix list to incorporate these graphs into a Word file called Individual_Amount_Excreted.doc.

Note: In cases where there is more than one value in the Matrix column in the study data, the first Matrix value is the value displayed in the output. This can result in incorrect Y-axis labels for graphs. You may have to remove all of the rows for the first Matrix value in order to obtain the correct Y-axis labels.

***Amount_Excreted_Trt_Lin/Log**

Spaghetti plot of amount excreted by treatment vs. midpoint or end time; linear and logarithmic scaling available.

Amount_Excreted_Trt_GroupBy-Strat_[Demog]_Lin/Log[a]

Spaghetti individual amount excreted plot, one graph per unique treatment or period. Can contain variability data, separated by All or demographic variables (e.g., All Mean, Male Mean, Female Mean).

***Summary_Amount_Excreted_Trt_Lin/Log**

Line plot of the summary amount excreted by treatment vs. midpoint or end time; linear and logarithmic scaling available, as are error bars.

Summary_Amount_Excreted_Lin/Log[a]

Amount excreted summary, all treatments or periods on one graph.

Summary_Amount_Excreted_Trt_GroupBy-Strat-[Demog]_Lin/Log[a]

Amount excreted summary, all treatments or periods on one graph with demographic variables in the legend (e.g. Treatment 1 Male, Treatment 1 Female).

Summary_Amount_Excreted_Strat-[Demog][Value]_Lin/Log

Amount excreted summary, one graph per demographic variable value (e.g. Male) with all treatments or periods in the legend (e.g. Treatment 1, Treatment 2).

Time Concentration Graphs — Trough

Conc_by_Subject_Lin/Log

Individual trough time-concentration, one subject per graph. Activate **Individual Trough Concentration** checkbox in the Appendix list to incorporate these graphs into a Word file called Individual_Trough_Concentration.doc.

Conc_Trt_Lin/Log[a]

Spaghetti trough individual time-concentration plot, one graph per unique treatment, period. Can have variability data (e.g. mean, median).

Conc_Trt_GroupBy-Strat-[Demog]_Lin/Log[a]

Spaghetti trough individual time-concentration plot, one graph per unique treatment, period. Can contain variability data, separated by All or demographic variables (e.g. All Mean, Male Mean, Female Mean).

Summary_Conc_Trt_Lin/Log[a]

Trough time-concentration summary, all treatments or periods on one graph.

Summary_Conc_Trt_GroupBy-Strat-[Demog]_Lin/Log[a]

Trough time-concentration summary, all treatments or periods on one graph with demographic variables in the legend (e.g. Treatment 1 Male, Treatment 1 Female).

Summary_Conc_Strat-[Demog][Value]_Lin/Log[a]

Trough time-concentration summary, one graph per demographic variable value (e.g. Male) with all treatments or periods in the legend (e.g. Treatment 1, Treatment 2).

PK Parameter Graphs — Plasma and Urine

***[PKParam]**

PK parameter vs. categorical treatment or period.

[PKParam]_Norm-[Demog]

Normalized PK parameter vs. categorical treatment or period.

***[PKParam]_Trt_GroupBy-Strat-[Demog]**[a]

PK parameter stratified by discrete demographic; categorical X-axis is demographic values with one graph per treatment or period.

[PKParam]_Strat-[Demog][Value]

PK parameter stratified by discrete demographic; categorical X-axis is treatment or period values with one graph per demographic value (e.g. Male, Female).

[PKParam]_Norm-[Demog]_Trt_GroupBy-Strat-[Demog][a]

Normalized PK parameter stratified by discrete demographic; categorical X-axis is demographic values with one graph per treatment or period.

[PKParam]_Norm-[Demog]_Strat-[Demog][Value]

Normalized PK parameter stratified by discrete demographic; categorical X-axis is treatment or period values with one graph per demographic value (e.g. Male, Female).

***Box_[PKParam]**

Box and whisker plot of PK parameter vs. categorical t

Box_[PKParam]_Norm-[Demog]

Box and whisker plot of normalized PK parameter vs. categorical treatment or period.

Box_[PKParam]_Trt_GroupBy-Strat-[Demog][a]

Box and whisker plot of PK parameter stratified by discrete demographic; categorical X-axis is demographic values with one graph per treatment or period.

Box_[PKParam]_Strat_[Demog][Value]

Box and whisker plot of PK parameter stratified by discrete demographic; categorical X-axis is treatment or period values with one graph per demographic value (e.g. Male, Female).

Box_[PKParam]_Norm-[Demog]_Trt_GroupBy-Strat-[Demog][a]

Box and whisker plot of normalized PK parameter stratified by discrete demographic; categorical X-axis is demographic values with one graph per treatment or period.

Box[PKParam]_Norm-[Demog]_Strat-[Demog][Value]

Box and whisker plot of normalized PK parameter stratified by discrete demographic; categorical X-axis is treatment or period values with one graph per demographic value (e.g. Male, Female).

***[PKParam]_by-Dose**

PK parameter vs. continuous dose X-variable.

[PKParam]_Norm-[Demog]_vs-Dose

Normalized PK parameter vs. continuous dose X-variable.

Box_[PKParam]_vs-Dose

Box and whisker plot of PK parameter vs. continuous dose X-variable.

Box_[PKParam]_Norm-[Demog]_vs-Dose

Box and whisker plot of normalized PK parameter vs. continuous dose X-variable.

***[PKParam]_ vs-Cont-[Demog]**

PK parameter vs. continuous demographic X-variable; all individual subjects for all treatments or periods are displayed on same graph.

[PKParam]_Norm-[Demog]_vs-Cont-[Demog]

Normalized PK parameter vs. continuous demographic X-variable; all individual subjects for all treatments or periods are displayed on same graph.

***[PKParam]_ Trt_vs-Cont-[Demog]**[a]

PK parameter vs. continuous demographic X-variable; a separate graph is created for each unique treatment or period.

[PKParam]_Norm-[Demog]_Trt_vs-Cont-[Demog][a]

Normalized PK parameter vs. continuous demographic X-variables, where a separate graph is created for each unique treatment or period.

[PKParam]_Strat-[Demog]_vs-Cont-[Demog]

PK parameter vs. continuous demographic X-variables; all individual subjects for all treatments or periods are displayed on same graph, legend includes stratified demographic values (e.g. Male, Female).

[PKParam]_Norm-[Demog]_Strat-[Demog]_vs-Cont-[Demog]

Normalized PK Parameter vs. continuous demographic X-variables; all individual subjects for all treatments or periods are displayed on same graph, legend includes stratified demographic values (e.g. Male, Female).

[PKParam]_Trt_GroupBy-Strat-[Demog]_vs-Cont-[Demog][a]

PK parameter vs. continuous demographic X-variables; a separate graph is created for each unique treatment or period, legend includes stratified demographic values (e.g. Male, Female).

[PKParam]_Norm-[Demog]_Trt_GroupBy-Strat-[Demog]_vs-Cont-[Demog][a]

Normalized PK parameter vs. continuous demographic X-variables; a separate graph is created for each unique treatment or period, legend includes stratified demographic values (e.g. Male, Female).

[PKParam]_Strat-[Demog][Value]_vs-Cont-[Demog]

PK parameter vs. continuous demographic X-variables; a separate graph is created for each unique demographic variable value (e.g. Male or Female), legend includes treatments or periods.

[PKParam]_Norm-[Demog]_Strat-[Demog][Value]_vs-Cont-[Demog]

Normalized PK parameter vs. continuous demographic X-variables; a separate graph is created for each unique demographic variable value (e.g. Male or Female), legend includes treatments or periods.

[a]For replicated studies, _Per appears after _Trt to indicate the specific period the graph is representing.

[b]For stratifications, if legend is "Summary only" or "Individual and Summary," Variable symbols are applied to Summary lines so each is distinguishable.

PK Automation Graphs by Study Design, Dosing, and Matrix

The following table details which graphs are available for each study type, dosing, and matrix. Abbreviations in the table include:

SD: Single-Dose applies to Plasma
MD: Multiple-Dose applies to Plasma
TR: Trough
UR: Urine

Graph	Study Design and Dosing/Matrix							
	Crossover				Parallel			
	SD	MD	TR	UR	SD	MD	TR	UR
Time Concentration Graphs — Plasma								
Conc_by_Subject_Lin/Log	X	X			X	X		
Conc_by_Trt or _Per_Lin/Log	X	X			X	X		
Conc_Strat_[Demog]_by_Trt or _Per_Lin/Log	X	X			X	X		
Summary_Conc_Lin/Log	X	X			X	X		
Summary_Conc_Strat_[Demog]_Lin/Log	X	X			X	X		
Summary_Conc_Strat_by_[Demog](Value)_Lin/Log	X	X			X	X		
Time Concentration Graphs — Urine								
Excretion_Rate_by_Subject_Lin/Log				X				X
Excretion_Rate_by_Trt or _Per_Lin/Log				X				X
Excretion_Rate_Strat_[Demog]_by_Trt or _Per_Lin/Log				X				X
Summary_Excretion_Rate_Lin/Log				X				X
Summary_Excretion_Rate_Strat_[Demog]_Lin/Log				X				X

Graph	Study Design and Dosing/Matrix							
	Crossover				Parallel			
	SD	MD	TR	UR	SD	MD	TR	UR
Summary_Excretion_Rate_Strat_by_[Demog](Value)_Lin/Log				X				X
Percent_Dose_Remaining_by_Subject_Lin/Log				X				X
Percent_Dose_Remaining_by_Trt or _Per_Lin/Log				X				X
Percent_Dose_Remaining_Strat_[Demog]_by_Trt or _Per_Lin/Log				X				X
Summary_Percent_Dose_Remaining_Lin/Log				X				X
Summary_Percent_Dose_Remaining_Strat_[Demog]_Lin/Log				X				X
Summary_Percent_Dose_Remaining_Strat_by[Demog]_(Value)_Lin/Log				X				X
Cumulative_Amount_Excreted_by_Subject_Lin/Log				X				X
Cumulative_Amount_Excreted_by_Treatment_Lin/Log				X				X
Summary_Cumulative_Amount_Excreted_Lin/Log				X				X
Individual_Cumulative_Amount_Excreted_Lin/Log				X				X
Amount_Excreted_by_Subject_Lin/Log				X				X
Amount_Excreted_by_Treatment_Lin/Log				X				X
Summary_Amount_Excreted_Lin/Log				X				X
Individual_Amount_Excreted_Lin/Log				X				X
Time Concentration Graphs — Trough								
Conc_by_Subject_Lin/Log			X				X	
Conc_by_Trt or _Per_Lin/Log			X				X	
Conc_Strat_[Demog]_by_Trt or _Per_Lin/Log			X				X	
Summary_Conc_Lin/Log			X				X	
Summary_Conc_Strat_[Demog]_Lin/Log			X				X	
Summary_Conc_Strat_by_[Demog]_[Value]_Lin/Log			X				X	
PK Parameter Graphs — Plasma and Urine								
[PKParam]	X	X		X	X	X		X
[PKParam]_Norm-[Demog]	X	X		X	X	X		X
[PKParam]_Trt or _Per_GroupBy-Strat-[Demog]	X	X		X	X	X		X

Graph	Study Design and Dosing/Matrix							
	Crossover				Parallel			
	SD	MD	TR	UR	SD	MD	TR	UR
[PKParam]_Norm-[Demog]_Trt or _Per_GroupBy-Strat-[Demog]	X	X		X	X	X		X
[PKParam]_Strat-[Demog][Value]	X	X		X	X	X		X
[PKParam]_Norm-[Demog]_Strat-[Demog][Value]	X	X		X	X	X		X
Box_[PKParam]	X	X		X	X	X		X
Box_[PKParam]_Norm-[Demog]	X	X		X	X	X		X
Box_[PKParam]_Trt or _Per_GroupBy-Strat-[Demog]	X	X		X	X	X		X
Box_[PKParam]_Norm-[Demog]_Trt or _Per_GroupBy-Strat-[Demog]	X	X		X	X	X		X
Box_[PKParam]_Strat-[Demog][Value]	X	X		X	X	X		X
Box_[PKParam]_Norm-[Demog]_Strat-[Demog][Value]	X	X		X	X	X		X
[PKParam]_by-Dose	X	X		X	X	X		X
[PKParam]_Norm-[Demog]_vs_Dose	X	X		X	X	X		X
[PKParam]_Trt or _Per_GroupBy-Strat-[Demog]_by-Dose	X	X		X	X	X		X
[PKParam]_Norm-[Demog]_Trt or _Per_GroupBy-Strat-[Demog]_by-Dose	X	X		X	X	X		X
[PKParam]_Strat-[Demog][Value]_by-Dose	X	X		X	X	X		X
[PKParam]_Norm-[Demog]_Strat-[Demog][Value]_by-Dose	X	X		X	X	X		X
Box_[PKParam]_vs_Dose	X	X		X	X	X		X
Box_[PKParam]_Normal-ized_[Demog]_vs_Dose	X	X		X	X	X		X
Box_[PKParam]_Trt or _Per_GroupBy-Strat-[Demog]_by-Dose	X	X		X	X	X		X
Box_[PKParam]_Norm-[Demog]_Trt or _Per_GroupBy-Strat-[Demog]_by-Dose	X	X		X	X	X		X
Box_[PKParam]_Strat-[Demog][Value]_by-Dose	X	X		X	X	X		X
Box_[PKParam]_Norm-[Demog]_Strat-[Demog][Value]_by-Dose	X	X		X	X	X		X
[PKParam]_ vs_Cont_[Demog]	X	X		X	X	X		X
[PKParam]_ Norm-[Demog]_vs-Cont-[Demog]	X	X		X	X	X		X
PKParam]_Trt or _Per_GroupBy-Strat-[Demog]_vs-Cont-[Demog]	X	X		X	X	X		X

Graph	Study Design and Dosing/Matrix							
	Crossover				Parallel			
	SD	MD	TR	UR	SD	MD	TR	UR
[PKParam]_Norm-[Demog]_Trt or _Per_GroupBy-Strat-[Demog]_vs-Cont-[Demog]	X	X		X	X	X		X
[PKParam]_Strat-[Demog][Value]_vs-Cont-[Demog]_vs-Cont-[Demog]	X	X		X	X	X		X
[PKParam]_Norm-[Demog]_Strat-[Demog][Value]_vs-Cont-[Demog]	X	X		X	X	X		X

PK Comparison graphs

Depending on Admin and interface settings, PK Comparison projects can produce combinations of the graphs listed below. The table following the list summarizes the availability of each graph by comparison type. Graph file names marked with an asterisk have example output graphs located in “Comparison Output Examples”.

***Comp_Conc_by_Subject_Lin/Log**

Overlay time-concentration graph of all treatment and period with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…) per subject. One graph per subject independent of number of treatments and analytes. Activate **Comparison Individual Time Conc** checkbox in the Appendix list to incorporate these graphs into a Word file called Comparison_Individual_Time_Conc.doc.

***Comp_Summary_Conc_Lin/Log**

Summary overlay time-concentration graph of all treatments and periods with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…). One graph per run independent of number of subjects, treatments, and analytes.

***Comp_Excretion_Rate_by_Subject_Lin/Log**

Overlay excretion rate graph of all treatments and periods with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…) per subject. One graph per subject independent of number of treatments and analytes. Activate **Comparison Individual Excretion Rate by Subject** checkbox in the Appendix list to incorporate these graphs into a Word file called Comparison_Individual_Excretion_Rate.doc.

***Comp_Summary_Excretion_Rate_Lin/Log**

Summary overlay excretion rate graph of all treatments and periods with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…). One graph per run independent of number of subjects, treatments, and analytes.

***Comp_Cumulative_Amount_Excreted_by_Subject_Lin/Log**

Overlay of the cumulative amount of urine excreted by subject for all treatments and periods with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…). One graph per subject independent of number of treatments and analytes. Activate **Comparison Individual Cumulative Amount Excreted by Subject** checkbox in the Appendix list to incorporate these graphs into a Word file called Comparison_Individual_Cumulative_Amount_Excreted.doc.

***Comp_Summary_Cumulative_Amount_Excreted_Lin/Log**

Summary overlay line graph of the cumulative amount of urine excreted by treatment vs. midpoint or end time. Error bars are available.

***Comp_Amount_Excreted_by_Subject_Lin/Log**

Overlay line graph of the amount excreted by subject per treatment vs. midpoint or end time.

***Comp_Summary_Amount_Excreted_Lin/Log**

Comparison overlay line graph of the summary amount excreted vs. the midpoint or end time. Error bars are available.

***Comp_Percent_Dose_Remaining_by_Subject_Lin/Log**

Overlay line graph of the percent dose remaining by subject per treatment vs. midpoint or end time.

***Comp_Summary_Percent_Dose_Remaining_Lin/Log**

Comparison overlay line graph of the summary percent dose remaining vs. the midpoint or end time. Error bars are available.

***Comp_Trough_Conc_by_Subject_Lin/Log**

Overlay trough time-concentration graph of all treatments and periods with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…) per subject. One graph per subject independent of number of treatments and analytes. Activate **Comparison Individual Trough Time** checkbox in the Appendix list to incorporate these graphs into a Word file called Comparison_Individual_Trough_Time.doc.

***Comp_Summary_Conc_Lin/Log** (Trough)

Summary overlay trough time-concentration graph of all treatments and periods with all possible analyte combinations (e.g., Treatment 1 Analyte 1, Treatment 1 Analyte 1, Treatment 2 Analyte 1…). One graph per run independent of number of subjects, treatments, and analytes.

***Comp_[PKParam]**

Individual and summary overlay PK parameter graph of all treatments and periods with all possible Analyte (Analyte–Plasma/Urine), Day (Accumulation), Absolute Bioavail (Treatment), Clinical Renal (Treatment) combinations displayed on X-axis. One graph per PK parameter per run independent of number of treatments or periods, analytes, days, or subjects. All Comparison types included.

Comp_[PKParam]_Norm-[Demog]

Individual and summary overlay normalized PK parameter graph of all treatments and periods with all possible Analyte (Analyte–Plasma/Urine), Day (Accumulation), Absolute Bioavail (Treatment), Clinical Renal (Treatment) combinations displayed on X-axis. One graph per PK parameter per run independent of number of treatments or periods, analytes, days, or subjects.

***Comp_Box_[PKParam]**

Box & whisker plot of PK parameter for all treatments and periods with all possible Analyte (Analyte–Plasma/Urine), Day (Accumulation), Absolute Bioavail (Treatment), Clinical Renal (Treatment) combinations displayed on X-axis. One graph per PK parameter per run independent of number of treatments or periods, analytes, days, or subjects. All Comparison types included. Requires at least three subjects in the study.

Comp_Box_[PKParam]_Norm-[Demog]

Box & whisker plot of normalized PK parameter for all treatments and periods with all possible Analyte (Analyte–Plasma/Urine), Day (Accumulation), Absolute Bioavail (Treatment), Clinical

Renal (Treatment) combinations displayed on X-axis. One graph per PK parameter per run independent of number of treatments, periods, analytes, days, or subjects. Requires at least three subjects in the study.

***Comp_[PKParam]_vs-Cont-[Demog]**

Individual scatter plot of PK parameter graph vs. continuous demographic of all treatments and periods with all possible Analyte (Analyte–Plasma/Urine), Day (Accumulation), Absolute Bioavail (Treatment), Clinical Renal (Treatment) combinations displayed on legend. One graph per PK parameter per run independent of number of treatments periods, analytes, days, or subjects.

Comp_[PKParam]_Norm-[Demog]_vs-Cont-[Demog]

Individual scatter plot of PK parameter graph vs. continuous demographic all each treatment and period with all possible Analyte (Analyte–Plasma/Urine), Day (Accumulation), Absolute Bioavail (Treatment), Clinical Renal (Treatment) combinations displayed on legend. One graph per PK parameter per run independent of number of treatments, periods, analytes, days, or subjects.

***Comp_[PKParam]_Trt or _Per_vs-Cont-[Demog]**

Individual scatter plot PK parameter graph vs. continuous demographic of each treatment or period with all possible Analyte (Analyte–Plasma/Urine) or Day (Accumulation) combinations displayed on legend. One graph per PK parameter per treatment or period per run independent of number of analytes, days, or subjects.

Comp_[PKParam]_Norm-[Demog]_Trt or _Per_vs-Cont-[Demog]

Individual scatter plot PK parameter graph vs. continuous demographic of each treatment or period with all possible Analyte (Analyte–Plasma/Urine) or Day (Accumulation) combinations displayed on legend. One graph per PK parameter per treatment or period per run independent of number of analytes, days, or subjects.

Comparison Graphs by Type and Matrix

The following table details the graphs that are available for each comparison study type and matrix.

(In the following table “Pl” = Plasma, “Ur” = Urine, “Tr” = Trough, “Acc” = Accumulation, “AbBio” = Absolute Bioavailability, “RenCl” = Renal Clearance.)

Filenames (*.jpg, *.emf, *.wmf)	Analyte			Acc	AbBio	RenCl
	Pl	Ur	Tr			
Time-Concentration Graphs — Plasma						
Comp_Conc_by_Subject_Lin/Log	X			X	X	
Comp_Summary_Conc_Lin/Log	X			X	X	
Time-Concentration Graphs — Urine						
Comp_Excretion_Rate_by_Subject_Lin/Log		X				
Comp_Summary_Excretion_Rate_Lin/Log		X				
Comp_Cumulative_Amount_Excreted_by_Subject_Lin/Log		X				
Comp_Summary_Cumulative_Amount_Excreted_Lin/Log		X				
Comp_Amount_Excreted_by_Subject_Lin/Log		X				
Comp_Summary_Amount_Excreted_Lin/Log		X				

Filenames (*.jpg, *.emf, *.wmf)	Analyte			Acc	AbBio	RenCl
	Pl	Ur	Tr			
Comp_Percent_Dose_Remaining_by_Subject_Lin/Log		X				
Comp_Summary_Percent_Dose_Remaining_Lin/Log		X				
Time-Concentration Graphs — Trough						
Comp_Trough_Conc_by_Subject_Lin/Log			X			
Comp_Summary_Conc_Lin/Log (Trough)			X			
PK Parameter Graphs — Plasma and Urine						
Comp_[PKParam]	X	X		X	X	X[a]
Comp_[PKParam]_Norm-[Demog]	X	X		X	X	X[a]
Comp_Box_[PKParam]	X	X		X	X	X[a]
Comp_Box_[PKParam]_Norm-[Demog]	X	X		X	X	X[a]
Comp_[PKParam]_vs-Cont-[Demog]	X	X		X	X	X[a]
Comp_[PKParam]_Norm-[Demog]_vs-Cont-[Demog]	X	X		X	X	X[a]
Comp_[PKParam]_Trt or _Per_vs-Cont-[Demog]	X	X		X		
Comp_[PKParam]_Norm-[Demog]_Trt or _Per_vs-Cont-[Demog]	X	X		X		

a. Only one PK parameter is available for graphs in this comparison type (CLr).

There are two types of appendix output: PK Automation appendix output and PK Comparison appendix output.

PK Automation appendix output

PK Automation can create the following output as Microsoft Word documents.

Time-Concentration/Excretion Rate/Percent Dose Remaining (one document per subject graph)

Individual_Time_Concentration.doc
Individual_Excretion_Rate.doc
Individual_Percent_Dose_Remaining.doc
Individual_Cumulative_Amount_Excreted.doc
Individual_Amount_Excreted.doc

PK Parameter

Summary_PK_Text.doc: Individual regression fit, one subject per graph and listing of the individual PK parameter values selected for display in the tables.

If Phoenix cannot create a regression line (for instance, when concentration increases over time), AutoPilot Toolkit cannot generate this document, since it is based. To force a regression line, set the start and stop times in Phoenix larger than t_{last}.

Any selections made to the X-axis scaling, including uniform vs. non-uniform scaling, user-defined tick mark settings, and any options to start the X-axis at time=0, are only applied to the JNB, WMF, and EMF output objects and not to the charts in this document.

PK Automation appendix output by study design, dosing, and matrix

The following table details the Word documents that are available by study design, dosing, and matrix.

Word Document	Study Design and Dosing/Matrix							
	Crossover				Parallel			
	SD	MD	TR	UR	SD	MD	TR	UR
Time-Concentration/Excretion Rate/Percent Dose Remaining								
Individual_Time_Concentration.doc	X	X	X		X	X	X	
Individual_Excretion_Rate.doc				X				X
Individual_Percent_Dose_Remaining.doc				X				X
Individual_Cumulative_Amount_Excreted.doc				X				
Individual_Amount_Excreted.doc				X				
PK Parameter								
Summary_PK_Text.doc	X	X		X	X	X		X

Each Individual Time-Concentration, Excretion Rate, or Percent Dose Remaining document is a single Word document containing individual graphs with one subject per graph. The legend indicates all treatments and periods. The graphs are created by Phoenix and inserted, in Windows Metafile format, into the Word document.

Each page of the Summary PK Text document contains a graph and a table of PK parameter values for one profile, where a profile is defined as one unique combination of values for the sort variable(s) selected in the NCA model (e.g., Treatment_Description, Period, Day). The graph is displayed at the top of the page, with the PK parameters below. The graph is a copy of the regression fit created during the NCA run.

Note: The Summary PK Text document only includes values for parameters from non-excluded tables (PK Parameter, Intext, Lambda_Z tables). If only stratified and excluded tables are created, the document will not include the table of PK parameters per profile.

The display names for the graphs and tables, the parameters available for inclusion in the output and the option of including source information in the document are all Admin settings. If source information is included in the document is presented as one footnote per automation run. The footnote is displayed in the right lower margin of page. See “Managing footnotes” for further details.

PK Comparison appendix output

The following table details the Word documents that are available by comparison type and matrix.

(In the following table “Pl” = Plasma, “Ur” = Urine, “Tr” = Trough, “Acc” = Accumulation, “AbBio” = Absolute Bioavailability, “RenCl” = Renal Clearance.)

Filenames (*.doc)	Analyte			Acc	AbBio	RenCl
	Pl	Ur	Tr			
Time-Concentration Graphs						
Comparison_Individual_Time_Conc.doc	X			X	X	
Comparison_Individual_Trough_Time.doc			X			

Filenames (*.doc)	Analyte			Acc	AbBio	RenCl
	Pl	Ur	Tr			
Comparison_Individual_Excretion_Rate.doc		X				
Comparison_Individual_Cumulative_Amount_Excreted.doc		X				

The Individual Time-Concentration and Excretion Rate documents combine individual graphs, one subject per graph, with all combinations of analytes, days, treatments, periods in the legend. The graphs are created by Phoenix and inserted in Windows Metafile format into a Word document. The user settings for the text objects from the automation runs used apply.

AutoPilot File Explorer

AutoPilot File Explorer, which is located in the *Reporting* tab, loads the graphs and tables from AutoPilot Toolkit project output files and exports them as pictures into Microsoft Word documents and PowerPoint presentations. File Explorer also allows users to insert files as editable objects. This section contains the following topics:

Caution: Close Microsoft Word and Excel before using AutoPilot File Explorer.

File Explorer user interface

- After an Automation or Comparison run is complete, select the *Reporting* tab in the AutoPilot Toolkit object.

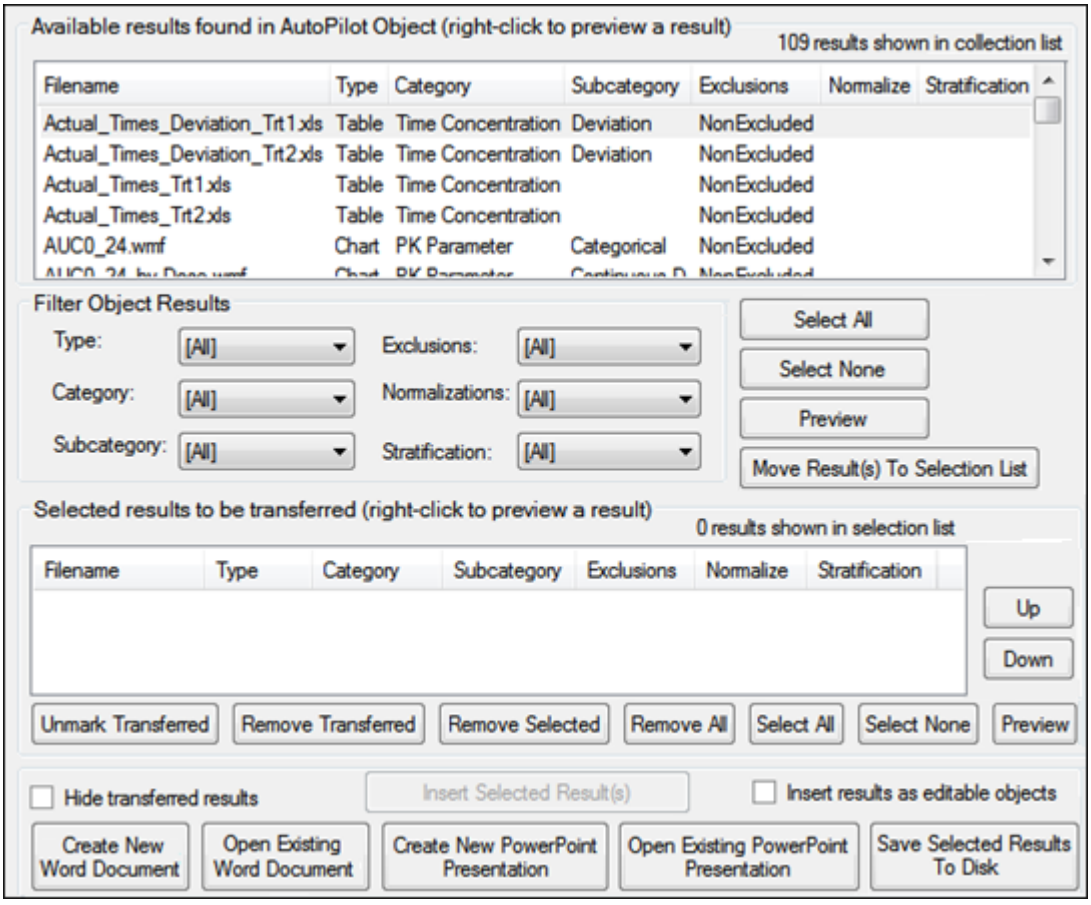


Figure 10-1. Reporting tab

The *Reporting* tab several groups of options to help select the output files to insert into Word documents or PowerPoint presentations, or to save to the file system.

Available results found in AutoPilot Toolkit object

All available `jpg`, `emf`, `wmf`, and `xls` files created during the execution of the AutoPilot Toolkit object selected in the hierarchical list are displayed in this table.

- Click on the **Filename**, **Type**, **Category**, **Subcategory**, **Exclusions**, **Normalize**, and **Stratification** column headers to sort the file list by the different fields.

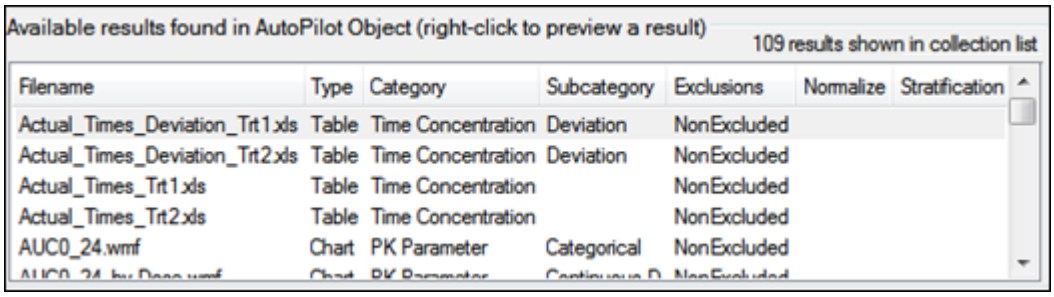


Figure 10-2. List of files created during execution

Filter object results

- Choose from the options in the pull-down menus to filter the files shown in the Available Results list.

Figure 10-3. Filter Object Results section of Reporting tab

Type: Show **All** file types, only **Chart** types, or only **Table** types.

Category: Show files for **All** categories, or only those for a particular category (e.g., **Time Concentration**, **PK Parameter**).

Subcategory: Show files for **All** subcategories, or only those for a particular subcategory (e.g., **Summary**, **Individual**)

Exclusions: Show **All** files, only those involving exclusions (**Excluded**), or only those created with no exclusions (**NonExcluded**).

Normalization: Show **All** files, or only those involving normalization by a particular demographic variable (e.g., **Age**, **Height**).

Stratification: Show **All** files, or only those involving stratification using a particular criteria (e.g., **Gender**, **Race**).

File selection and previewing options

Use the file selection and file preview buttons underneath the Available Results list to preview files and select files to be transferred to Word or PowerPoint.

- Click **Select All** to select all available result files.
- Click **Select None** to deselect all selected result files.
- Click **Preview** (or right-click a file) to preview selected `jpg`/`emf`/`wmf` files in Microsoft Word and `xls` files in Microsoft Excel.
- Click **Move Result(s) To Selection List** to move the selected files to the selection list.

  The selected files are displayed in the **Selected Results to be Transferred** list.

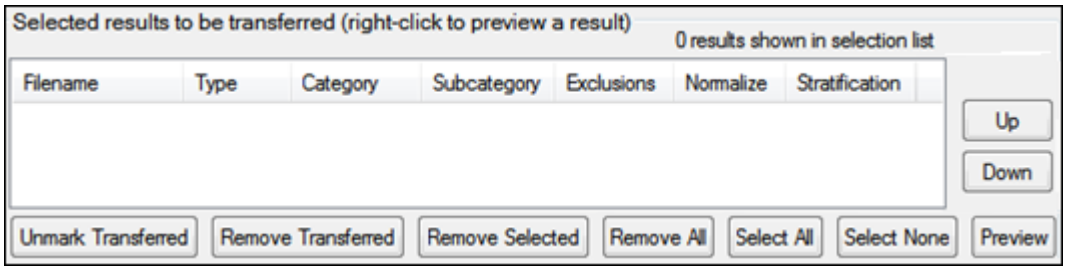


Figure 10-4. Selected Results section of Reporting tab

- Click any of the column headers to sort by the values in that column.
- Select a file and click **Up** and **Down** to modify the file order.

The following buttons are available below the Selected files list:

Unmark Transferred: Remove the asterisk that identifies files as having been successfully transferred.
Remove Transferred: Remove transferred files from the Selected files list.
Remove Selected: Remove the selected file(s) from the Selected files list.
Remove All: Clear the Selected files list.
Select All: Select all files in the Selected files list.
Select None: Deselect all selected files in the Selected files list.
Preview: Load selected `jpg`/`emf`/`wmf` files into a Microsoft Word document and `xls` files into a Microsoft Excel spreadsheet. Right-clicking a selected file also previews the file.

Export options

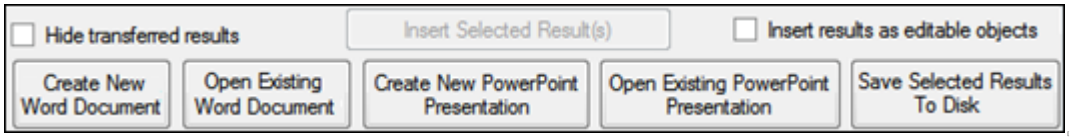


Figure 10-5. Export section of Reporting tab

The bottom portion of the *Reporting* tab contains a number of options for handling the files in the Selected file list.

Note: AutoPilot File Explorer allows only one document/presentation to be open at a time.

- **Hide transferred results**: Check this box to remove files from the Selected files list after they have been transferred (the **Unmark Transferred Files and Remove Transferred Files** buttons also become unavailable).

  Uncheck to add transferred files back in the list (the **Unmark Transferred Files and Remove Transferred Files** buttons become available again).

- **Insert Selected Result(s)**: Insert the selected file(s) into an existing Word document or PowerPoint presentation. This button becomes available only after the **Open Existing Word Document** or **Open Existing PowerPoint Presentation** button has been used to select and open a document or spreadsheet.
- **Insert results as editable objects**: Check this box if post-insertion editing such as adding titles or footnotes is needed.
- **Create New Word Document**: Insert the file or files into a new Microsoft Word document. AutoPilot File Explorer automatically inserts a caption above each table or graph image when a new document is created. The caption is based on the type of table or graph that was inserted.
- **Open Existing Word Document**: Display the *Select Document Source* dialog to choose whether the Word document is located in the **File System** or within the current **Phoenix Project**.
  - **File System**: Display the *Open* dialog for navigating and selecting a Word document from the file system.
  - **Phoenix Project**: Display the *Select Object* dialog for selecting a Word document that is part of the current project.
- **Create New PowerPoint Presentation**: Insert the file or files into a new PowerPoint presentation.
- **Open Existing PowerPoint Presentation**: Display the *Select Document Source* dialog to choose whether the PowerPoint presentation is located in the **File System** or within the current **Phoenix Project**.
  - **File System**: Display the *Open* dialog for navigating and selecting a PowerPoint presentation from the file system.
  - **Phoenix Project**: Display the *Select Object* dialog for selecting a PowerPoint presentation that is part of the current project.
- **Save Selected Results to Disk**: Display the *Browse for Folder* dialog for selecting the file system folder in which to save the selected file(s).

Notes on inserting files

- If a table is too wide to fit on a single page, File Explorer resizes the table before it is inserted into Microsoft Word or PowerPoint. However, tables too wide to fit on one page ***ARE NOT*** automatically resized if they are inserted as editable objects. This retains font sizes and other characteristics in their original format.
- If a very wide table is inserted as an editable object, then the table flows over the page margins. To insert a very wide table as an editable object, do the following:
  - Create an AP Automation or AP Analyte Comparison project and select the **Display** tab.
  - Select the **Display Options** tab, and select the **Automatic Splitting** checkbox in the Table column.
- Any changes made to tables or charts inserted as editable objects are only reflected in Word and PowerPoint. The source files that were created by AutoPilot Toolkit and inserted into Word or PowerPoint are not affected.

  For this reason the source files are not required to be located on the same computer that is to be used to edit the objects. However, Excel and SigmaPlot are required on any computer used to edit table and chart objects, respectively.
- When inserting AutoPilot Toolkit templates, executing the node prior to saving it as a template can prevent the template from being exported to Word. Create the template before executing the node.

Steps to insert and save files

Inserting files into a new Word document

- Select the files to insert into a Word document.
- Click **Create New Word Document** to insert the selected file(s) into a new document.

Successfully transferred files are marked with an asterisk.

Inserting files into an existing Word document

Note: When inserting Automation or Comparison results into an existing Word document, it is recommended that only one document is open at the time.

AutoPilot File Explorer allows only one document to be opened at a time.

- Select the files to insert into a Word document.
- Click **Open Existing Word Document** to insert the selected file(s) into an existing Word document.
- In the *Select Document Source* dialog, choose the source where the document is located and click **OK**.
  - If **File System** is selected, the *Open* dialog is displayed. Select the Word file and click **Open**.
  - If **Phoenix Project** is selected, the *Select Object* dialog is displayed. Select a Word file and click **Select**.
- In the *Reporting* tab, select the file or files in the order they are to be inserted into the specified Word document and click **Insert Selected Result(s)**.

  The file(s) are imported into the Word document and inserted in the order in which they are listed in the Selected files list. The insertion point in the Word file is determined by the cursor location.

  A message is displayed that confirms the file export.
- Click **OK** to continue.

Successfully transferred files are marked with an asterisk.

Inserting files into a new presentation

Note: Close any open presentations before creating a new one.

- Select the files to insert into a Microsoft PowerPoint presentation.
- Click **Create New PowerPoint Presentation** to insert the file or files into a new Microsoft PowerPoint presentation.

  AutoPilot File Explorer automatically inserts a caption above each table or graph image when a new presentation is created. The caption is based on the type of table or graph that was inserted.

Successfully transferred files are marked with an asterisk.

Inserting files into an existing presentation

AutoPilot File Explorer allows only one presentation to be opened at a time.

- Select the files to insert into a PowerPoint presentation.
- Click **Open Existing PowerPoint Presentation** to insert the selected file(s) into an existing PowerPoint presentation.

  The *Select Document Source* dialog is displayed.
- Choose the source where the document is located and click **OK**.
  - If **File System** is selected, the *Open* dialog is displayed. Select the PowerPoint file and click **Open**.
  - If **Phoenix Project** is selected, the *Select Object* dialog is displayed. Select a PowerPoint file and click **Select**.
- In the *Reporting* tab, select the file or files in the order they are to be inserted into the specified PowerPoint presentation and click **Insert Selected Result(s)**.

  The file(s) are imported into the PowerPoint presentation and inserted in the order in which they are listed in the Selected files list. The insertion point in the PowerPoint file is determined by the cursor location.

  A message is displayed that confirms the file export.
- Click **OK** to continue.

Successfully transferred files are marked with an asterisk.

Saving results to disk

- Click **Save Selected Results To Disk**.
- In the *Browse for Folder* dialog, select a folder and click **OK**.
  If the folder contains any files, then a message is displayed:
- Click **Yes** to continue.

The selected results are saved in the folder.

Note: If you want to save a Word 2010 document to disk, it is recommended that you first save the Word document to Phoenix, then export the document to disk.

Editable objects

When all desired files are selected, they can be exported into a Microsoft Word document or a Microsoft PowerPoint presentation.

By default, inserting tables and charts into Microsoft Word or PowerPoint creates image objects in those applications. The image objects are easy to insert and create a relatively small document size, but there are limits as to what can be done with the output after it has been created.

If post-insertion editing such as adding additional titles or footnotes is necessary in the output document, select the **Insert results as editable objects** checkbox prior to inserting the files.

Using this feature allows AutoPilot File Explorer to embed copies of the files into Microsoft Word or PowerPoint so that they can be edited using the original application that created the object. Tables are inserted as Microsoft Excel objects and charts are inserted as SigmaPlot chart objects.

Editing inserted tables

The same editing options are available in Microsoft Word and PowerPoint.

There are two options for editing a table that has been inserted as editable: edit directly in Word or open an instance of Microsoft Excel and edit the table using Excel.

Edit Directly in Microsoft Word

- Click anywhere in the table object in Microsoft Word to directly edit the table.

	A	B	C	D	
1	Mean ± SD	Day Comparison - Plasma OH_Carterolol			
2	Treatment	Carterolol PO Form A		Carterolol PO Form B	
3	Day	Day 1	Day 14	Day 1	Day 14
4	N	12	12	12	11
5	$t_{1/2}$ (hr)	6.97 ± 2.12	8.50 ± 2.33[c]	6.68 ± 2.70	7.52 ± 2.62
7	T_{max}[a] (hr)	0.58 (0.25 - 1.00)	0.66 (0.25 - 1.50)	0.69 (0.50 - 1.00)	0.73 (0.25 - 1.50)
9	C_{max} (ng/ml)	156 ± 300	170 ± 297	228 ± 430	294 ± 490
11	AUC_{last} (ng•hr/ml)	927 ± 1880	1270 ± 2230	1520 ± 3120	2670 ± 5270
13	AUC_{∞} (ng•hr/ml)	1010 ± 2020	1430 ± 2390[c]	1710 ± 3540	2730 ± 5330
15	AUC_{τ} (ng•hr/ml)	NC ± NC[b]	1190 ± 2090	NC ± NC[b]	2400 ± 4780
17	CL/F (ml/hr)	1030000 ± 1640000	NC ± NC[b]	624000 ± 1050000	NC ± NC[b]
19	CL_{ss}/F (ml/hr)	NC ± NC[b]	1220000 ± 2420000	NC ± NC[b]	463000 ± 860000

Figure 10-6. Table being edited in Microsoft Word

- When the edits are complete, click anywhere in the Microsoft Word document other than in the table. The table automatically updates in Word.

Edit in Microsoft Excel

- Right-click the table and select **Worksheet Object > Open** in the context menu.

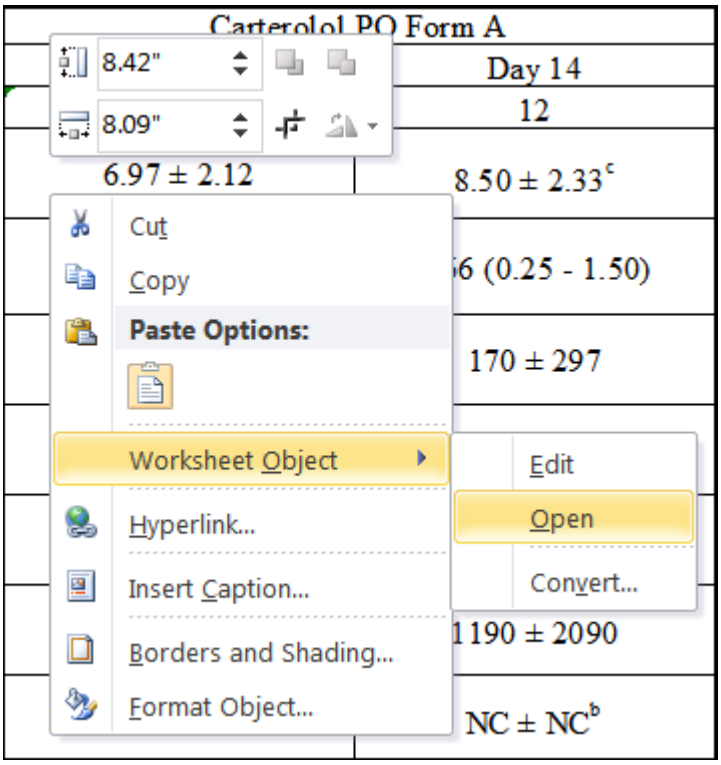


Figure 10-7. Right-click menu option to edit a table in Microsoft Excel

A new instance of Microsoft Excel opens and the selected table loads into Excel.

- Edit the table within Excel.
- When the edits are finished, close Excel. Any changes made to the table are reflected in the Word document.

The same editing options are also available in Microsoft PowerPoint.

Editing inserted charts

The same methods used to edit tables can be used to edit charts and the same editing options are available in Microsoft Word and PowerPoint.

There are two options to edit a chart that has been inserted as editable: edit directly in Word or open an instance of SigmaPlot and edit the table using SigmaPlot.

Edit directly in Microsoft Word

- Click anywhere in the chart object in Microsoft Word to directly edit the chart.

  During in-place editing, full access to SigmaPlot context menus and dialog boxes is available by right-clicking on any object within the chart. In the example above the legend text has been selected for editing within the *SigmaPlot Edit Text* dialog.

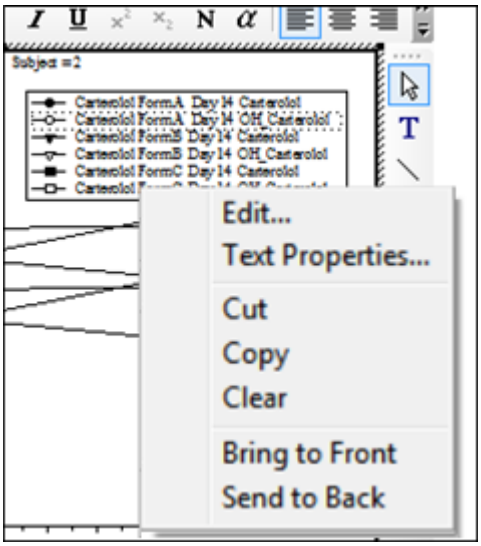


Figure 10-8. Right-click menu options when editing a chart in Microsoft Word

- When the edits are complete, click anywhere in the Microsoft Word document other than in the chart. The chart automatically updates in Word.

Edit in SigmaPlot

- Right-click the chart and select **SPW xx Graph Object > Open** from the context menu (**xx**: the SigmaPlot version number).

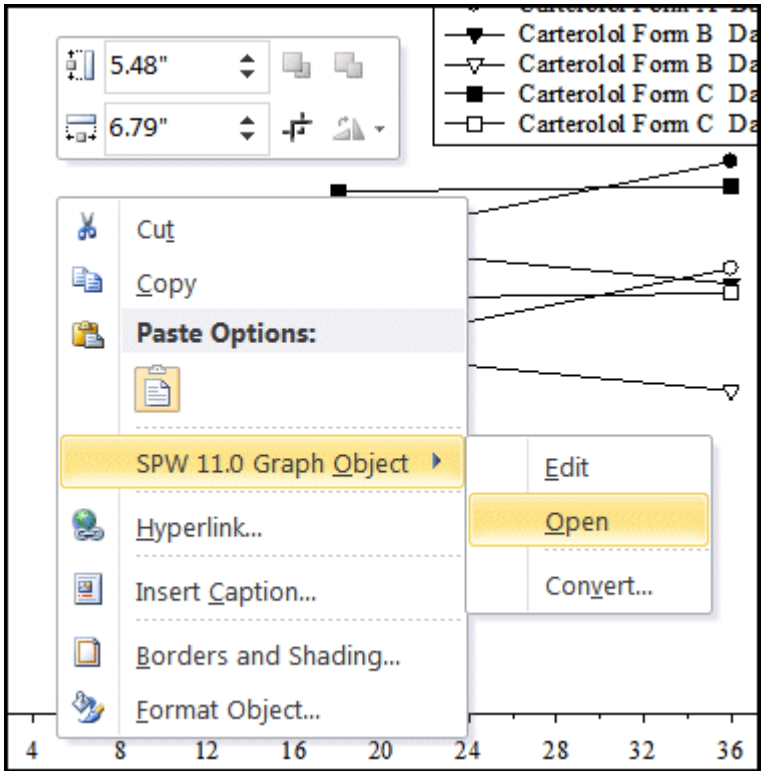


Figure 10-9. Right-click menu option to edit a chart in SigmaPlot directly

A new instance of SigmaPlot opens and the selected chart is loaded.

- Edit the chart in SigmaPlot.

- When the edits are finished, close SigmaPlot. Any changes made to the chart are reflected in the Word document.

Note: Due to a known issue in SigmaPlot 12.x, graphs may not completely get exported from SigmaPlot as editable objects into Word or PowerPoint.

Undoing edits

To undo any unwanted changes made to a table or chart, select **Undo Object** from the Word or PowerPoint **Edit** menu. This reverts the last change or set of changes that were made to the object during editing. Microsoft Word and PowerPoint keep track of all changes and allows multiple undo operations.

PK Parameters

Using AutoPilot Toolkit, the administrator can select which output (tables, graphs, and appendices) is available for selection in the Automation and Comparison interfaces. In addition, an administrator can filter which PK parameters are available and provide defaults for each table, graph, or text type if they are displayed. “PK automation parameters” presents the full list of PK parameters that administrators can include in the PK tables and graphs from PK Automation projects. “PK comparison parameters” presents the PK parameters that are included in the output from PK Comparison projects.

PK automation parameters

The following table lists the available PK parameters that can be selected for output from automation projects and their treatment in the default output, including the tables PKParameter_A, PKParameter_B, Intext_PK_Parameter_I, Urine_PK_Parameter, Urine_Intext_PK_Parameter, PK_Ratios, Urine_PK_Ratios, PK_Stats, Urine_PK_Stats, and Lambda_Z. The list of available parameters varies by NCA model and whether the study contains single-dose (SD) or multiple-dose (MD) data.

Note: For the NCA Model 220, Lambda Z values calculated in Phoenix may differ slightly from results calculated using WinNonlin version 5.x and earlier due to the default setting for the slope being changed from **Time Ranges** to **Best Fit**.

Definitions for terms appearing in the table:

WNL Name: Name (column header) provided by NCA model output.

Def Disp Name: Default name displayed in the final output (tables, graphs, and text).

Mod: Parameter is available for a specific NCA Model (e.g., 200 Ext) and regimen (Single-Dose (1D) or Multiple-Dose (MD)).

Def Table: Parameter displays in a specific table by default (LZ = Lambda Z).

Def Graph: Parameter is used for the creation of PK parameter graphs by default.

Ratios/Stats: Parameter displays in the PK Ratios and PK Stats tables by default.

Div/Sub: Parameter is set to show differences in the PK Ratios table based on subtraction (e.g., Trt 2 – Trt 1) or division (Trt 2/Trt 1).

Def Precision: Default precision regarding the type (significant figures or decimal places) and value (e.g., 0) to display in tables.

Normalization: If parameter can have normalization applied to it.

Def Summary / Error: Default summary (e.g. mean) and error term (e.g., SD) per PK parameter for graphs.

Cfg: Default values are configurable in the Administrator Module.

WNL Name [Def Display] (Cfg)	Mod 200 (Ext)		Mod 201 (IV bolus)		Mod 202 (IV infusion)		Mod 210–212	Def Table (Cfg)	Def Graph (Cfg)	Ratio/Stats (Cfg)	Div/Sub	Def Precision Type/Value (Cfg)	Normalization	Def Summary / Error (Cfg)
	1D	MD	1D	MD	1D	MD	1DMD							
Accumulation_Index [Accumulation]		X		X		X		N	N	N	S	dec/0	N	Mean/SD
Amount_Recovered [Ae]							X	Urine Intext	Y	Y	D	sig/3	Y	Mean/SD
AUC_%Back_Ext_obs [AUC % Back Extrap]			X	X				N	N	N	S	dec/0	N	Mean/SD
AUC_%Back_Ext_pred [AUC % Back Extrap]			X	X				N	N	N	S	dec/0	N	Mean/SD
AUC_%Extrap_obs [AUC % Extrap]	X	X	X	X	X	X		PKA	N	N	S	dec/0	N	Mean/SD
AUC_%Extrap_pred [AUC % Extrap]	X	X	X	X	X	X		N	N	N	S	dec/0	N	Mean/SD
AUC_TAU [AUC_{τ}]		X		X		X		PKA, Intext	Y	Y	D	sig/3	Y	Mean/SD
AUCall [AUC_{all}]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
AUCINF_D_obs [AUC_{∞}/D]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
AUCINF_D_pred [AUC_{∞}/D]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
AUCINF_obs [AUC_{∞}]	X	X	X	X	X	X		PKA, Intext	Y	Y	D	sig/3	Y	Mean/SD
AUCINF_pred [AUC_{∞}]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
AUClast [AUC_{last}]	X	X	X	X	X	X		PKA, Intext	Y	Y	D	sig/3	Y	Mean/SD
AUMC_%Extrap_obs [AUMC % Extrap]	X		X		X			N	N	N	S	dec/0	N	Mean/SD
AUMC_%Extrap_pred [AUMC % Extrap]	X		X		X			N	N	N	S	dec/0	N	Mean/SD
AUMC_TAU [$AUMC_{\tau}$]		X		X		X		N	N	N	D	sig/3	Y	Mean/SD
AUMCINF_obs [$AUMC_{\infty}$]	X		X		X			N	N	N	D	sig/3	Y	Mean/SD

WNL Name [Def Display] (Cfg)	Mod 200 (Ext)		Mod 201 (IV bolus)		Mod 202 (IV infusion)		Mod 210–212	Def Table (Cfg)	Def Graph (Cfg)	Ratio/Stats (Cfg)	Div/Sub	Def Precision Type/Value (Cfg)	Normalization	Def Summary / Error (Cfg)
	1D	MD	1D	MD	1D	MD	1D MD							
AUMCINF_pred [$AUMC_{\infty}$]	X		X		X			N	N	N	D	sig/3	Y	Mean/SD
AUMClast [$AUMC_{last}$]	X		X		X			N	N	N	D	sig/3	Y	Mean/SD
AURC_%Extrap_obs [AURC % Extrap]							X	N	N	N	S	dec/0	N	Mean/SD
AURC_%Extrap_pred [AURC % Extrap]							X	N	N	N	S	dec/0	N	Med/Min-Max Mean/SD
AURC_all [$AURC_{all}$]							X	N	N	N	D	sig/3	Y	Mean/SD
AURC_INF_obs [$AURC_{\infty}$]							X	N	N	N	D	sig/3	Y	Mean/SD
AURC_INF_pred [$AURC_{\infty}$]							X	N	N	N	D	sig/3	Y	NA
AURC(x-y) [$AURC^{a}$]							X	N	N	N	D	sig/3	Y	NA
AURClast [$AURC_{last}$]							X	N	N	N	D	sig/3	Y	Mean/SD
C0 [C_0]			X	X				N	N	N	D	sig/3	Y	Mean/SD
Cavg [C_{avg}]		X		X		X		PKB	Y	N	D	sig/3	Y	Mean/SD
Cl_F_obs [CL/F]	X							PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
Cl_F_pred [CL/F]	X							N	N	N	D	sig/3	Y	Mean/SD
Cl_obs [CL]			X		X			PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
Cl_pred [CL]			X		X			N	N	N	D	sig/3	Y	Mean/SD
Clast [C_{last}]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD

WNL Name [Def Display] (Cfg)	Mod 200 (Ext)		Mod 201 (IV bolus)		Mod 202 (IV infusion)		Mod 210–212	Def Table (Cfg)	Def Graph (Cfg)	Ratio/Stats (Cfg)	Div/Sub	Def Precision Type/Value (Cfg)	Normalization	Def Summary / Error (Cfg)
	1D	MD	1D	MD	1D	MD	1DMD							
CLss [CL_{ss}]				X		X		PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
CLss_F [CL_{ss}/F]		X						PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
Cmax [C_{max}]	X	X	X	X	X	X		PKA, Intext	Y	Y	D	sig/3	Y	Mean/SD
Cmax_D [C_{max}/Dose]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
Cmin [C_{min}]		X		X		X		N	N	N	D	sig/3	Y	Mean/SD
Corr_XY [Correlation]	X	X	X	X	X	X		N	N	N	S	sig/3	N	Med/Min-Max
Fluctuation% [Fluctuation %]		X		X		X		PKB, Intext	Y	N	S	dec/0	N	Mean/SD
HL_Lambda_z [$t_{1/2}$]	X	X	X	X	X	X		PKB, Intext	Y	N	D	dec/2	Y	Mean/SD
Lambda_z [λ_z]	X	X	X	X	X	X		LZ	Y	N	D	sig/3	N	Mean/SD
Lambda_z_lower [$\lambda_{z\ Lower}$]	X	X	X	X	X	X		LZ	N	N	S	dec/2	N	Med/Min-Max
Lambda_z_upper [$\lambda_{z\ Upper}$]	X	X	X	X	X	X		LZ	N	N	S	dec/2	N	Med/Min-Max
Max_Rate [Max Rate]							X	N	N	N	S	sig/3	Y	Med/Min-Max
Mid_Pt_last [Midpoint]							X	N	N	N	S	dec/2	N	Med/Min-Max
MRTINF_obs [MRT_{∞}]	X	X	X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
MRTINF_pred [MRT_{∞}]	X	X	X	X	X	X		N	N	N		sig/3	Y	Mean/SD
MRTlast [MRT_{last}]	X		X		X			N	N	N	D	sig/3	Y	Mean/SD
No_points_lambda_z [Number of Points]	X	X	X	X	X	X		LZ	N	N	S	dec/0	N	Med/Min-Max

WNL Name [Def Display] (Cfg)	Mod 200 (Ext)		Mod 201 (IV bolus)		Mod 202 (IV infusion)		Mod 210–212	Def Table (Cfg)	Def Graph (Cfg)	Ratio/Stats (Cfg)	Div/Sub	Def Precision Type/Value (Cfg)	Normalization	Def Summary / Error (Cfg)
	1D	MD	1D	MD	1D	MD	1D MD							
Partial_Area [AUC[a]]	X	X	X	X	X	X		PKB	Y	N	D	sig/3	Y	Mean/SD
Percent_Recovered [fe]							X	Urine Intext	Y	Y	S	dec/0	Y	Mean/SD
Rate_last [Last Rate]							X	N	N	N	S	sig/3	Y	Med/Min-Max
Rsq [R^2]	X	X	X	X	X	X		N	N	N	S	sig/3	N	Med/Min-Max
Rsq_adjusted [R^2 Adjusted]	X	X	X	X	X	X		X	N	N	S	sig/3	N	Med/Min-Max
Tlag [T_{lag}]	X	X						PKB	N	N	S	dec/2	N	Med/Min-Max
Tlast [T_{last}]	X	X	X	X	X	X		N	N	N	S	dec/2	N	Med/Min-Max
Tmax [T_{max}]	X	X	X	X	X	X		PKA, Intext	Y	N	S	dec/2	N	Med/Min-Max
Tmax_Rate [T_{max} Rate]							X	N	N	N	S	dec/2	N	Med/Min-Max
Tmin [T_{min}]		X		X		X		N	N	N	S	dec/2	N	Med/Min-Max
Vol_UR [Volume]							X	N	N	N	D	dec/0	Y	Mean/SD
Vss_obs [V_{ss}]			X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
Vss_pred [V_{ss}]			X	X	X	X		N	N	N	D	sig/3	Y	Mean/SD
Vss/F_obs [V_{ss}/F]	X	X						N	N	N	D	sig/3	Y	NA
Vss/F_pred [V_{ss}/F]	X	X						N	N	N	D	sig/3	Y	NA
Vz [V_z]				X		X		PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
Vz_F [V_z/F]		X						PKB, Intext	Y	N	D	sig/3	Y	Mean/SD

WNL Name [Def Display] (Cfg)	Mod 200 (Ext)		Mod 201 (IV bolus)		Mod 202 (IV infusion)		Mod 210–212	Def Table (Cfg)	Def Graph (Cfg)	Ratio/Stats (Cfg)	Div/Sub	Def Precision Type/Value (Cfg)	Normalization	Def Summary / Error (Cfg)
	1D	MD	1D	MD	1D	MD	1DMD							
Vz_F_obs [V_Z/F]	X							PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
Vz_F_pred [V_Z/F]	X							N	N	N	D	sig/3	Y	Mean/SD
Vz_obs [V_Z]			X		X			PKB, Intext	Y	N	D	sig/3	Y	Mean/SD
Vz_pred [V_Z]			X		X			N	N	N	D	sig/3	Y	Mean/SD

a. The display name is amended by the time period for the AUC calculation, for example, AUC0-24.

PK comparison parameters

PK Comparison projects calculate the following additional PK parameters, which the user can select to include for a given comparison run. This includes analyte, accumulation, absolute bioavailability, and renal clearance comparisons.

(In the following table "Accum" = Accumulation, "AbBio" = Absolute Bioavailability, "RenCl" = Renal Clearance.)

PK Parameter	Equation	Precision Type /Default	Comparison Type				
			Plasma	Trough	Accum	AbBio	RenCl
CLr	Ae(URN)/AUClast	Sig/3					X
DoseExt	NA	Dec/0				X	X
DoseIV	NA	Dec/0				X	X
Fabs	AUCinf(PO)*Dose(IV)/ AUCnf(IV)*Dose(PO)*100	Dec/0				X	X
LI	AUCtau(MD)/AUCinf(SD)	Dec/3			X		
RA[a]	AUCtau(MD)/AUCtau(SD)	Dec/3			X		

a. RA is calculated from the equation RA=AUCtau(MD)/AUCtau(SD). Since Phoenix does not calculate AUCtau for SD, the user needs to create a Partial AUC for the SD model that is equal to the interval of the tau. When RA is calculated, AutoPilot Toolkit checks that the parameter Tlast for MD is the same as the interval for the Partial Area set up in the SD model (e.g., tlast=AUC Partial Interval). If these are the same, RA is calculated using the above equation. If these values do not match, RA is calculated using the equation, RA=AUCtau (MD)/AUClast (SD).

Summary Statistics

During automation runs, Phoenix WinNonlin analysis generates summary statistics that can be included in tabular and graphical output. The following list shows display names for all available statistics, a brief description, and the default precision selected (in parentheses). The AutoPilot Toolkit administrator can filter the list to make only certain summary statistics available to the user.

The precisions listed below, in decimal places (dec) or significant figures (sig), are used to display the values in tabular output. Some of the summary statistics are defaulted (can be configured) for tables and graphs, but these are on a table by table or graph by graph basis.

N: Number of observations with non-missing data (dec/0)

NMiss: Number of observations with missing data (dec/0)

NObs: Number of observations (dec/0)

Mean: Arithmetic Average (Per PK parameter)

SD: Standard Deviation (Per PK parameter)

SE: Standard Error (Per PK parameter)

Variance: Unbiased sample variance (Per PK parameter)

Min: Minimum (Per PK parameter)

Median: Median (Per PK parameter)

Max: Maximum (Per PK parameter)

Range: Range of values, maximum value minus minimum value (Per PK parameter)

Percentiles1: The Pth percentile divides the distribution at a point such that P percent of the distribution are below this point. (Per PK parameter)

CV%: Coefficient of Variation (dec/0)

Geometric Mean: Geometric Mean (Per PK parameter)

Harmonic Mean: Reciprocal of the arithmetic mean of the reciprocals of the observations (Per PK parameter)

Mean of Logs: Arithmetic average of the natural logs of the observations (Per PK parameter)

SD of the Logs: Arithmetic average of the natural logs of the observations (Per PK parameter)

Geometric CV%: Geometric coefficient of variation (dec/0)

95% CI Lower Mean: Lower limit of an 95% confidence interval for the mean (Per PK parameter)

95% CI Upper Mean: Upper limit of an 95% confidence interval for the mean (Per PK parameter)

95% CI Lower Var: Lower limit of an 95% confidence interval for the variance (Per PK parameter)

95% CI Upper Var: Upper limit of an 95% confidence interval for the variance (Per PK parameter)

Skewness: Coefficient of skewness (Per PK parameter)

Kurtosis: Coefficient of excess (Per PK parameter)

Pseudo SD: Jackknife estimate of the standard deviation of the harmonic mean. (Per PK parameter)

K-S p-value: Kolmogorov-Smirnov normality test p value (Per PK parameter)

Lower 68% bound: Lower range value based on one standard deviation from the geometric mean (Per PK parameter)

Upper 68% bound: Upper range value based on one standard deviation from the geometric mean. (Per PK parameter)

All the summary statistics are available for display in tabular output. For graphical output, however, only the following summary statistics are available for summary terms:

mean
median
geometric mean
harmonic mean

Only the following are available for error terms in graphical output:

SD
SE
variance
min/max
68% Range

Automation Output Examples

For each example, images of the output table/graph and settings used when creating the table are included.

Demographics tables

Subject	Gender	Race	Smoke	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m2)	BSA (m2)	CrCL (mL/min)
1	Female	Hispanic	No	44	72.7	158	29.3	1.81	74
2	Male	Hispanic	No	34	88.6	178	28	2.11	170
3	Female	Hispanic	No	47	65.6	158	26.4	1.72	72
4	Male	Hispanic	No	44	76.4	173	25.6	1.93	102
5	Female	Hispanic	No	30	70.9	158	28.6	1.79	74
6	Male	Hispanic	No	43	80.5	178	25.5	2.01	130
7	Female	Black	Yes	44	85.9	173	28.8	2.05	88
8	Male	Hispanic	Yes	21	60	170	20.7	1.69	109
9	Male	Caucasian	Yes	50	88.6	180	27.3	2.12	122
10	Male	Black	Yes	35	76.8	168	27.3	1.91	134
11	Male	Caucasian	Yes	48	90	170	31.1	2.09	150
12	Female	Caucasian	Yes	47	65	160	25.4	1.72	64
N				12	12	12	12	12	12
Mean				41	76.8	168	27	1.91	107
SD				9	10.2	8	2.6	0.16	34.3
SE				3	2.9	2	0.8	0.05	9.9
Min				21	60	158	20.7	1.69	64
Median				44	76.6	170	27.3	1.92	106
Max				50	90	180	31.1	2.12	170
CV%				21	13	5	10	9	32
Geometric Mean				40	76.1	168	26.9	1.9	102

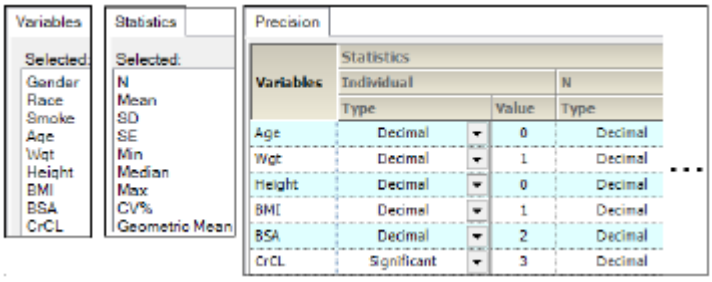


Figure 13-1. Demographic

Treatment = Carterolol IV											
Subject	Gender	Race	Smoke	Genotype	Alcohol	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m^2)	BSA (m^2)	CrCL (yr)
1	Male	White	Yes	2D6 EM	Yes	25	82	180	40.6	2.02	122
2	Female	Black	No	2D6 EM	Yes	18	67.1	176	37.1	1.81	165
3	Female	White	No	2D6 EM	Yes	23	82.2	182	40.3	2.04	58
4	Male	Black	No	2D6 EM	Yes	25	87.4	185	41.4	2.11	NR
5	Male	White	No	2D6 PM	Yes	24	72.1	177	38.4	1.88	99
6	Male	Black	No	2D6 EM	No	22	70.6	179	37.6	1.88	105
7	Male	White	Yes	2D6 EM	No	19	71.6	185	37.3	1.92	103
8	Female	Black	No	2D6 EM	No	21	81.9	174	41.2	1.99	88
9	Male	Black	NR	2D6 EM	NR	21	68	168	38.2	1.78	64
10	Male	Black	No	2D6 PM	No	42	81	175	40.9	1.98	65
11	Male	Black	No	2D6 EM	No	77	NR	180	41.9	2.14	100
12	NR	NR	Yes	2D6 EM	No	21	68.8	178	37.2	1.85	102
N						12	11	12	12	12	11
Mean						28	75.7	178	39.3	1.95	97.4
SD						17	7.2	5	1.9	0.12	30.2
SE						5	2.2	1	0.5	0.03	9.1
Min						18	67.1	168	37.1	1.78	58
Median						23	72.1	179	39.3	1.95	100
Max						77	87.4	185	41.9	2.14	165
CV%						59	10	3	5	6	31
Geometric Mean						26	75.4	178	39.3	1.95	93.3
NR = Not Recorded											

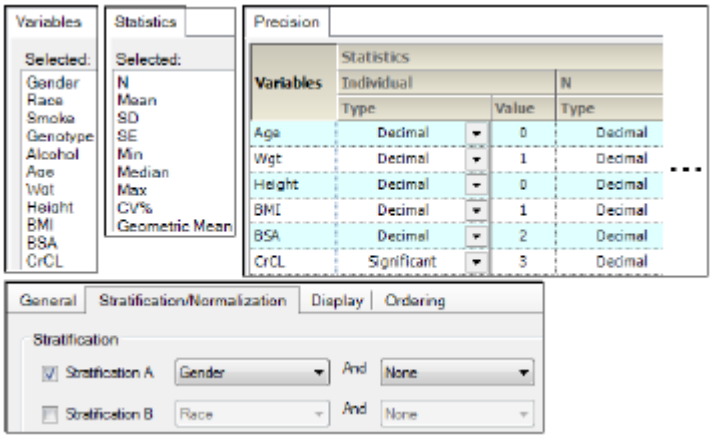


Figure 13-2. Demographic stratified by group

Plasma time concentration tables

Actual times
Actual times stratified by group
Actual times deviation
Actual times deviation stratified by group
Concentration
Concentration stratified by group

Treatment = Carterolol										
Plasma Carterolol										
	Actual Time (hr) over Nominal Time (hr)									
Subject	0	0.5	1	2	4	8	12	24	48	72
1	0	0.5	1	2	4	8	12	24	48	72
2	0	0.5	1	2	4	8	12	24	48	69
3	0	0.5	1	2	4	8	12	23.75	48	72
4	0	0.5	1	2	4.25	8	12	24	48	72
5	0	0.65	1	2	4	8	12	24	48	72
6	0	0.5	1	2	4	8	12	24	47	72
7	0	0.5	1	2.15	4	8	12	24	48	72
8	0	0.5	1	2	4	8	12	24	48	72
9	0	0.5	1	2	4	7.75	12	24	48	72
10	0	0.5	1	2	4	8	12	24	48	72
11	0	0.5	1.15	2	4	8	11.75	24	48	72
12	0	0.5	1	2	4	8	12	24.25	48	72
N	12	12	12	12	12	12	12	12	12	12
Mean	0	0.51	1.01	2.01	4.02	7.98	11.98	24	47.92	71.75
SD	0	0.04	0.04	0.04	0.07	0.07	0.07	0.11	0.29	0.87
SE	0	0.01	0.01	0.01	0.02	0.02	0.02	0.03	0.08	0.25
Min	0	0.5	1	2	4	7.75	11.75	23.75	47	69
Median	0	0.5	1	2	4	8	12	24	48	72
Max	0	0.65	1.15	2.15	4.25	8	12	24.25	48	72
CV%	NA	8	4	2	2	1	1	0	1	1
Geometric Mean	NA	0.51	1.01	2.01	4.02	7.98	11.98	24	47.92	71.75
NA = Not Applicable										

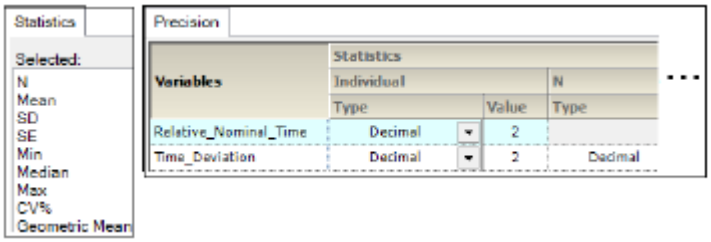


Figure 13-3. Actual times

Treatment = Carterolol Form A (Day = 14)															
Plasma Howerolol															
	Actual Time (hr) over Nominal Time (hr)														
Subject	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
1	-1.00	0.35	0.65	0.85	1.25	1.75	3.00	5.00	9.00	14.00	20.00	28.00	34.00	38.00	50.00
2	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
3	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
4	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
5	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
6	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
7	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
8	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
9	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
10	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
11	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
12	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	-0.08	0.26	0.51	0.76	1.02	1.52	2.08	4.08	8.08	12.17	16.33	24.33	30.33	36.17	48.17
SD	0.29	0.03	0.04	0.03	0.07	0.07	0.29	0.29	0.29	0.58	1.15	1.15	1.15	0.58	0.58
SE	0.08	0.01	0.01	0.01	0.02	0.02	0.08	0.08	0.08	0.17	0.33	0.33	0.33	0.17	0.17
Min	-1.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
Median	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
Max	0.00	0.35	0.65	0.85	1.25	1.75	3.00	5.00	9.00	14.00	20.00	28.00	34.00	38.00	50.00
CV%	-346	11	8	4	7	5	14	7	4	5	7	5	4	2	1
Geometric Mean	NA	0.26	0.51	0.76	1.02	1.52	2.07	4.08	8.08	12.16	16.30	24.31	30.31	36.16	48.16
NA = Not Applicable															

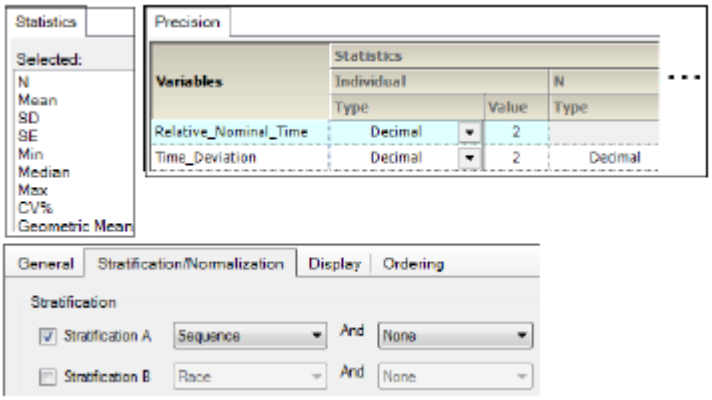


Figure 13-4. Actual times stratified by group

Treatment = Carterolol										
Plasma Carterolol										
	Actual Time Deviation (%) from Nominal Time (hr)									
Subject	0	0.5	1	2	4	8	12	24	48	72
1	NS	0	0	0	0	0	0	0	0	0
2	NS	0	0	0	0	0	0	0	0	-4.17
3	NS	0	0	0	0	0	0	-1.04	0	0
4	NS	0	0	0	6.25	0	0	0	0	0
5	NS	*30.00	0	0	0	0	0	0	0	0
6	NS	0	0	0	0	0	0	0	-2.08	0
7	NS	0	0	7.5	0	0	0	0	0	0
8	NS	0	0	0	0	0	0	0	0	0
9	NS	0	0	0	0	-3.13	0	0	0	0
10	NS	0	0	0	0	0	0	0	0	0
11	NS	0	15	0	0	0	-2.08	0	0	0
12	NS	0	0	0	0	0	0	1.04	0	0
N	0	12	12	12	12	12	12	12	12	12
Mean	NC	2.5	1.25	0.63	0.52	-0.26	-0.17	0	-0.17	-0.35
SD	NC	8.66	4.33	2.17	1.8	0.9	0.6	0.44	0.6	1.2
SE	NC	2.5	1.25	0.63	0.52	0.26	0.17	0.13	0.17	0.35
Min	NC	0	0	0	0	-3.13	-2.08	-1.04	-2.08	-4.17
Median	NC	0	0	0	0	0	0	0	0	0
Max	NC	30	15	7.5	6.25	0	0	1.04	0	0
CV%	NC	346	346	346	346	-346	-346	NA	-346	-346
Geometric Mean	NC	NA	NA	NA	NA	NA	NA	NA	NA	NA
* = Actual sampling time exceeds ±15% of nominal sampling time threshold.										
NS = No Sample										
NC = Not Calculated										
NA = Not Applicable										

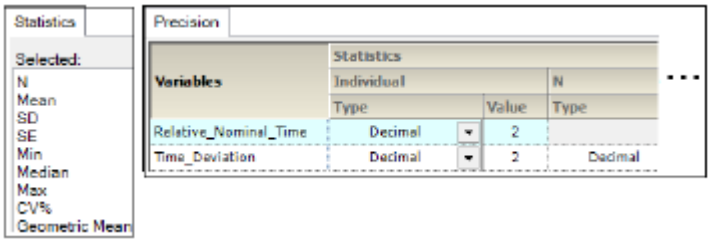


Figure 13-5. Actual times deviation

Treatment = Carterolol Form A (Day = 14)															
Plasma Howerolol															
	Actual Time Deviation (%) from Nominal Time (hr)														
Subject	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00	30.00	36.00	48.00
1	NS	*40.00	*30.00	13.33	*25.00	*16.67	*50.00	*25.00	12.50	*16.67	*25.00	*16.67	13.33	5.56	4.17
2	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
7	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
8	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
9	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
11	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
12	NS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	0	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	NC	3.33	2.50	1.11	2.08	1.39	4.17	2.08	1.04	1.39	2.08	1.39	1.11	0.46	0.35
SD	NC	11.55	8.66	3.85	7.22	4.81	14.43	7.22	3.61	4.81	7.22	4.81	3.85	1.60	1.20
SE	NC	3.33	2.50	1.11	2.08	1.39	4.17	2.08	1.04	1.39	2.08	1.39	1.11	0.46	0.35
Min	NC	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Median	NC	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max	NC	40.00	30.00	13.33	25.00	16.67	50.00	25.00	12.50	16.67	25.00	16.67	13.33	5.56	4.17
CV%	NC	346	346	346	346	346	346	346	346	346	346	346	346	346	346
Geometric Mean	NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
* = Actual sampling time exceeds ±15% of nominal sampling time threshold.															
NS = No Sample															
NC = Not Calculated															
NA = Not Applicable															

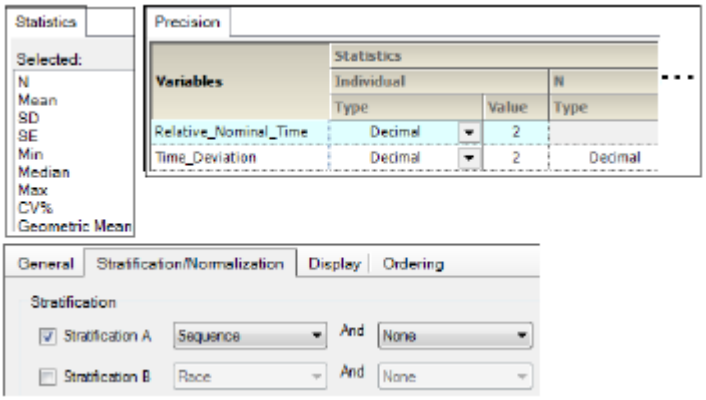


Figure 13-6. Actual times deviation stratified by group

Treatment = Carterolol									
Plasma Carterolol									
	Concentration (ng/ml) over Nominal Time (hr)								
Subject	0	0.5	1	2	4	8	12	24	48	72
1	0	50.9	235	191	145	109	81.8	40.8	22.3	13.3
2	0	53.6	124	170	134	87.4	63.2	31.2	13.9	6.74
3	0	280	218	186	176	133	87.6	47.2	23	12
4	0	1.81	2.88	125	142	108	80.9	40.9	21.8	10.8
5	0	178	232	184	164	136	95.3	52.8	30.2	18.8
6	0	19.9	73.5	181	147	114	94.2	64.3	42.4	29
7	0	176	184	170	145	120	87.5	59.2	41.3	24.9
8	0	265	212	196	158	138	97.7	51.2	25.7	14
9	0	127	143	115	107	75.7	59.9	34.2	19.6	11.5
10	0	245	189	152	142	133	99.5	63.2	41.1	28.6
11	0	231	183	146	135	104	63.1	28	13.3	7.28
12	0	290	216	175	131	106	68.2	36.3	18.9	10.4
N	12	12	12	12	12	12	12	12	12	12
Mean	0	160	168	166	144	114	81.6	45.8	26.1	15.6
SD	0	106	70.7	26.1	17.5	19.6	14.5	12.5	10.4	7.87
SE	0	30.7	20.4	7.52	5.04	5.65	4.2	3.6	3	2.27
Min	0	1.81	2.88	115	107	75.7	59.9	28	13.3	6.74
Median	0	177	187	173	144	112	84.7	44.1	22.7	12.7
Max	0	290	235	196	176	138	99.5	64.3	42.4	29
CV%	NA	66	42	16	12	17	18	27	40	50
Geometric Mean	NA	94	124	164	143	112	80.3	44.2	24.3	14
NA = Not Applicable										

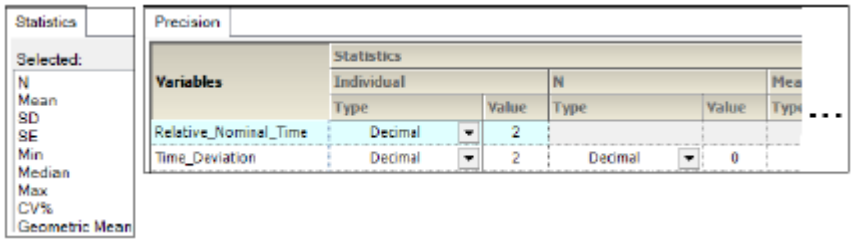


Figure 13-7. Concentration

Treatment = Carterolol Form A (Sequence = A, Genotype = 2D6 EM)

Plasma OH_Carterolol

	Concentration (ng/ml) over Nominal Time (hr)											
Subject	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00
1	0.00	0.970	2.31	1.78	1.60	1.34	1.17	1.04	0.610	0.390	0.280	0.120
2	0.00	10.6	15.1	11.9	10.5	10.0	8.63	7.45	7.43	5.70	3.98	2.55
3	0.00	95.3	158	131	120	101	82.5	69.8	44.3	27.8	18.0	7.50
4	0.00	43.2	222	166	167	138	131	107	49.2	33.6	16.8	0.00
N	4	4	4	4	4	4	4	4	4	4	4	4
Mean	0.00	37.5	99.2	77.4	74.7	62.5	55.8	46.3	25.4	16.9	9.76	2.54
SD	0.00	42.5	108	82.9	81.6	67.4	62.0	50.9	24.9	16.3	8.96	3.51
SE	0.00	21.3	54.0	41.4	40.8	33.7	31.0	25.4	12.4	8.14	4.48	1.75
Min	0.00	0.970	2.31	1.78	1.60	1.34	1.17	1.04	0.610	0.390	0.280	0.00
Median	0.00	26.9	86.3	71.2	65.3	55.3	45.6	38.6	25.8	16.7	10.4	1.34
Max	0.00	95.3	222	166	167	138	131	107	49.2	33.6	18.0	7.50
CV%	NA	113	109	107	109	108	111	110	98	97	92	138
Geometric Mean	NA	14.3	33.2	26.0	24.1	20.8	18.2	15.5	9.96	6.75	4.28	NA

NA = Not Applicable

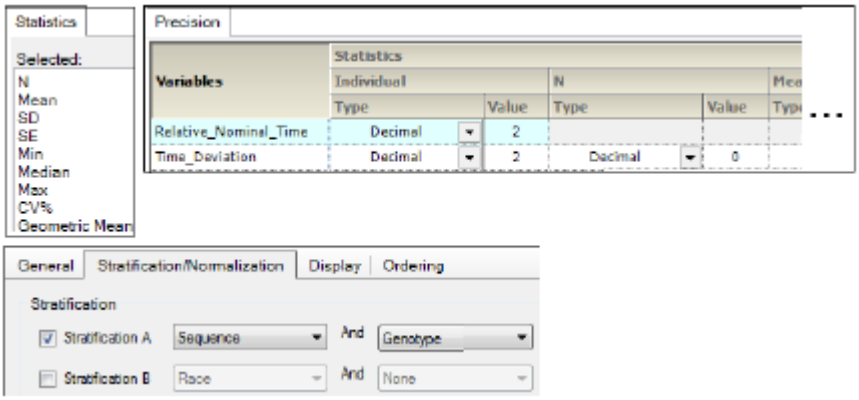


Figure 13-8. Concentration stratified by group

Trough time concentration tables

Trough actual times
Trough concentration
Trough concentrations stratified by group

Treatment = Carterolol PO Form A			
Plasma Carterolol			
	Day		
	4	8	11
	Nominal Time (hr)		
Subject	0.00	0.00	0.00
1	-1.00	-1.00	-1.00
2	0.00	0.00	0.00
3	0.00	0.00	0.00
4	0.00	0.00	0.00
5	0.00	0.00	0.00
6	0.00	0.00	0.00
7	0.00	0.00	0.00
8	0.00	0.00	0.00
9	0.00	0.00	0.00
10	0.00	0.00	0.00
11	0.00	0.00	0.00
12	0.00	0.00	0.00
N	12	12	12
Mean	-0.08	-0.08	-0.08
SD	0.29	0.29	0.29
SE	0.08	0.08	0.08
Min	-1.00	-1.00	-1.00
Median	0.00	0.00	0.00
Max	0.00	0.00	0.00
CV%	-346	-346	-346
Geometric Mean	NA	NA	NA
Nominal Times instead of Actual Times			
NA = Not Applicable			

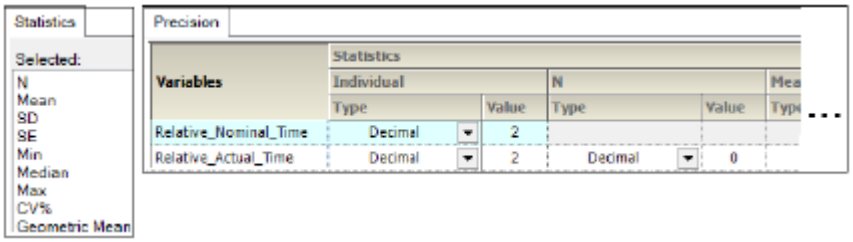


Figure 13-9. Trough actual times

Treatment = Carterolol PO Form A			
Plasma NS			
	Concentration over Day (Nominal Time)		
Subject	Day 4 (0 hr)	Day 8 (0 hr)	Day 11 (0 hr)
1	1.88	1.29	1.19
2	33.8	38.0	38.5
3	122	85.5	84.0
4	118	124	113
5	12.0	15.5	12.6
6	198	188	210
7	26.0	23.0	28.7
8	22.1	20.2	24.9
9	910	943	918
10	62.0	55.0	55.0
11	6.08	7.28	6.96
12	13.2	8.11	7.92
N	12	12	12
Mean	127	126	125
SD	254	263	257
SE	73.3	76.0	74.1
Min	1.88	1.29	1.19
Median	29.9	30.5	33.6
Max	910	943	918
CV%	200	210	205
Geometric Mean	36.5	33.7	33.9
Nominal Times instead of Actual Times			

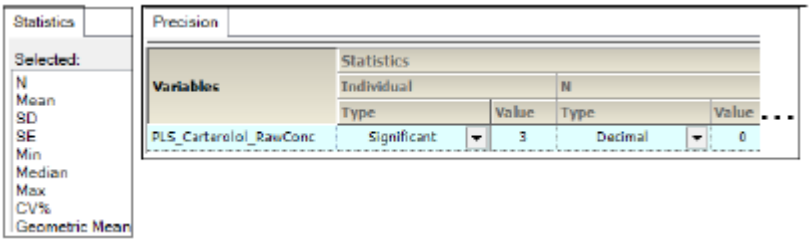


Figure 13-10. Trough concentration

Treatment = Carterolol PO Form A (Gender = Male, Race = Black)			
Plasma NS			
	Concentration over Day (Nominal Time)		
Subject	Day 4 (0 hr)	Day 8 (0 hr)	Day 11 (0 hr)
4	118	124	113
6	198	188	210
9	910	943	918
10	62.9	55.0	55.0
11	6.08	7.28	6.96
N	5	5	5
Mean	259	263	261
SD	371	386	375
SE	166	173	168
Min	6.08	7.28	6.96
Median	118	124	113
Max	910	943	918
CV%	143	147	144
Geometric Mean	95.7	97.4	96.5
Nominal Times instead of Actual Times			

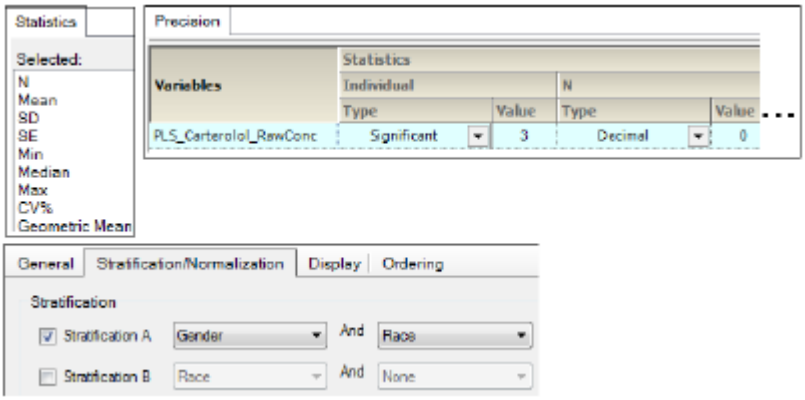


Figure 13-11. Trough concentrations stratified by group

Urine time concentration tables

Urine amount
Urine amount stratified by group
Urine cumulative amount
Urine cumulative amount stratified by group
Urine actual times

Analyte = Urine OH-Carterolol			
	Amount Excreted (ng) over the Nominal Collection Interval (hr)		
Subject	0 - 12	12 - 24	24 - 48
1	1395	10192.5	24522.75
2	459.85	13414.2	40886.06
3	NC	9835.5	23665.64
4	1377.6	8283.8	21213.36
5	508.8	9211	49497.84
6	4456.8	NC	14064.96
7	2407.5	5467.5	26082
8	550.4	2101.6	43388.1
9	5157.5	13662	28690.2
10	7618	36592.5	67620
11	1197.65	12786.15	29762.46
12	1021.2	11516.8	9428.16
N	11	11	12
Mean	2459.12	12096.69	31568.46
SD	2313.34	8834.56	16251.53
SE	697.5	2663.72	4691.41
Min	459.85	2101.6	9428.16
Median	1395	10192.5	27386.1
Max	7618	36592.5	67620
CV%	94.07	73.03	51.48
Geometric Mean	1645.86	9872.08	27830.29

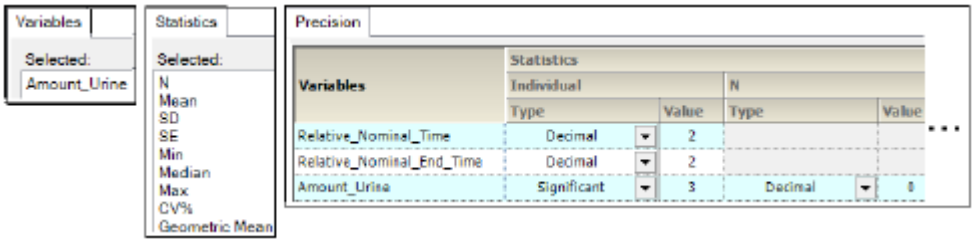


Figure 13-12. Urine amount

Treatment = Carterolol Form A (Sequence = B)										
Urine OH_Carterolol										
	Nominal Time (hr)									
	0.00 - 12.00					12.00 - 24.00				
Subject	Concentration (ng/ml)	Midpoint Time (hr)	Volume (ml)	Amount (ng)	Rate (ng/hr)	Concentration (ng/ml)	Midpoint Time (hr)	Volume (ml)	Amount (ng)	Rate (ng/hr)
5	0.490	6.00	120	58.8	4.90	0.870	18.00	1220	1060	88.5
6	0.710	6.00	720	511	42.6	0.310	18.00	1820	564	47.0
7	1.11	6.00	250	278	23.1	0.470	18.00	1350	635	52.9
8	0.200	6.00	NS	NS	NS	0.170	18.00	1420	241	20.1
N	4	4	3	3	3	4	4	4	4	4
Mean	0.628	6.00	363	283	23.5	0.455	18.00	1453	625	52.1
SD	0.384	0.00	316	226	18.9	0.303	0.00	259	337	28.1
SE	0.192	0.00	182	131	10.9	0.151	0.00	129	169	14.1
Min	0.200	6.00	120	58.8	4.90	0.170	18.00	1220	241	20.1
Median	0.600	6.00	250	278	23.1	0.390	18.00	1385	599	49.9
Max	1.11	6.00	720	511	42.6	0.870	18.00	1820	1060	88.5
CV%	61	0	87	80	80	67	0	18	54	54
Geometric Mean	0.527	6.00	278	203	16.9	0.383	18.00	1436	550	45.9
NS = No Sample										

24.00 - 48.00				
Concentration (ng/ml)	Midpoint Time (hr)	Volume (ml)	Amount (ng)	Rate (ng/hr)
2.22	36.00	2562	5690	237
0.420	36.00	3822	1610	66.9
1.06	36.00	2835	3010	125
1.67	36.00	2982	4980	207
4	4	4	4	4
1.34	36.00	3050	3820	159
0.776	0.00	543	1860	77.6
0.388	0.00	272	931	38.8
0.420	36.00	2562	1610	66.9
1.37	36.00	2909	3990	166
2.22	36.00	3822	5690	237
58	0	18	49	49
1.13	36.00	3016	3420	142

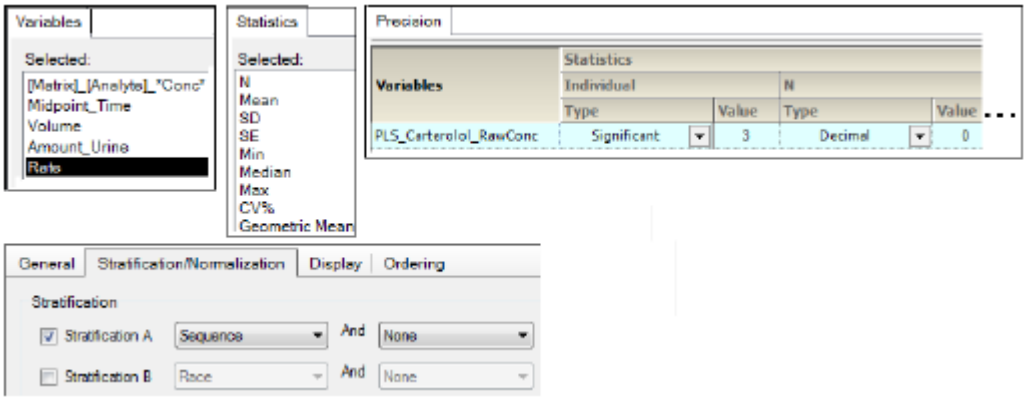


Figure 13-13. Urine amount stratified by group

Treatment = Carterolol IV (Day = 14)

Urine OH-Carterolol

Subject	Amount Excreted (ng) over the Nominal Collection Interval (hr) 12.00 - 24.00	12.00 - 48.00
1	14000.0	62700.0
2	26800.0	55700.0
3	39800.0	124000.0
4	28500.0	67700.0
5	NS	46600.0
6	29300.0	61700.0
7	21500.0	66100.0
8	18400.0	80200.0
9	24600.0	105000.0
10	7620.0	44200.0
11	25800.0	117000.0
12	22200.0	113000.0
N	11.0	12.0
Mean	23300.0	78700.0
SD	8360.0	28600.0
SE	2520.0	8260.0
Min	7620.0	44200.0
Median	24600.0	66900.0
Max	39800.0	124000.0
CV%	36.0	36.0
Geometric Mean	21700.0	74100.0

NS = No Sample
Source = C:\Testing
Date/Time = 5/19/2008 11:57:06 AM

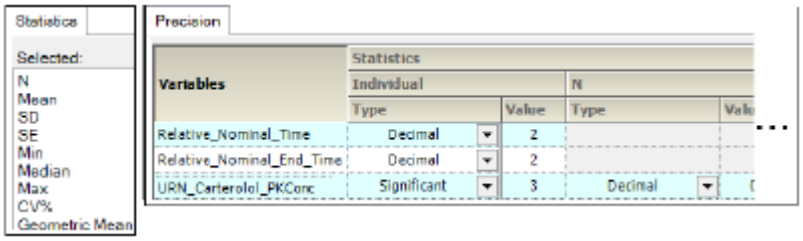


Figure 13-14. Urine cumulative amount

Treatment = Carterolol IV (Day = 14, Gender = Male, Race = White)		
Urine OH-Carterolol		
	Amount Excreted (ng) over the Nominal Collection Interval (hr)	
Subject	12.00 - 24.00	12.00 - 48.00
1	14000.0	62700.0
5	NS	46600.0
7	21500.0	66100.0
N	2.0	3.0
Mean	17800.0	58500.0
SD	5320.0	10400.0
SE	3760.0	6010.0
Min	14000.0	46600.0
Median	17800.0	62700.0
Max	21500.0	66100.0
CV%	30.0	18.0
Geometric Mean	17400.0	57800.0
NS = No Sample		
Source = CATesting		
Date/Time = 5/19/2008 11:57:06 AM		

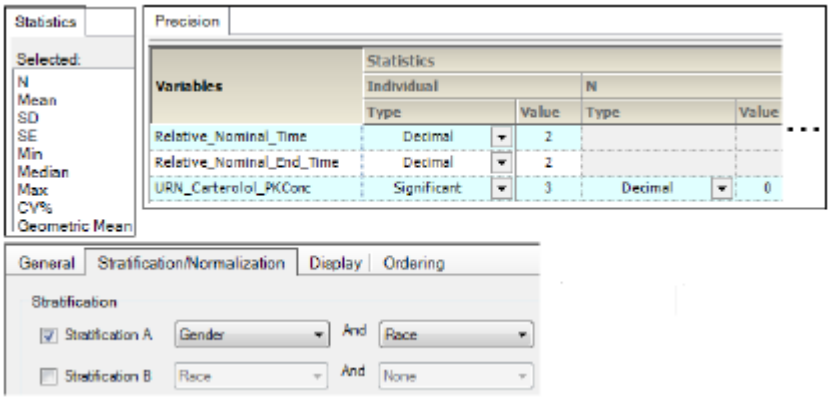


Figure 13-15. Urine cumulative amount stratified by group

Treatment = Carterolol Form A						
Urine Carterolol						
	Actual Time (hr) over Nominal Time (hr)					
	0.00 - 12.00		12.00 - 24.00		24.00 - 48.00	
Subject	Start Time (hr)	Stop Time (hr)	Start Time (hr)	Stop Time (hr)	Start Time (hr)	Stop Time (hr)
1	-1.00	12.00	14.00	30.00	28.00	50.00
2	0.00	12.00	12.00	24.00	24.00	48.00
3	0.00	12.00	12.00	24.00	24.00	48.00
4	0.00	12.00	12.00	24.00	24.00	48.00
5	0.00	12.00	12.00	24.00	24.00	48.00
6	0.00	12.00	12.00	24.00	24.00	48.00
7	0.00	12.00	12.00	24.00	24.00	48.00
8	0.00	12.00	12.00	24.00	24.00	48.00
9	0.00	12.00	12.00	24.00	24.00	48.00
10	0.00	12.00	12.00	24.00	24.00	48.00
11	0.00	12.00	12.00	24.00	24.00	48.00
12	0.00	12.00	12.00	24.00	24.00	48.00
N	12	12	12	12	12	12
Mean	-0.08	12.00	12.17	24.50	24.33	48.17
SD	0.29	0.00	0.58	1.73	1.15	0.58
SE	0.08	0.00	0.17	0.50	0.33	0.17
Min	-1.00	12.00	12.00	24.00	24.00	48.00
Median	0.00	12.00	12.00	24.00	24.00	48.00
Max	0.00	12.00	14.00	30.00	28.00	50.00
CV%	-346	0	5	7	5	1
Geometric Mean	NA	12.00	12.16	24.45	24.31	48.16
Nominal Time used as time variable for NCA						
NA = Not Applicable						

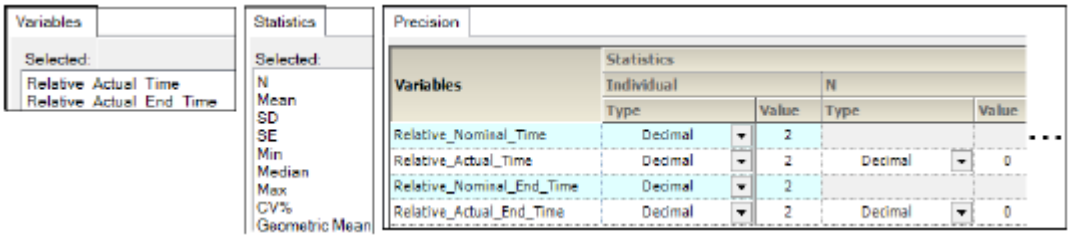


Figure 13-16. Urine actual times

PK parameter tables

Lambda_Z
Lambda_Z stratified by group
Cumulative AUC
Cumulative AUC stratified by group
Plasma PK parameter
Plasma PK parameter stratified by group
Urine PK parameter
Urine PK parameter stratified by group

Treatment = Carteolol
Plasma Carteolol
Regression Points Used in Lambda Z Calculation

Subject	λ_zLower (hr)	λ_zUpper (hr)	Number of Points	R^2
1	24	72	3	0.998
2	24	69	3	1
3	23.75	72	3	0.999
4	24	72	3	0.999
5	24	72	3	0.998
6	24	72	3	0.997
7	24	72	3	0.991
8	24	72	3	0.999
9	24	72	3	1
10	24	72	3	0.998
11	24	72	3	0.996
12	24.25	72	3	0.999
N	12	12	12	12
Mean	24	71.75	3	0.998
SD	0.11	0.87	0	0.00251
SE	0.03	0.25	0	0.000724
Min	23.75	69	3	0.991
Median	24	72	3	0.998
Max	24.25	72	3	1
CV%	0	1	0	0
Geometric Mean	24	71.75	3	0.998

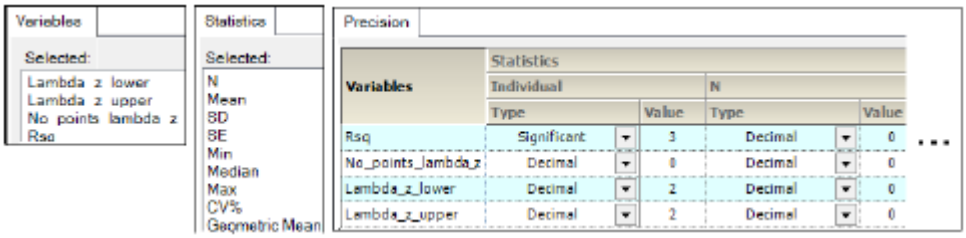


Figure 13-17. Lambda_Z

Treatment = Carterolol Form A (Smoke = No, Alcohol = No)				
Plasma OH_Carterolol				
Regression Points Used in Lambda Z Calculation				
Subject	λ_zLower (hr)	λ_zUpper (hr)	Number of Points	R^2
6	1.00	16.00	7	0.992
8	8.00	24.00	4	0.989
10	0.75	24.00	9	0.981
11	1.50	24.00	7	0.995
N	4	4	4	4
Mean	2.81	22.00	7	0.989
SD	3.47	4.00	2	0.00588
SE	1.74	2.00	1	0.00294
Min	0.75	16.00	4	0.981
Median	1.25	24.00	7	0.991
Max	8.00	24.00	9	0.995
CV%	123	18	31	1
Geometric Mean	1.73	21.69	6	0.989

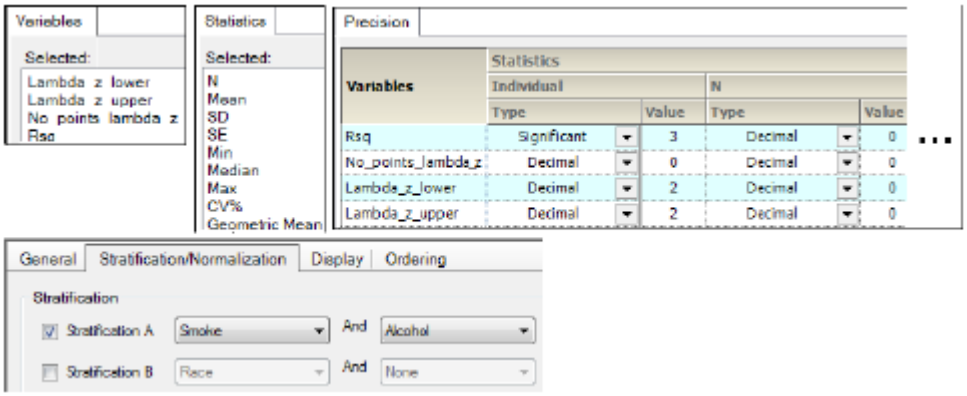


Figure 13-18. Lambda_Z stratified by group

Treatment = Carterolol										
Plasma Carterolol										
AUC (ng*hr/ml) over Nominal Time (hr)										
Subject	0	0.5	1	2	4	8	12	24	48	72
1	0	12.73	84.2	296.44	630.33	1134.91	1513.91	2221.22	2956.2	3374.14
2	0	13.4	57.8	204.8	507.37	943.56	1242.15	1786.14	2299.67	2507.4
3	0	70	193.85	395.43	757.34	1371.33	1806.23	2573.87	3390.19	3795.97
4	0	0.45	1.63	65.57	365.94	831.79	1206.98	1910.71	2639.23	3015.1
5	0	57.85	120.6	336.67	684.29	1282.54	1740.33	2603.98	3574.86	4152.09
6	0	4.98	28.33	155.58	482.4	1001.6	1416.74	2356.35	3565.98	4447.9
7	0	44	134	337.44	628.21	1156.63	1568.21	2437.38	3630.52	4408.4
8	0	66.25	185.01	388.9	741.54	1332.64	1799.41	2662.97	3550.89	4013.16
9	0	31.75	99.25	227.74	449.65	788.83	1075.67	1625.94	2255.37	2619.97
10	0	61.25	169.15	338.97	632.86	1182.66	1644.43	2604.21	3836.85	4664.2
11	0	57.75	191.69	330.93	611.78	1087.09	1394.04	1923.23	2397.15	2636.89
12	0	72.5	198.09	392.87	696.75	1168.99	1511.83	2131.51	2764.7	3106.2
N	12	12	12	12	12	12	12	12	12	12
Mean	0	41.08	122.72	289.28	599.04	1106.88	1493.33	2236.46	3071.8	3561.79
SD	0	27.04	68.45	104.27	122.09	185.77	236.85	358.25	582.97	781.61
SE	0	7.81	19.76	30.1	35.25	53.63	68.37	103.42	168.29	225.63
Min	0	0.45	1.63	65.57	365.94	788.83	1075.67	1625.94	2255.37	2307.4
Median	0	50.88	131.8	333.8	629.27	1145.77	1512.88	2288.79	3173.19	3585.06
Max	0	72.5	198.09	395.43	757.34	1371.33	1806.23	2662.97	3836.85	4664.2
CV%	NA	66	56	36	20	17	16	16	19	22
Geometric Mean	NA	24.02	81.74	262.81	586.4	1091.75	1475.33	2208.83	3019.01	3481.1
NA = Not Applicable										

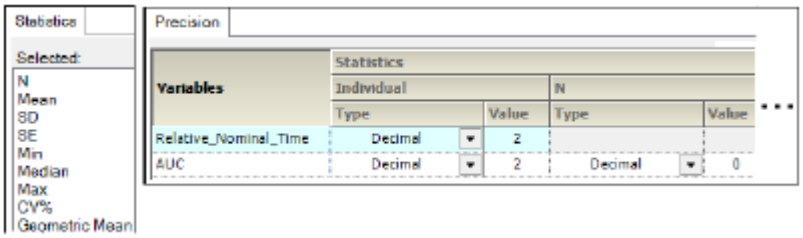


Figure 13-19. Cumulative AUC

Treatment = Carterolol Form A (Smoke = No, Alcohol = No)

Plasma OH_Carterolol

AUC (ng*hr/ml) over Nominal Time (hr)

Subject	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00
6	0.00	9.19	54.94	126.93	193.01	309.91	411.64	743.11	1159.54	1364.87	1483.25	1579.25
8	0.00	2.32	6.48	9.80	12.45	17.05	21.24	36.10	57.67	70.90	80.47	93.14
10	0.00	26.41	94.22	169.45	233.59	346.87	448.36	781.99	1167.97	1358.45	1460.24	1559.91
11	0.00	1.57	5.30	8.71	11.21	15.53	19.07	30.76	48.08	58.30	63.71	68.83
N	4	4	4	4	4	4	4	4	4	4	4	4
Mean	0.00	9.87	40.23	78.72	112.56	172.34	225.08	397.99	608.32	713.13	771.92	825.28
SD	0.00	11.55	42.78	82.07	117.49	180.82	237.10	421.26	641.39	748.88	808.17	859.54
SE	0.00	5.77	21.39	41.04	58.75	90.41	118.55	210.63	320.70	374.44	404.09	429.77
Min	0.00	1.57	5.30	8.71	11.21	15.53	19.07	30.76	48.08	58.30	63.71	68.83
Median	0.00	5.75	30.71	68.36	102.73	163.48	216.44	389.61	608.61	714.68	770.35	826.52
Max	0.00	26.41	94.22	169.45	233.59	346.87	448.36	781.99	1167.97	1364.87	1483.25	1579.25
CV%	NA	117	106	104	104	105	105	106	105	105	105	104
Geometric Mean	NA	5.45	20.53	36.81	50.09	73.04	92.98	159.38	247.54	295.89	324.62	354.50

NA = Not Applicable

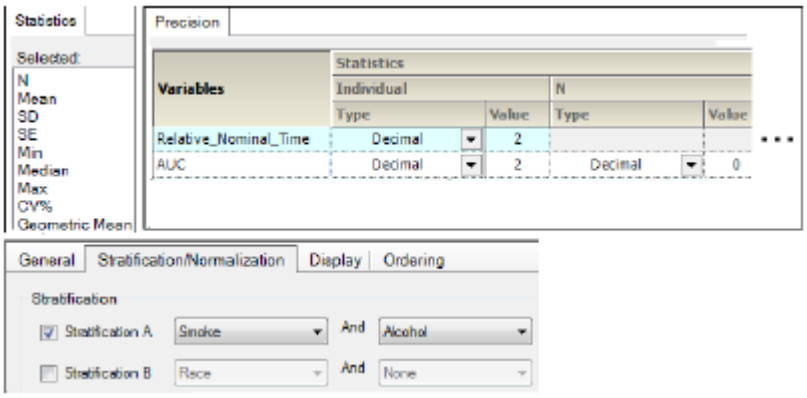


Figure 13-20. Cumulative AUC stratified by group

Treatment = Carterolol					
Plasma Carterolol					
Subject	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng*hr/ml)	AUC_{∞} (ng*hr/ml)	AUC % Extrap (%)
1	1	235	3370	3940	14
2	2	170	2510	2710	7
3	0.5	280	3800	4220	10
4	4.25	142	3020	3400	11
5	1	232	4150	5030	17
6	2	181	4450	6200	28
7	1	184	4410	5790	24
8	0.5	265	4010	4530	11
9	1	143	2620	3130	16
10	0.5	245	4660	6400	27
11	0.5	231	2640	2900	9
12	0.5	290	3110	3500	11
N	12	12	12	12	12
Mean	1.23	217	3560	4310	16
SD	1.09	51.2	782	1290	7
SE	0.32	14.8	226	372	2
Min	0.5	142	2510	2710	7
Median	1	232	3590	4080	13
Max	4.25	290	4660	6400	28
CV%	89	24	22	30	46
Geometric Mean	0.95	211	3480	4140	14

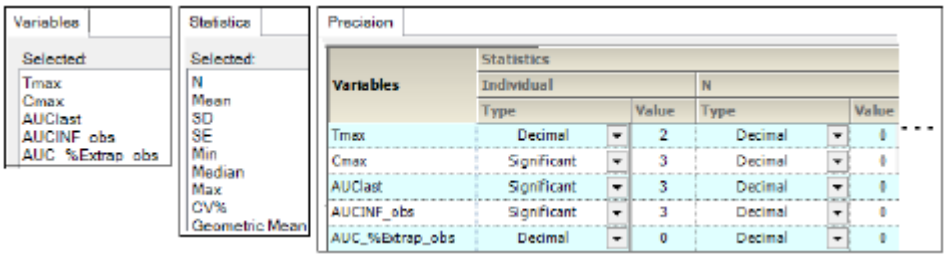


Figure 13-21. Plasma PK parameter

Treatment = Carterolol (Smoke = Yes)					
Plasma Carterolol					
Subject	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng*hr/ml)	AUC_{∞} (ng*hr/ml)	AUC % Extrap (%)
7	1.00	184	4410	5790	24
8	0.50	265	4010	4530	11
9	1.00	143	2620	3130	16
10	0.50	245	4660	6400	27
11	0.50	231	2640	2900	9
12	0.50	290	3110	3500	11
N	6	6	6	6	6
Mean	0.67	226	3570	4370	16
SD	0.26	54.1	904	1460	7
SE	0.11	22.1	369	595	3
Min	0.50	143	2620	2900	9
Median	0.50	238	3560	4020	14
Max	1.00	290	4660	6400	27
CV%	39	24	25	33	45
Geometric Mean	0.63	220	3480	4180	15

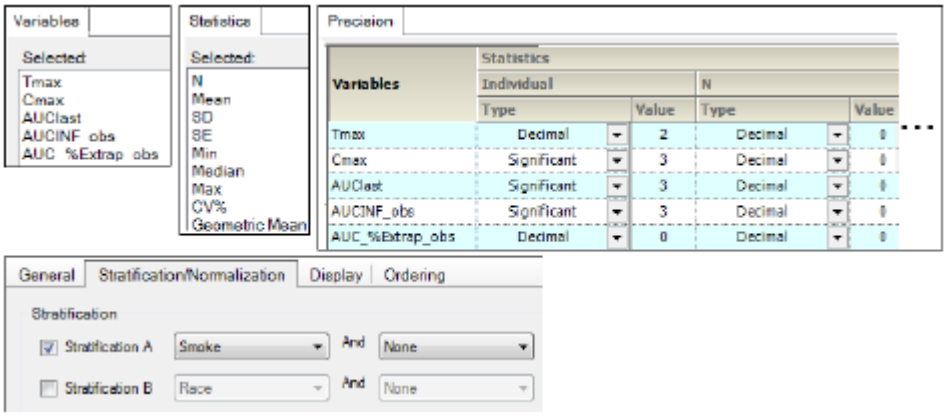


Figure 13-22. Plasma PK parameter stratified by group

Treatment = Carterolol Form A (Day 14)

Urine OH_Carterolol

Subject	Ae (ng)	fe (%)
1	34700	3.47
2	54800	5.48
3	33500	3.35
4	30900	3.09
5	59200	5.92
6	18500	1.85
7	34000	3.40
8	46000	4.60
9	47500	4.75
10	112000	11.18
11	43700	4.37
12	22900	2.29
N	12	12
Mean	44800	4.48
SD	24400	2.44
SE	7030	0.70
Min	18500	1.85
Median	39200	3.92
Max	112000	11.18
CV%	54	54
Geometric Mean	40200	4.02

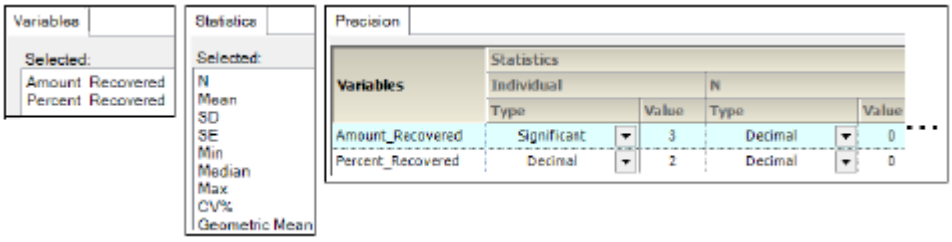


Figure 13-23. Urine PK parameter

Treatment – Carterolol Form A (Sequence – B)		
Urine OH_Carterolol		
Subject	Ae (ng)	fe (%)
5	6810	0.68
6	2680	0.27
7	3920	0.39
8	5220	0.52
N	4	4
Mean	4660	0.47
SD	1770	0.18
SE	885	0.09
Min	2680	0.27
Median	4570	0.46
Max	6810	0.68
CV%	38	38
Geometric Mean	4400	0.44

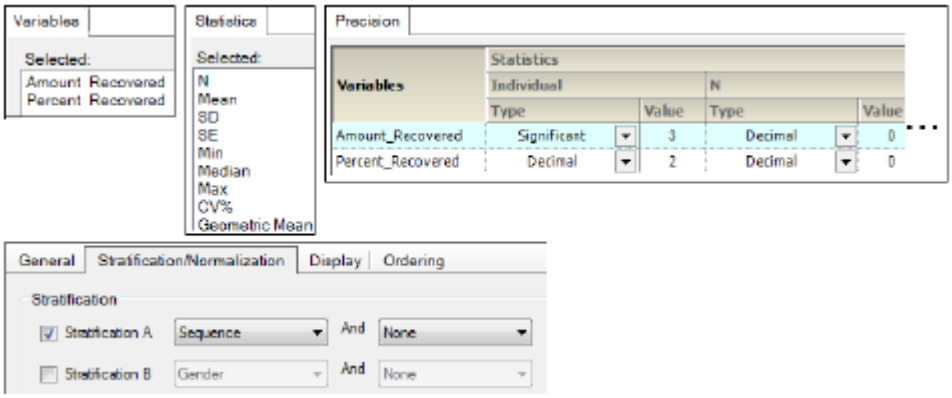


Figure 13-24. Urine PK parameter stratified by group

Intext tables

Plasma intext PK parameter
Urine intext PK parameter

Mean ± SD	Plasma Carterolol	
	Carterolol	Carterolol + Rifampin
N	12	12
$t_{1/2}$ (hr)	30.10 ± 7.18	30.25 ± 4.87
T_{max} [a] (hr)	1.23 (0.50 - 4.25)	1.10 (0.50 - 4.00)
C_{max} (ng/ml)	217 ± 51.2	199 ± 47.1
AUC_{last} (ng•hr/ml)	3560 ± 782	3350 ± 853
AUC_{∞} (ng•hr/ml)	4310 ± 1290	4040 ± 1280
CL/F (L/hr)	7.54 ± 2.17	8.09 ± 2.41
V_z/F (L)	310 ± 49.9	344 ± 83.3
[a] Mean (Min - Max)		

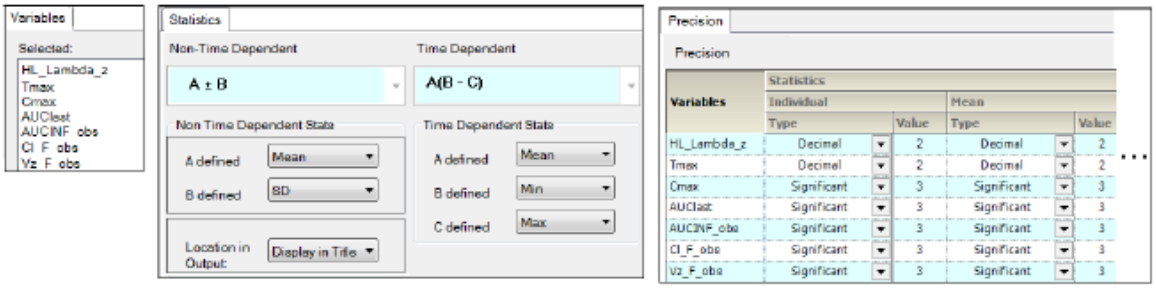


Figure 13-25. Plasma intext PK parameter

Mean ± SD	Urine Carterolol		
	Carterolol Form A	Carterolol Form B	Carterolol Form C
N	12	12	12
Ae (ng)	21900 ± 13700	35000 ± 13900	47100 ± 14600
fe (%)	2.19 ± 1.37	3.50 ± 1.39	4.71 ± 1.46

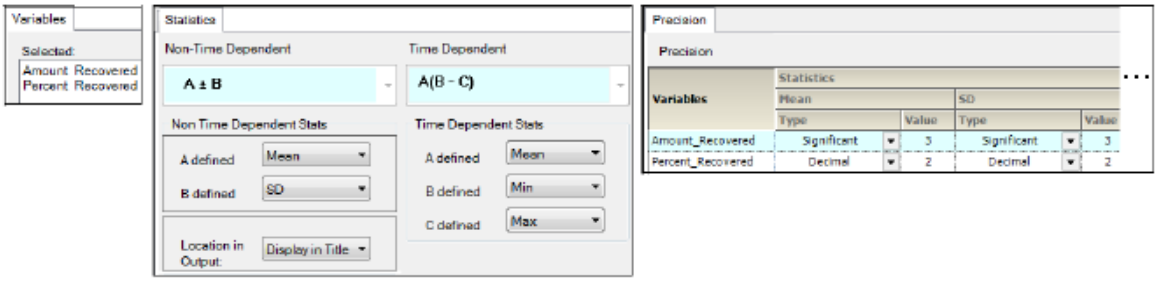


Figure 13-26. Urine intext PK parameter

PK statistics tables

Plasma PK ratios
Urine PK ratios
Plasma PK statistics
Plasma PK statistics
Plasma PK statistics table with multiple tabs of data.
Urine PK statistics
Urine PK statistics table with multiple tabs of data.

PK Parameter Ratios (Test/Reference)				
Subject	C_{max} (µg/ml)	AUC_{last} (µg•hr/ml)	AUC_{∞} (µg•hr/ml)	AUC_{τ} (µg•hr/ml)
1	1.98	3.47	3.13	3.08
2	6.81	4.42	4.26	5.28
3	1.16	0.704	0.702	0.744
4	0.860	0.971	0.932	0.915
5	0.862	0.766	0.729	0.889
6	0.170	0.135	0.131	0.134
7	2.32	3.23	3.13	3.13
8	11.3	5.87	5.43	6.35
9	1.67	2.33	2.28	2.28
10	1.00	1.00	1.00	1.00
11	37.2	77.3	76.8	60.7
12	NC	NC	NC	NC
N	11	11	11	11
Mean	5.93	9.11	8.95	7.69
SD	10.9	22.7	22.5	17.7
SE	3.28	6.84	6.80	5.34
Min	0.170	0.135	0.131	0.134
Median	1.67	2.33	2.28	2.28
Max	37.2	77.3	76.8	60.7
CV%	183	249	252	230
Geometric Mean	2.08	2.11	2.04	2.11
NC = Not calculated				
Test = Carterolol PO Form B				
Reference = Carterolol PO Form A				
Values are calculated by division (Test/Ref)				

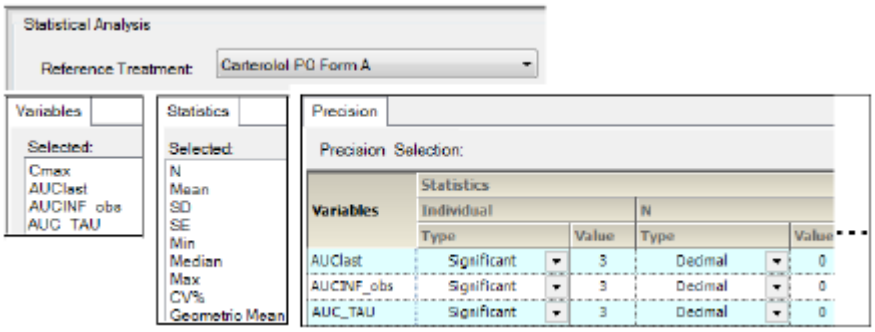


Figure 13-27. Plasma PK ratios

PK Parameter Ratios (Test/Reference)		
Urine Carterolol		
Subject	Ae (ng)	fe # (%)
1	4.62	16.76
2	0.401	-14.90
3	0.364	-9.68
4	3.88	39.07
5	1.06	1.64
6	4.51	24.18
7	1.85	12.45
8	2.59	31.51
9	1.63	12.57
10	0.43	-29.10
11	1.59	11.53
12	3.58	25.39
N	12.00	12.00
Mean	2.21	10.12
SD	1.59	20.03
SE	0.46	5.78
Min	0.36	-23.32
Median	0.36	12.51
Max	0.36	39.07
CV%	0.36	198.00
Geometric Mean	0.36	NA
NA = Not Applicable Test = Carterolol Form B Reference = Carterolol Form A # Values are calculated by subtraction (Test - Ref)		

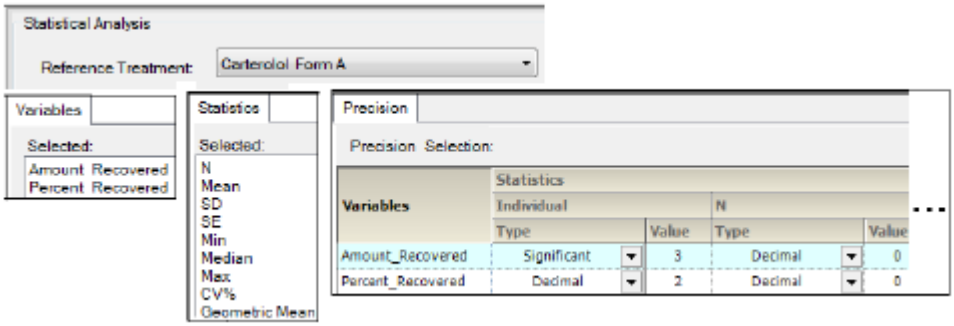


Figure 13-28. Urine PK ratios

PK Stats: Statistical Comparison for a (Multiple-Dose) Crossover Design				
	P-Values from Log-Transformed Analysis of Variance			
Factor	C_{max} (µg/ml)	AUC_{last} (µg•hr/ml)	AUC_{∞} (µg•hr/ml)	AUC_{τ} (µg•hr/ml)
Treatment	0.267	0.278	0.359	0.252
Intrasubject CV%	458	453	473	461
	Pair-wise Comparison: Carterolol PO Form B (Test) vs. Carterolol PO Form A (Ref)			
Ratio of Least Square Geometric Means (%)	231	226	204	238
90% Confidence Interval around Ratio	65-816	64-796	55-752	67-842
Probability < 80%	0.0817	0.0852	0.116	0.0768
Probability > 125%	0.794	0.786	0.737	0.804
Total Probability (<80%,>125%)	0.875	0.872	0.853	0.881
Statistical Power (%)	11.3	11.4	11.3	11.3
Treatments = [Carterolol PO Form A, Carterolol PO Form B]				

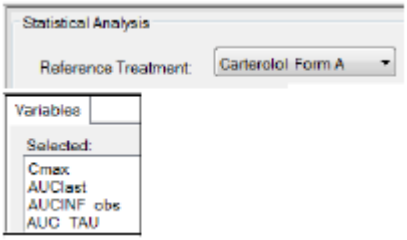


Figure 13-29. Plasma PK statistics

Dependent	Units	Diagnostic	Value
Ln(Cmax)	ng/ml	Total Observations	24
Ln(Cmax)	ng/ml	Observations Used	24
Ln(Cmax)	ng/ml	Obs. Missing Model Terms	0
Ln(Cmax)	ng/ml	Residual SS	1.262242343
Ln(Cmax)	ng/ml	Residual df	22
Ln(Cmax)	ng/ml	Residual Variance	0.057374652
Ln(Cmax)	ng/ml	REML log(likelihood)	0.223021445
Ln(Cmax)	ng/ml	-2 * REML log(likelihood)	-0.446042889
Ln(Cmax)	ng/ml	Akaike's Information Criterion	5.553957111
Ln(Cmax)	ng/ml	Schwarz's Bayesian Criterion	8.827084471
Ln(Cmax)	ng/ml	Hessian eigenvalue	3341.585341
Ln(AUClast)	hr*ng/ml	Total Observations	24
Ln(AUClast)	hr*ng/ml	Observations Used	24

Diagnostics | Sequential Tests | Partial Tests ...

Figure 13-30. Plasma PK statistics table with multiple tabs of data.

PK Stats: Statistical Comparison for a (Multiple-Dose) Crossover Design		
	P-Values from Log-Transformed Analysis of Variance	
	Ae	fe
Factor	(ng)	(%)
Period	0.763	0.763
Sequence	< 0.05	< 0.05
Treatment	< 0.05	< 0.05
Intersubject CV%	NC	NC
Intrasubject CV%	63.4	63.4
	Pair-wise Comparison: Carterolol Form B (Test) vs. Carterolol Form A (Ref)	
Ratio of Least Square Geometric Means (%)	160	160
90% Confidence Interval around Ratio	102-251	102-251
Probability < 80%	0.00730	0.00730
Probability > 125%	0.825	0.825
Total Probability (<80%,>125%)	0.832	0.832
Statistical Power (%)	20.7	20.7
	Pair-wise Comparison: Carterolol Form C (Test) vs. Carterolol Form A (Ref)	
Ratio of Least Square Geometric Means (%)	231	231
90% Confidence Interval around Ratio	148-362	148-362
Probability < 80%	0.000285	0.000285
Probability > 125%	0.986	0.986
Total Probability (<80%,>125%)	0.986	0.986
Statistical Power (%)	20.7	20.7
Treatments = [Carterolol Form A, Carterolol Form B, Carterolol Form C]		
NC - Not Calculated		

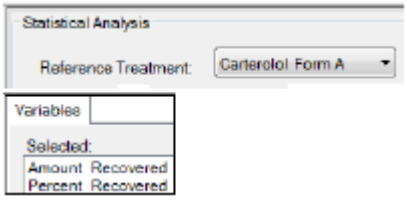
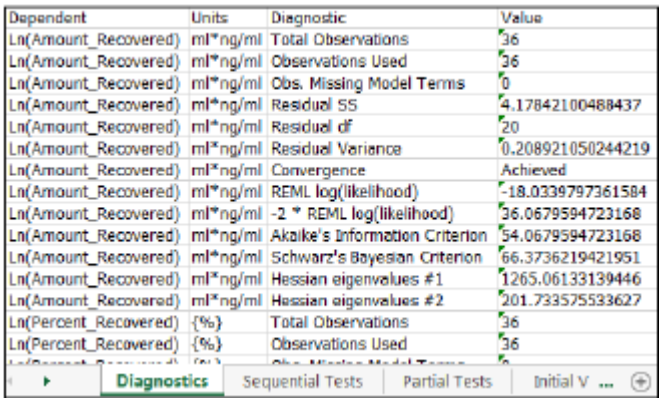


Figure 13-31. Urine PK statistics

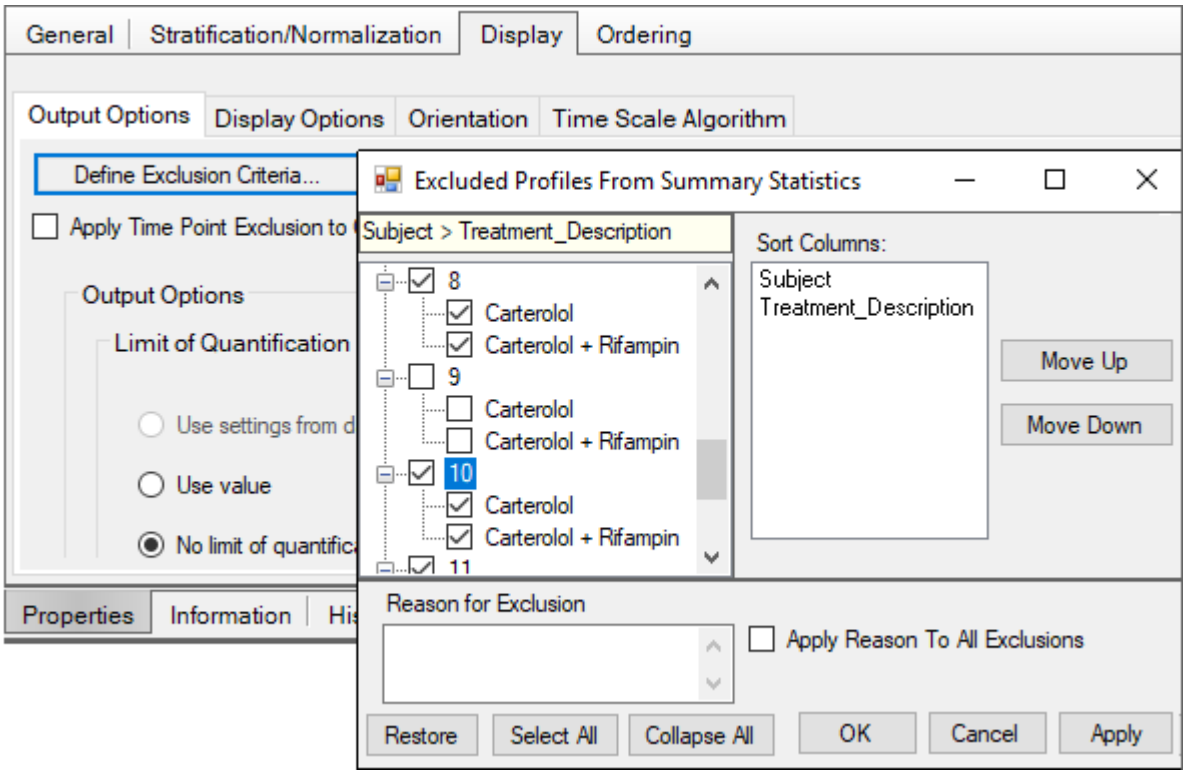


Dependent	Units	Diagnostic	Value
Ln(Amount_Recovered)	ml*ng/ml	Total Observations	36
Ln(Amount_Recovered)	ml*ng/ml	Observations Used	36
Ln(Amount_Recovered)	ml*ng/ml	Obs. Missing Model Terms	0
Ln(Amount_Recovered)	ml*ng/ml	Residual SS	4.17842100488437
Ln(Amount_Recovered)	ml*ng/ml	Residual df	20
Ln(Amount_Recovered)	ml*ng/ml	Residual Variance	0.208921050244219
Ln(Amount_Recovered)	ml*ng/ml	Convergence	Achieved
Ln(Amount_Recovered)	ml*ng/ml	REML log(likelihood)	-18.0339797361584
Ln(Amount_Recovered)	ml*ng/ml	-2 * REML log(likelihood)	36.0679594723168
Ln(Amount_Recovered)	ml*ng/ml	Akaike's Information Criterion	54.0679594723168
Ln(Amount_Recovered)	ml*ng/ml	Schwarz's Bayesian Criterion	66.3736219421951
Ln(Amount_Recovered)	ml*ng/ml	Hessian eigenvalues #1	1265.06133139446
Ln(Amount_Recovered)	ml*ng/ml	Hessian eigenvalues #2	201.733575533627
Ln(Percent_Recovered)	{%}	Total Observations	36
Ln(Percent_Recovered)	{%}	Observations Used	36

Figure 13-32. Urine PK statistics table with multiple tabs of data.

Profile exclusions table

Profile Exclusions	
Subject	Treatment
8	Carterolol
8	Carterolol + Rifampin
10	Carterolol
10	Carterolol + Rifampin
11	Carterolol
11	Carterolol + Rifampin
12	Carterolol
12	Carterolol + Rifampin



Plasma time concentration graphs

Concentration by subject
Concentration by treatment

Concentration by treatment, sorted by treatment and strat. by group

Summary concentration by treatment

Summary conc. by treatment, sorted by treatment, and strat. by group
Summary conc. by treatment, sorted and strat. by group

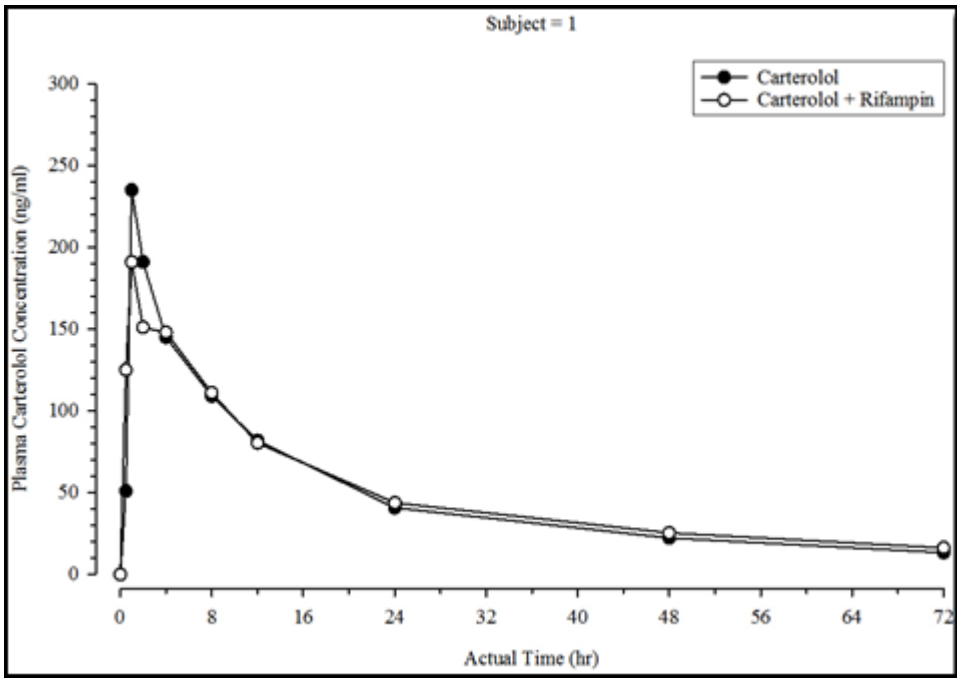
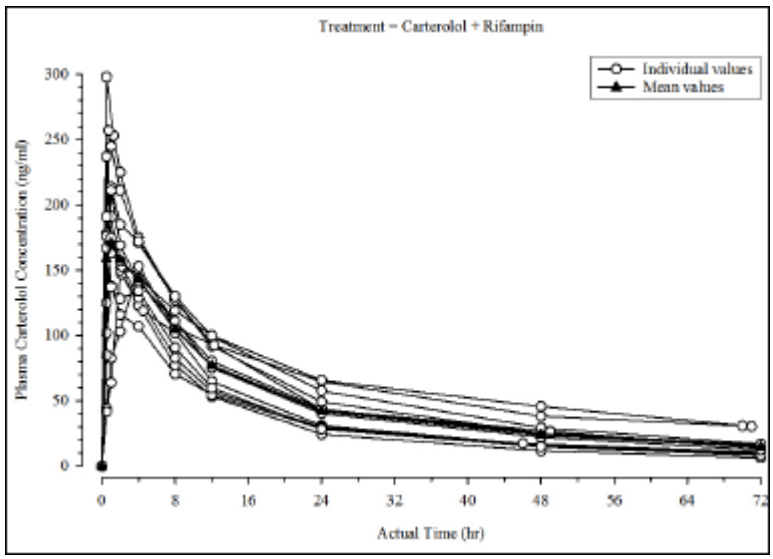


Figure 13-33. Concentration by subject



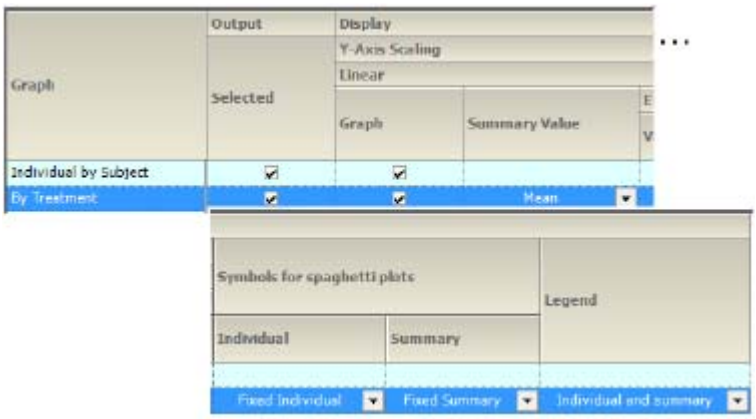
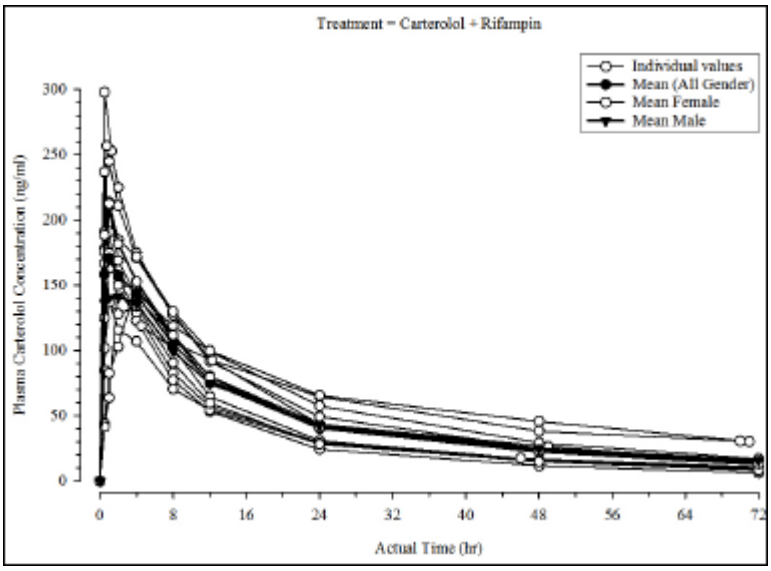


Figure 13-34. Concentration by treatment



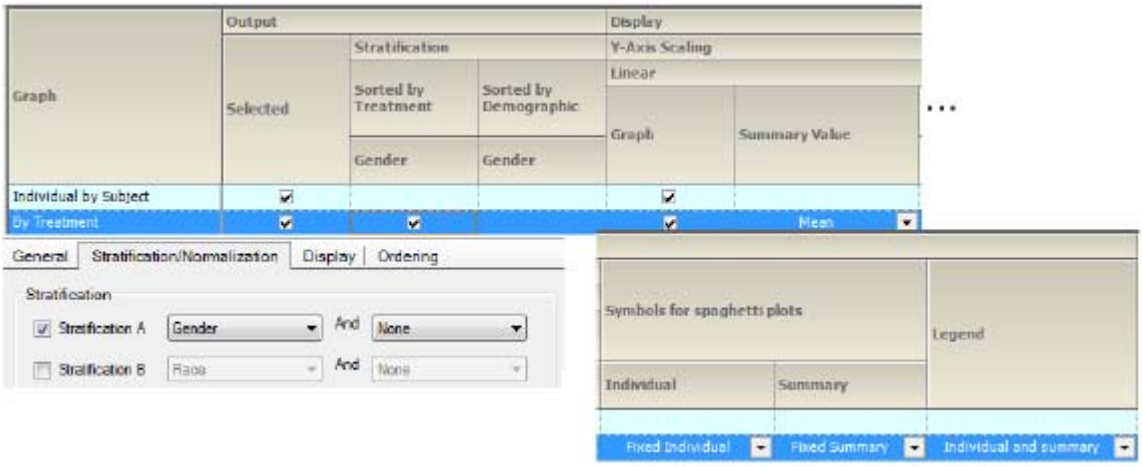
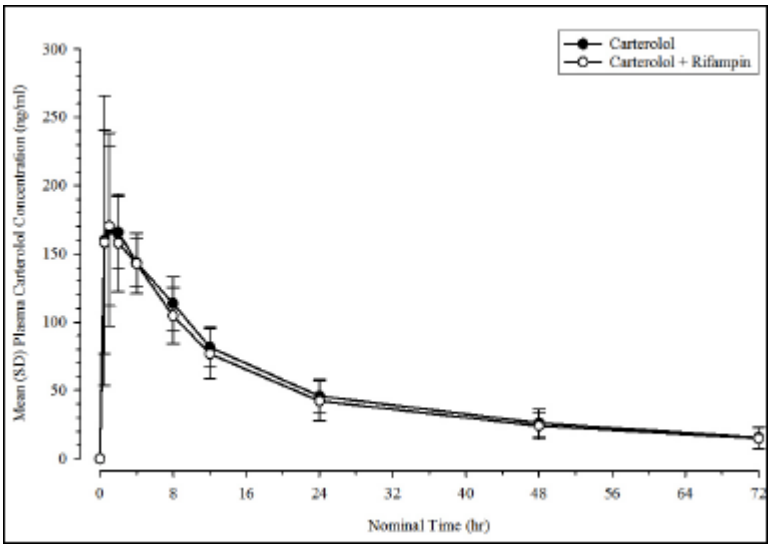
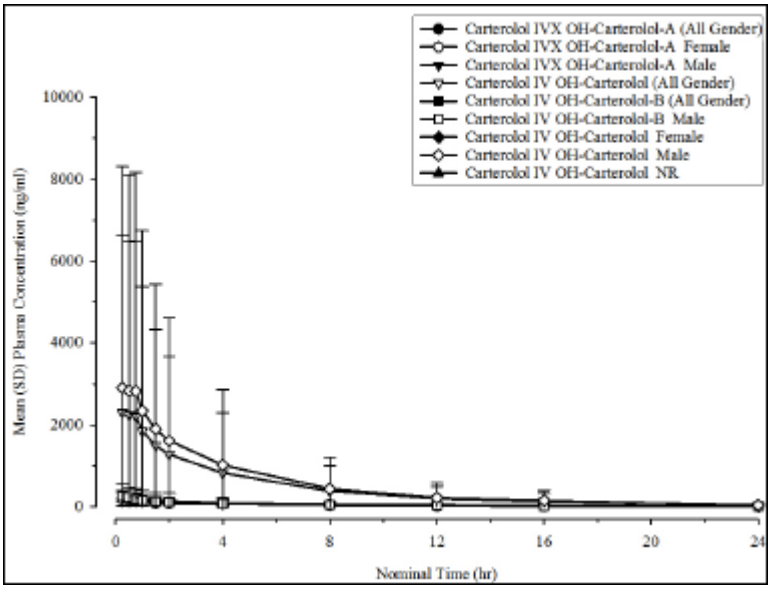


Figure 13-35. Concentration by treatment, sorted by treatment and strat. by group



Graph	Output	Display			
	Selected	Y-Axis Scaling			
		Linear			
		Graph	Summary Value	Error	
				Value	Direction
Individual by Subject	☑	☑			
By Treatment	☑	☑	Mean		
Summary by Treatment	☑	☑	Mean	SD	Both

Figure 13-36. Summary concentration by treatment



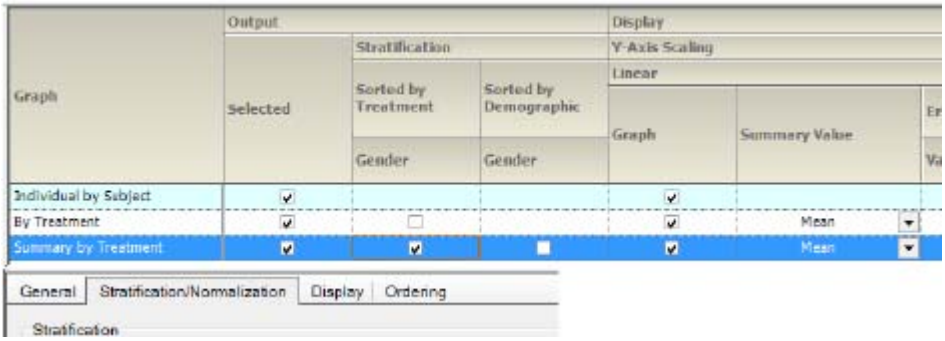
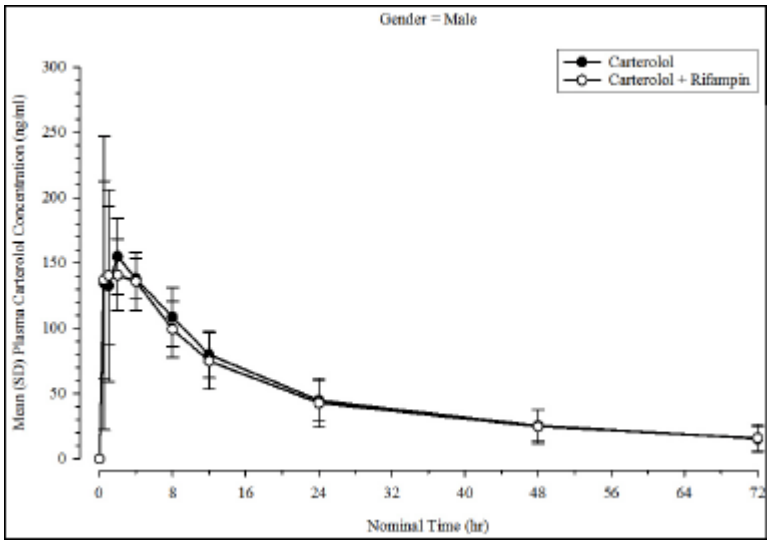


Figure 13-37. Summary conc. by treatment, sorted by treatment, and strat. by group



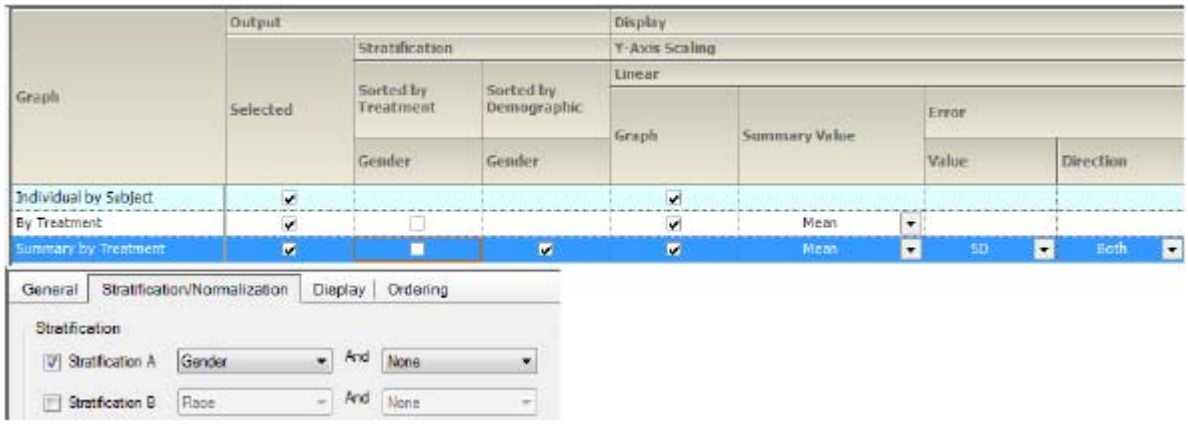


Figure 13-38. Summary conc. by treatment, sorted and strat. by group

Urine time concentration graph

Excretion rate by subject
Excretion rate by treatment
Excretion rate by treatment, sorted by treatment, and strat. by group

Summary excretion rate by treatment
Summary excretion rate by treatment, sorted by treatment, and strat. by group
Summary excretion rate by treatment, sorted and strat. by group

Percent dose remaining by subject
Percent dose remaining by treatment

Percent dose remaining by treatment, sorted by treatment, and strat. by group

Summary percent dose remaining by treatment

Summary percent dose remaining by treatment, sorted by treatment, and strat. by group
Summary percent dose remaining by treatment, sorted and strat. by group

Cumulative amount excreted by subject
Cumulative amount excreted by treatment

Cumulative amt. excreted by treatment, sorted by treatment, and strat. by group

Summary cum. amt. excreted by treatment

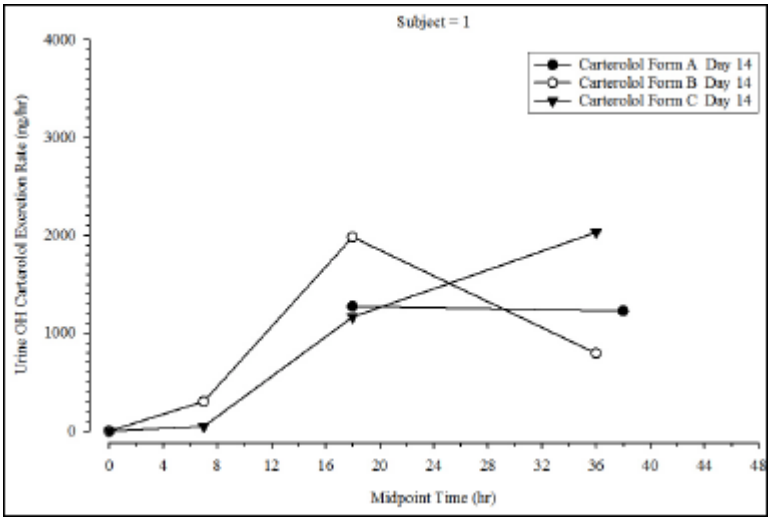
Summary cum. amt. excreted by treatment, sorted by treatment, and strat. by group
Summary cum. amt. excreted by treatment, sorted and strat. by group

Amount excreted by subject
Amount excreted by treatment

Amount excreted by treatment, sorted by treatment, and strat. by group

Summary amount excreted by treatment

Summary amt. excreted by treatment, sorted by treatment, and strat. by group
Summary amt. excreted by treatment, sorted and strat. by group



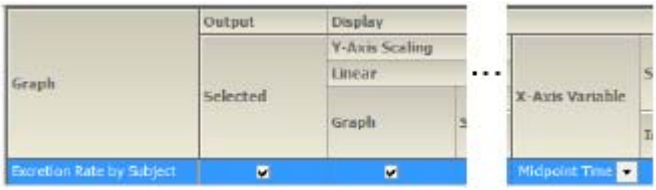
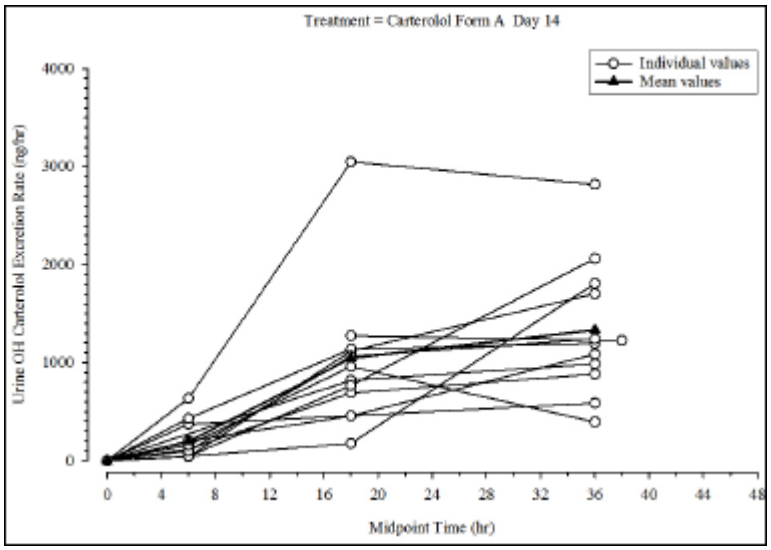


Figure 13-39. Excretion rate by subject



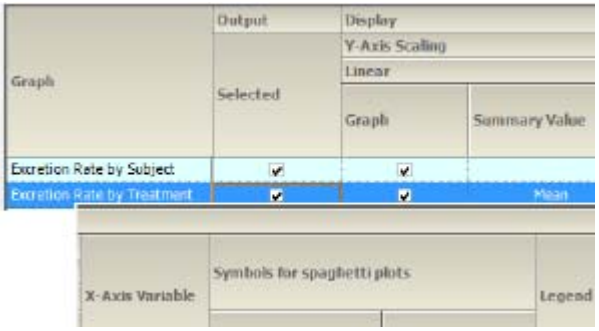
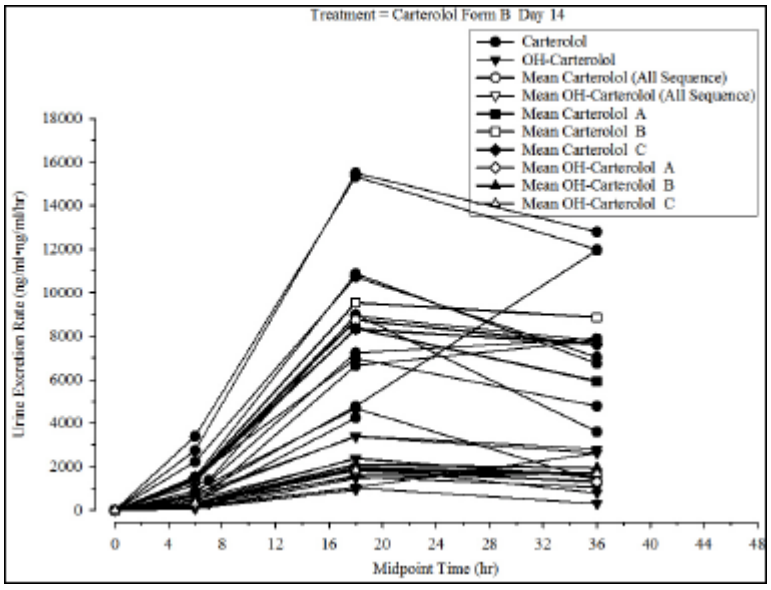


Figure 13-40. Excretion rate by treatment



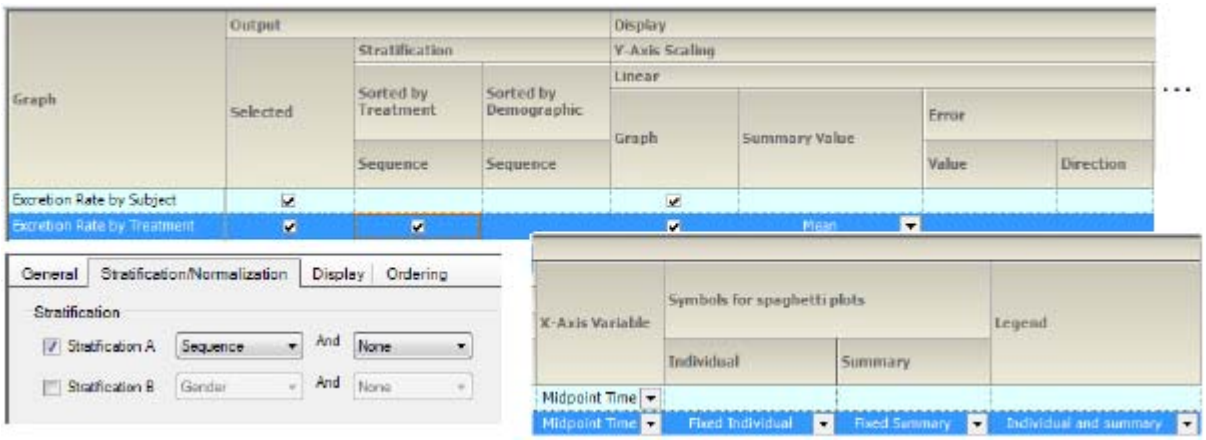
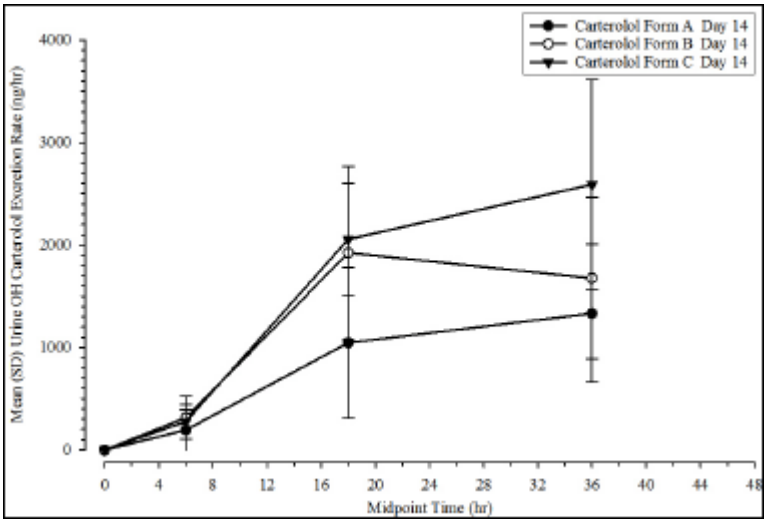


Figure 13-41. Excretion rate by treatment, sorted by treatment, and strat. by group



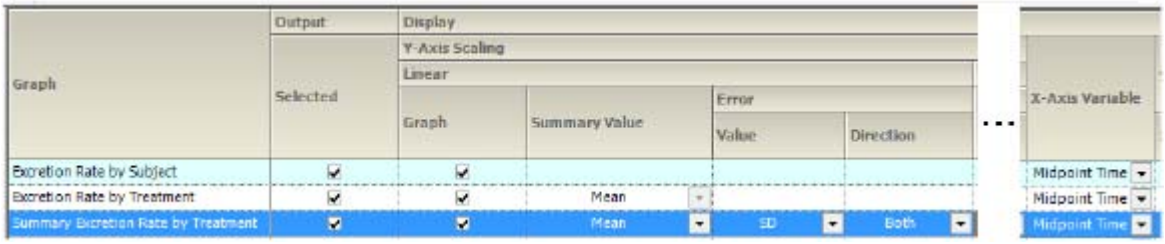


Figure 13-42. Summary excretion rate by treatment

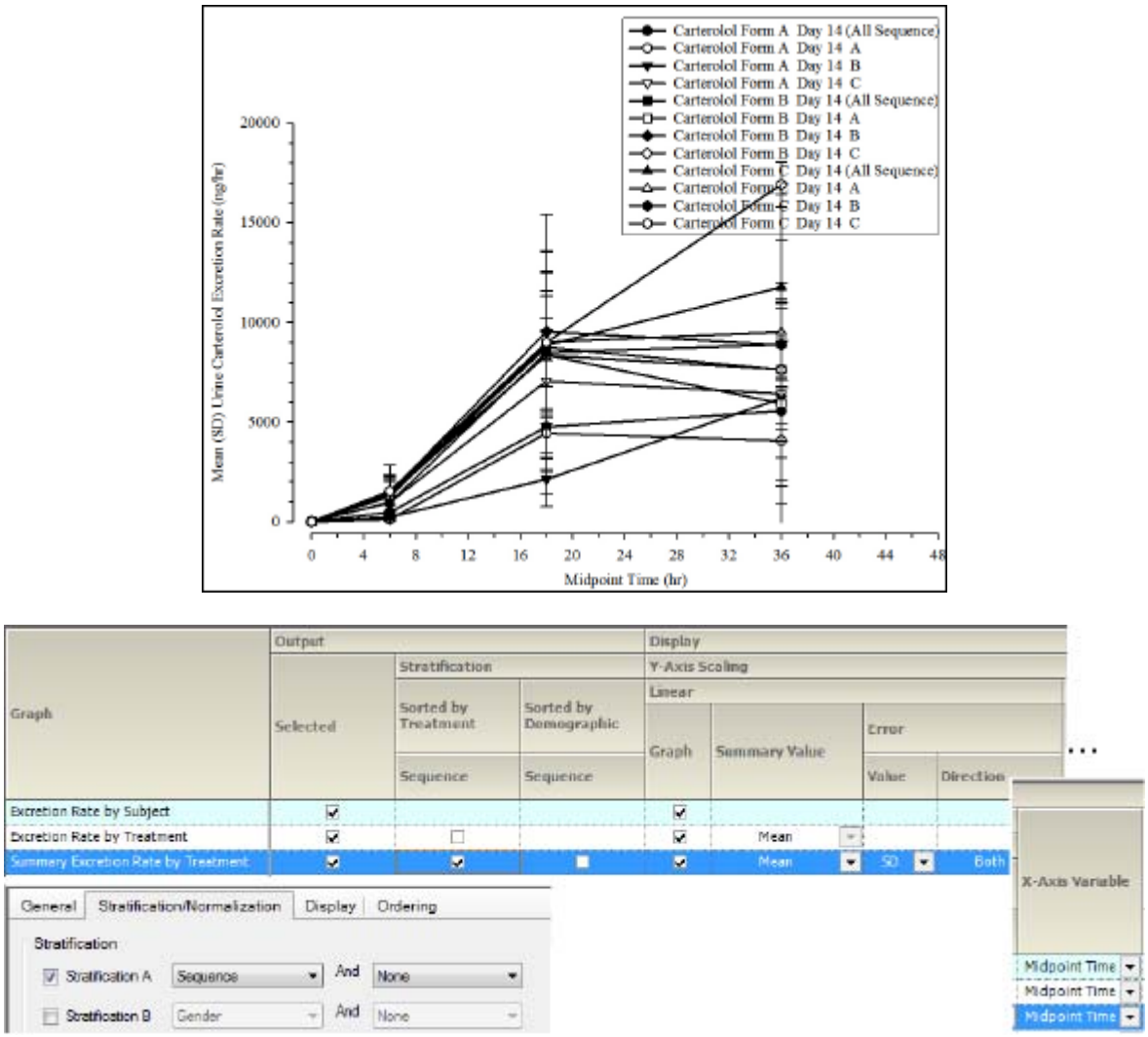
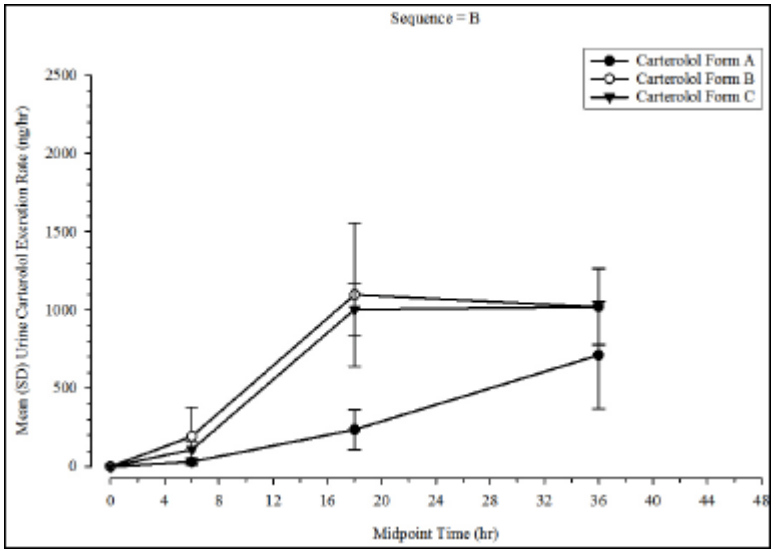


Figure 13-43. Summary excretion rate by treatment, sorted by treatment, and strat. by group



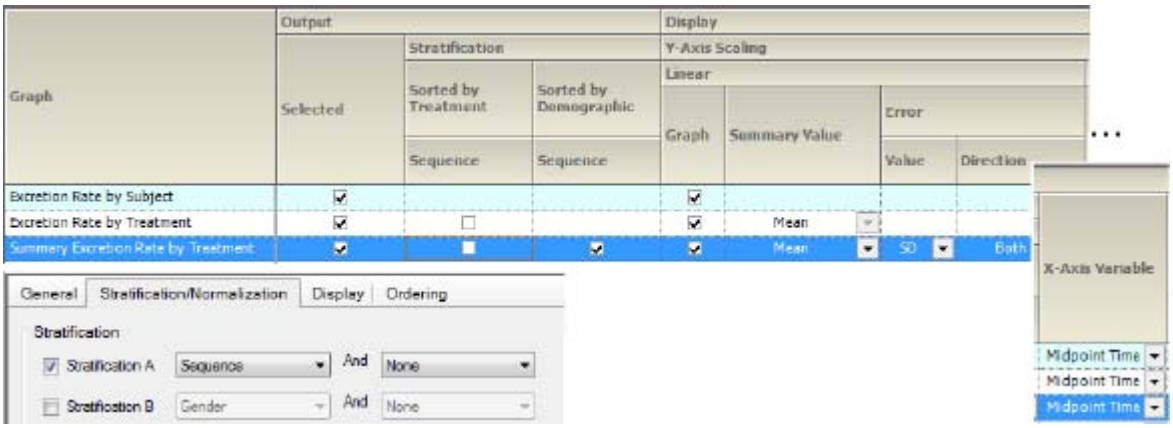
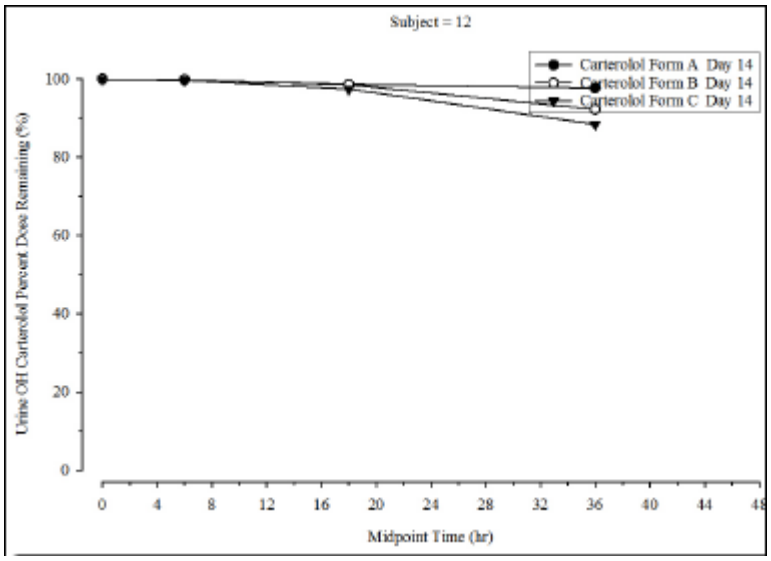


Figure 13-44. Summary excretion rate by treatment, sorted and strat. by group



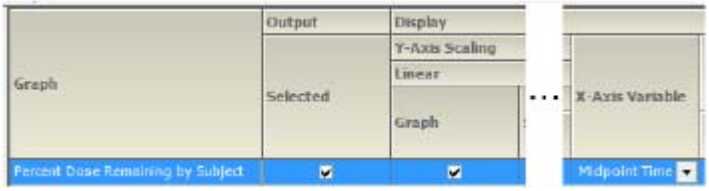
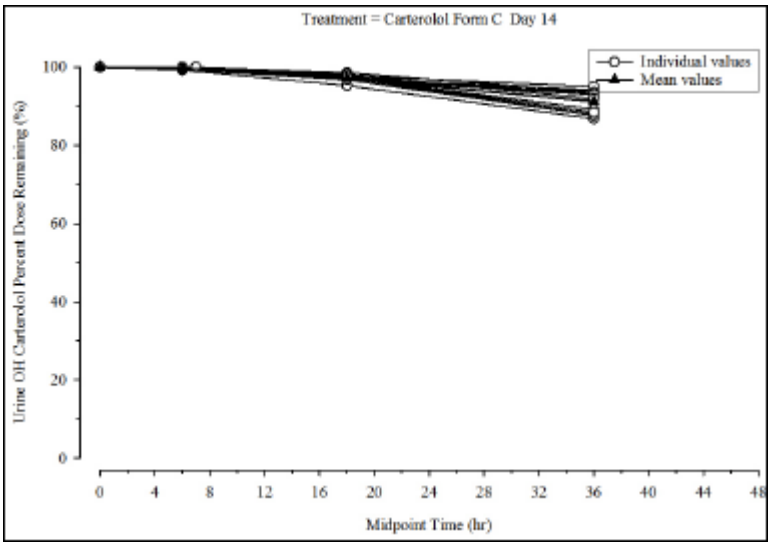


Figure 13-45. Percent dose remaining by subject



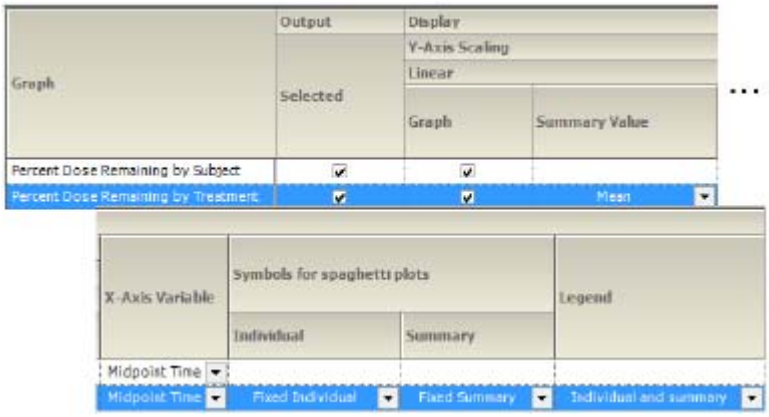
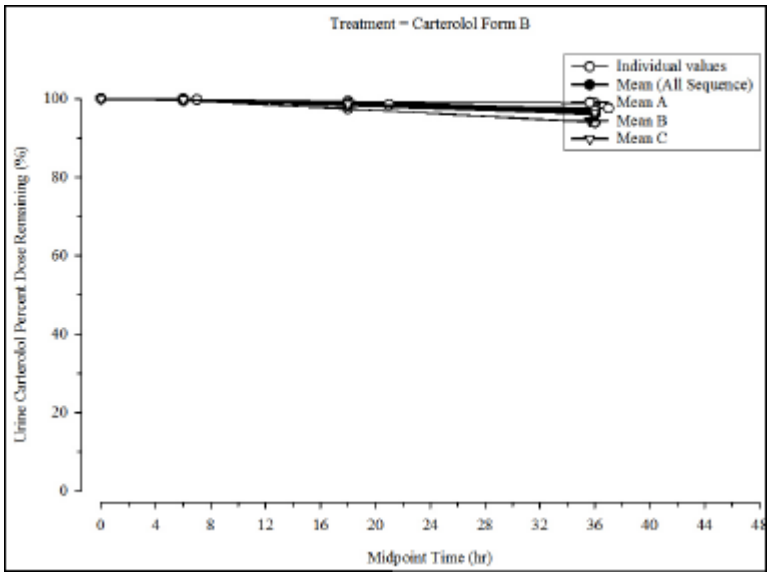


Figure 13-46. Percent dose remaining by treatment



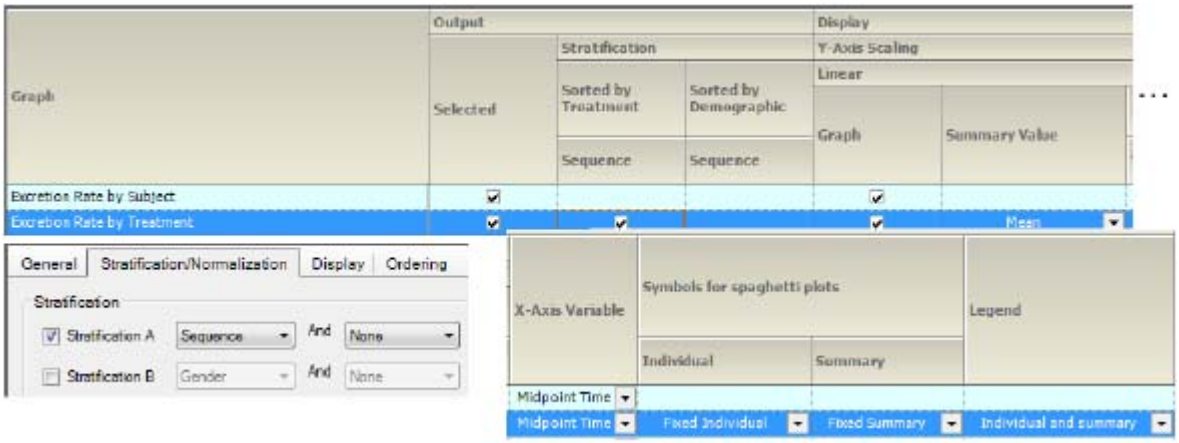
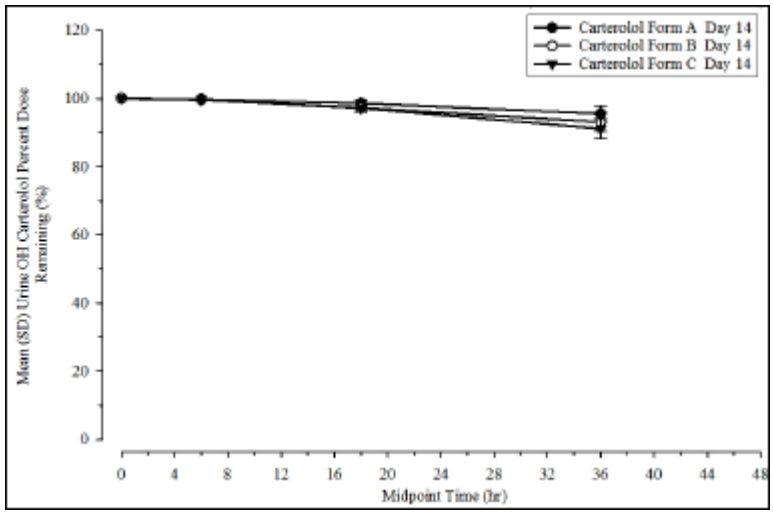


Figure 13-47. Percent dose remaining by treatment, sorted by treatment, and strat. by group



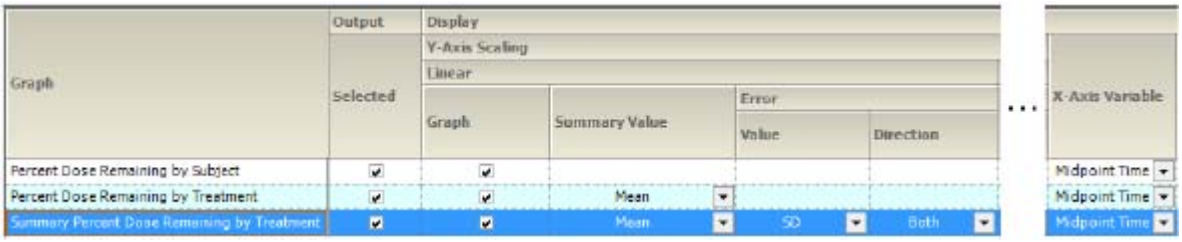


Figure 13-48. Summary percent dose remaining by treatment

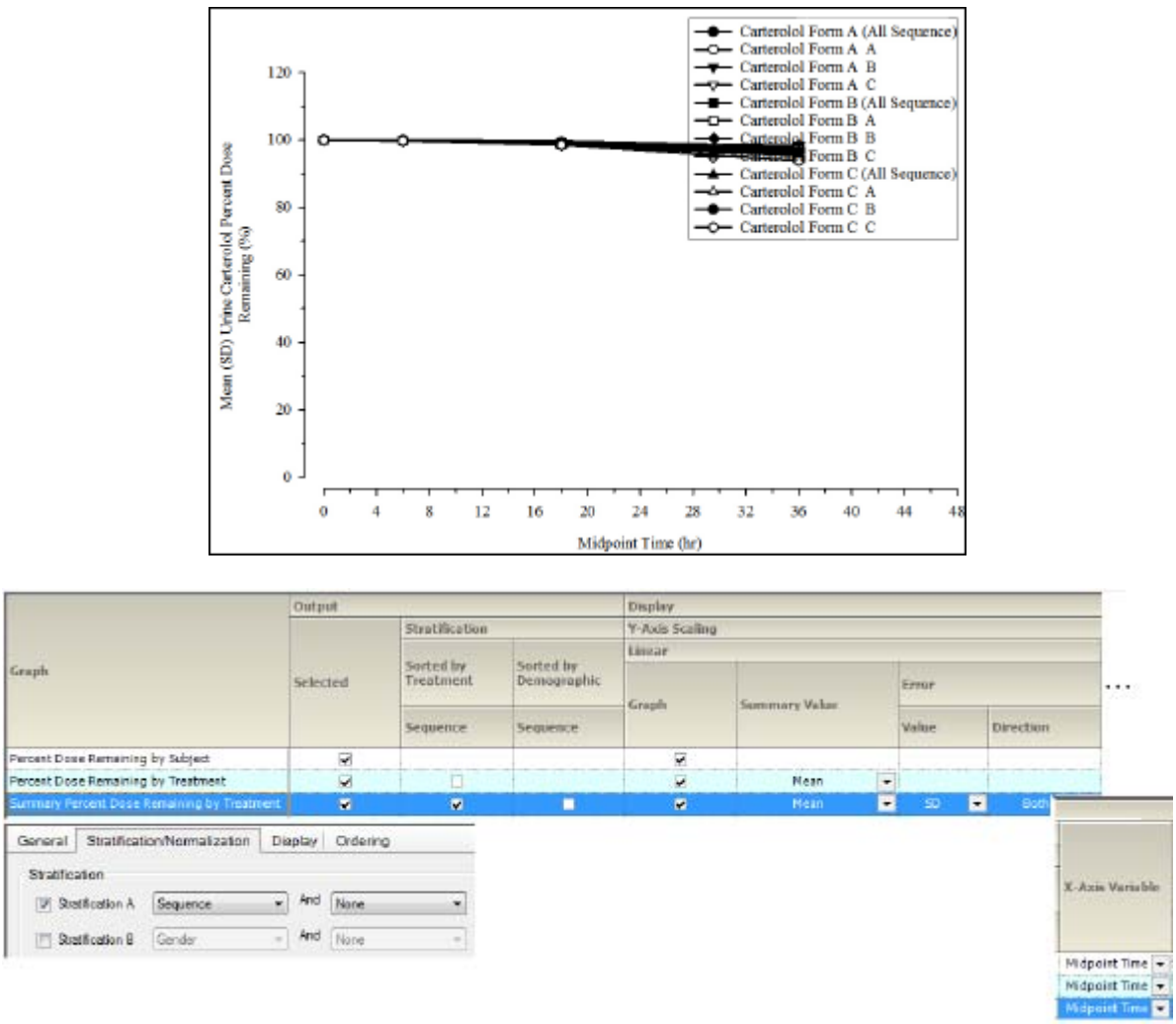
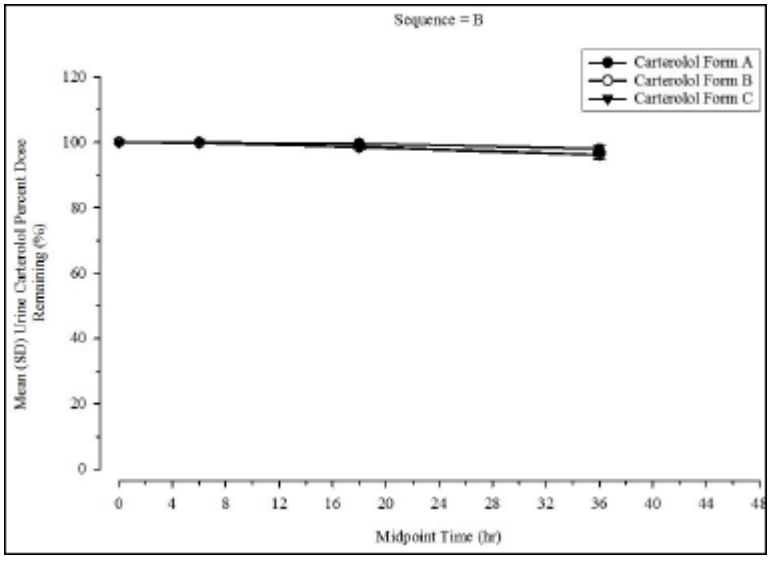


Figure 13-49. Summary percent dose remaining by treatment, sorted by treatment, and strat. by group



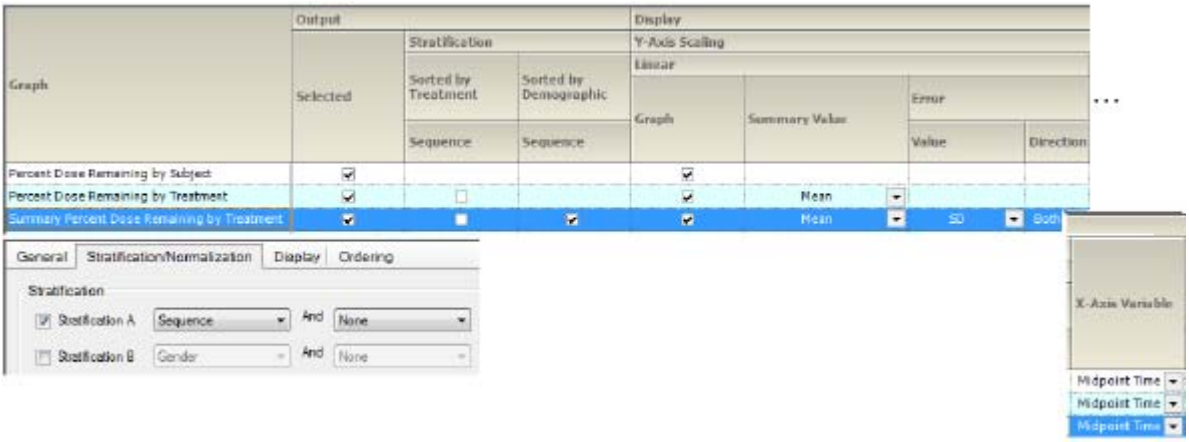
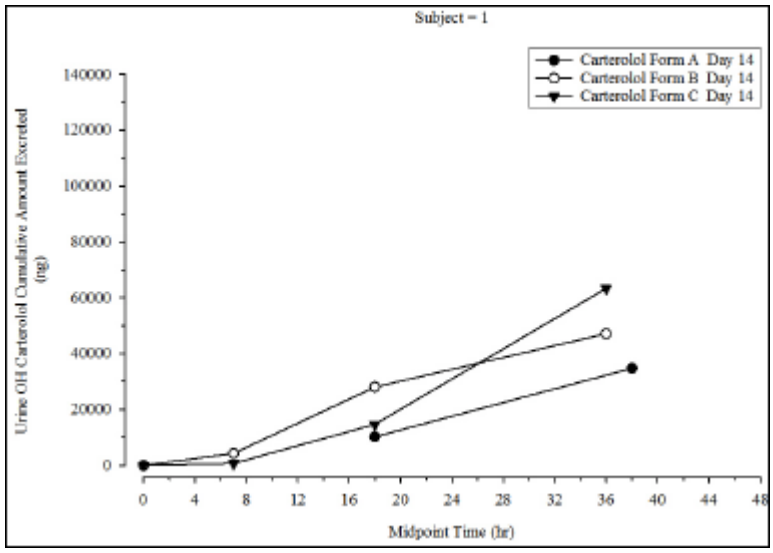


Figure 13-50. Summary percent dose remaining by treatment, sorted and strat. by group



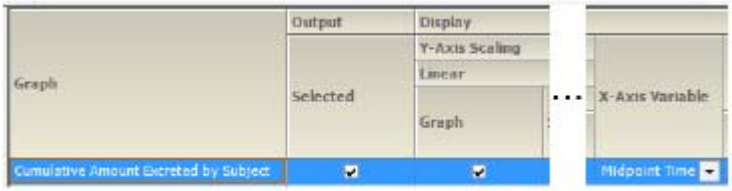
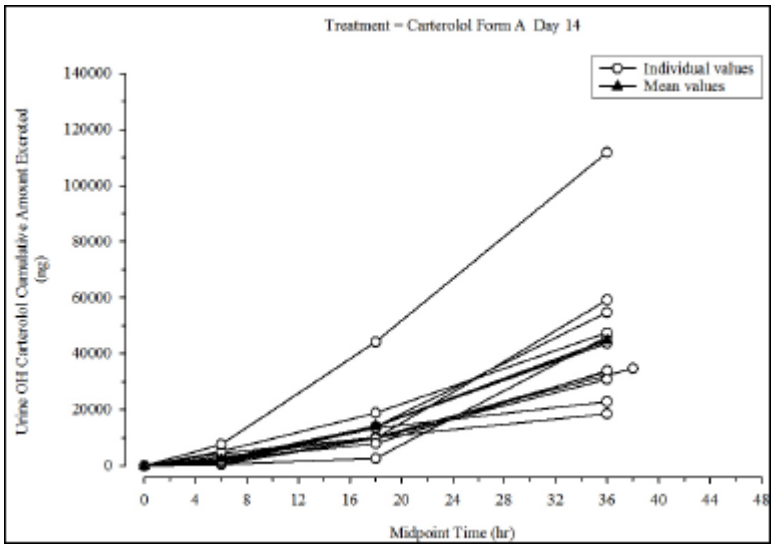


Figure 13-51. Cumulative amount excreted by subject



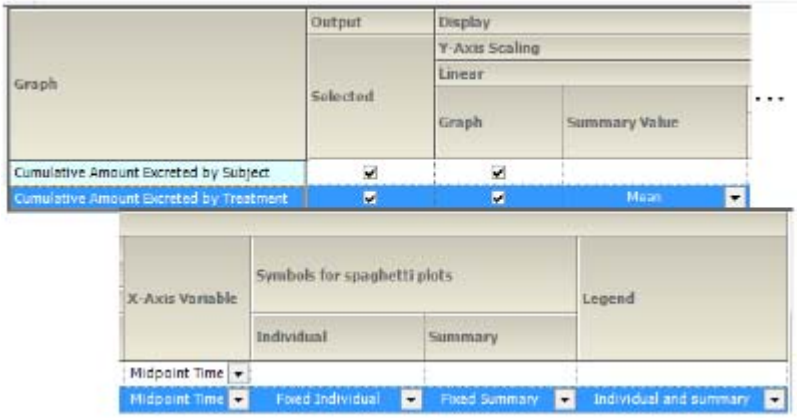
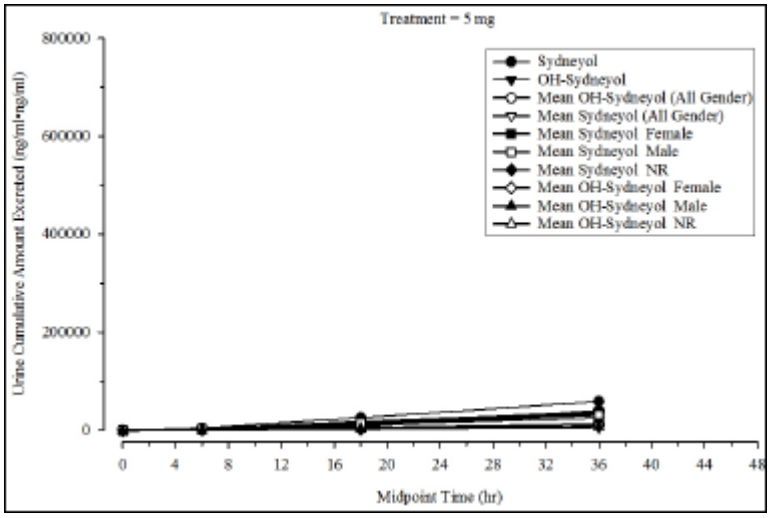


Figure 13-52. Cumulative amount excreted by treatment



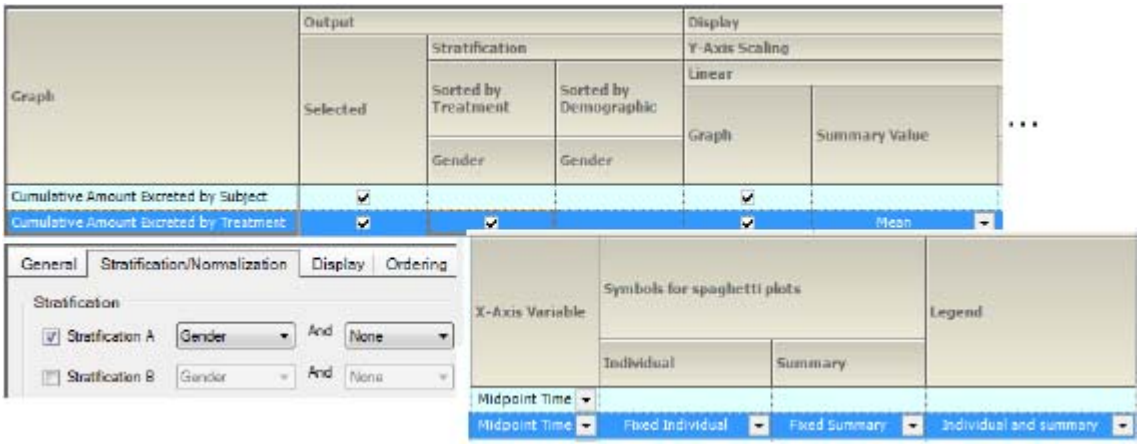
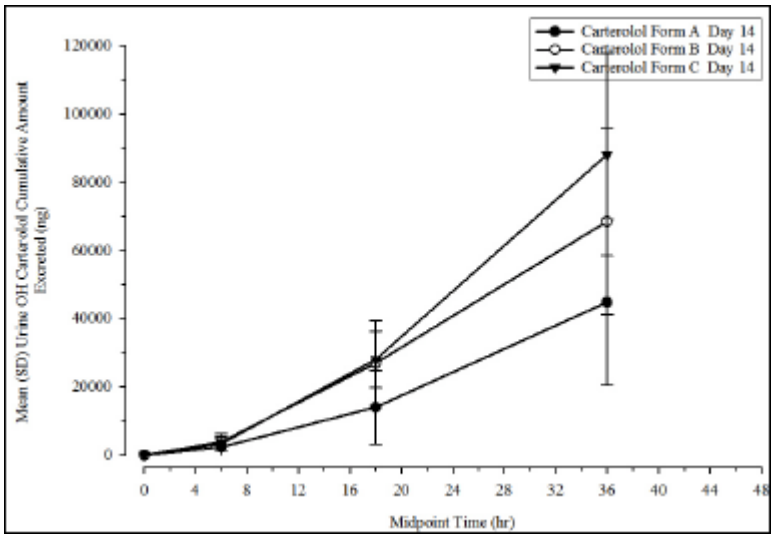


Figure 13-53. Cumulative amt. excreted by treatment, sorted by treatment, and strat. by group



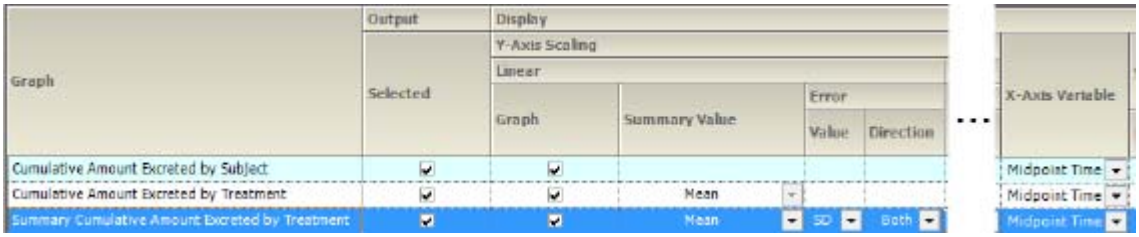


Figure 13-54. Summary cum. amt. excreted by treatment

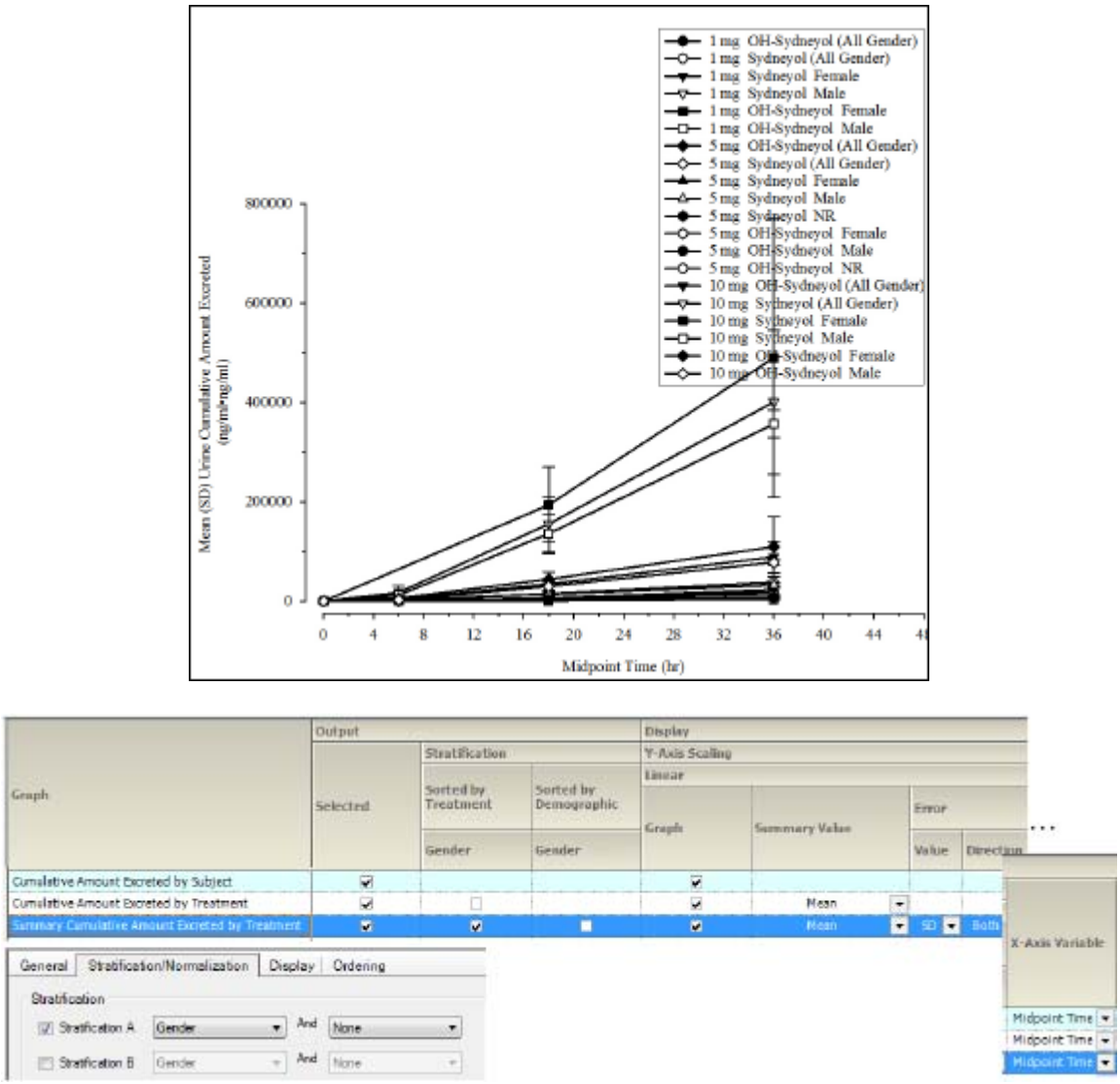


Figure 13-55. Summary cum. amt. excreted by treatment, sorted by treatment, and strat. by group

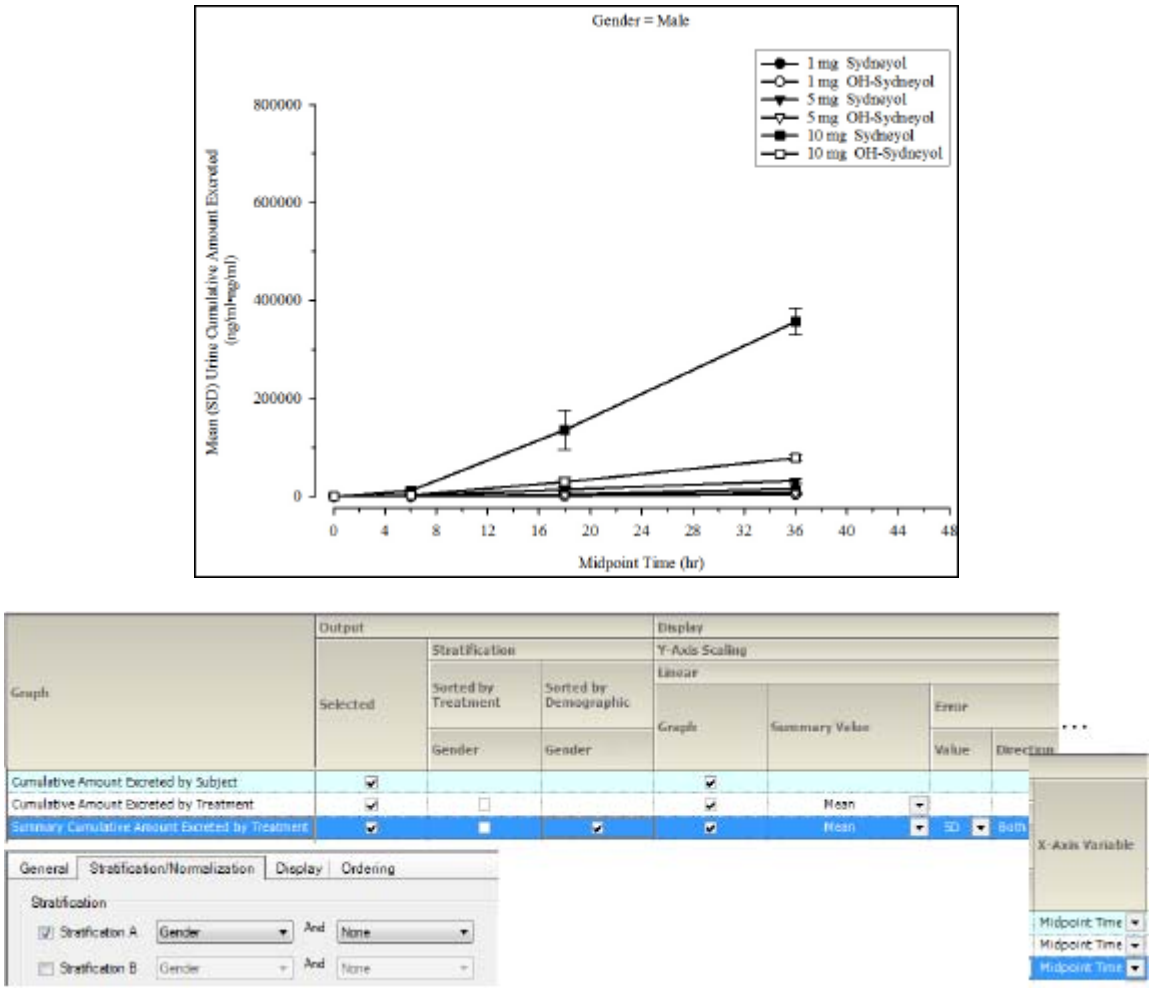
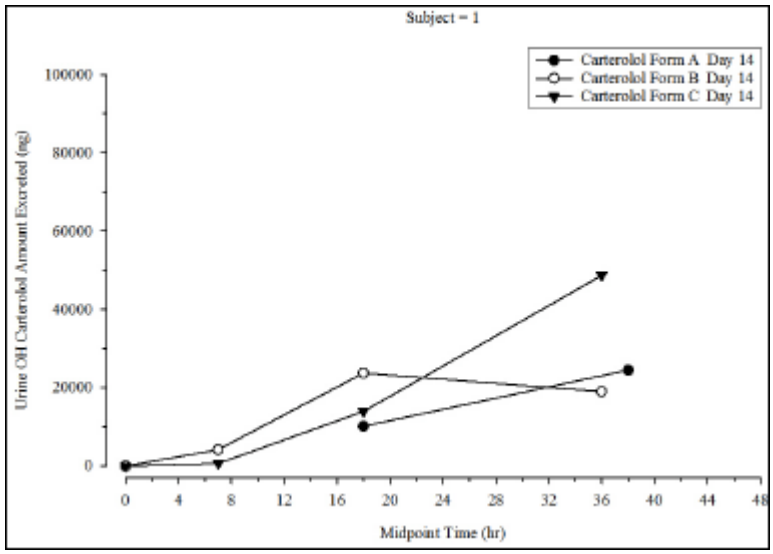


Figure 13-56. Summary cum. amt. excreted by treatment, sorted and strat. by group



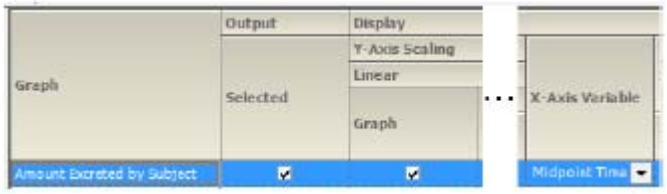
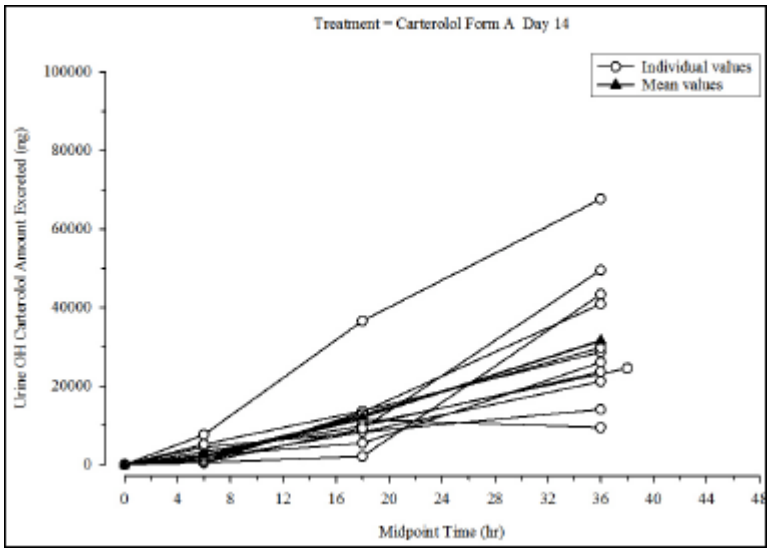


Figure 13-57. Amount excreted by subject



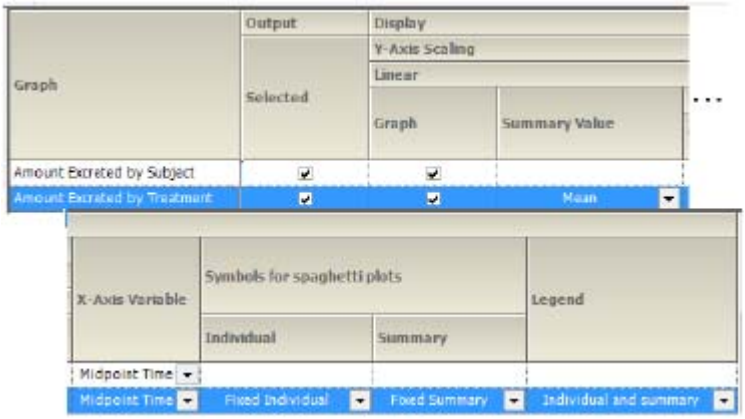


Figure 13-58. Amount excreted by treatment

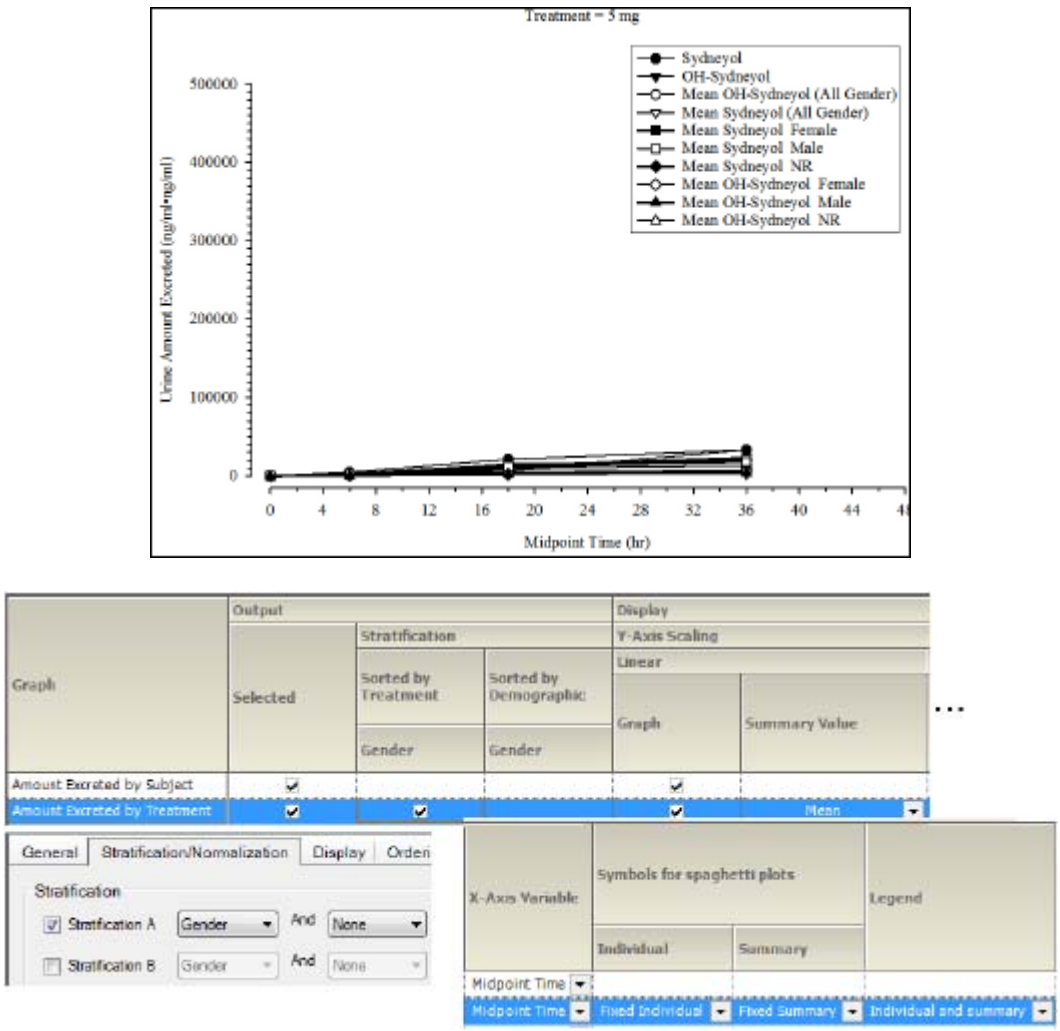
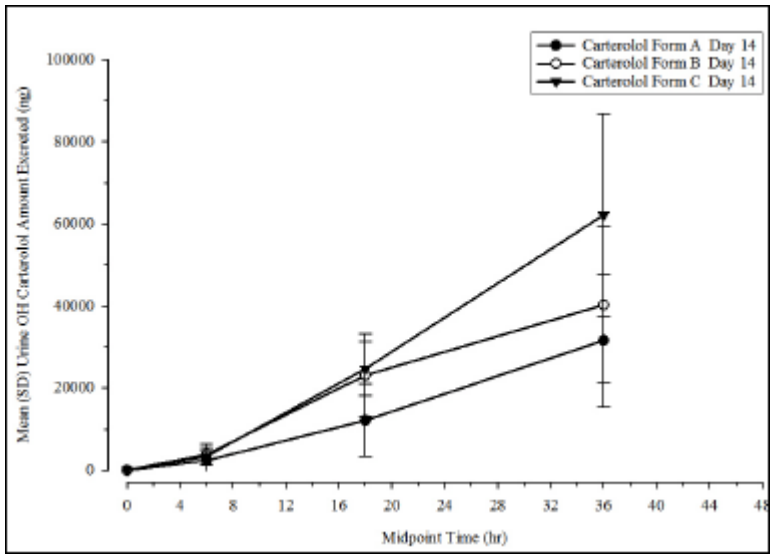
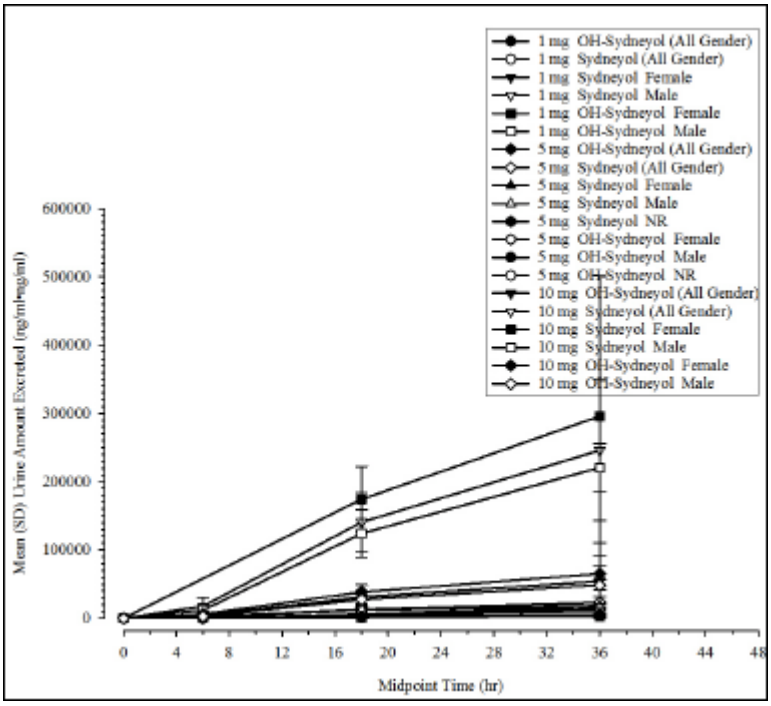


Figure 13-59. Amount excreted by treatment, sorted by treatment, and strat. by group



Graph	Output	Display						X-Axis Variable
	Selected	Y-Axis Scaling						
		Linear						
		Graph	Summary Value	Error				
				Value	Direction			
Amount Excreted by Subject	☑	☑						Midpoint Time
Amount Excreted by Treatment	☑	☑	Mean					Midpoint Time
Summary Amount Excreted by Treatment	☑	☑	Mean	SD	Both			Midpoint Time

Figure 13-60. Summary amount excreted by treatment



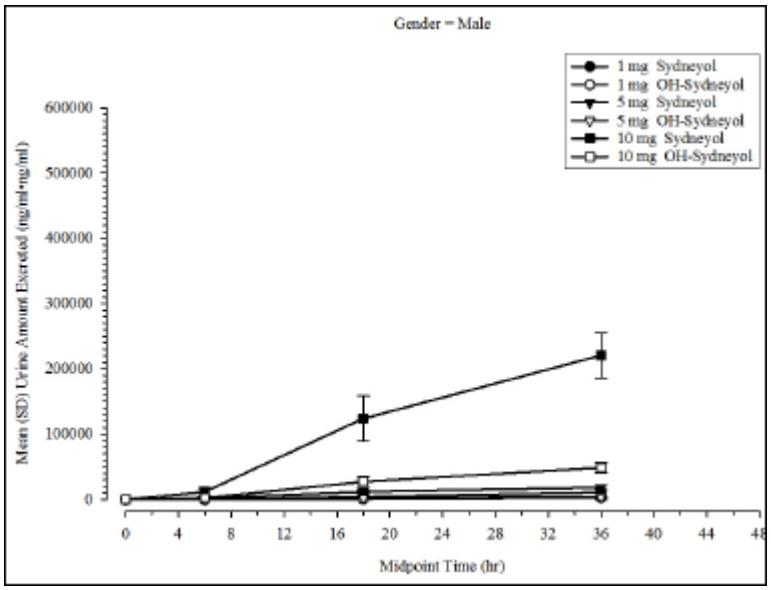
Graph	Output		Display		
	Selected	Stratification		Y-Axis Scaling	
				Linear	
		Sorted by Treatment	Sorted by Demographic	Graph	Summary Value	Error
		Gender	Gender			Value
Amount Excreted by Subject	☑			☑		
Amount Excreted by Treatment	☑	☐		☑	Mean	
Summary Amount Excreted by Treatment	☑	☑	☐	☑	Mean	SD

General | Stratification/Normalization | Display | Ordering

Stratification

☑ Stratification A: Gender And None

Figure 13-61. Summary amt. excreted by treatment, sorted by treatment, and strat. by group



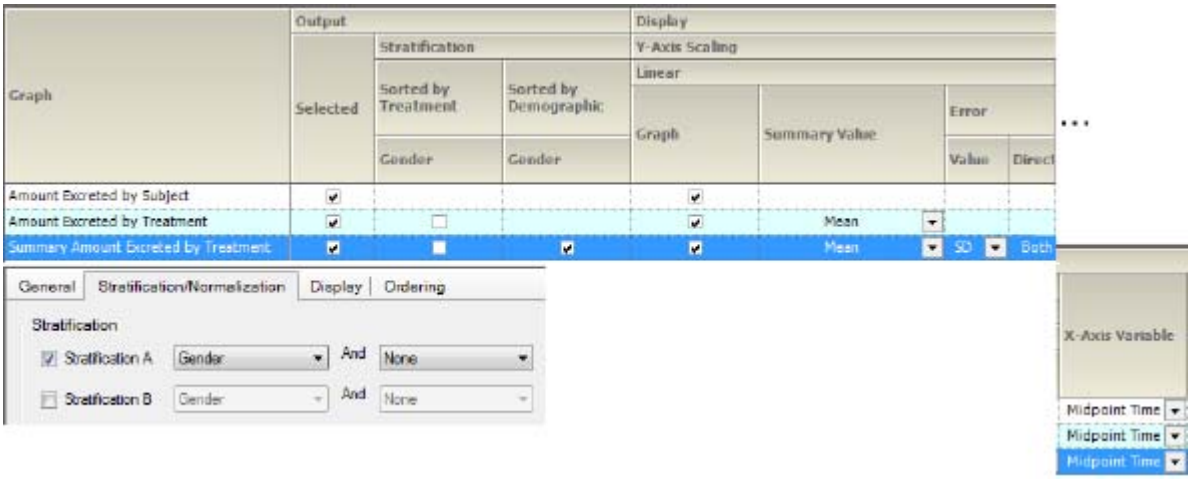


Figure 13-62. Summary amt. excreted by treatment, sorted and strat. by group

Trough time concentration graphs

Concentration by subject
Concentration by treatment

Concentration by treatment, sorted by treatment, and strat. by group

Summary concentration by treatment

Summary conc. by treatment and strat. by group
Summary conc. by treatment and strat. by group value

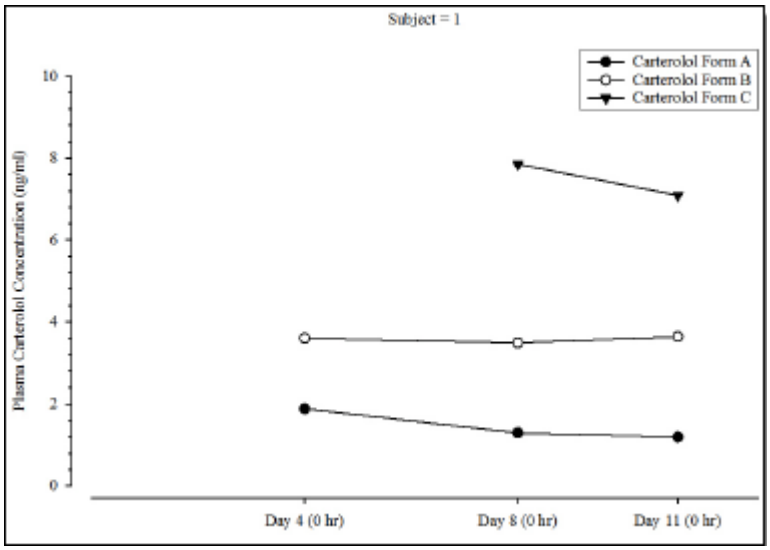
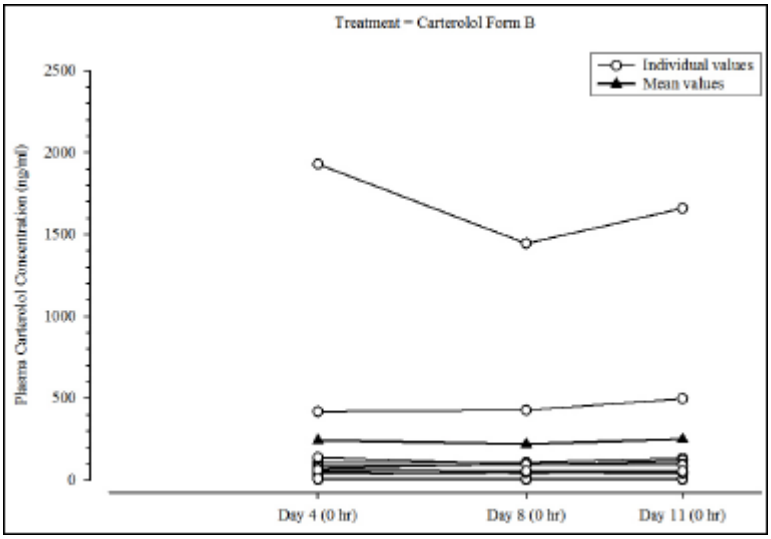


Figure 13-63. Concentration by subject



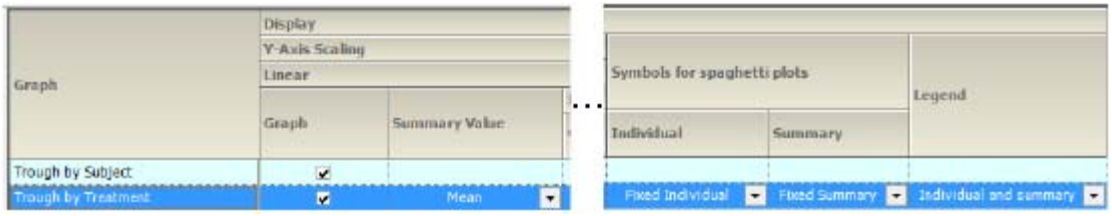


Figure 13-64. Concentration by treatment

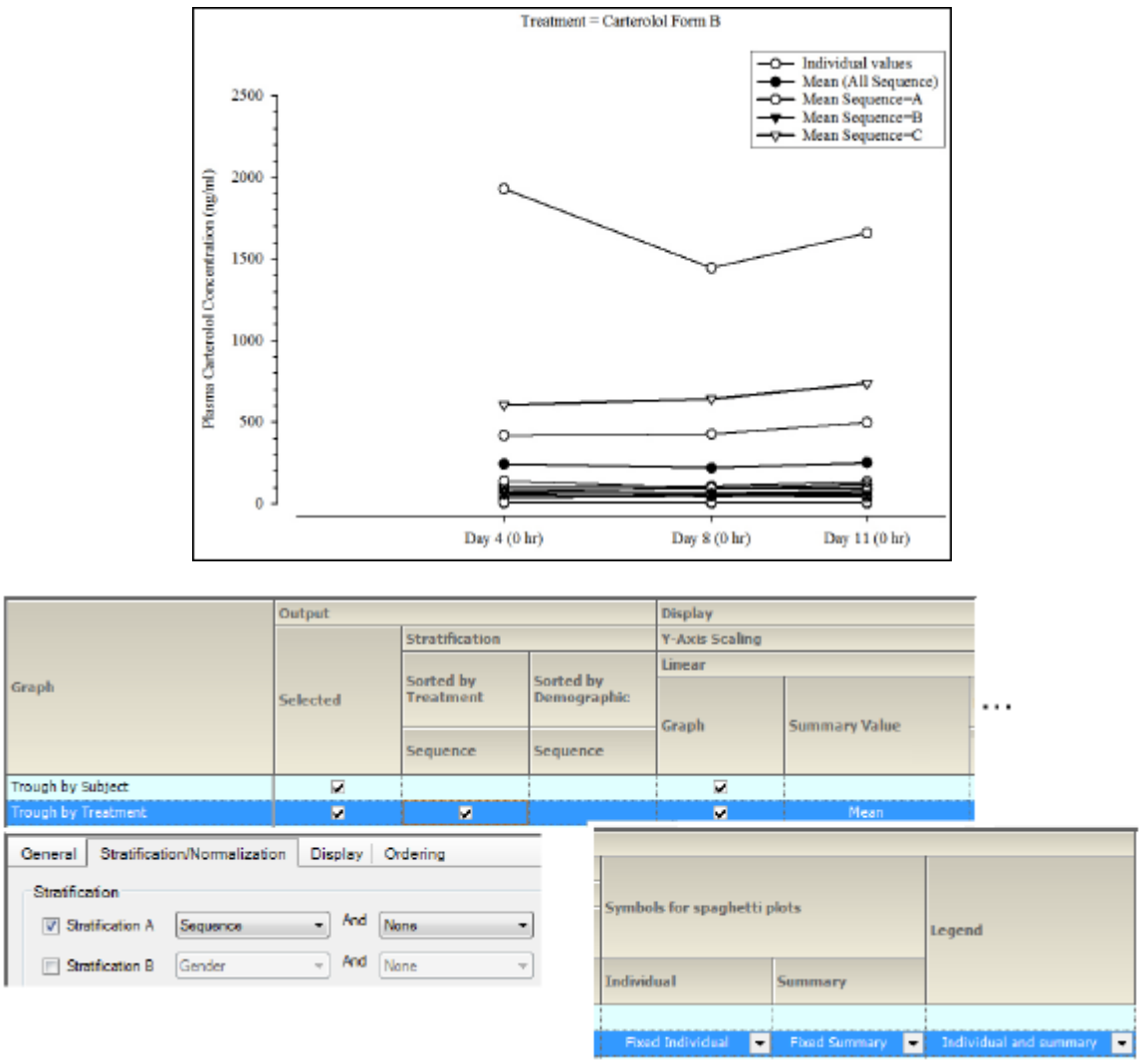
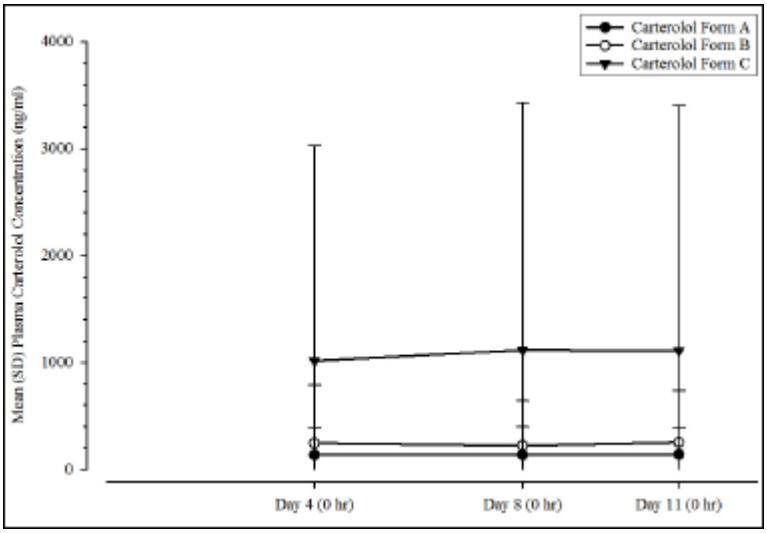
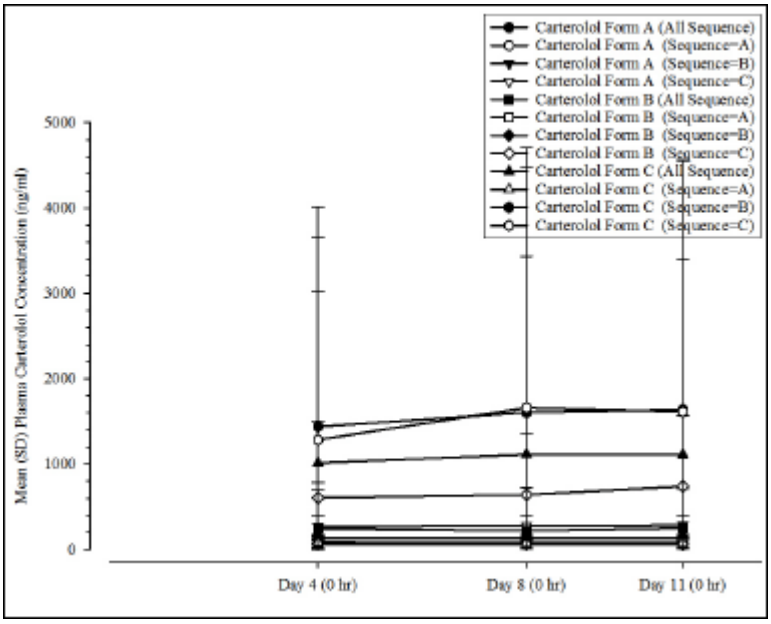


Figure 13-65. Concentration by treatment, sorted by treatment, and strat. by group



Graph	Output	Display			
	Selected	Y-Axis Scaling			
		Linear			
		Graph	Summary Value	Error	
				Value	Direction
Trough by Subject	☑	☑			
Trough by Treatment	☑	☑	Mean		
Trough Summary by Treatment	☑	☑	Mean	SD	Both

Figure 13-66. Summary concentration by treatment



Graph	Output			Display				
	Selected	Stratification		Y-Axis Scaling				
		Sorted by Treatment	Sorted by Demographic	Linear				
				Graph	Summary Value	Error		
		Sequence	Sequence			Value	Direction	
Trough by Subject	☑			☑				
Trough by Treatment	☑	☐		☑	Mean			
Trough Summary by Treatment	☑	☑	☐	☑	Mean	SD	Both	

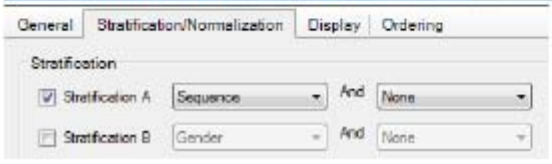


Figure 13-67. Summary conc. by treatment and strat. by group

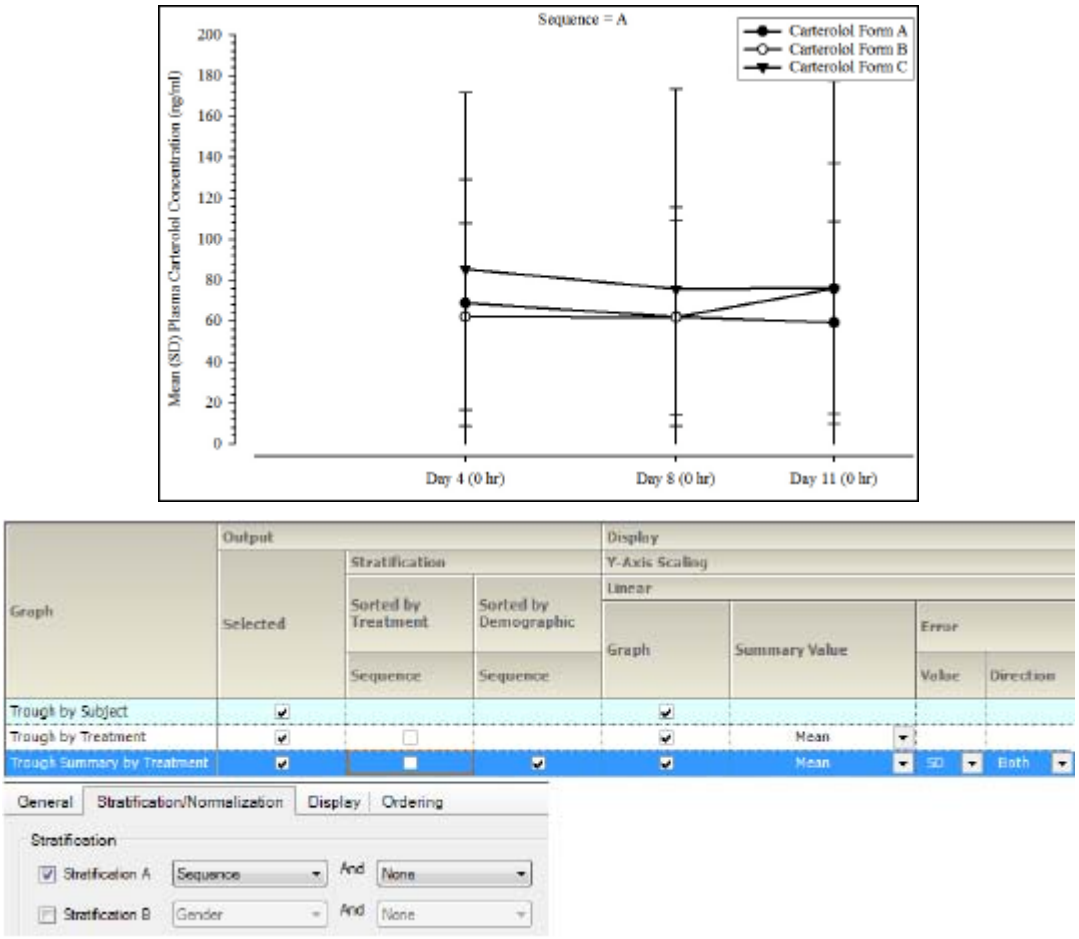


Figure 13-68. Summary conc. by treatment and strat. by group value

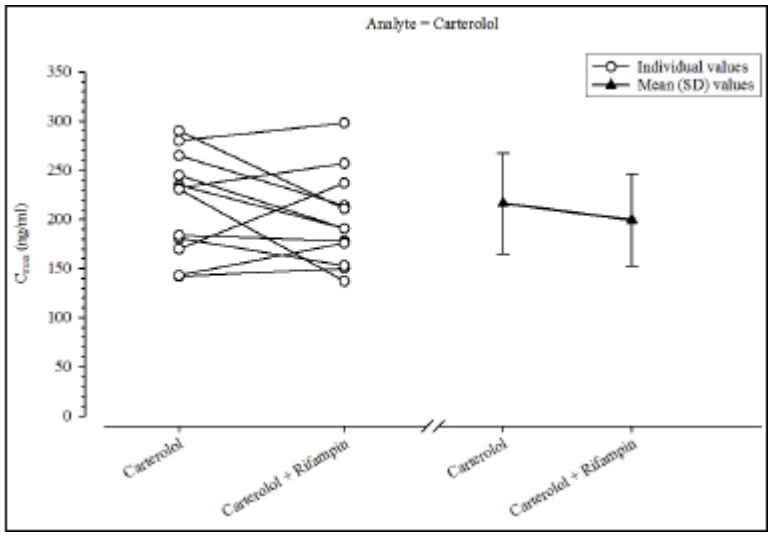
Plasma and urine categorical standard PK parameter graphs

PK parameter split

PK parameter offset

PK parameter sorted by treatment and strat. by group

PK parameter strat. by group



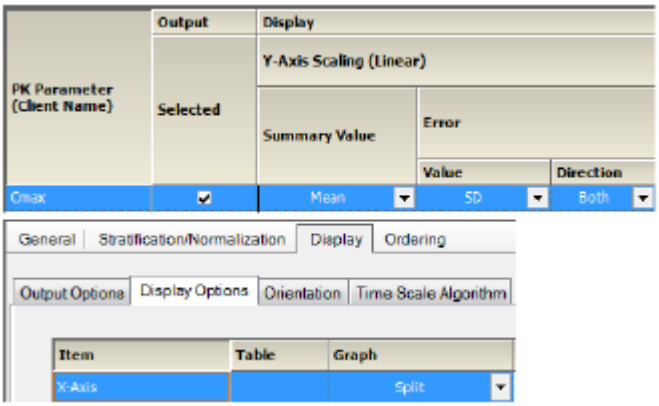
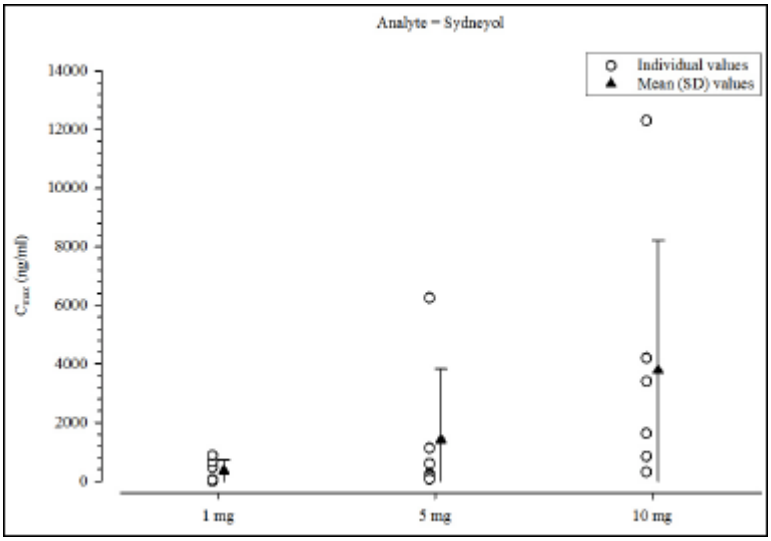


Figure 13-69. PK parameter split



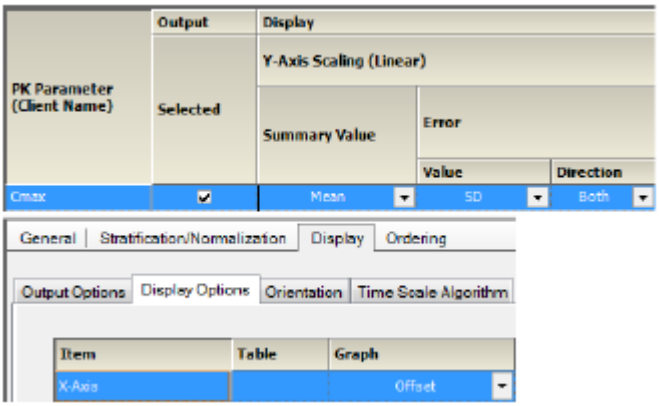
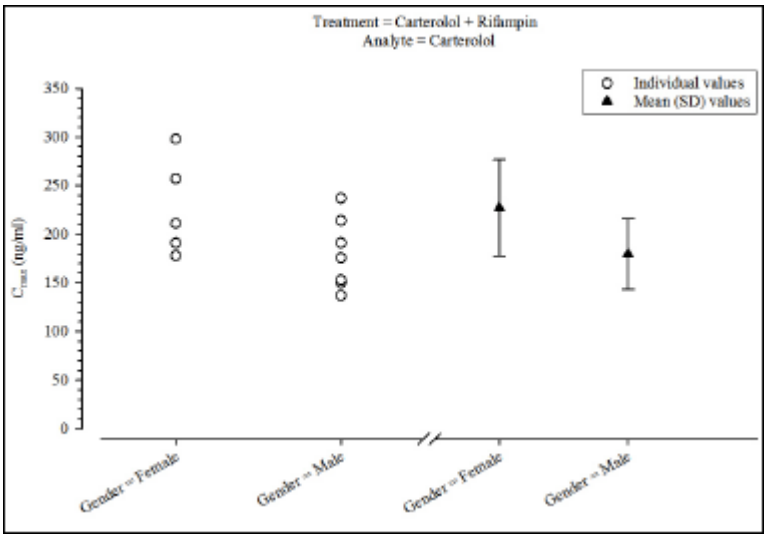


Figure 13-70. PK parameter offset



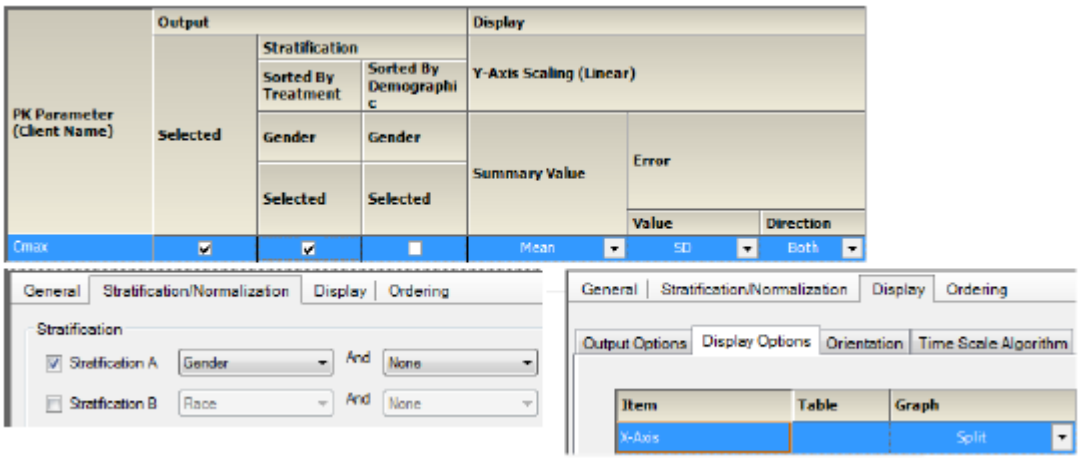
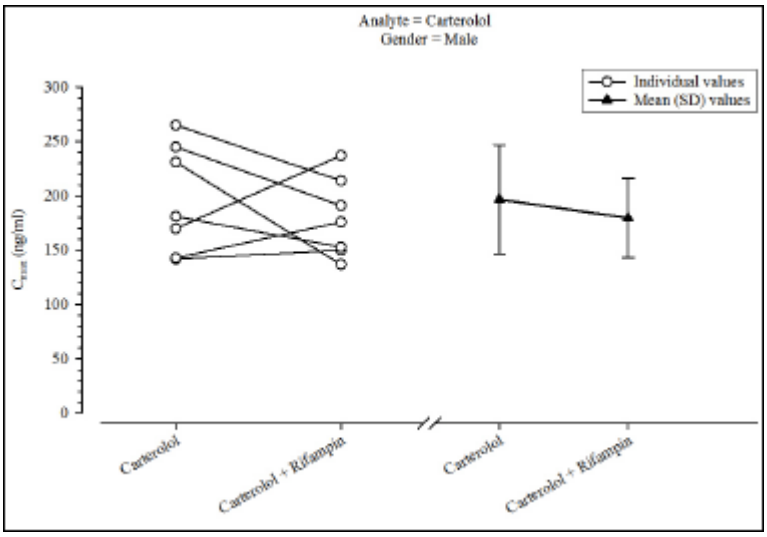


Figure 13-71. PK parameter sorted by treatment and strat. by group



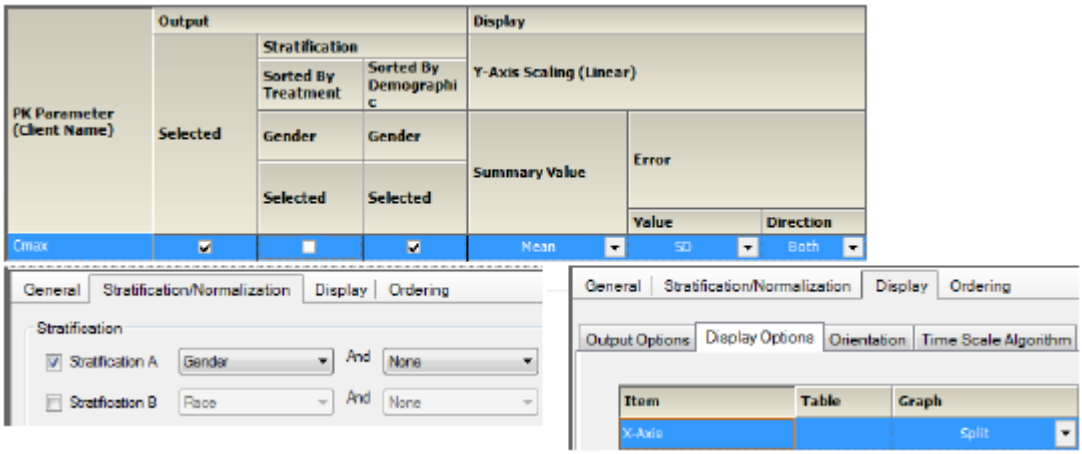
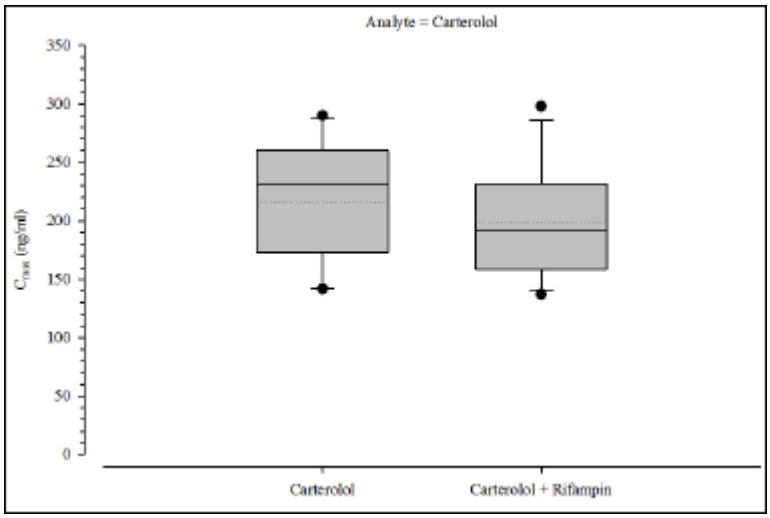


Figure 13-72. PK parameter strat. by group

Plasma and urine categorical box and whisker PK parameter graphs

Box and whisker PK parameter
Box and whisker PK parameter sorted by treatment and strat. by group
Box and whisker PK parameter sorted and strat. by group



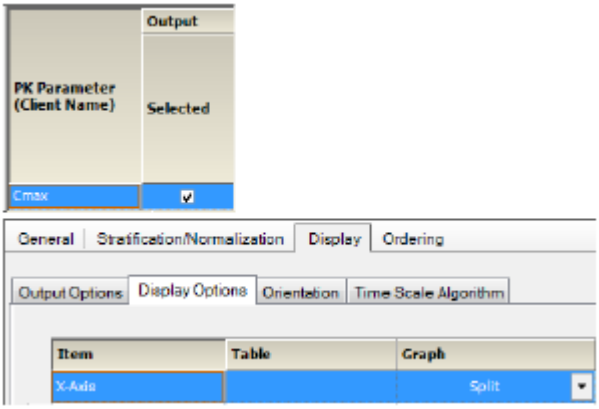
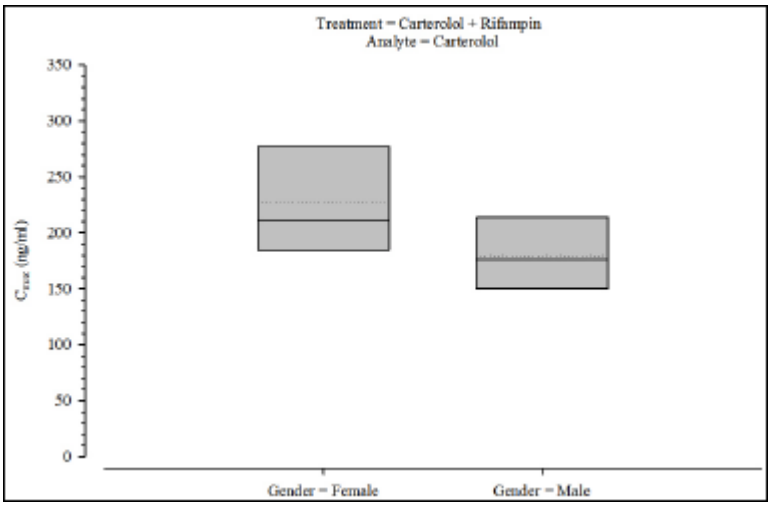


Figure 13-73. Box and whisker PK parameter



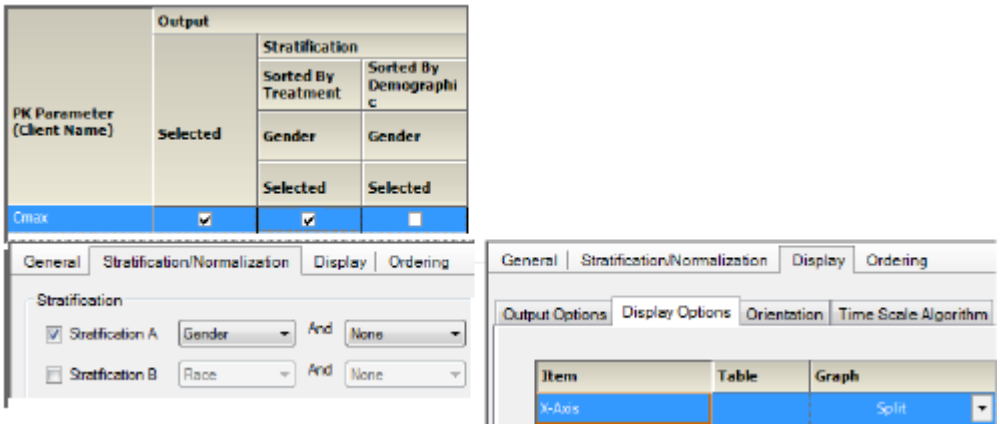


Figure 13-74. Box and whisker PK parameter sorted by treatment and strat. by group

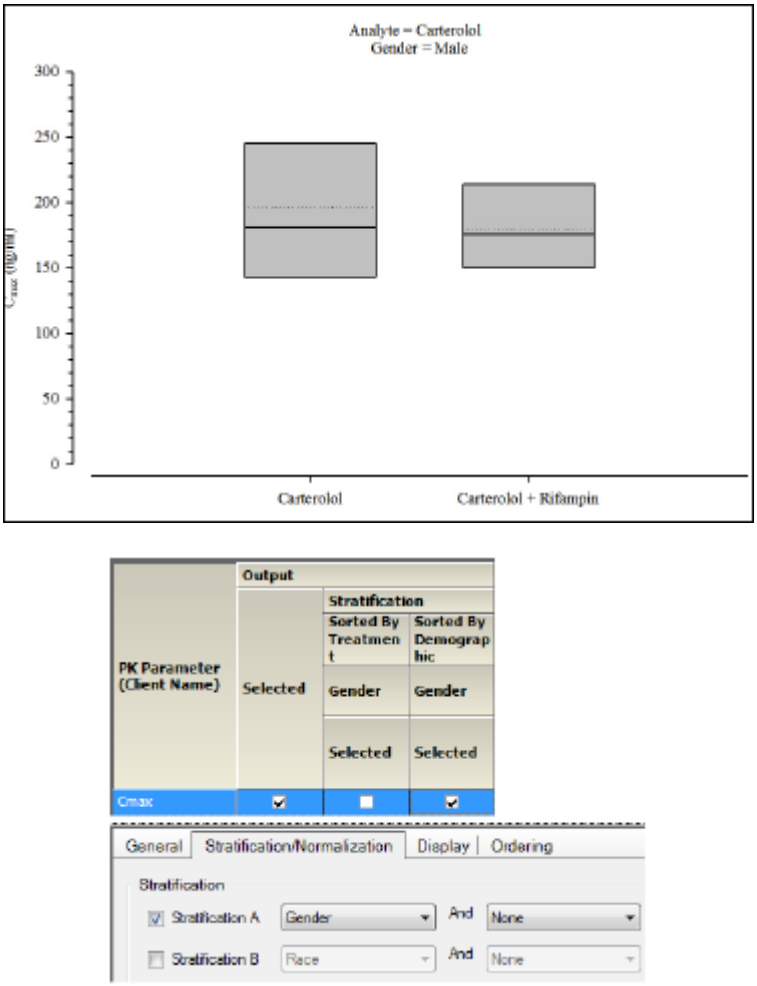
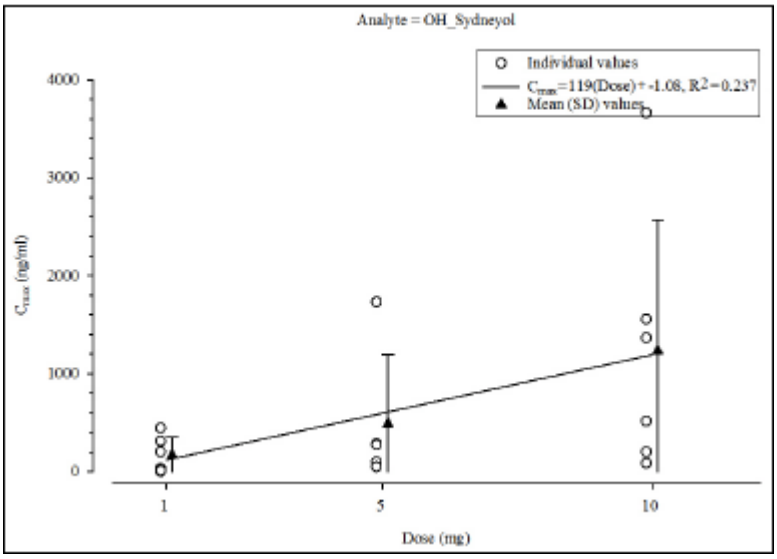


Figure 13-75. Box and whisker PK parameter sorted and strat. by group

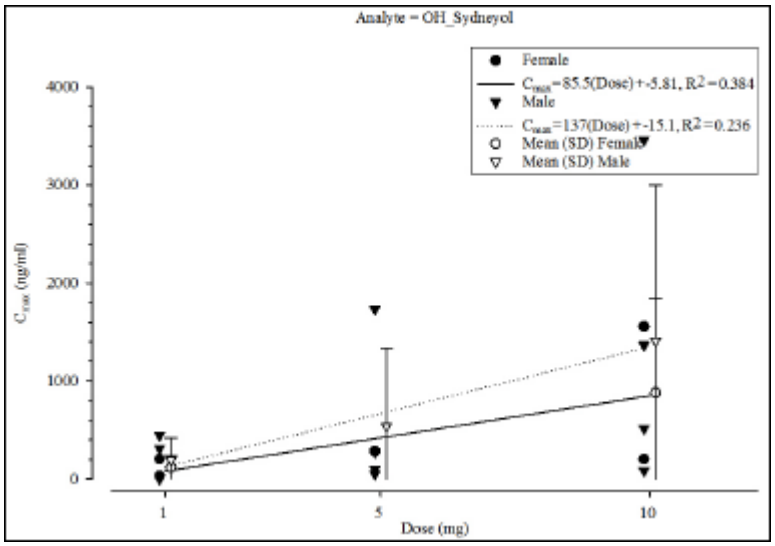
Plasma and urine continuous dose standard PK parameter graphs

PK parameter by dose
PK parameter by dose sorted by treatment and strat. by group
PK parameter by dose sorted and strat. by group



PK Parameter (Client Name)	Output	Display				
	Selected	Y-Axis Scaling (Linear)			Regression	
		Summary Value	Error			
			Value	Direction	Line	Equation
Cmax	☑	Mean	SD	Both	☑	☑

Figure 13-76. PK parameter by dose



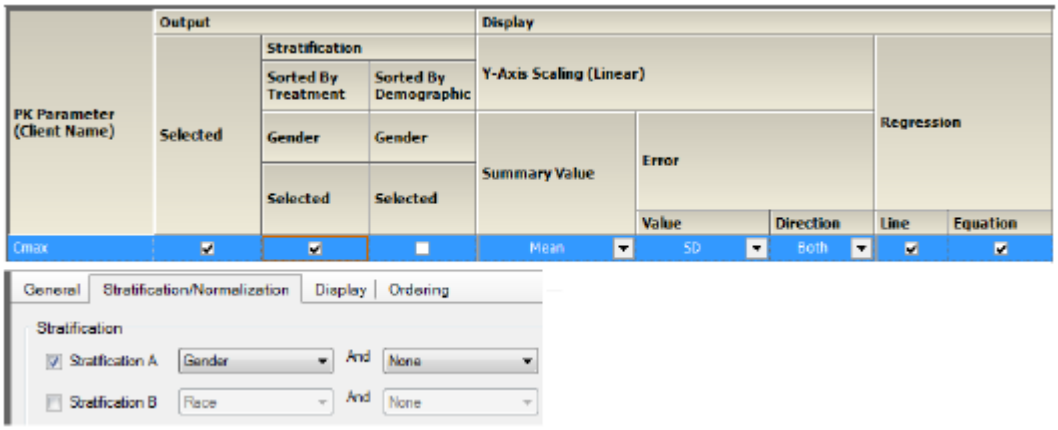
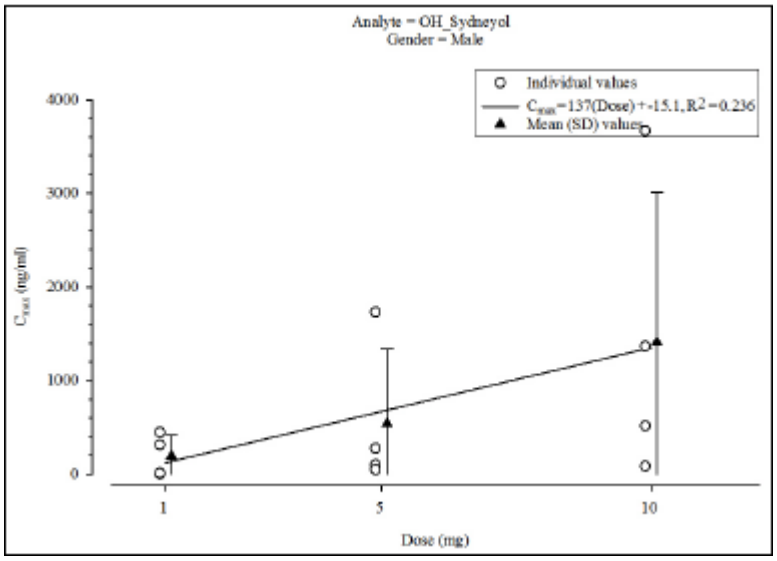


Figure 13-77. PK parameter by dose sorted by treatment and strat. by group



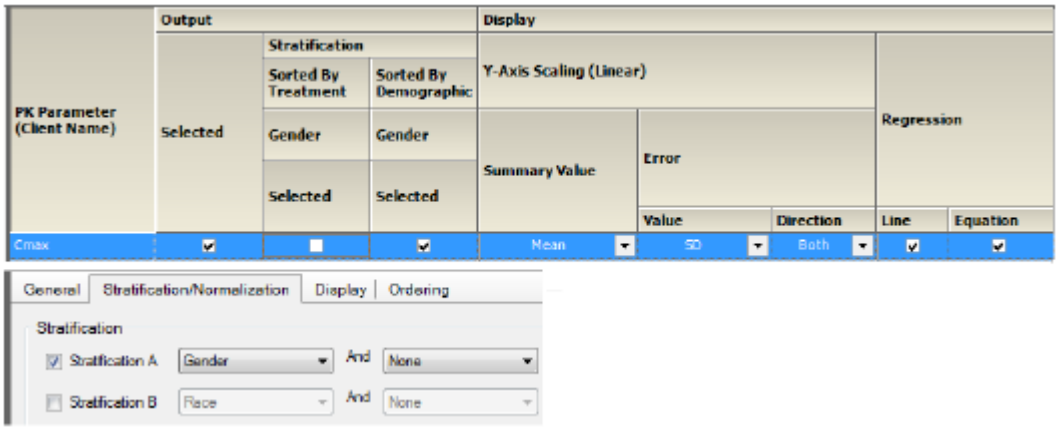


Figure 13-78. PK parameter by dose sorted and strat. by group

Plasma and urine continuous dose box and whisker PK parameter graphs

Box and whisker PK parameter by dose
Box and whisker PK parameter by dose and strat. by group

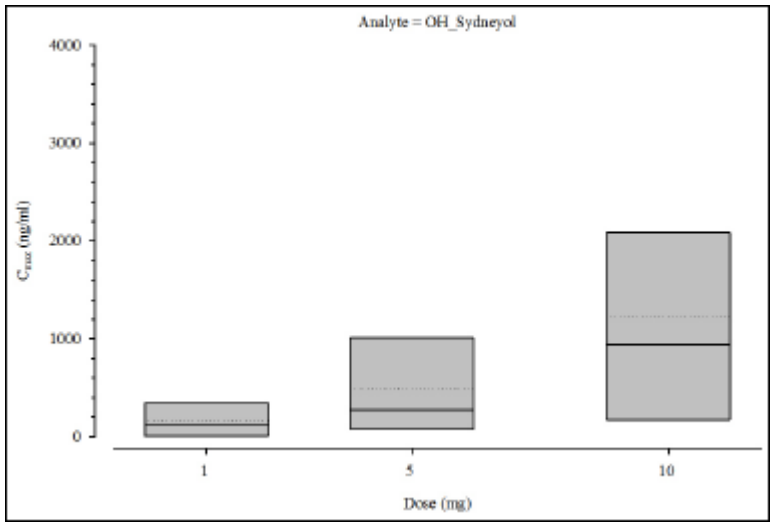
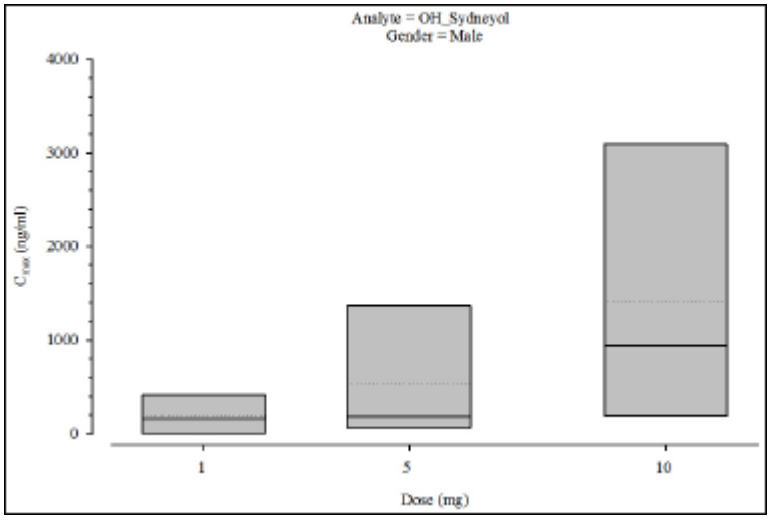


Figure 13-79. Box and whisker PK parameter by dose



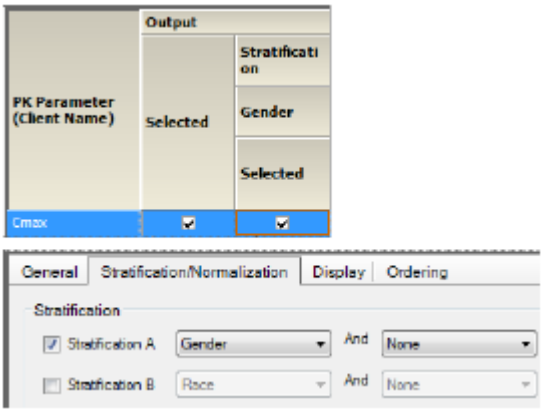


Figure 13-80. Box and whisker PK parameter by dose and strat. by group

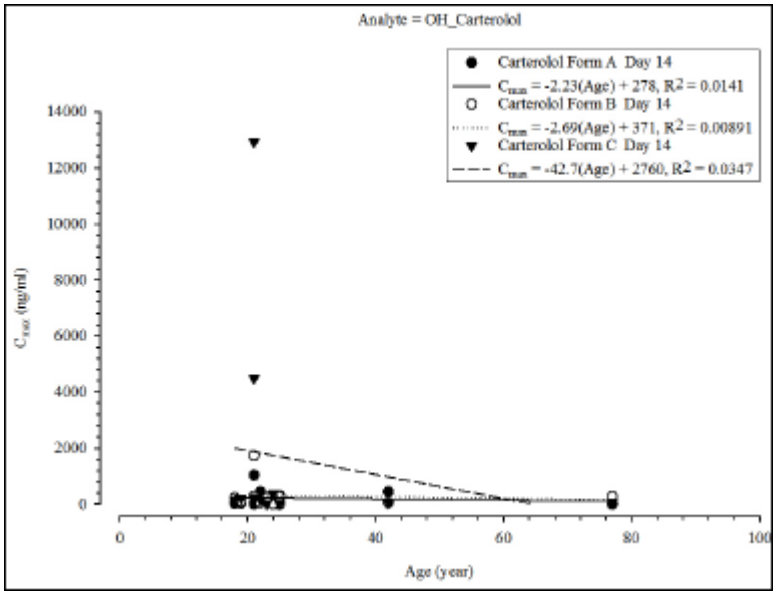
Plasma and urine continuous demographic PK parameter graphs

PK parameter vs. continuous demographic

PK parameter vs. continuous demographic sorted by treatment and strat. by group

PK parameter vs. continuous demographic by treatment

- PK parameter vs. continuous demographic by treatment, sorted by treatment and strat. by group
  PK parameter vs. continuous demographic by treatment, sorted and strat. by group



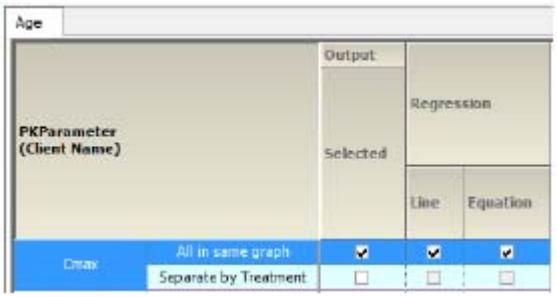


Figure 13-81. PK parameter vs. continuous demographic

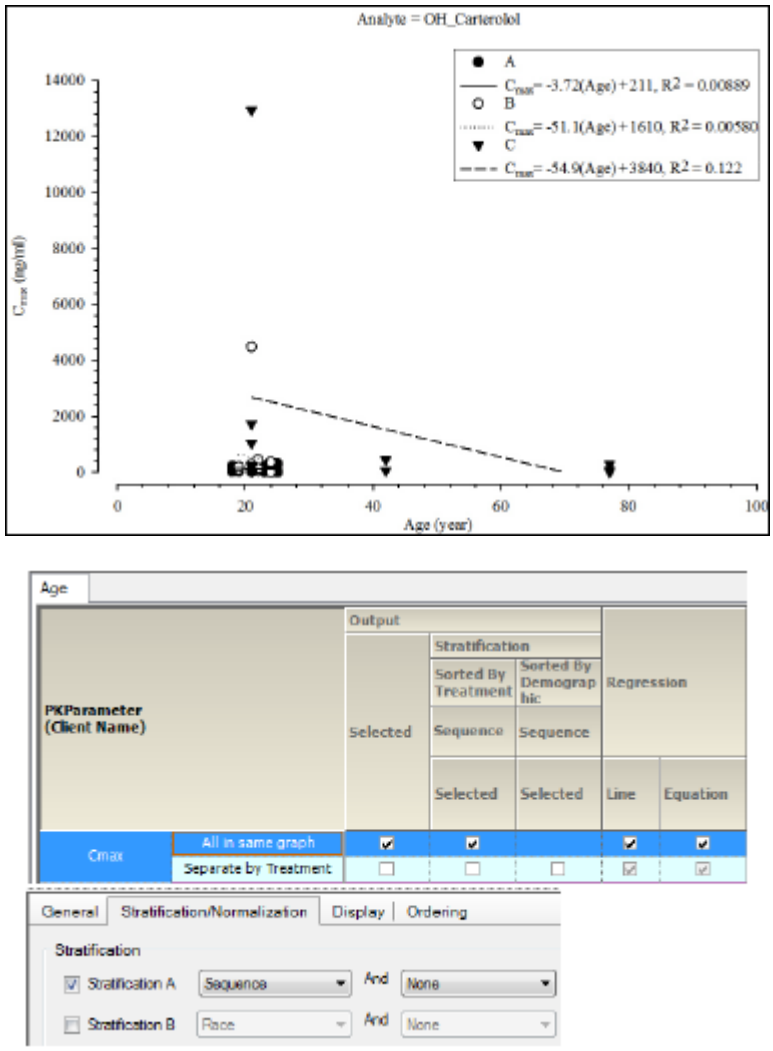
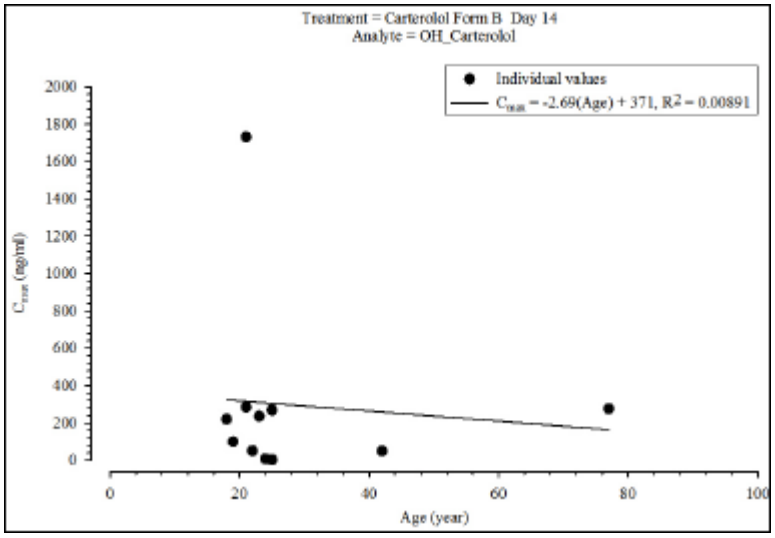


Figure 13-82. PK parameter vs. continuous demographic sorted by treatment and strat. by group



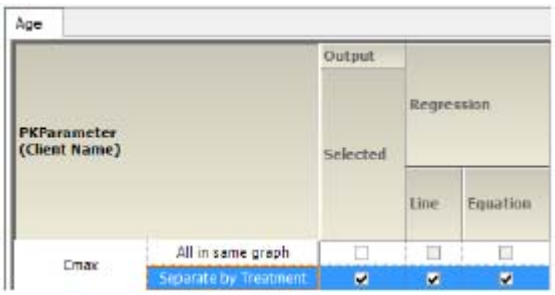
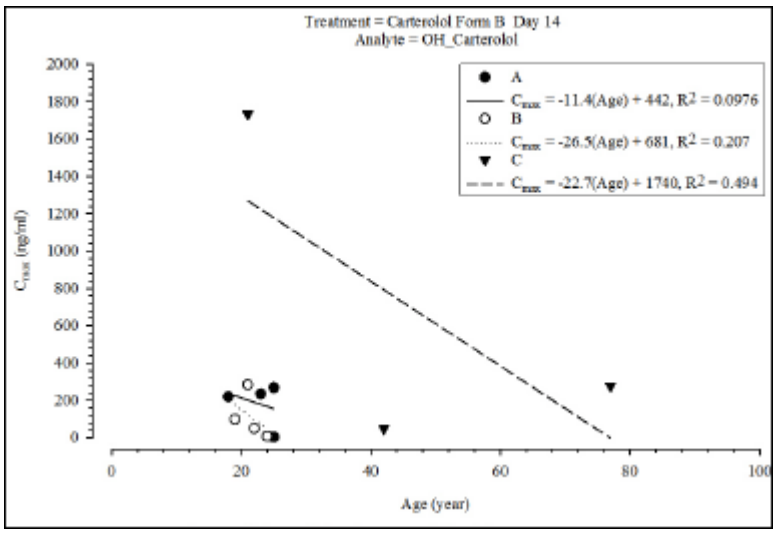


Figure 13-83. PK parameter vs. continuous demographic by treatment



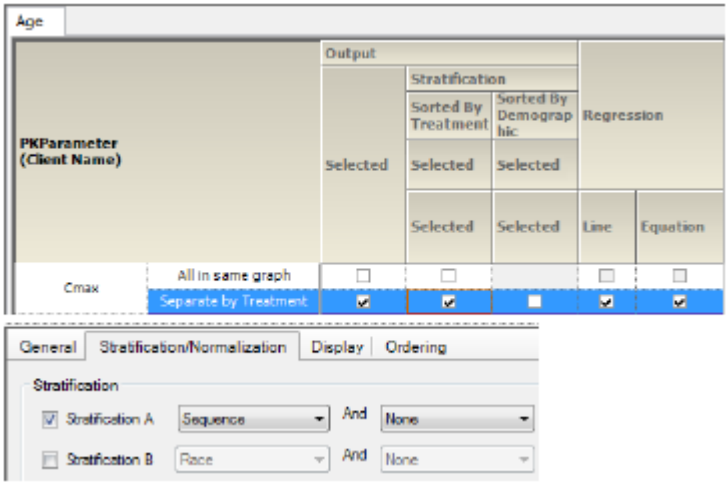
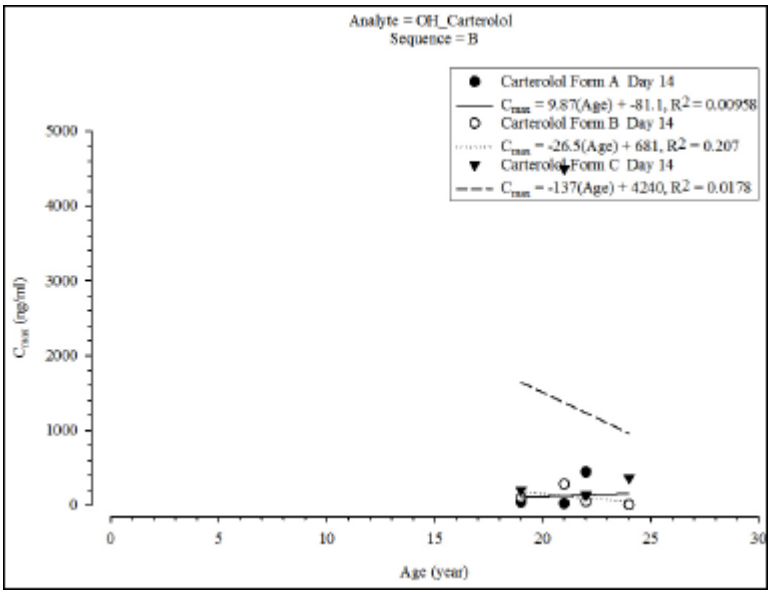


Figure 13-84. PK parameter vs. continuous demographic by treatment, sorted by treatment and strat. by group



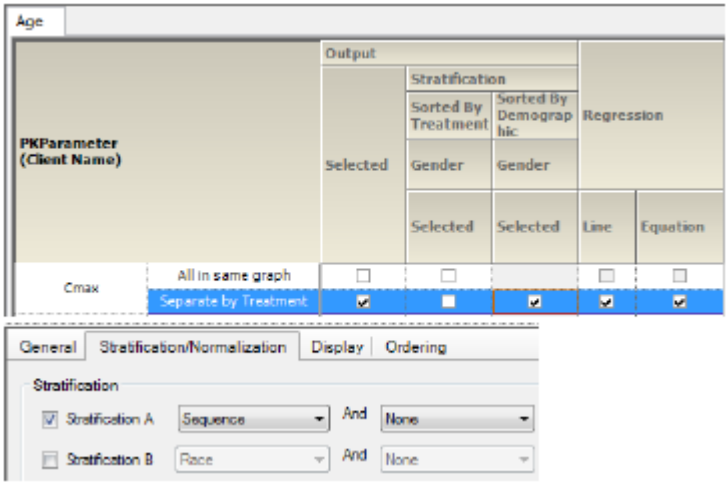


Figure 13-85. PK parameter vs. continuous demographic by treatment, sorted and strat. by group

Comparison Output Examples

For each table example, images of the output table/graph and settings used when creating the table are included.

Comparison time concentration tables

Analyte Comparison (Metabolite/Parent)

Treatment = Carterolol Form A

Plasma

Concentration Ratio over Nominal Time (hr)

Subject	0.00	0.25	0.50	0.75	1.00	1.50	2.00	4.00	8.00	12.00	16.00	24.00
1	NS	NS	0.334	0.333	NS	0.334	0.333	NS	0.332	0.336	0.332	0.336
2	NS	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.333	0.333	0.333	0.334
3	NS	0.334	0.334	0.333	0.333	0.333	0.333	0.335	0.333	0.333	0.333	0.327
4	NS	0.333	0.333	0.333	0.333	0.333	0.332	0.333	0.333	0.333	0.331	NS
5	NS	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.408	0.333	0.333	0.332
6	NS	0.333	0.333	0.334	0.333	0.334	0.332	0.332	0.336	0.336	0.338	NS
7	NS	0.333	0.333	0.334	0.334	0.333	0.333	0.333	0.333	0.336	0.337	0.326
8	NS	0.333	0.333	0.334	0.332	0.334	0.332	0.335	0.333	0.338	0.332	0.334
9	NS	0.250	0.250	0.250	0.408	0.333	0.334	0.333	0.333	0.333	0.331	0.333
10	NS	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.333
11	NS	0.333	0.408	0.333	0.334	0.334	0.333	0.334	0.335	0.336	0.340	0.338
12	NS	0.250	0.250	0.250	0.408	0.333	0.333	0.334	0.335	0.331	0.331	0.320
N	0	11	12	12	11	12	12	11	12	12	12	10
Mean *	NC	0.295	0.305	0.299	0.324	0.313	0.312	0.311	0.333	0.327	0.327	0.331
SD *	NC	0.0434	0.0527	0.0429	0.0557	0.0378	0.0375	0.0390	0.0338	0.0244	0.0243	0.00544
SE *	NC	0.0131	0.0152	0.0124	0.0168	0.0109	0.0108	0.0118	0.00976	0.00704	0.00702	0.00172
Min *	NC	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.320
Median *	NC	0.333	0.333	0.333	0.333	0.333	0.333	0.333	0.333	0.333	0.332	0.333
Max *	NC	0.334	0.408	0.334	0.408	0.334	0.334	0.335	0.408	0.338	0.340	0.338
CV% *	NC	15	17	14	17	12	12	13	10	7	7	2
Geometric Mean *	NC	0.293	0.301	0.296	0.320	0.310	0.310	0.308	0.331	0.326	0.326	0.331

Metabolite=OH_Carterolol
Parent=Carterolol
NS = No Sample
NC = Not Calculated
* = Small sample size rule applied to calculation of summary variable

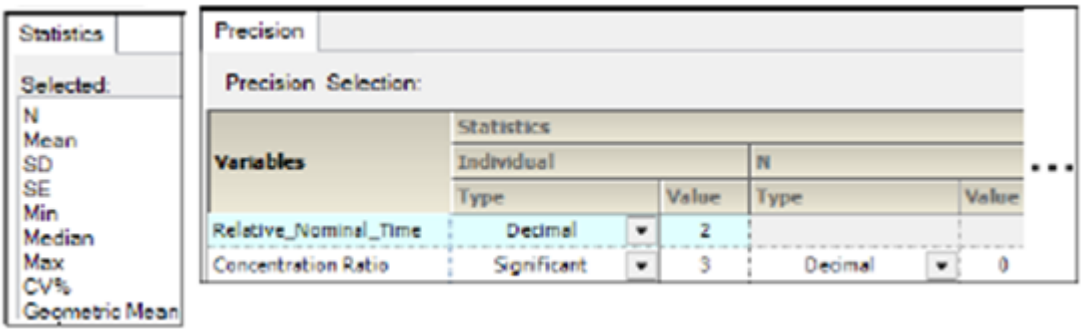


Figure 14-1. Plasma concentration ratios comparison

Analyte Comparison (Metabolite/Parent)			
Treatment = Carterolol Form A			
Plasma			
	Concentration Ratio over Day and Nominal Time (hr)		
Subject	Day 4 (0hr)	Day 8 (0hr)	Day 11 (0hr)
1	1.00	1.00	1.00
2	1.00	1.00	1.00
3	1.00	1.00	1.00
4	1.00	1.00	1.00
5	1.00	1.00	1.00
6	1.00	1.00	1.00
7	1.00	1.00	1.00
8	1.00	1.00	1.00
9	1.00	1.00	1.00
10	1.00	1.00	1.00
11	1.00	1.00	1.00
12	1.00	1.00	1.00
N	12	12	12
Mean	1.00	1.00	1.00
SD	0.00	0.00	0.00
SE	0.00	0.00	0.00
Min	1.00	1.00	1.00
Median	1.00	1.00	1.00
Max	1.00	1.00	1.00
CV%	0	0	0
Geometric Mean	1.00	1.00	1.00
Metabolite=Carterolol Parent=Carterolol Nominal Time used as time variable for NCA			

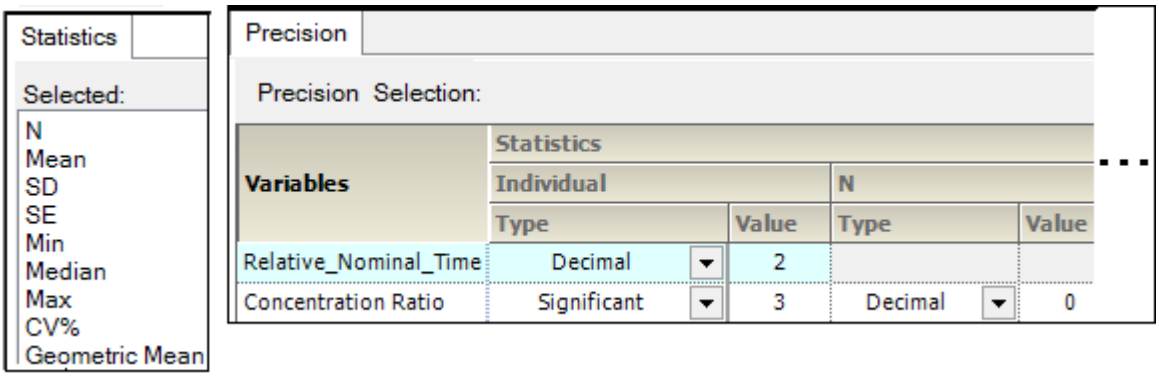


Figure 14-2. Trough concentration ratios comparison

Analyte Comparison (Metabolite/Parent)			
Treatment = Carterolol Form A			
Urine			
	Amount Excreted (ng) over the Nominal Collection Interval (hr)		
Subject	0 - 12	12 - 24	24 - 48
1	0.340	0.220	NS
2	0.220	0.220	0.220
3	NS	0.220	0.220
4	0.777	0.220	0.220
5	0.220	0.220	0.220
6	0.900	NS	0.220
7	0.934	0.220	0.220
8	0.455	0.220	0.232
9	0.800	0.220	0.220
10	0.220	0.220	0.220
11	0.512	0.220	0.220
12	0.600	0.220	0.220
N	11	11	11
Mean	0.544	0.220	0.221
SD	0.277	0.000162	0.00369
SE	0.0835	0.0000490	0.00111
Min	0.220	0.220	0.220
Median	0.512	0.220	0.220
Max	0.934	0.220	0.232
CV%	51	0	2
Geometric Mean	0.473	0.220	0.221
Metabolite=OH_Carterolol Parent=Carterolol NS = No Sample			

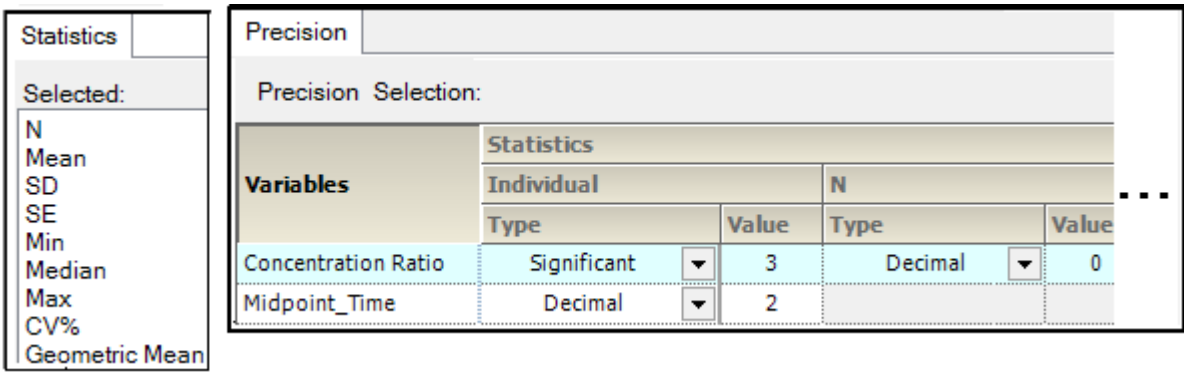


Figure 14-3. Urine amount ratios comparison

Analyte Comparison (Metabolite/Parent)			
Treatment = Carterolol Form A			
Urine			
	Amount Excreted (ng) over the Nominal Collection Interval		
Subject	0 - 12	0 - 24	0 - 48
1	0.340	0.230	0.716
2	0.220	0.220	0.220
3	NS	0.220	0.220
4	0.777	0.245	0.227
5	0.220	0.220	0.220
6	0.900	0.900	0.269
7	0.934	0.287	0.233
8	0.455	0.246	0.233
9	0.800	0.275	0.239
10	0.220	0.220	0.220
11	0.512	0.231	0.223
12	0.600	0.242	0.232
N	11	12	12
Mean	0.544	0.295	0.271
SD	0.277	0.192	0.141
SE	0.0835	0.0554	0.0407
Min	0.220	0.220	0.220
Median	0.512	0.237	0.230
Max	0.934	0.900	0.716
CV%	51	65	52
Geometric Mean	0.473	0.267	0.253
Metabolite=OH_Carterolol			
Parent=Carterolol			
NS = No Sample			
Source = compare [C:\Users\ladams\Documents\Pharsight Projects\compare.phxproj]			
Date/Time = 12/19/2011 1:33:47 PM			

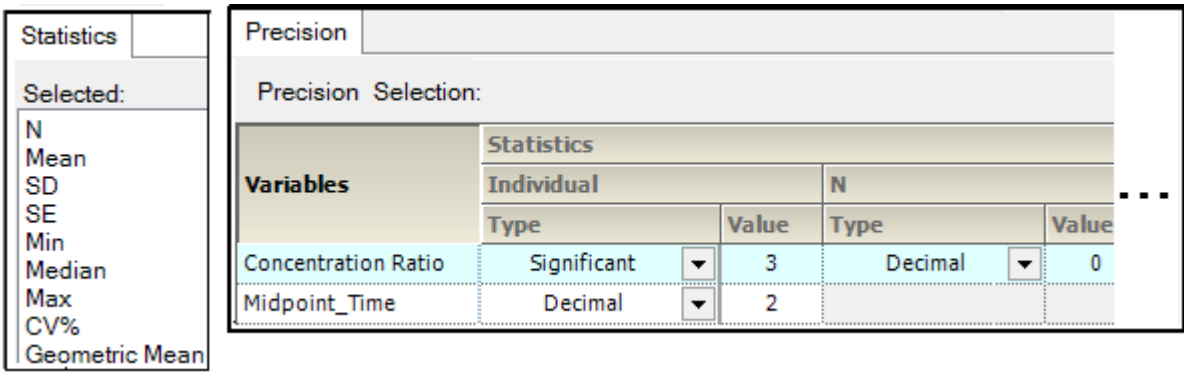


Figure 14-4. Cumulative urine amount ratios comparison

Comparison PK parameter tables

PK parameter ratios plasma comparison
PK parameter ratios urine comparison
PK parameter ratios accumulation comparison
PK parameter ratios absolute bioavailability comparison
PK parameter ratios renal comparison

Analyte Comparison (Metabolite/Parent)					
Plasma					
Period = 1					
	OH_Carterolol vs Carterolol				
	Carterolol Form A				
Subject	T_{max} # (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap # (%)
1	0.00	0.334	0.347	0.346	0
2	0.00	0.250	0.297	0.306	2
3	0.00	0.334	0.333	0.332	0
4	0.00	0.333	0.333	0.333	0
5	0.00	0.250	0.304	0.315	3
6	0.00	0.333	0.334	0.334	0
7	0.00	0.334	0.334	0.328	-2
8	0.00	0.333	0.334	0.342	2
9	0.50	0.305	0.327	0.327	0
10	0.00	0.250	0.252	0.254	1
11	0.00	0.408	0.338	0.338	0
12	0.50	0.271	0.325	0.325	0
N	12	12	12	12	12
Mean	0.08	0.311	0.321	0.323	1
SD	0.19	0.0480	0.0260	0.0243	1
SE	0.06	0.0139	0.00751	0.00703	0
Min	0.00	0.250	0.252	0.254	-2
Median	0.00	0.333	0.333	0.330	0
Max	0.50	0.408	0.347	0.346	3
CV%	234	15	8	8	248
Geometric Mean	NA	0.308	0.320	0.322	NA
NA = Not Applicable # Values are calculated by subtraction (Test - Ref)					

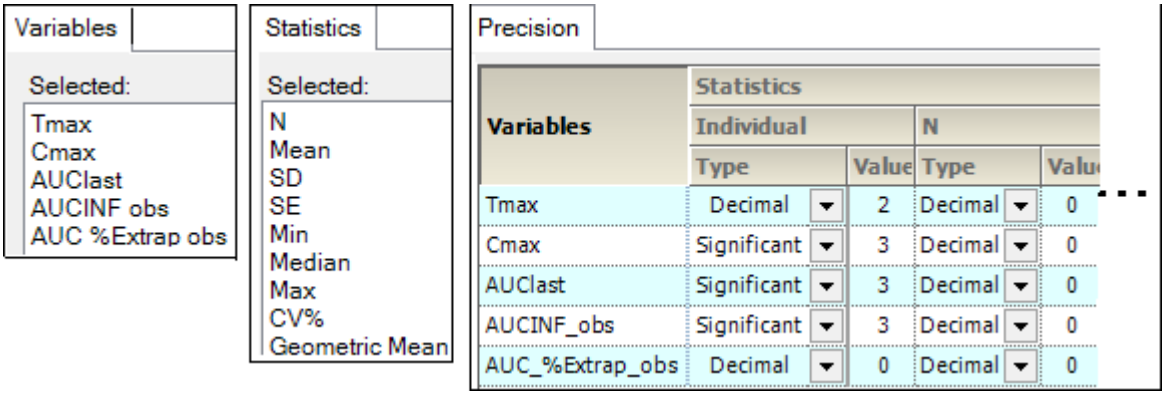


Figure 14-5. PK parameter ratios plasma comparison

Analyte Comparison (Metabolite/Parent)						
Urine						
	Carterolol		Carterolol Form B		Carterolol Form	
Subject	Ae (ng)	fe # (%)	Ae (ng)	fe # (%)	Ae (ng)	fe # (%)
1	0.749	-1.16	0.220	-16.69	0.282	-16.11
2	0.220	-19.41	0.220	-7.79	0.220	-20.76
3	0.220	-11.88	0.220	-4.33	0.220	-46.72
4	0.227	-10.50	0.220	-41.07	0.220	-24.88
5	0.220	-21.00	0.220	-22.28	0.220	-17.65
6	0.269	-5.04	0.220	-24.23	0.220	-22.90
7	0.233	-11.20	0.220	-21.10	0.220	-24.64
8	0.233	-15.16	0.220	-39.99	0.220	-28.70
9	0.239	-15.14	0.220	-25.32	0.220	-38.12
10	0.220	-39.65	0.220	-16.95	0.220	-43.18
11	0.223	-15.20	0.220	-24.26	0.220	-43.80
12	0.232	-7.56	0.220	-27.48	0.220	-41.08
N	12	12	12	12	12	12
Mean	0.274	-14.4	0.220	-22.6	0.225	-30.7
SD	0.150	9.77	0.0000597	10.9	0.0180	11.1
SE	0.0434	2.82	0.0000172	3.14	0.00520	3.21
Min	0.220	-39.6	0.220	-41.1	0.220	-46.7
Median	0.230	-13.5	0.220	-23.3	0.220	-26.8
Max	0.749	-1.16	0.220	-4.33	0.282	-16.1
CV%	55	-68	0	-48	8	-36
Geometric Mean	0.254	NA	0.220	NA	0.225	NA
NA = Not Applicable						
# Values are calculated by subtraction (Test - Ref)						

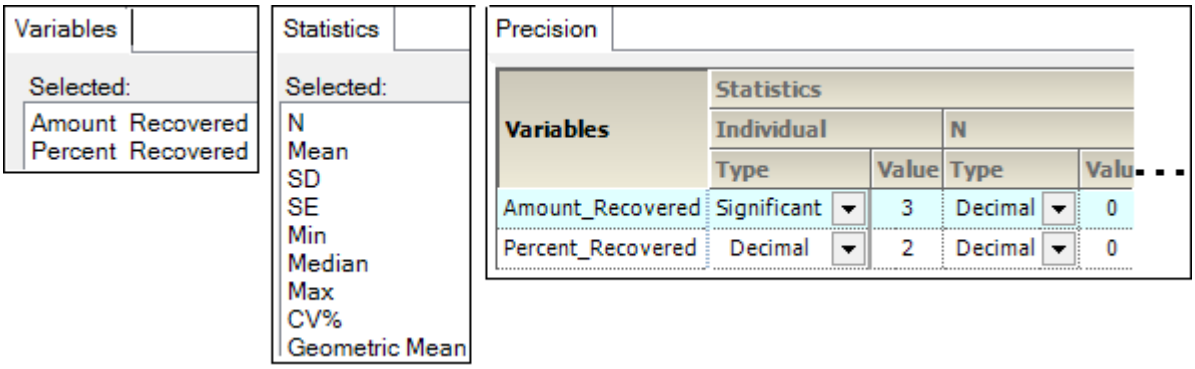


Figure 14-6. PK parameter ratios urine comparison

Carterolol PO Form A

Subject	Day 1 T_{max} (hr)	Day 1 C_{max} (ng/ml)	Day 1 AUC_{last} (ng•hr/ml)	Day 1 AUC_{∞} (ng•hr/ml)	Day 1 AUC % Extrap (%)	Day 14 T_{max} (hr)	Day 14 C_{max} (ng/ml)	Day 14 AUC_{last} (ng•hr/ml)	Day 14 AUC_{∞} (ng•hr/ml)	Day 14 AUC % Extrap (%)
1	0.65	2.31	15.4	16.8	8	0.65	2.17	11.1	12.7	12
2	0.50	15.1	137	175	22	0.25	32.4	329	353	7
3	0.50	158	915	984	7	0.75	203	1260	1310	3
4	0.50	222	1070	1180	10	0.50	313	1670	1760	5
5	0.25	9.30	56.2	66.9	16	0.50	10.6	109	115	5
6	0.50	293	1480	1630	9	0.75	300	2720	2860	5
7	0.75	19.2	166	179	8	0.50	43.3	303	317	4
8	0.25	18.6	93.1	107	13	0.75	25.3	234	254	8
9	1.00	1060	6690	7200	7	0.75	1040	7870	8130	3
10	0.50	44.8	321	388	17	0.75	49.5	551	566	3
11	0.50	17.3	68.8	71.9	4	0.25	7.44	48.1	53.0	9
12	1.00	19.1	106	108	2	1.50	14.7	174	NC	NC
N	12	12	12	12	12	12	12	12	11	11
Mean	0.58	156	927	1010	10	0.66	170	1270	1430	6
SD	0.24	300	1880	2020	6	0.32	297	2230	2390	3
SE	0.07	86.7	542	583	2	0.09	85.7	644	721	1
Min	0.25	2.31	15.4	16.8	2	0.25	2.17	11.1	12.7	3
Median	0.50	19.2	151	177	9	0.70	37.8	316	353	5
Max	1.00	1060	6690	7200	22	1.50	1040	7870	8130	12
CV%	42	192	203	200	56	49	175	175	167	49
Geometric Mean	0.53	40.3	243	271	9	0.59	45.9	366	417	5

NC = Not calculated

Day Comparison

Plasma OH_Carterolol

					Carterolol PO Form B										
					Day 1								Day 14		
AUC_τ (ng•hr/ml)	R_A	LI	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_∞ (ng•hr/ml)	AUC % Extrap (%)	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_∞ (ng•hr/ml)	AUC % Extrap (%)	AUC_τ (ng•hr/ml)	R_A	LI
11.6	0.750	0.691	1.00	3.16	24.3	28.0	13	0.25	4.30	38.5	39.7	3	35.6	1.47	1.27
261	1.90	1.49	0.75	168	1290	1340	4	1.50	221	1440	1490	3	1360	1.05	1.01
1230	1.34	1.25	0.50	202	680	717	5	0.50	236	881	909	3	904	1.33	1.26
1670	1.57	1.42	0.50	199	936	970	3	0.50	269	1620	1630	1	1530	1.63	1.58
87.3	1.55	1.31	1.00	7.62	59.8	64.0	6	0.75	9.12	82.4	82.9	1	76.6	1.28	1.20
2580	1.74	1.58	0.50	42.9	302	330	8	0.50	50.9	367	375	2	345	1.14	1.05
279	1.69	1.56	1.00	58.3	477	522	9	0.75	100	975	989	1	873	1.83	1.67
209	2.24	1.94	0.75	282	1440	1490	4	0.50	284	1350	1360	0	1310	0.907	0.875
7300	1.09	1.01	0.50	1560	11300	12800	12	1.00	1730	18300	18400	1	16600	1.47	1.30
465	1.45	1.20	0.50	44.8	319	386	17	0.75	49.5	551	566	3	465	1.46	1.20
48.1	0.698	0.669	0.75	148	1320	1790	26	1.00	277	3750	4090	9	2950	2.23	1.64
83.9	0.793	0.776	0.50	18.2	84.6	87.6	3	NC	NC	NC	NC	NC	NC	NC	NC
12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11
1190	1.40	1.24	0.69	228	1520	1710	9	0.73	294	2670	2730	2	2400	1.44	1.28
2090	0.486	0.394	0.22	430	3120	3540	7	0.34	490	5270	5330	2	4780	0.371	0.260
602	0.140	0.114	0.06	124	900	1020	2	0.10	148	1590	1610	1	1440	0.112	0.0785
11.6	0.698	0.669	0.50	3.16	24.3	28.0	3	0.25	4.30	38.5	39.7	0	35.6	0.907	0.875
270	1.50	1.28	0.63	103	579	620	7	0.75	221	975	989	2	904	1.46	1.26
7300	2.24	1.94	1.00	1560	11300	12800	26	1.50	1730	18300	18400	9	16600	2.23	1.67
176	35	32	31	189	205	207	75	47	167	198	196	93	199	26	20
319	1.32	1.18	0.66	72.6	464	513	7	0.66	106	824	845	2	756	1.39	1.25

Variables

Selected:

- Tmax
- Cmax
- AUClast
- AUCINF_obs
- AUC_%Extrap_obs

Statistics

Selected:

- N
- Mean
- SD
- SE
- Min
- Median
- Max
- CV%
- Geometric Mean

Precision

Variables	Statistics			
	Individual		N	
	Type	Value	Type	Value
Tmax	Decimal	2	Decimal	0
Cmax	Significant	3	Decimal	0
AUClast	Significant	3	Decimal	0
AUCINF_obs	Significant	3	Decimal	0
AUC_%Extrap_obs	Decimal	0	Decimal	0

Figure 14-7. PK parameter ratios accumulation comparison

Absolute Bioavailability Comparison											
Plasma OH_Carterolol											
	IV (Reference)						Extravascular (Test 1)				
Subject	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)	$Dose_{iv}$ (mg)	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)
1	0.25	8.88	65.1	71.9	9	100	0.65	2.31	15.4	16.8	8
2	0.25	150	645	743	13	100	0.50	15.1	137	175	22
3	0.25	223	1290	1440	10	100	0.50	158	915	984	7
4	0.25	450	2760	3030	9	100	0.50	222	1070	1180	10
5	0.25	320	1520	1600	5	100	0.25	9.30	56.2	66.9	16
6	0.25	187	808	878	8	100	0.50	293	1480	1630	9
7	0.25	125	494	503	2	100	0.75	19.2	166	179	8
8	0.25	2000	11100	11600	4	100	0.25	18.6	93.1	107	13
9	0.25	11000	47000	47700	1	100	1.00	1060	6690	7200	7
10	0.25	350	1640	1700	3	100	0.50	44.8	321	388	17
11	0.25	137	1760	2060	14	100	0.50	17.3	68.8	71.9	4
12	0.25	205	919	985	7	100	1.00	19.1	106	108	2
N	12	12	12	12	12	12	12	12	12	12	12
Mean	0.25	1260	5840	6030	7	100	0.58	156	927	1010	10
SD	0.00	3110	13300	13500	4	0	0.24	300	1880	2020	6
SE	0.00	898	3840	3890	1	0	0.07	86.7	542	583	2
Min	0.25	8.88	65.1	71.9	1	100	0.25	2.31	15.4	16.8	2
Median	0.25	214	1400	1520	7	100	0.50	19.2	151	177	9
Max	0.25	11000	47000	47700	14	100	1.00	1060	6690	7200	22
CV%	0	246	228	224	58	0	42	192	203	200	56
Geometric Mean	0.25	278	1500	1610	6	100	0.53	40.3	243	271	9

Extravascular (Test 2)								
F_{abs} (%)	$Dose_{Ext}$ (mg)	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)	F_{abs} (%)	$Dose_{Ext}$ (mg)
23	100	1.00	3.16	24.3	28.0	13	39	100
24	100	0.75	168	1290	1340	4	181	100
69	100	0.50	202	680	717	5	50	100
39	100	0.50	199	936	970	3	32	100
4	100	1.00	7.62	59.8	64.0	6	4	100
186	100	0.50	42.9	302	330	8	38	100
36	100	1.00	58.3	477	522	9	104	100
1	100	0.75	282	1440	1490	4	13	100
15	100	0.50	1560	11300	12800	12	27	100
23	100	0.50	44.8	319	386	17	23	100
3	100	0.75	148	1320	1790	26	87	100
11	100	0.50	18.2	84.6	87.6	3	9	100
12	12	12	12	12	12	12	12	12
36	100	0.69	228	1520	1710	9	50	100
51	0	0.22	430	3120	3540	7	51	0
15	0	0.06	124	900	1020	2	15	0
1	100	0.50	3.16	24.3	28.0	3	4	100
23	100	0.63	103	579	620	7	35	100
186	100	1.00	1560	11300	12800	26	181	100
141	0	31	189	205	207	75	101	0
17	100	0.66	72.6	464	513	7	32	100

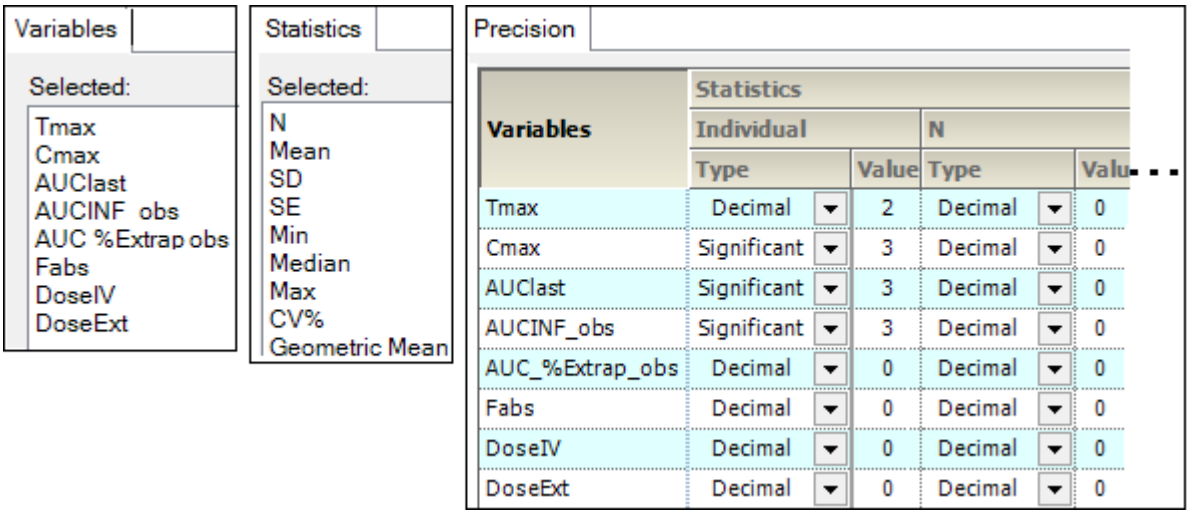


Figure 14-8. PK parameter ratios absolute bioavailability comparison

Renal Clearance Comparison			
	Treatment = Carterolol Form A	Treatment = Carterolol Form B	Treatment = Carterolol Form C
Subject	CL_r (ml/hr)	CL_r (ml/hr)	CL_r (ml/hr)
1	3120	1220	804
2	166	15.3	39.8
3	26.5	13.9	962
4	18.5	71.5	160
5	544	762	21.2
6	6.65	186	55.9
7	112	61	65.1
8	197	83.3	1.9
9	6.04	3.91	1.46
10	41.4	86.8	198
11	910	18.3	130
12	132	NC	65.1
N	12	11	12
Mean	440	230	209
SD	887	394	323
SE	256	119	93.1
Min	6.04	3.91	1.46
Median	122	71.5	65.1
Max	3120	1220	962
CV%	201	172	155
Geometric Mean	95.9	64.7	58.9
NC = Not calculated			

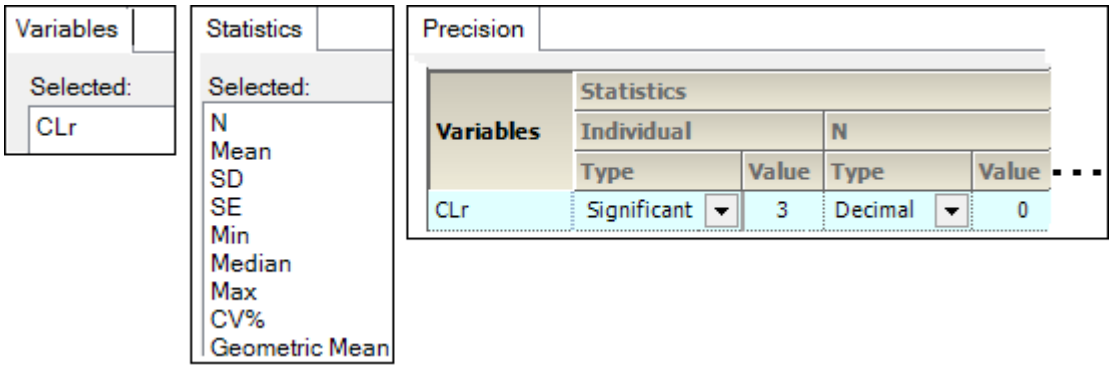


Figure 14-9. PK parameter ratios renal comparison

Comparison intext tables

Intext PK parameter plasma comparison
Intext PK parameter urine comparison
Intext PK parameter accumulation comparison
Intext PK parameter absolute bioavailability comparison
Intext PK parameter renal comparison

Mean ± SD	Analyte Comparison - Plasma					
Treatment	Carterolol Form A		Carterolol Form B		Carterolol Form C	
Analyte	OH_Carterolol	Carterolol	OH_Carterolol	Carterolol	OH_Carterolol	Carterolol
N	12	12	11	11	12	12
$t_{1/2}$ (hr)	8.35 ± 2.32[b]	10.70 ± 8.84	7.52 ± 2.62	7.35 ± 2.62	9.74 ± 5.78	8.92 ± 3.85
T_{max}[a] (hr)	0.62 (0.25 - 1.50)	0.49 (0.25 - 0.75)	0.73 (0.25 - 1.50)	0.64 (0.25 - 1.00)	0.52 (0.25 - 1.00)	0.56 (0.25 - 1.50)
C_{max} (ng/ml)	216 ± 311	678 ± 943	294 ± 490	1140 ± 1970	1560 ± 3800	6240 ± 15200
AUC_{last} (ng•hr/ml)	1460 ± 2260	4640 ± 6970	2670 ± 5270	9680 ± 19000	10500 ± 23300	40800 ± 90700
AUC_{∞} (ng•hr/ml)	1630 ± 2410[b]	5200 ± 7070	2730 ± 5330	9890 ± 19200	10700 ± 23400	41200 ± 91100
AUC_{τ} (ng•hr/ml)	1360 ± 2110	4350 ± 6530	2400 ± 4780	8820 ± 17500	9630 ± 21800	38000 ± 86300
CL_{ss}/F (L/hr)	12.1 ± 24.2	3.84 ± 8.05	4.63 ± 8.60	1.43 ± 2.79	2.61 ± 4.02	0.700 ± 1.10
V_z/F (L)	144 ± 280[b]	55.9 ± 95.2	45.8 ± 84.1	13.8 ± 27.2	28.3 ± 30.6	7.10 ± 8.07
Fluctuation % (%)	349 ± 71	350 ± 65	330 ± 134	358 ± 124	309 ± 91	326 ± 98

[a] Mean (Min - Max)

[b] n=11, Subject 12 not included in calculation of summary statistics
NC = Not calculated

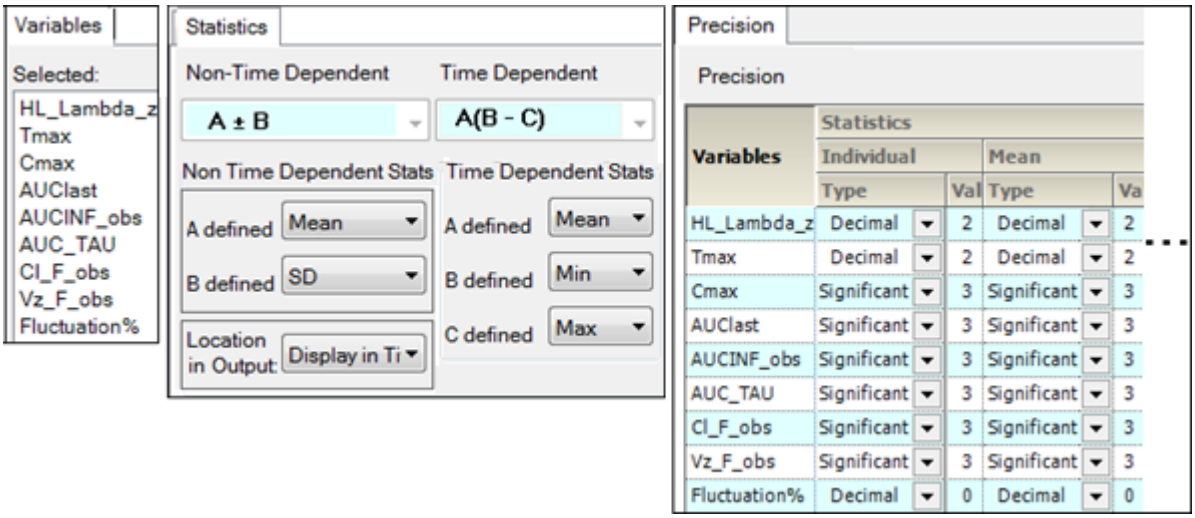
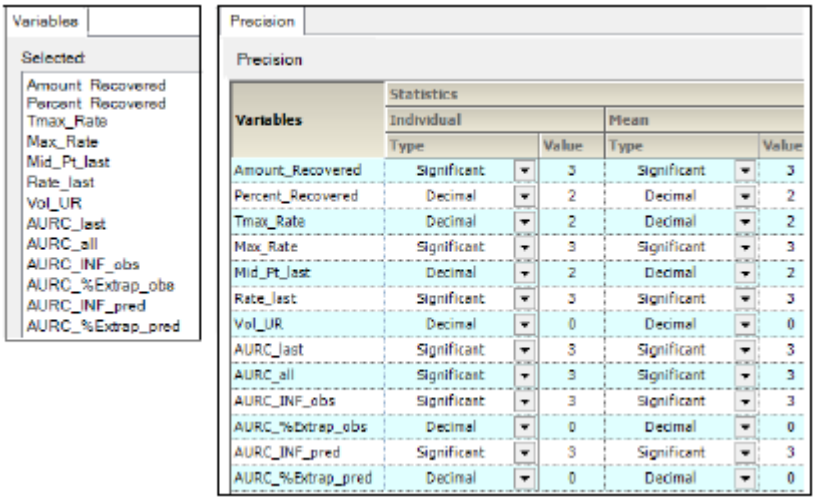


Figure 14-10. Intext PK parameter plasma comparison

Mean ± SD	Analyte Comparison					
	Carterolol Form A		Carterolol Form B		Carterolol Form C	
	Carterolol	OH-Carterolol	Carterolol	OH-Carterolol	Carterolol	OH-Carterolol
N	12	12	12	12	12	12
Ae (ng)	189000 ± 121000	44800 ± 24400	290000 ± 140000	63800 ± 30700	395000 ± 141000	88100 ± 29600
fe (%)	18.89 ± 12.11	4.48 ± 2.44	29.01 ± 13.95	6.38 ± 3.07	39.52 ± 14.07	8.81 ± 2.96
T_{max}Rate[a] (hr)	31.50 (18.00 - 36.00)	31.50 (18.00 - 36.00)	22.50 (18.00 - 36.00)	22.50 (18.00 - 36.00)	31.50 (18.00 - 36.00)	31.50 (18.00 - 36.00)
Max Rate (ng/hr)	6340 ± 3010	1400 ± 667	9500 ± 3600	2090 ± 793	12800 ± 3660	2810 ± 806
Midpoint[a] (hr)	34.50 (18.00 - 36.00)	36.17 (36.00 - 38.00)	34.50 (18.00 - 36.00)	34.50 (18.00 - 36.00)	36.00 (36.00 - 36.00)	36.00 (36.00 - 36.00)
Last Rate (ng/hr)	6040 ± 3030	1330 ± 672	7340 ± 3560	1610 ± 783	11800 ± 4670	2590 ± 1030
Volume (ml)	4274 ± 666	4274 ± 666	5140 ± 1427	5140 ± 1427	4804 ± 1007	4804 ± 1007
$AURC_{last}$ (ng)	125000 ± 80500[b]	29200 ± 16500	202000 ± 98700	44400 ± 21700	244000 ± 82300	55000 ± 15600
$AURC_{all}$ (ng)	123000 ± 76900	29200 ± 16500	202000 ± 98700	44400 ± 21700	244000 ± 82300	55000 ± 15600
$AURC_{\infty}$ (ng)	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]
AURC % Extra (%)	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]
$AURC_{\infty}$ (ng)	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]
AURC % Extra (%)	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]	NC ± NC[c]



Variables

Selected

- Amount_Recovered
- Percent_Recovered
- Tmax_Rate
- Max_Rate
- Mid_Pt_last
- Rate_last
- Vol_UR
- AURC_last
- AURC_all
- AURC_INF_obs
- AURC_%Extrap_obs
- AURC_INF_pred
- AURC_%Extrap_pred

Precision

Precision

Variables	Statistics			
	Individual		Mean	
	Type	Value	Type	Value
Amount_Recovered	Significant	3	Significant	3
Percent_Recovered	Decimal	2	Decimal	2
Tmax_Rate	Decimal	2	Decimal	2
Max_Rate	Significant	3	Significant	3
Mid_Pt_last	Decimal	2	Decimal	2
Rate_last	Significant	3	Significant	3
Vol_UR	Decimal	0	Decimal	0
AURC_last	Significant	3	Significant	3
AURC_all	Significant	3	Significant	3
AURC_INF_obs	Significant	3	Significant	3
AURC_%Extrap_obs	Decimal	0	Decimal	0
AURC_INF_pred	Significant	3	Significant	3
AURC_%Extrap_pred	Decimal	0	Decimal	0

Figure 14-11. Intext PK parameter urine comparison

Day Comparison

Plasma OH_Carterolol

Carterolol PO Form A

	Day 1					Day 14							
Subject	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)	AUC_{τ} (ng•hr/ml)	R_A	LI
1	0.65	2.31	15.4	16.8	8	0.65	2.17	11.1	12.7	12	11.6	0.750	0.691
2	0.50	15.1	137	175	22	0.25	32.4	329	353	7	261	1.90	1.49
3	0.50	158	915	984	7	0.75	203	1260	1310	3	1230	1.34	1.25
4	0.50	222	1070	1180	10	0.50	313	1670	1760	5	1670	1.57	1.42
5	0.25	9.30	56.2	66.9	16	0.50	10.6	109	115	5	87.3	1.55	1.31
6	0.50	293	1480	1630	9	0.75	300	2720	2860	5	2580	1.74	1.58
7	0.75	19.2	166	179	8	0.50	43.3	303	317	4	279	1.69	1.56
8	0.25	18.6	93.1	107	13	0.75	25.3	234	254	8	209	2.24	1.94
9	1.00	1060	6690	7200	7	0.75	1040	7870	8130	3	7300	1.09	1.01
10	0.50	44.8	321	388	17	0.75	49.5	551	566	3	465	1.45	1.20
11	0.50	17.3	68.8	71.9	4	0.25	7.44	48.1	53.0	9	48.1	0.698	0.669
12	1.00	19.1	106	108	2	1.50	14.7	174	NC	NC	83.9	0.793	0.776
N	12	12	12	12	12	12	12	12	11	11	12	12	12
Mean	0.58	156	927	1010	10	0.66	170	1270	1430	6	1190	1.40	1.24
SD	0.24	300	1880	2020	6	0.32	297	2230	2390	3	2090	0.486	0.394
SE	0.07	86.7	542	583	2	0.09	85.7	644	721	1	602	0.140	0.114
Min	0.25	2.31	15.4	16.8	2	0.25	2.17	11.1	12.7	3	11.6	0.698	0.669
Median	0.50	19.2	151	177	9	0.70	37.8	316	353	5	270	1.50	1.28
Max	1.00	1060	6690	7200	22	1.50	1040	7870	8130	12	7300	2.24	1.94
CV%	42	192	203	200	56	49	175	175	167	49	176	35	32
Geometric Mean	0.53	40.3	243	271	9	0.59	45.9	366	417	5	319	1.32	1.18

NC = Not calculated

Carterolol PO Form B

Day 1					Day 14							
T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)	T_{max} (hr)	C_{max} (ng/ml)	AUC_{last} (ng•hr/ml)	AUC_{∞} (ng•hr/ml)	AUC % Extrap (%)	AUC_{τ} (ng•hr/ml)	R_A	LI
1.00	3.16	24.3	28.0	13	0.25	4.30	38.5	39.7	3	35.6	1.47	1.27
0.75	168	1290	1340	4	1.50	221	1440	1490	3	1360	1.05	1.01
0.50	202	680	717	5	0.50	236	881	909	3	904	1.33	1.26
0.50	199	936	970	3	0.50	269	1620	1630	1	1530	1.63	1.58
1.00	7.62	59.8	64.0	6	0.75	9.12	82.4	82.9	1	76.6	1.28	1.20
0.50	42.9	302	330	8	0.50	50.9	367	375	2	345	1.14	1.05
1.00	58.3	477	522	9	0.75	100	975	989	1	873	1.83	1.67
0.75	282	1440	1490	4	0.50	284	1350	1360	0	1310	0.907	0.875
0.50	1560	11300	12800	12	1.00	1730	18300	18400	1	16600	1.47	1.30
0.50	44.8	319	386	17	0.75	49.5	551	566	3	465	1.46	1.20
0.75	148	1320	1790	26	1.00	277	3750	4090	9	2950	2.23	1.64
0.50	18.2	84.6	87.6	3	NC	NC	NC	NC	NC	NC	NC	NC
12	12	12	12	12	11	11	11	11	11	11	11	11
0.69	228	1520	1710	9	0.73	294	2670	2730	2	2400	1.44	1.28
0.22	430	3120	3540	7	0.34	490	5270	5330	2	4780	0.371	0.260
0.06	124	900	1020	2	0.10	148	1590	1610	1	1440	0.112	0.0785
0.50	3.16	24.3	28.0	3	0.25	4.30	38.5	39.7	0	35.6	0.907	0.875
0.63	103	579	620	7	0.75	221	975	989	2	904	1.46	1.26
1.00	1560	11300	12800	26	1.50	1730	18300	18400	9	16600	2.23	1.67
31	189	205	207	75	47	167	198	196	93	199	26	20
0.66	72.6	464	513	7	0.66	106	824	845	2	756	1.39	1.25

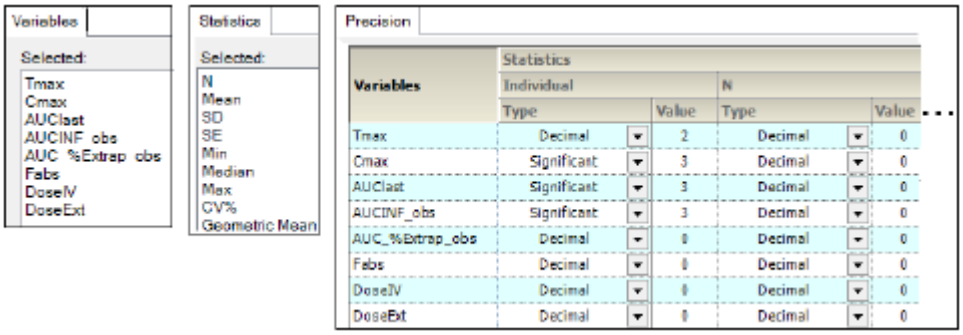


Figure 14-12. Intext PK parameter accumulation comparison

Mean ± SD	Absolute Bioavailability Comparison - Plasma OH_Carterolol		
Route	IV	Extravascular	
Treatment	Carterolol IV	Carterolol PO Form A	Carterolol PO Form B
N	12	12	11
$t_{1/2}$ (hr)	10.43 ± 5.93	8.50 ± 2.33[c]	7.52 ± 2.62
T_{max}[a] (hr)	0.27 (0.25 - 0.50)	0.66 (0.25 - 1.50)	0.73 (0.25 - 1.50)
C_{max} (ng/ml)	1680 ± 3780	170 ± 297	294 ± 490
AUC_{last} (ng•hr/ml)	11900 ± 23500	1270 ± 2230	2670 ± 5270
AUC_{∞} (ng•hr/ml)	12200 ± 23600	1430 ± 2390[c]	2730 ± 5330
AUC_{T} (ng•hr/ml)	10700 ± 22200	1190 ± 2090	2400 ± 4780
CL_{ss}/F (ml/hr)	NC ± NC[b]	1220000 ± 2420000	463000 ± 860000
CL_{ss} (ml/hr)	162000 ± 388000	NC ± NC[b]	NC ± NC[b]
V_z/F (ml)	NC ± NC[b]	14600000 ± 27900000[c]	4580000 ± 8410000
V_z (ml)	1630000 ± 2700000	NC ± NC[b]	NC ± NC[b]
Fluctuation % (%)	344 ± 170	323 ± 80	330 ± 134
F_{abs} (%)	NC ± NC[b]	35 ± 62[c]	54 ± 68
$Dose_{IV}$ (mg)	100 ± 0	NC ± NC[b]	NC ± NC[b]
$Dose_{Ext}$ (mg)	NC ± NC[b]	100 ± 0	100 ± 0

[a] Mean (Min - Max)

[b] n=0, Subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 not included in calculation of summary statistics

[c] n=11, Subject 12 not included in calculation of summary statistics
NC = Not calculated

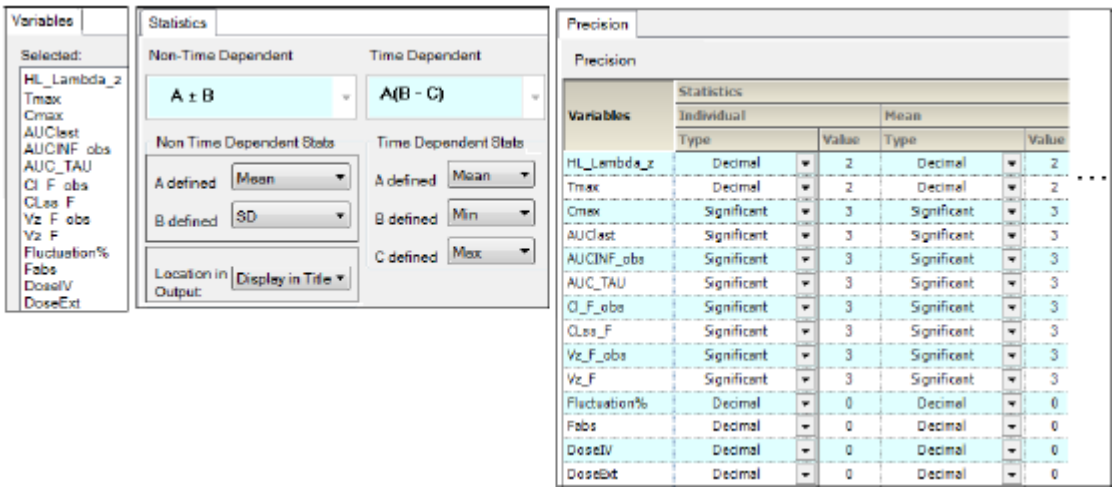


Figure 14-13. Intext PK parameter absolute bioavailability comparison

Mean ± SD	Renal Clearance Comparison		
	Carterolol Form A	Carterolol Form B	Carterolol Form C
N	12	11	12
CL_r (ml/hr)	440 ± 887	230 ± 394	209 ± 323

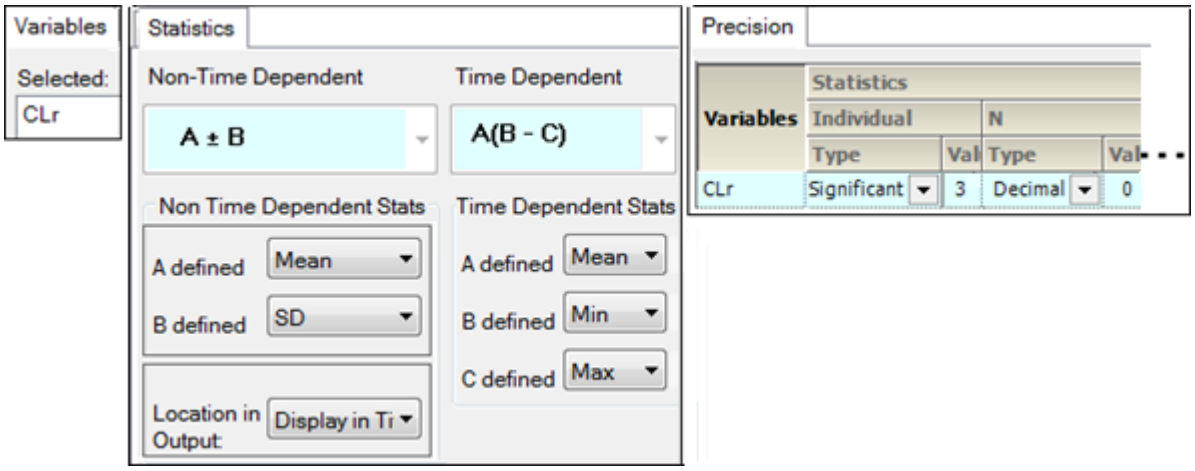


Figure 14-14. Intext PK parameter renal comparison

Plasma comparison time concentration

Individual analyte comparison by subject
Individual accum. comparison by subject
Individual absolute bioavail. comparison by subject
Analyte concentration comparison summary

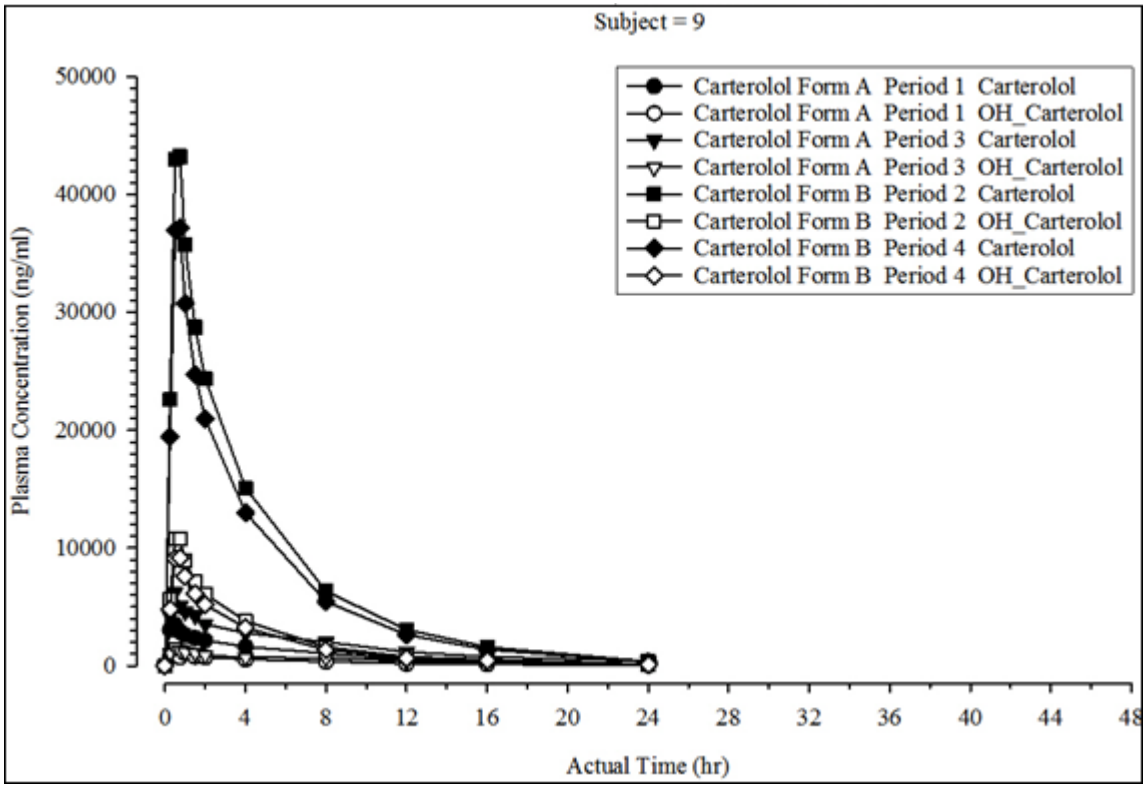
- Analyte conc. comp. summary by treatment and strat. by group
- Analyte conc. comp. summary sorted and strat. by group

Accumulation concentration comparison summary.

- Accumulation conc. comp. summary by treatment and strat. by group
- Accumulation conc. comp. summary sorted and strat. by group

Absolute bioavail. concentration comparison summary

- Absolute bioavail. conc. comp. summary by treatment and strat. by group
- Absolute bioavail. conc. comp. summary sorted and strat. by group



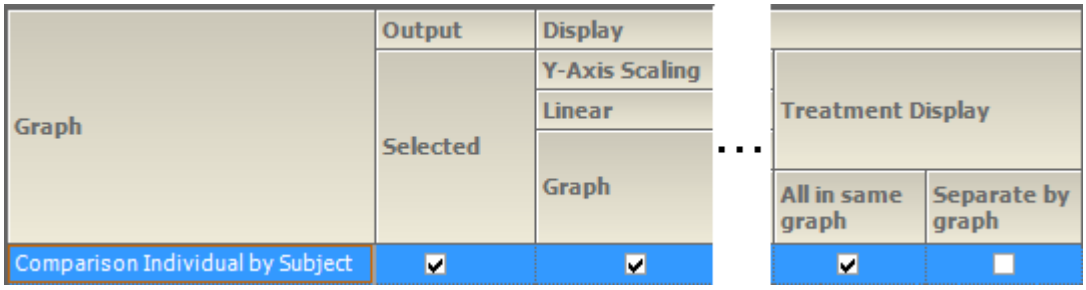
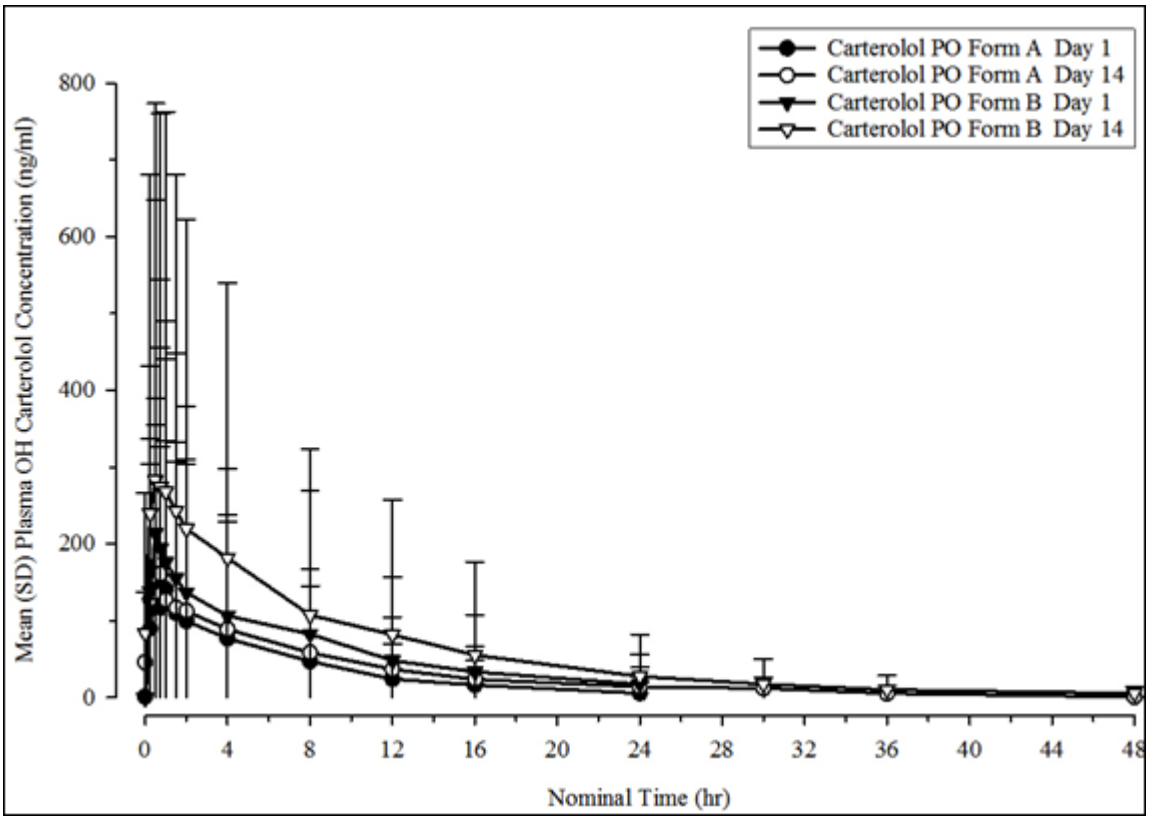
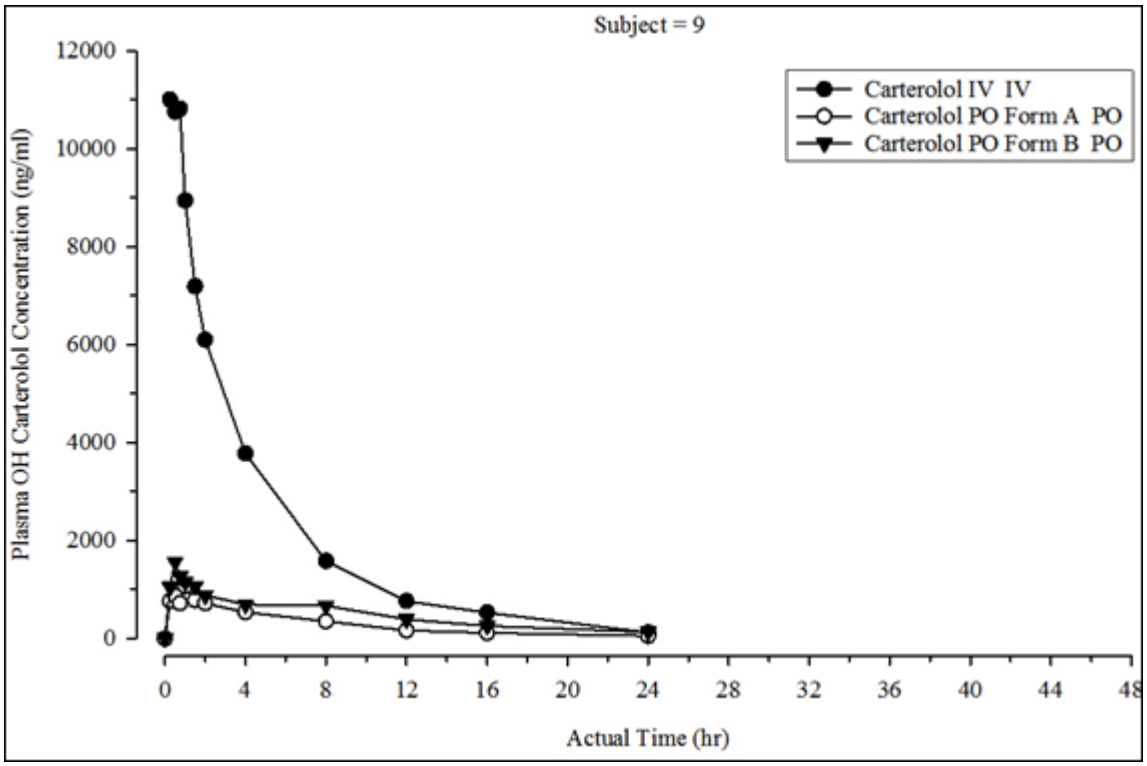


Figure 14-15. Individual analyte comparison by subject



Graph	Output	Display		LOQ	Treatment Display	
	Selected	Y-Axis Scaling				
		Linear				
		Graph	...		All in same graph	Separate by graph
Comparison Individual by Subject	☑	☑		☑	☑	☐

Figure 14-16. Individual accum. comparison by subject



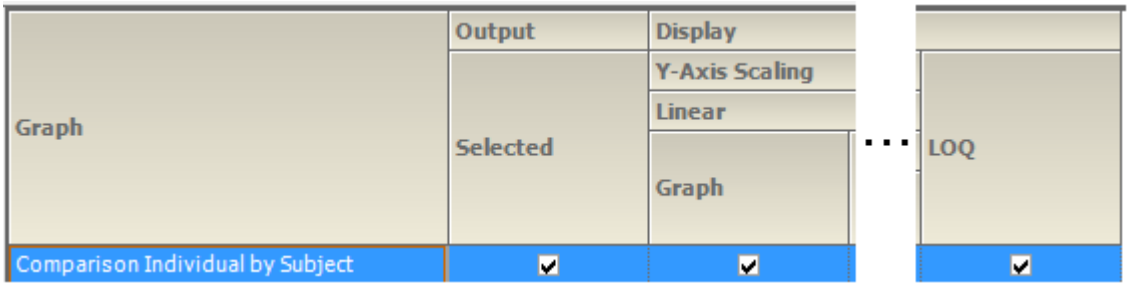
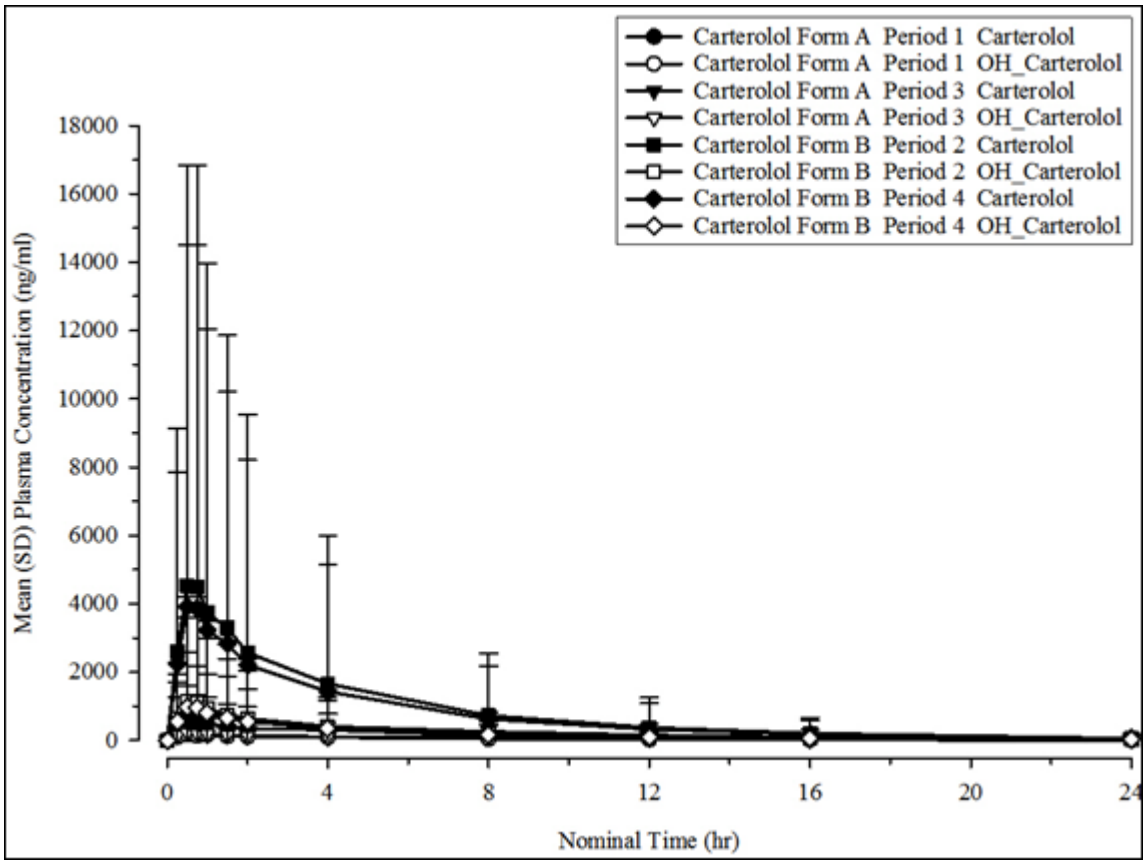
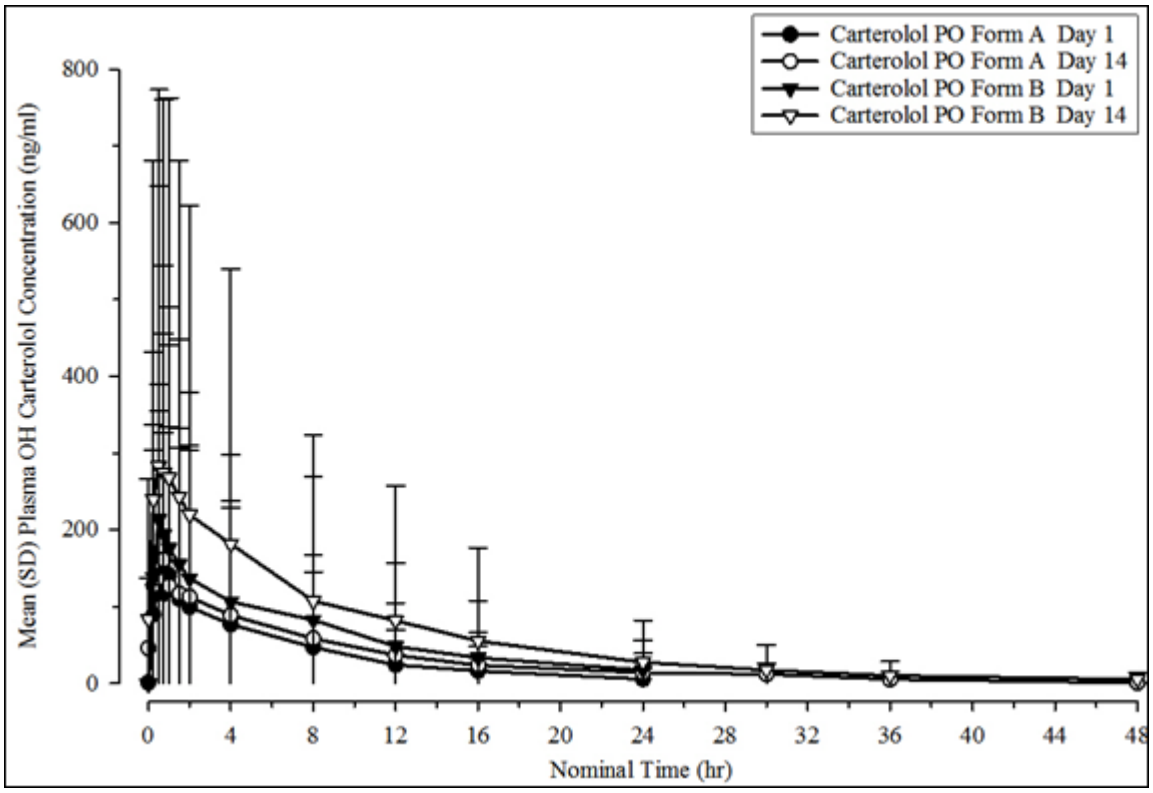


Figure 14-17. Individual absolute bioavail. comparison by subject



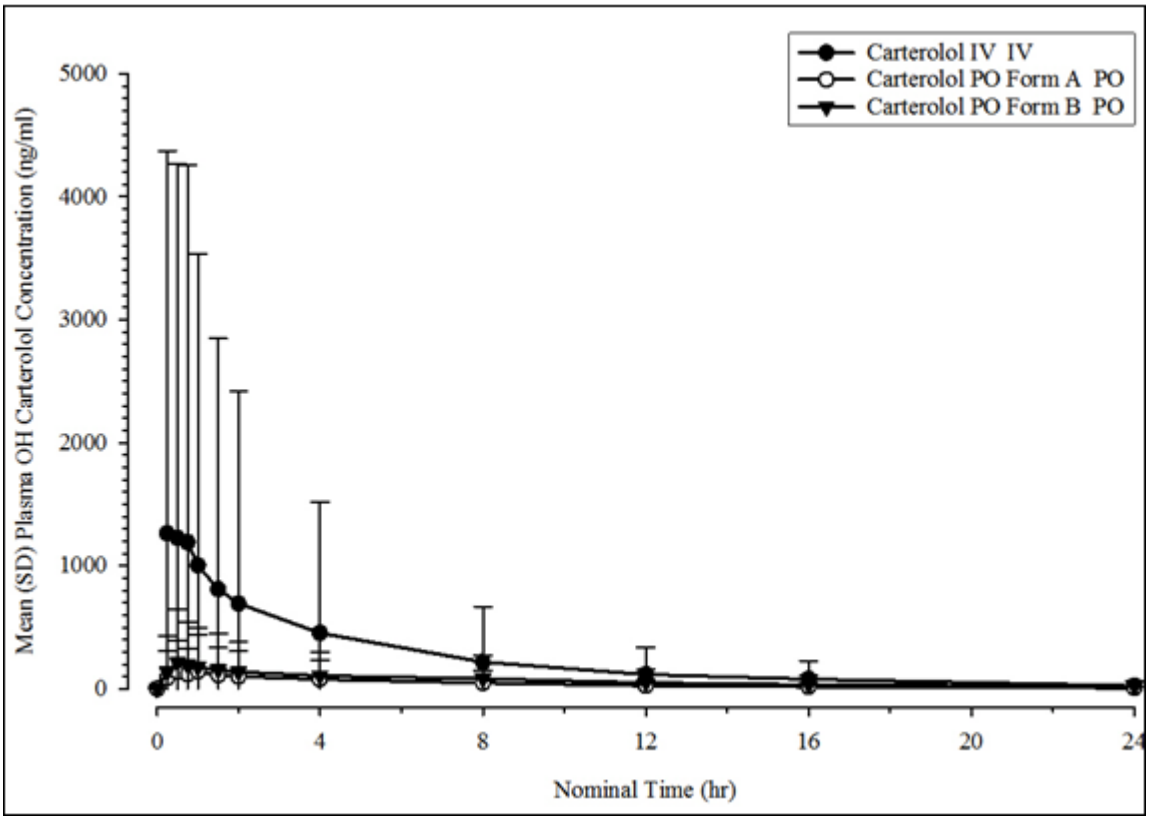
Graph	Output	Display							
	Selected	Y-Axis Scaling						Treatment Display	
		Linear							
		Graph	Summary Va		Error			All in san graph	Separate graph
					Value	Direction			
Comparison Individual by Subject	☑	☑						☑	☐
Comparison Summary by Treatment	☑	☑	Mean		SD	Both		☑	☐

Figure 14-18. Analyte concentration comparison summary



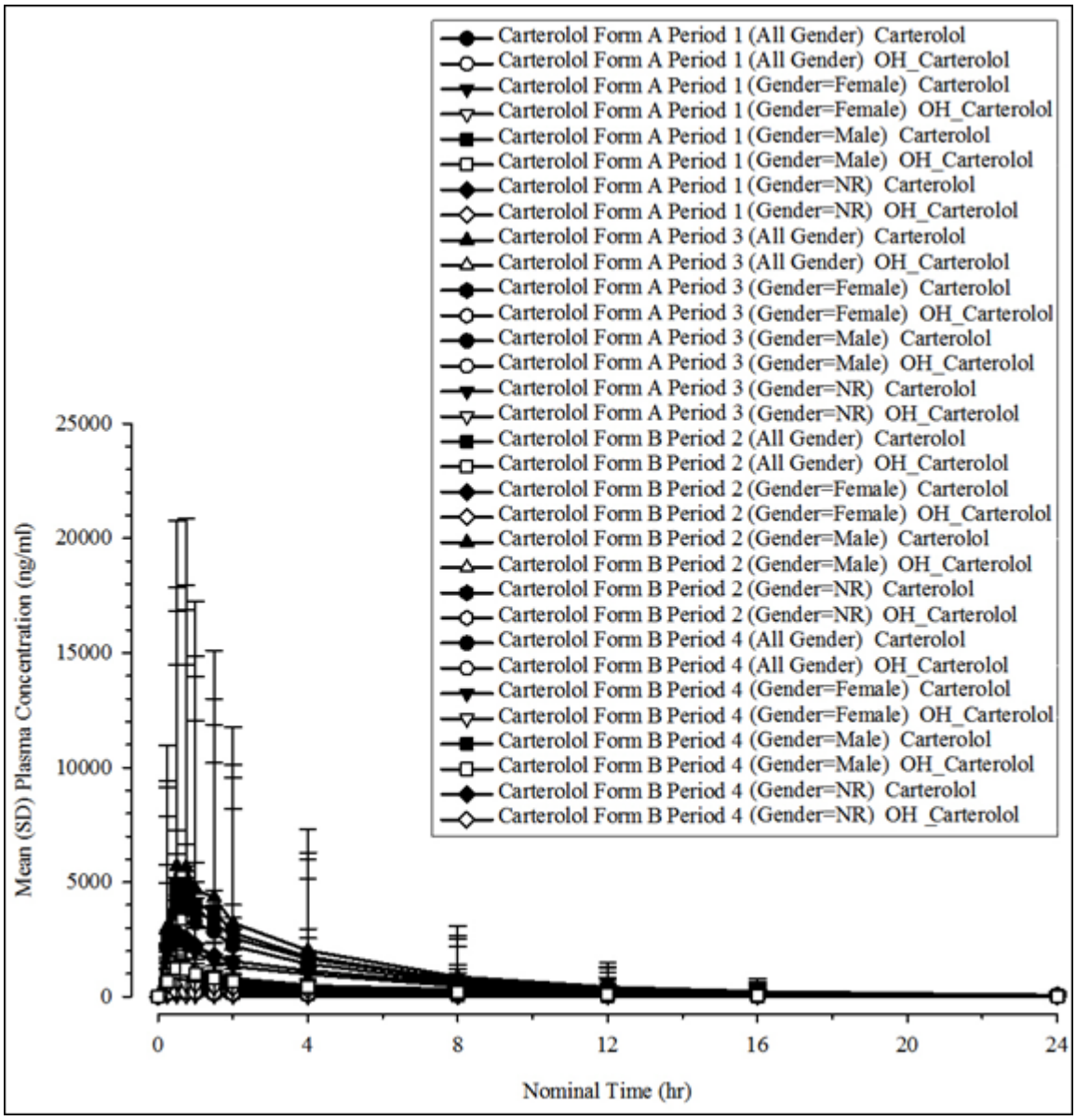
Graph	Output	Display							
	Selected	Y-Axis Scaling							
		Linear							
		Graph	Summary Val	Error		...	LOQ	Treatment Display	
				Value	Direction			All in same graph	Separate graph
Comparison Individual by Subject	☑	☑					☑	☑	☐
Comparison Summary by Treatment	☑	☑	Mean	SD	Both		☑	☑	☐

Figure 14-19. Accumulation concentration comparison summary.



Graph	Output	Display					...	
	Selected	Y-Axis Scaling						
		Linear						
		Graph	Summary Value	Error				LOQ
				Value	Direction			
Comparison Individual by Subject	☑	☑						☑
Comparison Summary by Treatment	☑	☑	Mean	SD	Both			☑

Figure 14-20. Absolute bioavail. concentration comparison summary


Carterolol Form A Period 1 (All Gender) Carterolol
Carterolol Form A Period 1 (All Gender) OH_Carterolol
Carterolol Form A Period 1 (Gender=Female) Carterolol
Carterolol Form A Period 1 (Gender=Female) OH_Carterolol
Carterolol Form A Period 1 (Gender=Male) Carterolol
Carterolol Form A Period 1 (Gender=Male) OH_Carterolol
Carterolol Form A Period 1 (Gender=NR) Carterolol
Carterolol Form A Period 1 (Gender=NR) OH_Carterolol
Carterolol Form A Period 3 (All Gender) Carterolol
Carterolol Form A Period 3 (All Gender) OH_Carterolol
Carterolol Form A Period 3 (Gender=Female) Carterolol
Carterolol Form A Period 3 (Gender=Female) OH_Carterolol
Carterolol Form A Period 3 (Gender=Male) Carterolol
Carterolol Form A Period 3 (Gender=Male) OH_Carterolol
Carterolol Form A Period 3 (Gender=NR) Carterolol
Carterolol Form A Period 3 (Gender=NR) OH_Carterolol
Carterolol Form B Period 2 (All Gender) Carterolol
Carterolol Form B Period 2 (All Gender) OH_Carterolol
Carterolol Form B Period 2 (Gender=Female) Carterolol
Carterolol Form B Period 2 (Gender=Female) OH_Carterolol
Carterolol Form B Period 2 (Gender=Male) Carterolol
Carterolol Form B Period 2 (Gender=Male) OH_Carterolol
Carterolol Form B Period 2 (Gender=NR) Carterolol
Carterolol Form B Period 2 (Gender=NR) OH_Carterolol
Carterolol Form B Period 4 (All Gender) Carterolol
Carterolol Form B Period 4 (All Gender) OH_Carterolol
Carterolol Form B Period 4 (Gender=Female) Carterolol
Carterolol Form B Period 4 (Gender=Female) OH_Carterolol
Carterolol Form B Period 4 (Gender=Male) Carterolol
Carterolol Form B Period 4 (Gender=Male) OH_Carterolol
Carterolol Form B Period 4 (Gender=NR) Carterolol
Carterolol Form B Period 4 (Gender=NR) OH _Carterolol
Mean (SD) Plasma Concentration (ng/ml)
25000
20000
15000
10000
5000
0
0
4
8
12
16
20
24
Nominal Time (hr)

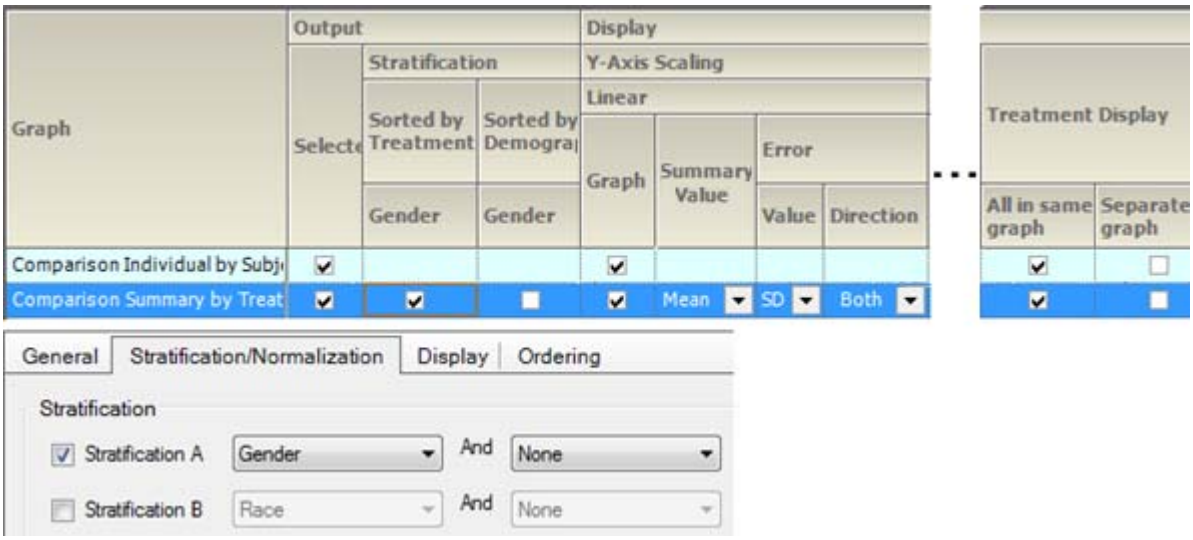
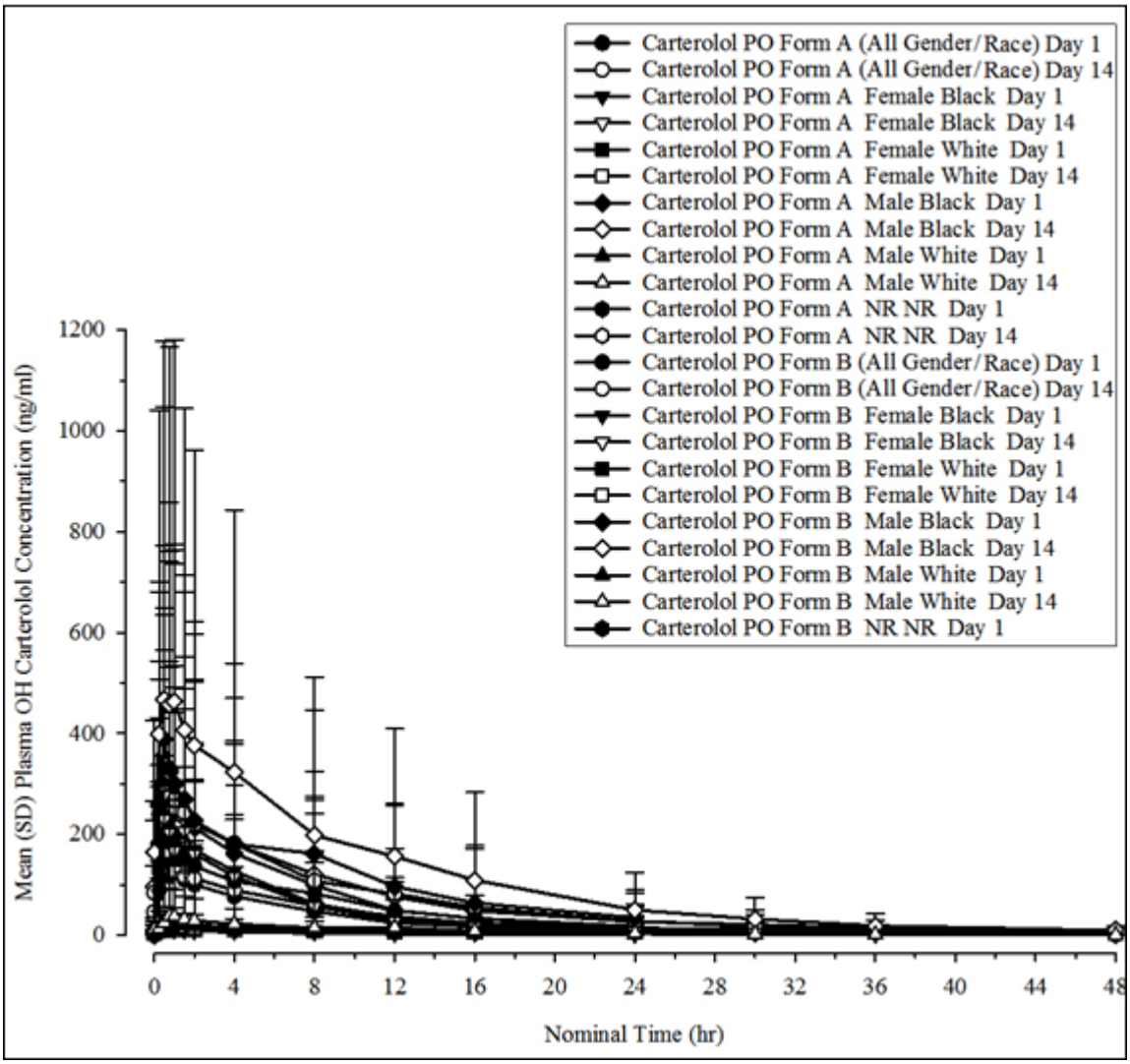


Figure 14-21. Analyte conc. comp. summary by treatment and strat. by group



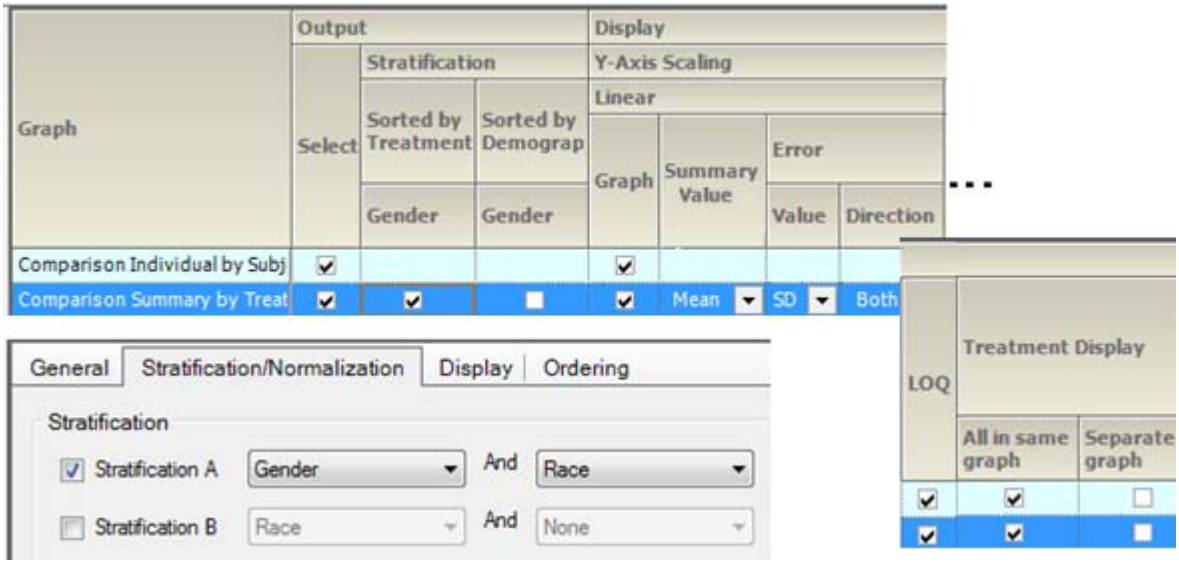
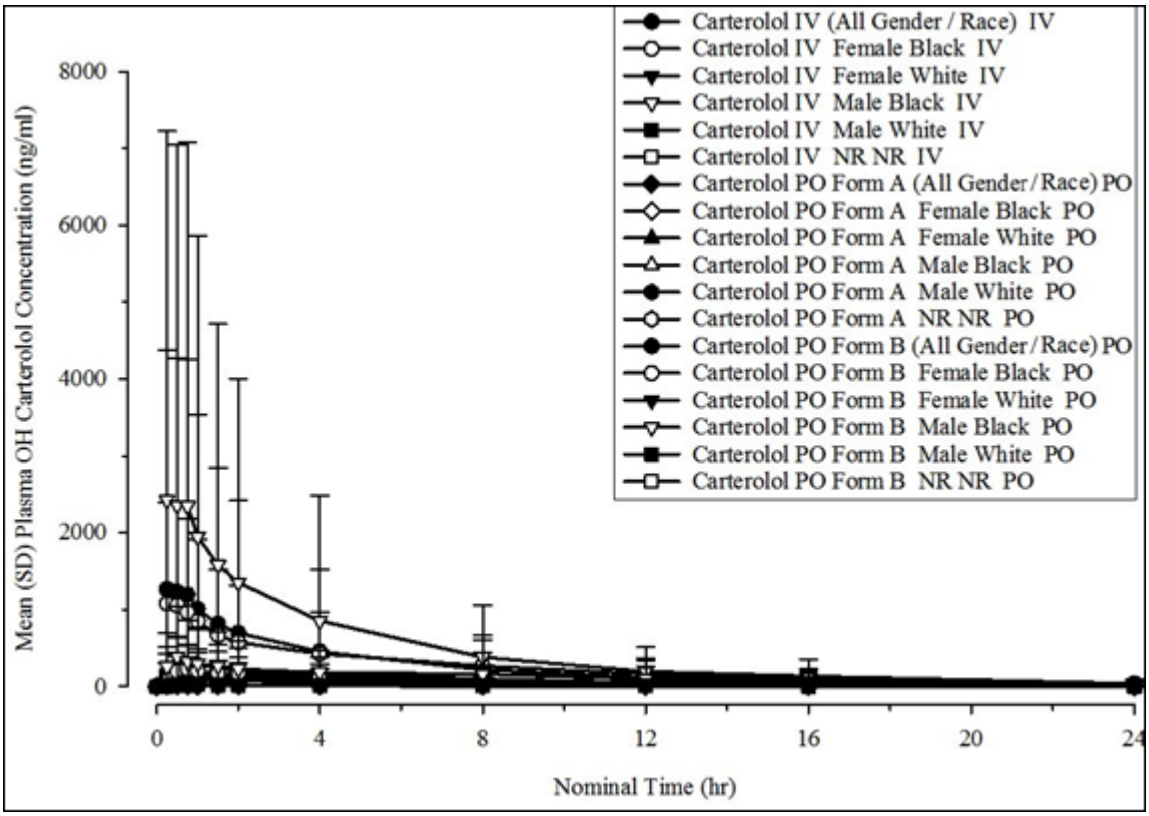


Figure 14-22. Accumulation conc. comp. summary by treatment and strat. by group



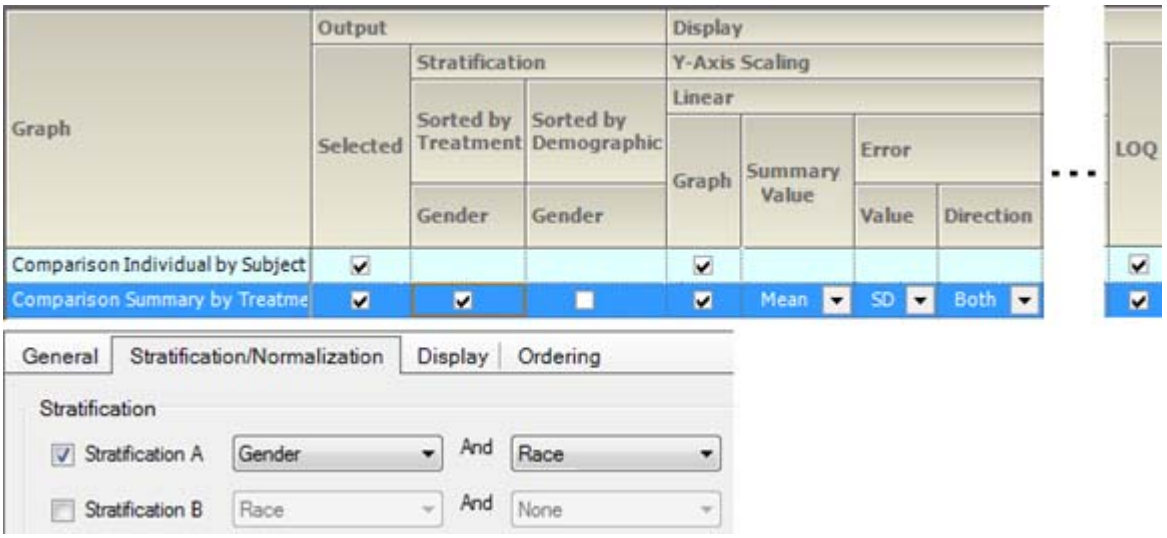
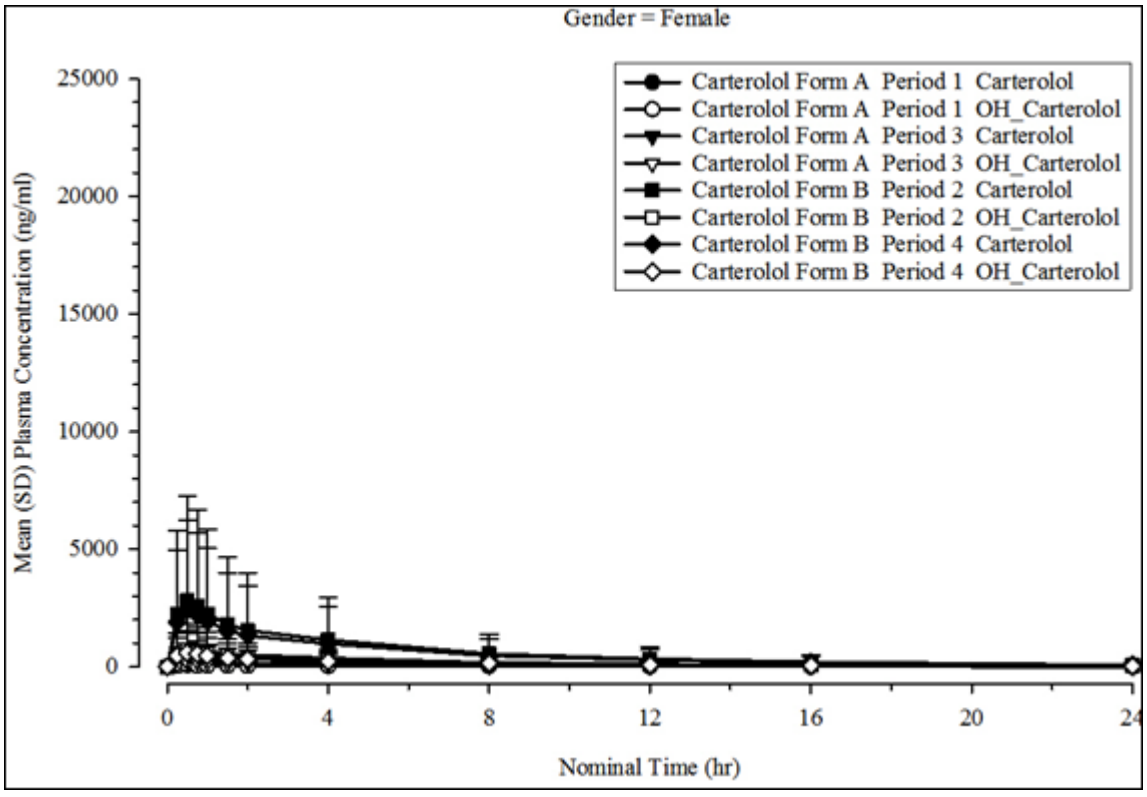


Figure 14-23. Absolute bioavail. conc. comp. summary by treatment and strat. by group



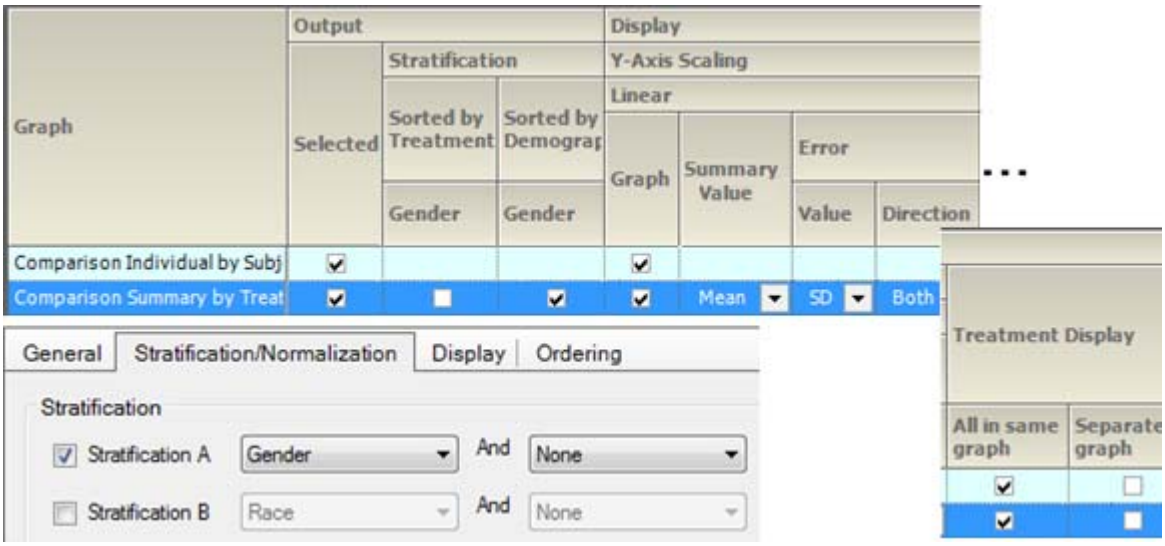
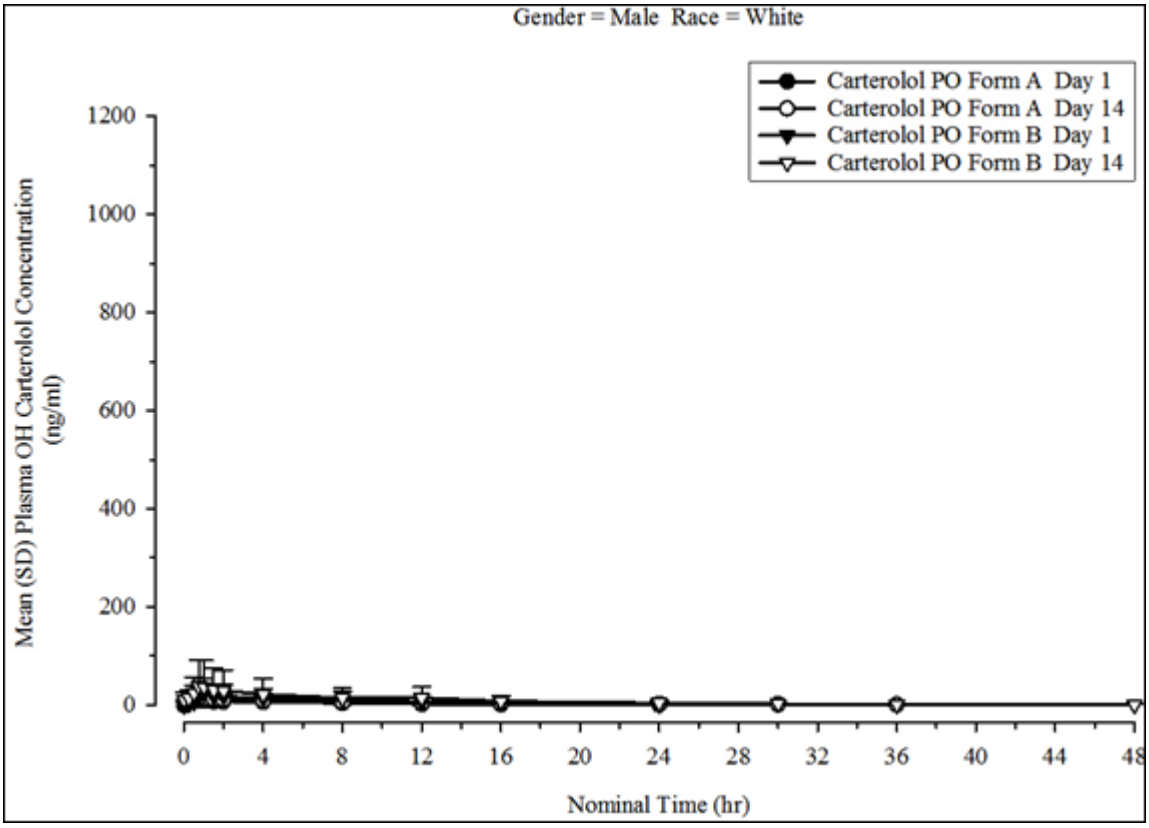


Figure 14-24. Analyte conc. comp. summary sorted and strat. by group



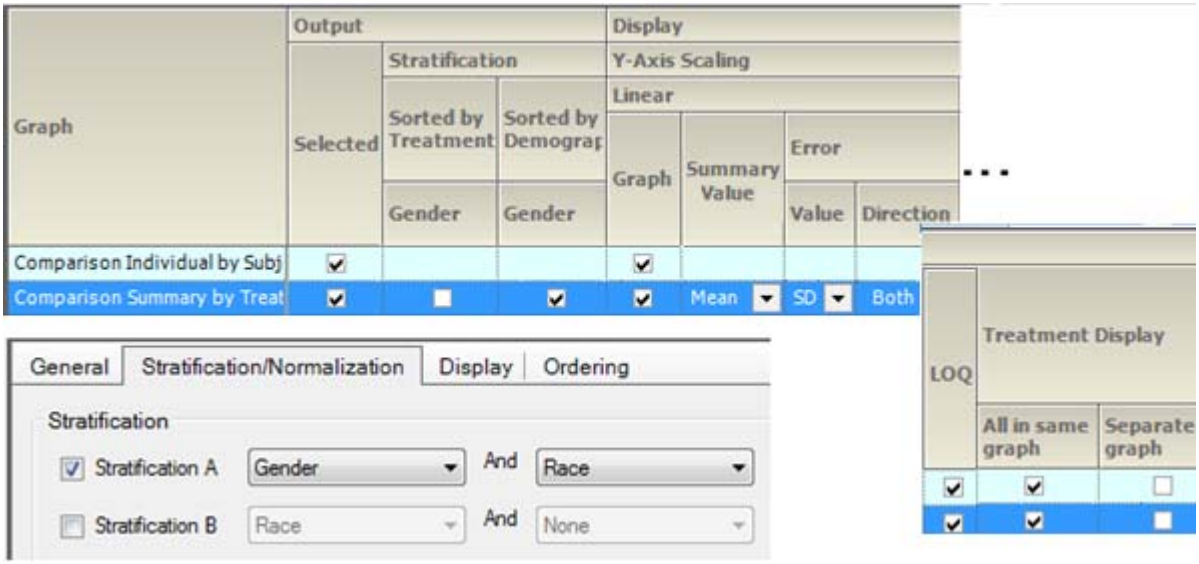
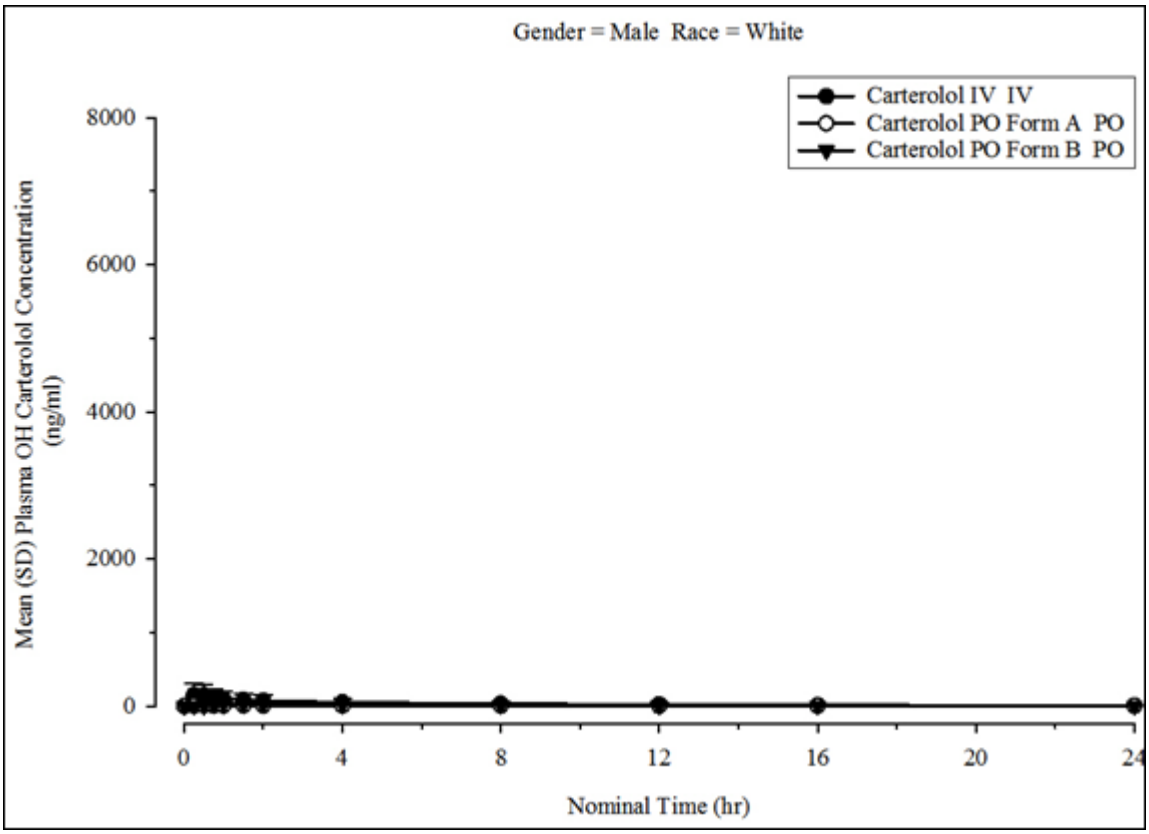


Figure 14-25. Accumulation conc. comp. summary sorted and strat. by group



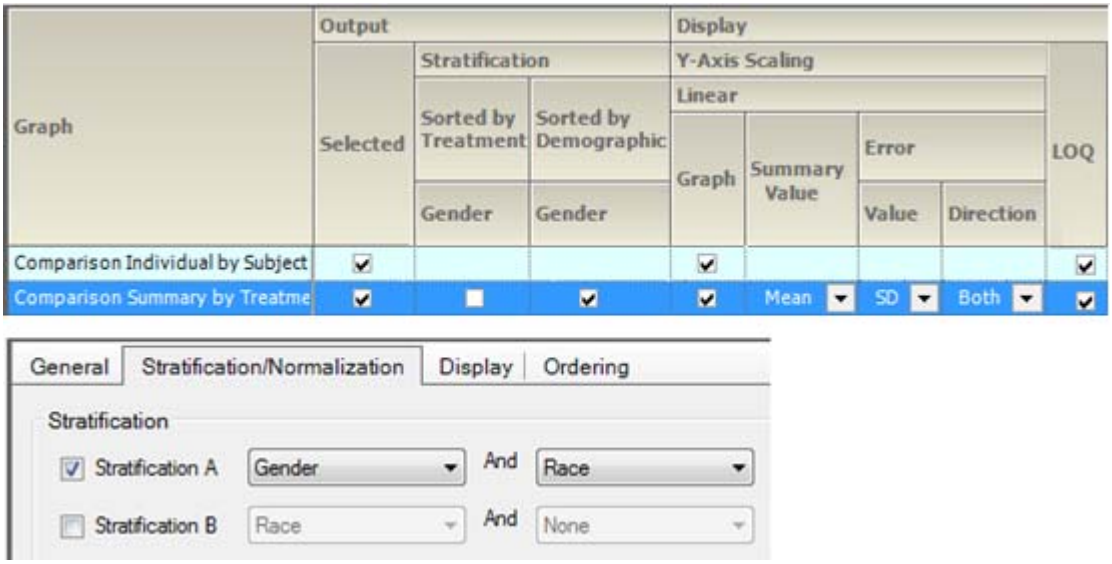


Figure 14-26. Absolute bioavail. conc. comp. summary sorted and strat. by group

Urine comparison time concentration

Excretion rate comparison by subject
Excretion comparison summary by treatment

- Excretion comp. summary by treatment, sorted by treatment, and strat. by group
- Excretion comp. summary by treatment, sorted and strat. by group

Cumulative amt. excreted comparison by subject
Cum. amt. excreted comp. summary by treatment, sorted by treatment, and strat. by group

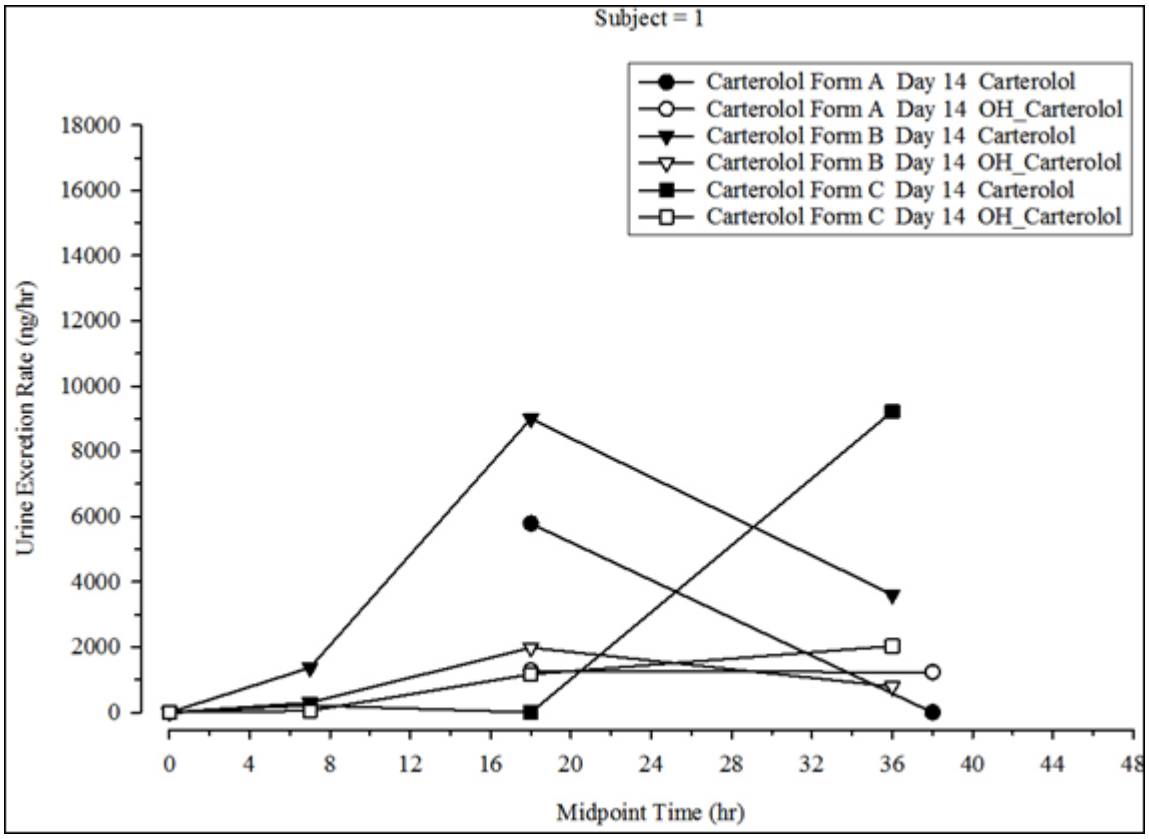
- Cum. amt. excreted comp. summary by treatment, sorted by treatment, and strat. by group
- Cum. amt. excreted comp. summary by treatment, sorted and strat. by group

Amount excreted comp. summary by subject
Amount excreted comp. summary by treatment

- Amt. excreted comp. summary by treatment, sorted by treatment, and strat. by group
- Amt. excreted comp. summary by treatment, sorted and strat. by group

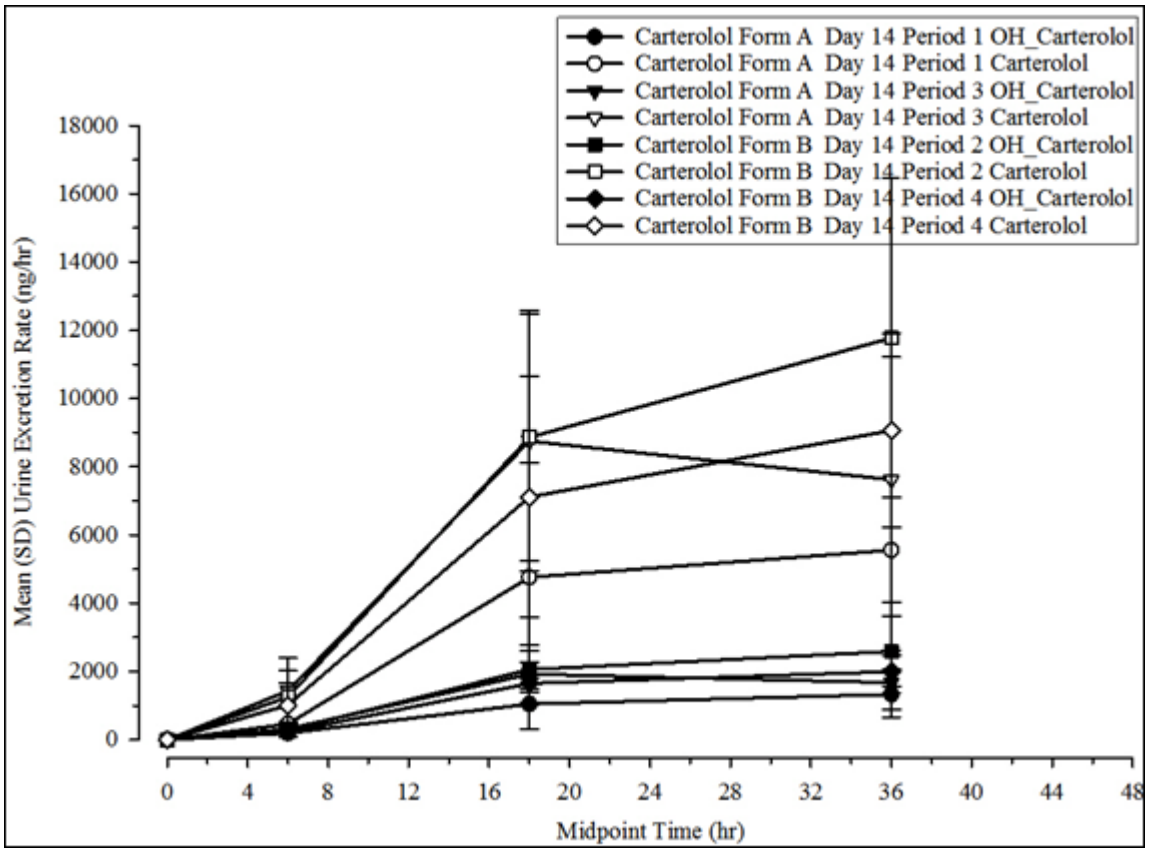
Percent dose remaining comp. by subject
Percent dose remaining comp. summary by treatment, sorted by treatment, and strat. by group

- Percent dose remaining comp. summary by treatment, sorted by treatment, and strat. by group
- Percent dose remaining comp. summary by treatment, sorted and strat. by group



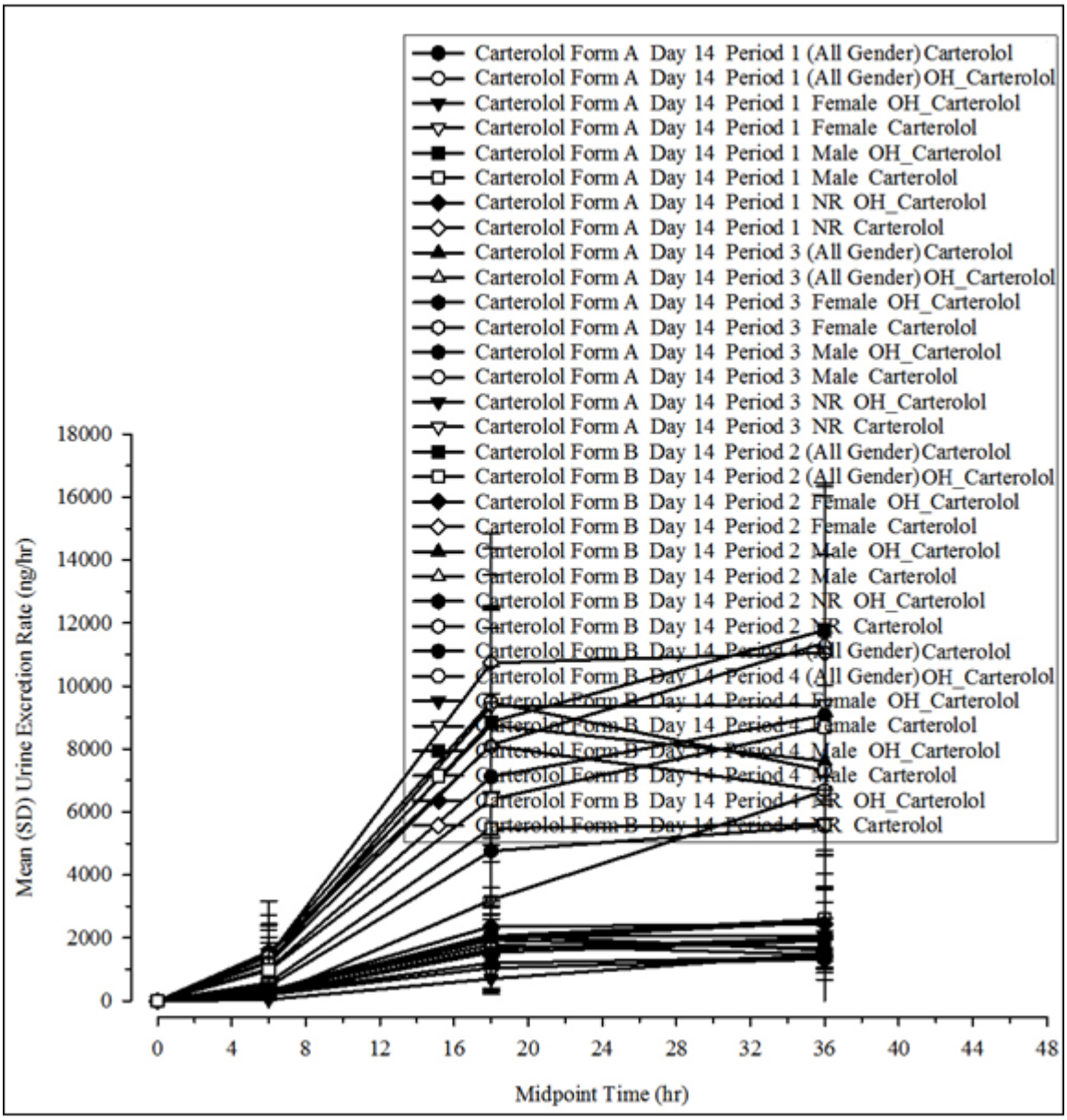
Graph	Output	Display		X-Axis Variable	Treatment Display	
	Selected	Y-Axis				
		Linear				
		Graph			All in same graph	Separate graph
Comparison Excretion Rate by Subject	☑	☑		Midpoint Time	☑	☐

Figure 14-27. Excretion rate comparison by subject



Graph	Output	Display		X-Axis Variable	Treatment Display	
	Selected	Y-Axis S				
		Linear				
		Graph			All in same graph	Separate graph
Comparison Excretion Rate by Subject	☑	☑		Midpoint Time	☑	☐

Figure 14-28. Excretion comparison summary by treatment


Carterolol Form A Day 14 Period 1 (All Gender) Carterolol
Carterolol Form A Day 14 Period 1 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 1 Female OH_Carterolol
Carterolol Form A Day 14 Period 1 Female Carterolol
Carterolol Form A Day 14 Period 1 Male OH_Carterolol
Carterolol Form A Day 14 Period 1 Male Carterolol
Carterolol Form A Day 14 Period 1 NR OH_Carterolol
Carterolol Form A Day 14 Period 1 NR Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 3 Female OH_Carterolol
Carterolol Form A Day 14 Period 3 Female Carterolol
Carterolol Form A Day 14 Period 3 Male OH_Carterolol
Carterolol Form A Day 14 Period 3 Male Carterolol
Carterolol Form A Day 14 Period 3 NR OH_Carterolol
Carterolol Form A Day 14 Period 3 NR Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 2 Female OH_Carterolol
Carterolol Form B Day 14 Period 2 Female Carterolol
Carterolol Form B Day 14 Period 2 Male OH_Carterolol
Carterolol Form B Day 14 Period 2 Male Carterolol
Carterolol Form B Day 14 Period 2 NR OH_Carterolol
Carterolol Form B Day 14 Period 2 NR Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 4 Female OH_Carterolol
Carterolol Form B Day 14 Period 4 Female Carterolol
Carterolol Form B Day 14 Period 4 Male OH_Carterolol
Carterolol Form B Day 14 Period 4 Male Carterolol
Carterolol Form B Day 14 Period 4 NR OH_Carterolol
Carterolol Form B Day 14 Period 4 NR Carterolol
Mean (SD) Urine Excretion Rate (ng/hr)
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Midpoint Time (hr)

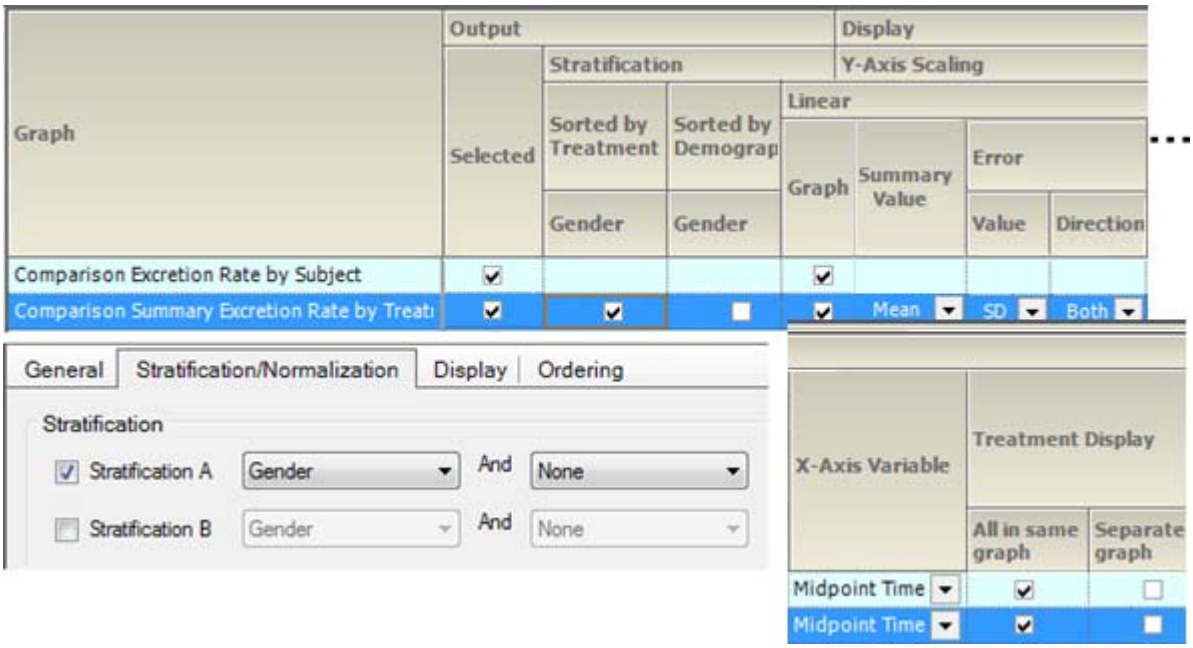
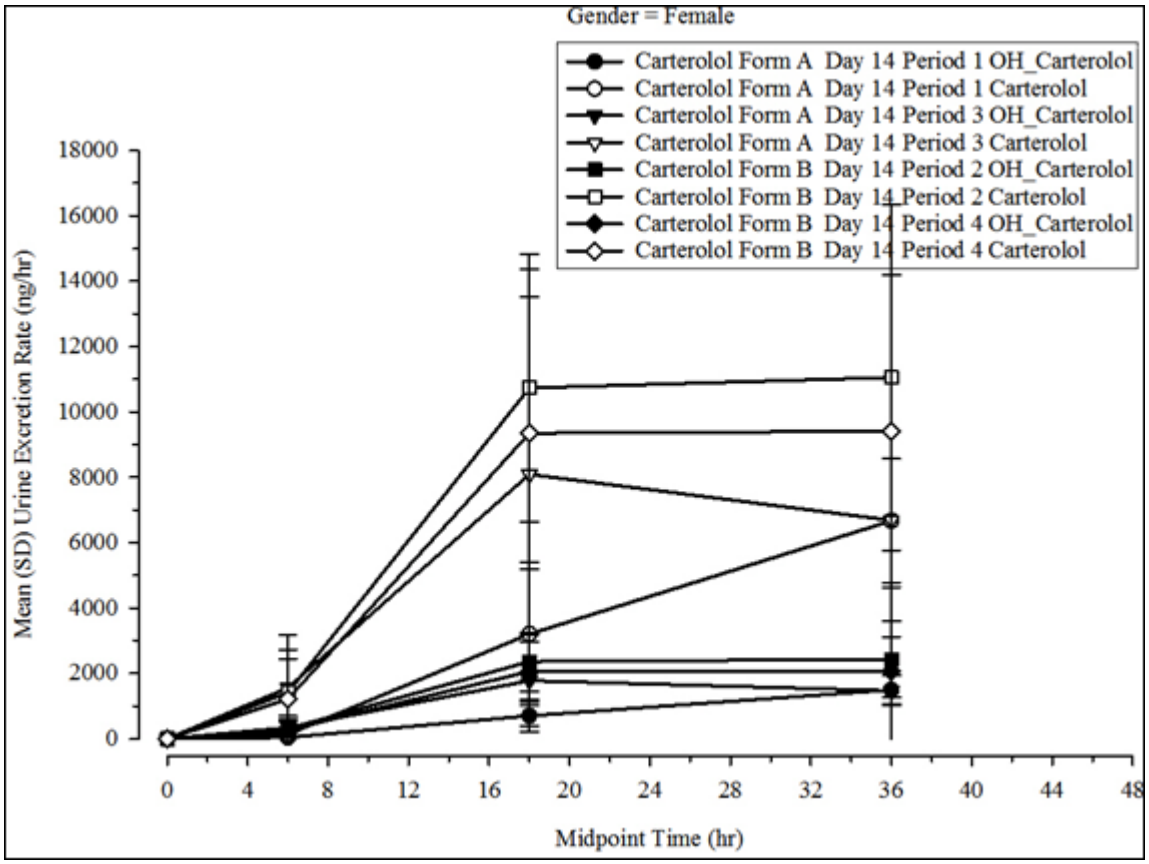


Figure 14-29. Excretion comp. summary by treatment, sorted by treatment, and strat. by group



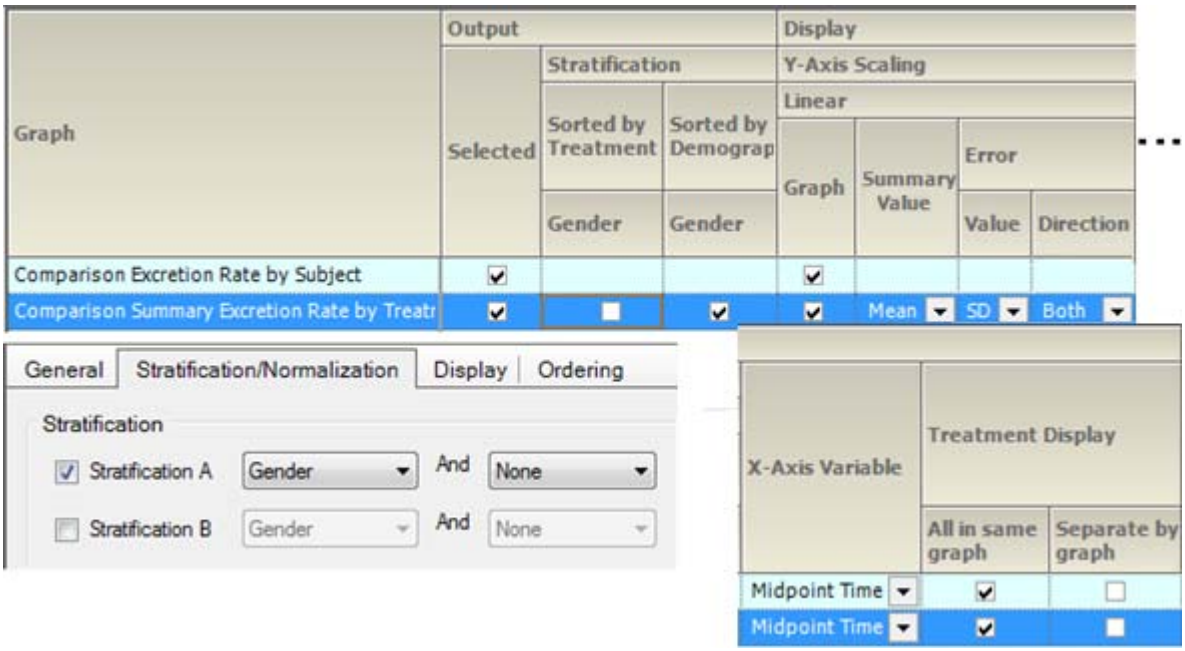
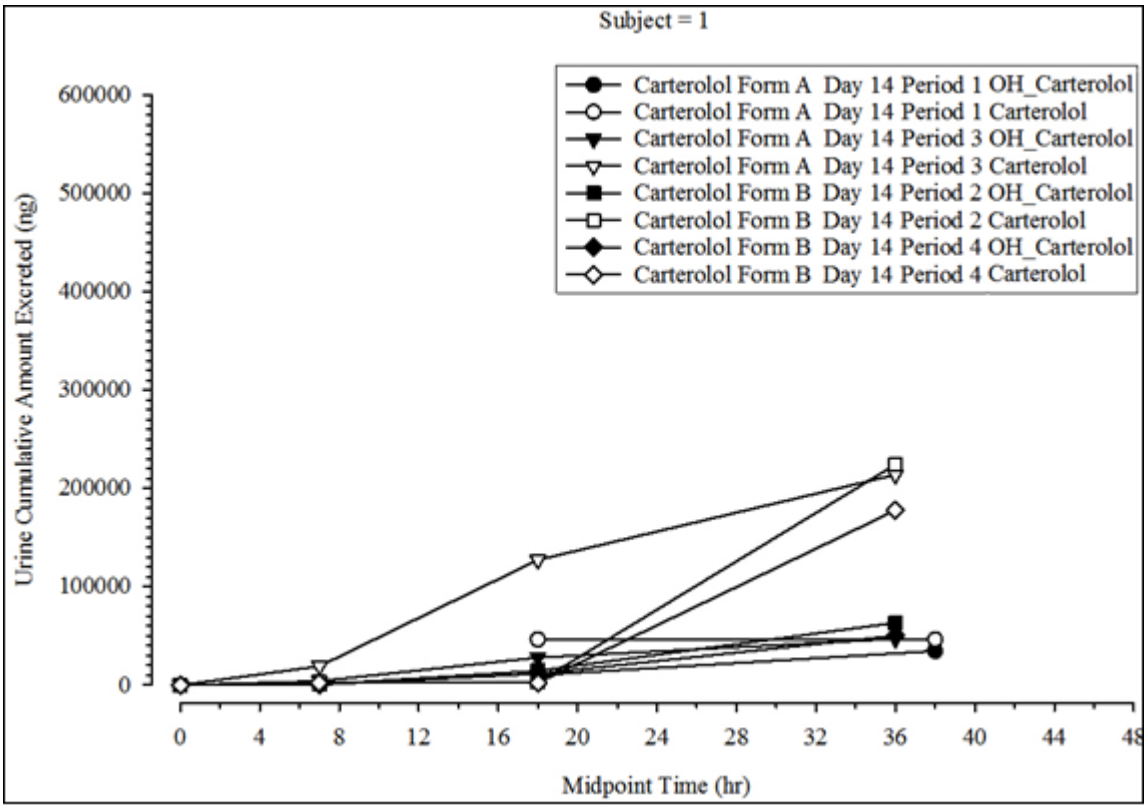
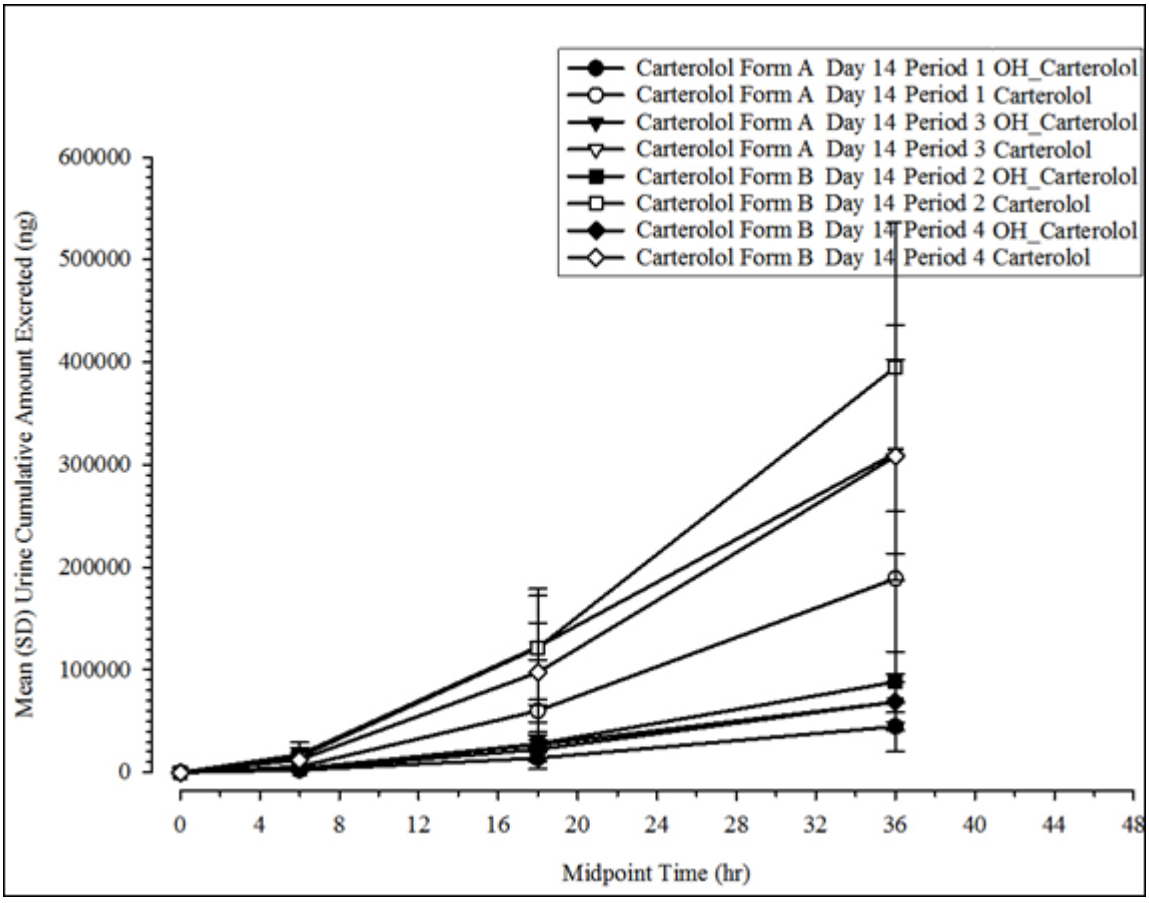


Figure 14-30. Excretion comp. summary by treatment, sorted and strat. by group



Graph	Output	Display			
	Selected	Y-Axis		Treatment Display	
		Linear	X-Axis Variable		
		Graph		All in sai graph	Separate graph
Comparison Excretion Rate by Subject	☑	☑	Midpoint Time	☑	☐
Comparison Summary Excretion Rate by Treatmen	☑	☑	Midpoint Time	☑	☐
Comparison Cumulative Amount Excreted by Subj	☑	☑	Midpoint Time	☑	☐

Figure 14-31. Cumulative amt. excreted comparison by subject



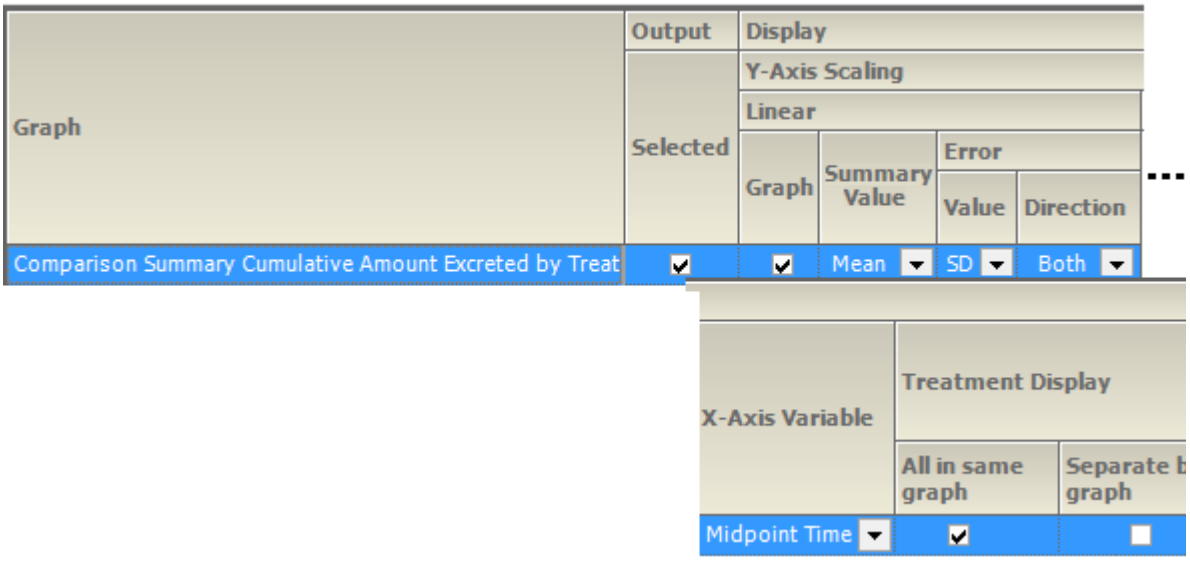
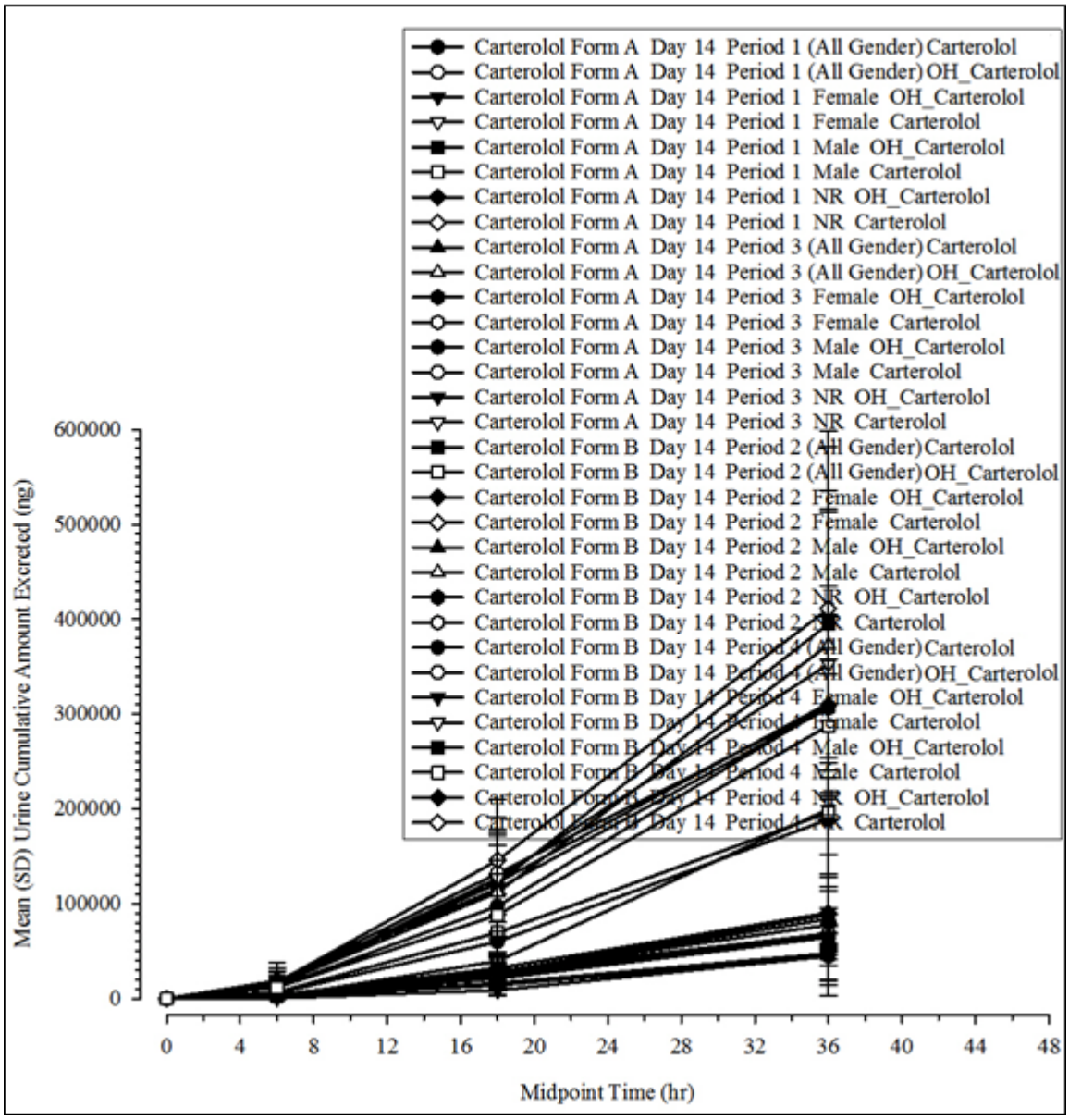


Figure 14-32. Cum. amt. excreted comp. summary by treatment, sorted by treatment, and strat. by group


Carterolol Form A Day 14 Period 1 (All Gender) Carterolol
Carterolol Form A Day 14 Period 1 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 1 Female OH_Carterolol
Carterolol Form A Day 14 Period 1 Female Carterolol
Carterolol Form A Day 14 Period 1 Male OH_Carterolol
Carterolol Form A Day 14 Period 1 Male Carterolol
Carterolol Form A Day 14 Period 1 NR OH_Carterolol
Carterolol Form A Day 14 Period 1 NR Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 3 Female OH_Carterolol
Carterolol Form A Day 14 Period 3 Female Carterolol
Carterolol Form A Day 14 Period 3 Male OH_Carterolol
Carterolol Form A Day 14 Period 3 Male Carterolol
Carterolol Form A Day 14 Period 3 NR OH_Carterolol
Carterolol Form A Day 14 Period 3 NR Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 2 Female OH_Carterolol
Carterolol Form B Day 14 Period 2 Female Carterolol
Carterolol Form B Day 14 Period 2 Male OH_Carterolol
Carterolol Form B Day 14 Period 2 Male Carterolol
Carterolol Form B Day 14 Period 2 NR OH_Carterolol
Carterolol Form B Day 14 Period 2 NR Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 4 Female OH_Carterolol
Carterolol Form B Day 14 Period 4 Female Carterolol
Carterolol Form B Day 14 Period 4 Male OH_Carterolol
Carterolol Form B Day 14 Period 4 Male Carterolol
Carterolol Form B Day 14 Period 4 NR OH_Carterolol
Carterolol Form B Day 14 Period 4 NR Carterolol
Mean (SD) Urine Cumulative Amount Excreted (ng)
600000
500000
400000
300000
200000
100000
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Midpoint Time (hr)

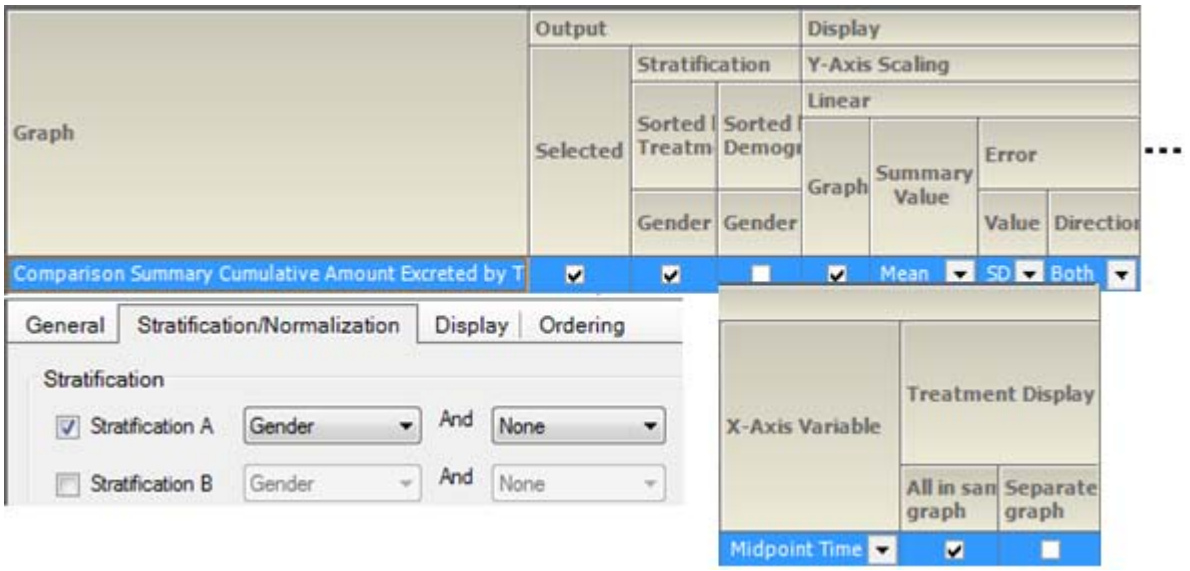


Figure 14-33. Cum. amt. excreted comp. summary by treatment, sorted by treatment, and strat. by group

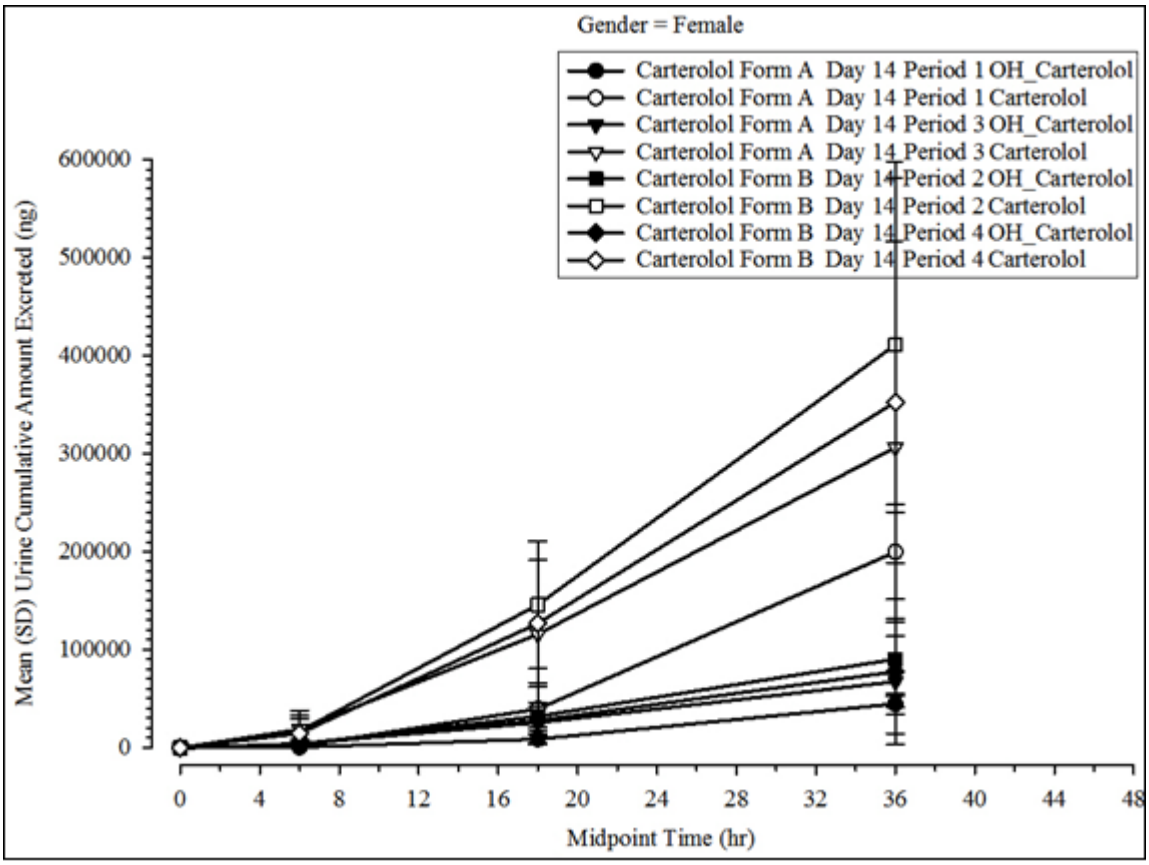
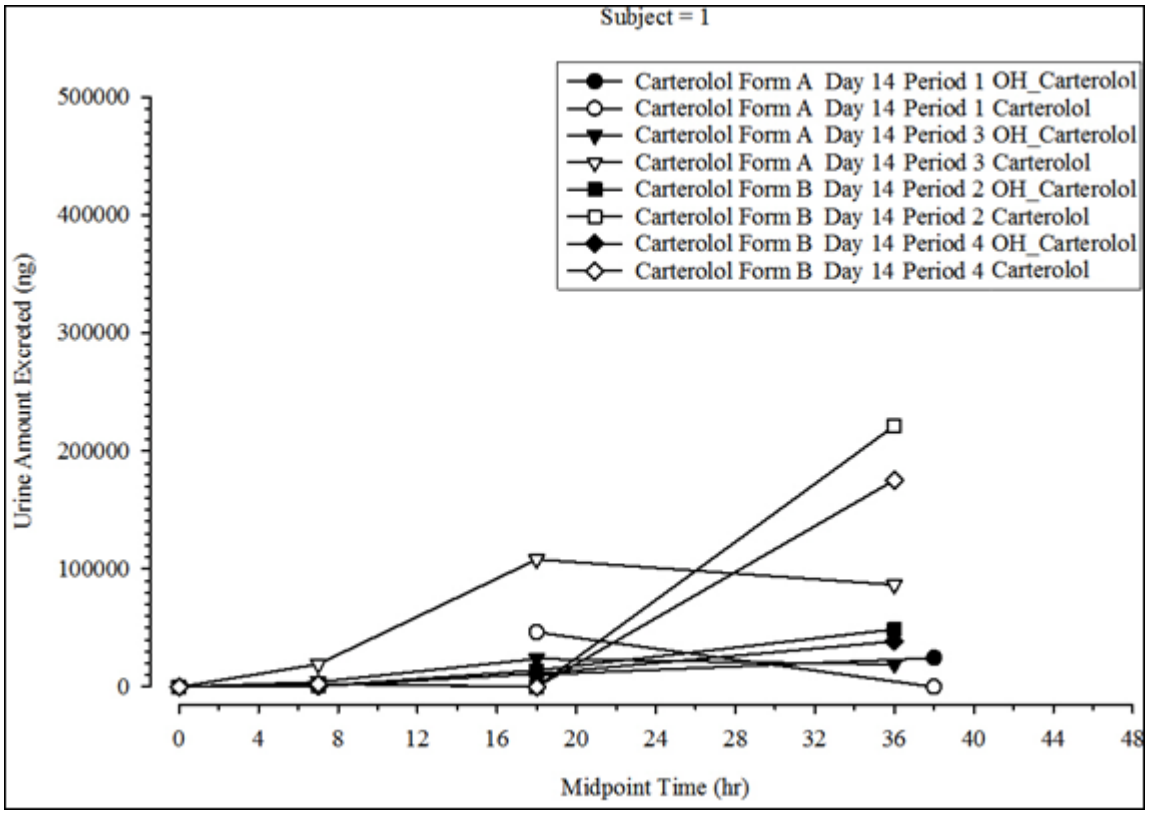
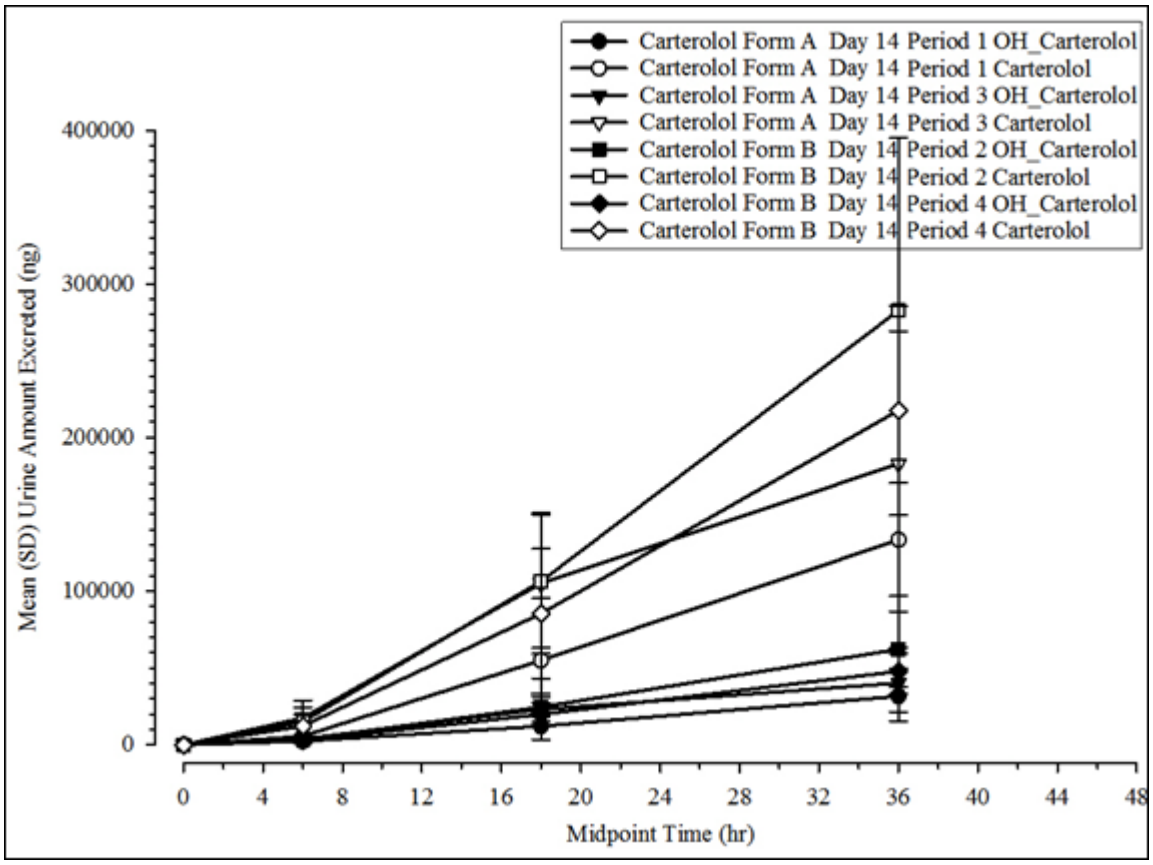


Figure 14-34. Cum. amt. excreted comp. summary by treatment, sorted and strat. by group



Graph	Output	Display		X-Axis Variable	Treatment Display	
	Selected	Y-Axis S				
		Linear				
		Graph	S		All in same graph	Separate by graph
Comparison Amount Excreted by Subject	☑	☑		Midpoint Time	☑	☐

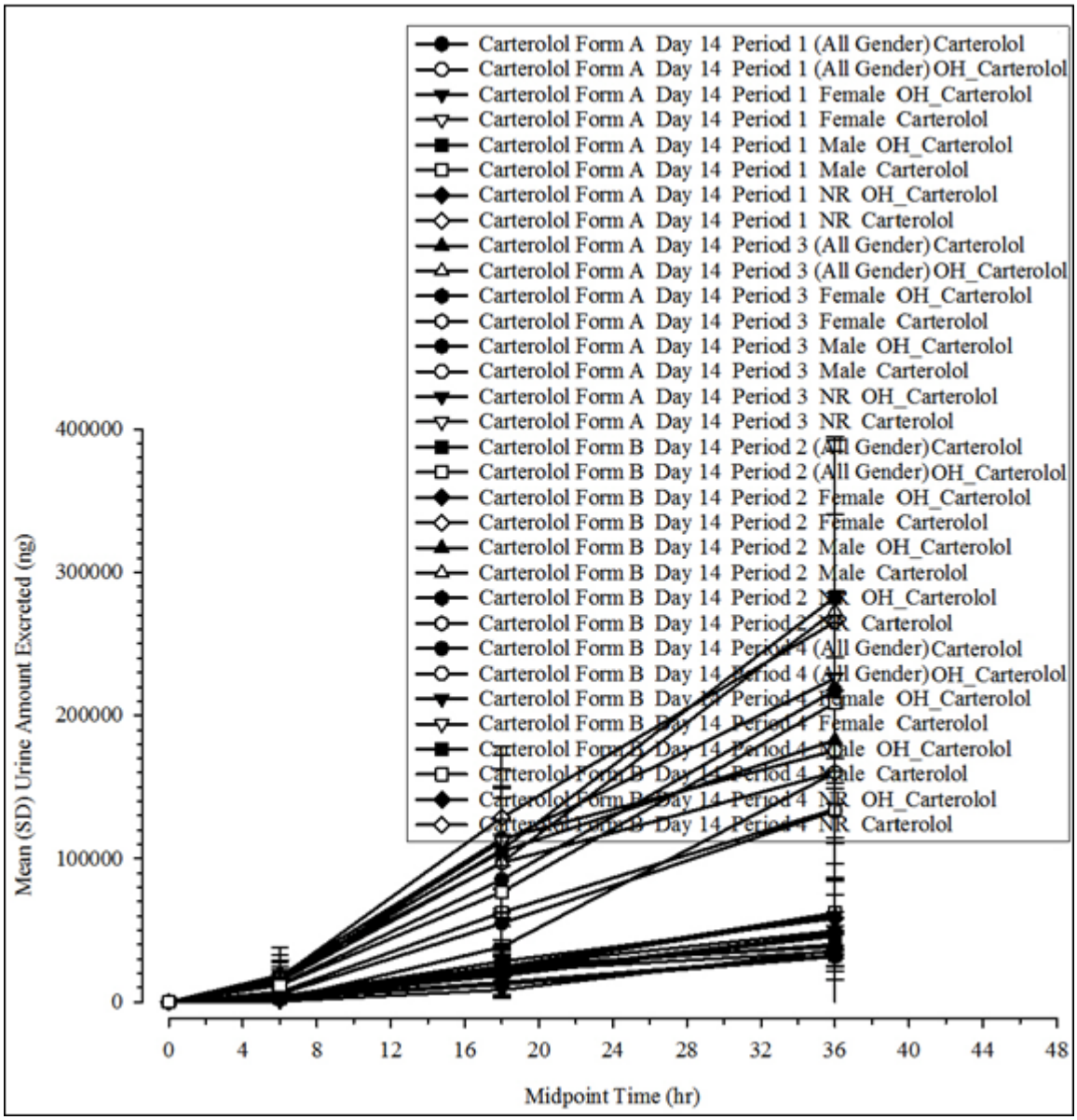
Figure 14-35. Amount excreted comp. summary by subject



Graph	Output	Display				
	Selected	Y-Axis Scaling				
		Linear				
		Graph	Summary Value	Error		
					Value	Direction
Comparison Amount Excreted by Subject	☑	☑				
Comparison Summary Amount Excreted by Treatment	☑	☑	Mean	SD	Both	

X-Axis Variable	Treatment Display	
	All in same graph	Separate by graph
Midpoint Time	☑	☐

Figure 14-36. Amount excreted comp. summary by treatment


Carterolol Form A Day 14 Period 1 (All Gender) Carterolol
Carterolol Form A Day 14 Period 1 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 1 Female OH_Carterolol
Carterolol Form A Day 14 Period 1 Female Carterolol
Carterolol Form A Day 14 Period 1 Male OH_Carterolol
Carterolol Form A Day 14 Period 1 Male Carterolol
Carterolol Form A Day 14 Period 1 NR OH_Carterolol
Carterolol Form A Day 14 Period 1 NR Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 3 Female OH_Carterolol
Carterolol Form A Day 14 Period 3 Female Carterolol
Carterolol Form A Day 14 Period 3 Male OH_Carterolol
Carterolol Form A Day 14 Period 3 Male Carterolol
Carterolol Form A Day 14 Period 3 NR OH_Carterolol
Carterolol Form A Day 14 Period 3 NR Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 2 Female OH_Carterolol
Carterolol Form B Day 14 Period 2 Female Carterolol
Carterolol Form B Day 14 Period 2 Male OH_Carterolol
Carterolol Form B Day 14 Period 2 Male Carterolol
Carterolol Form B Day 14 Period 2 NR OH_Carterolol
Carterolol Form B Day 14 Period 2 NR Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 4 Female OH_Carterolol
Carterolol Form B Day 14 Period 4 Female Carterolol
Carterolol Form B Day 14 Period 4 Male OH_Carterolol
Carterolol Form B Day 14 Period 4 Male Carterolol
Carterolol Form B Day 14 Period 4 NR OH_Carterolol
Carterolol Form B Day 14 Period 4 NR Carterolol
Mean (SD) Urine Amount Excreted (ng)
400000
300000
200000
100000
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Midpoint Time (hr)

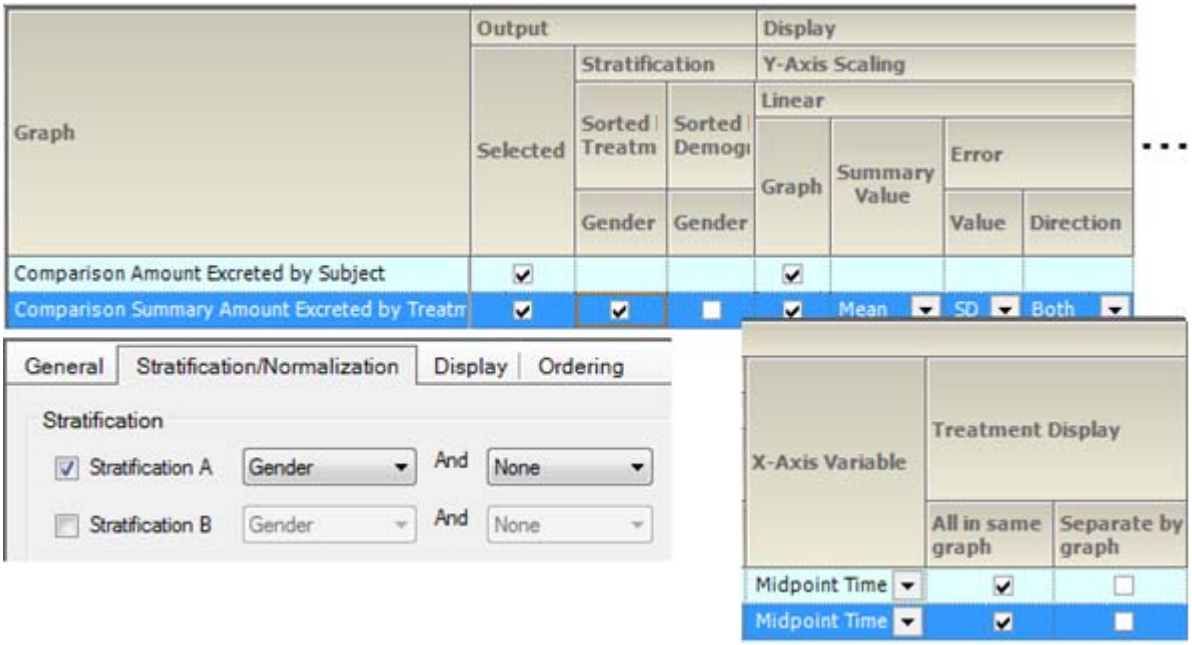
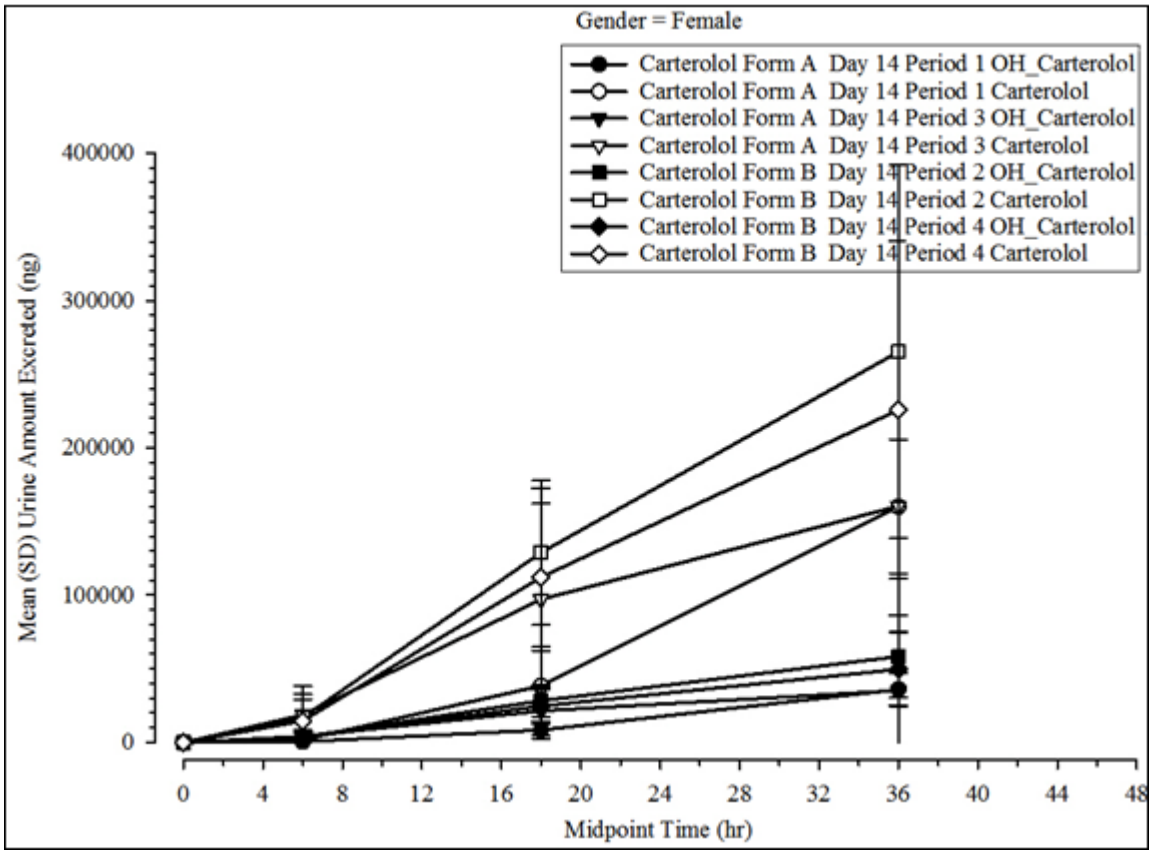


Figure 14-37. Amt. excreted comp. summary by treatment, sorted by treatment, and strat. by group



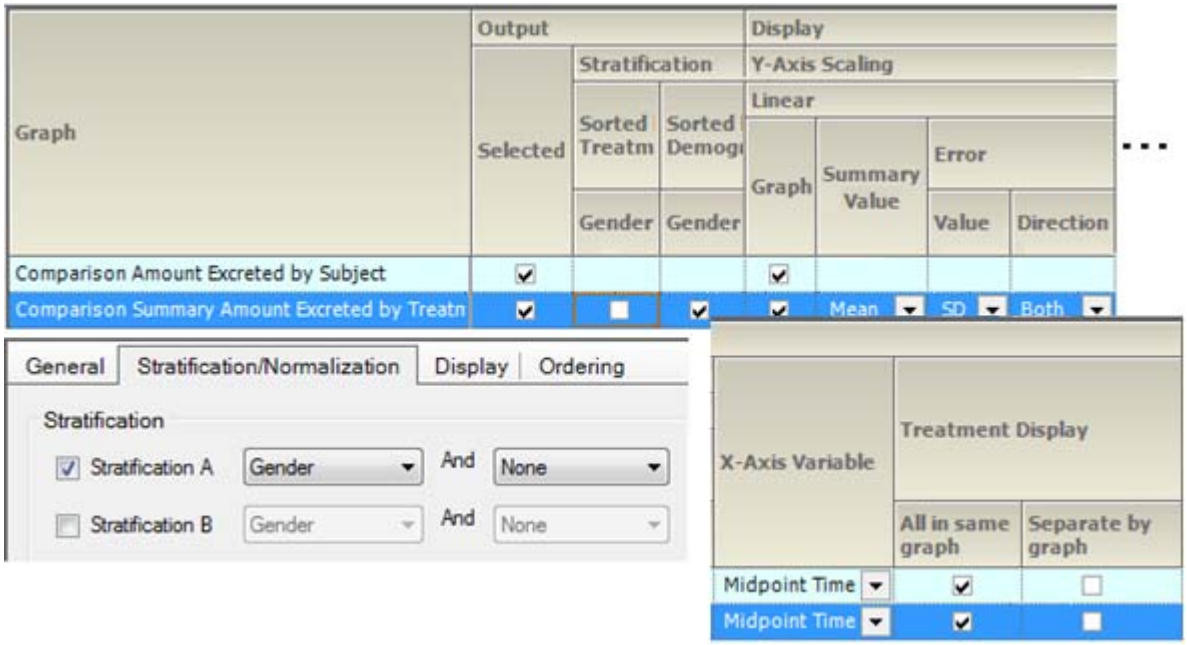
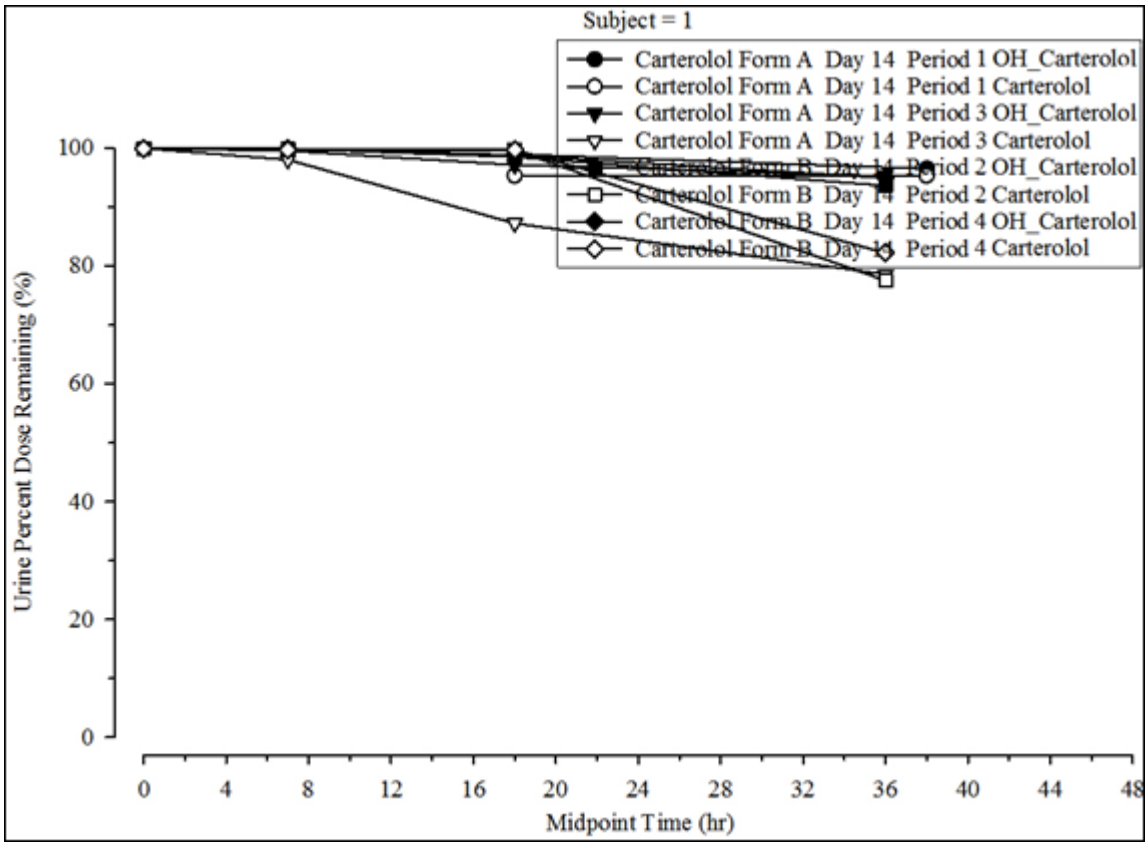


Figure 14-38. Amt. excreted comp. summary by treatment, sorted and strat. by group



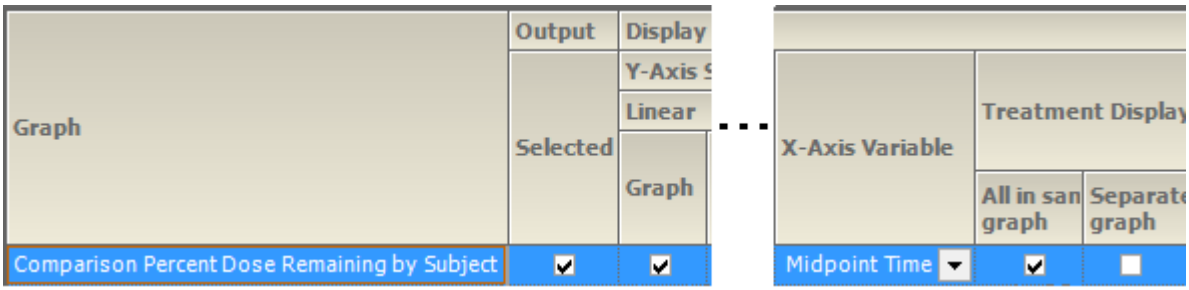
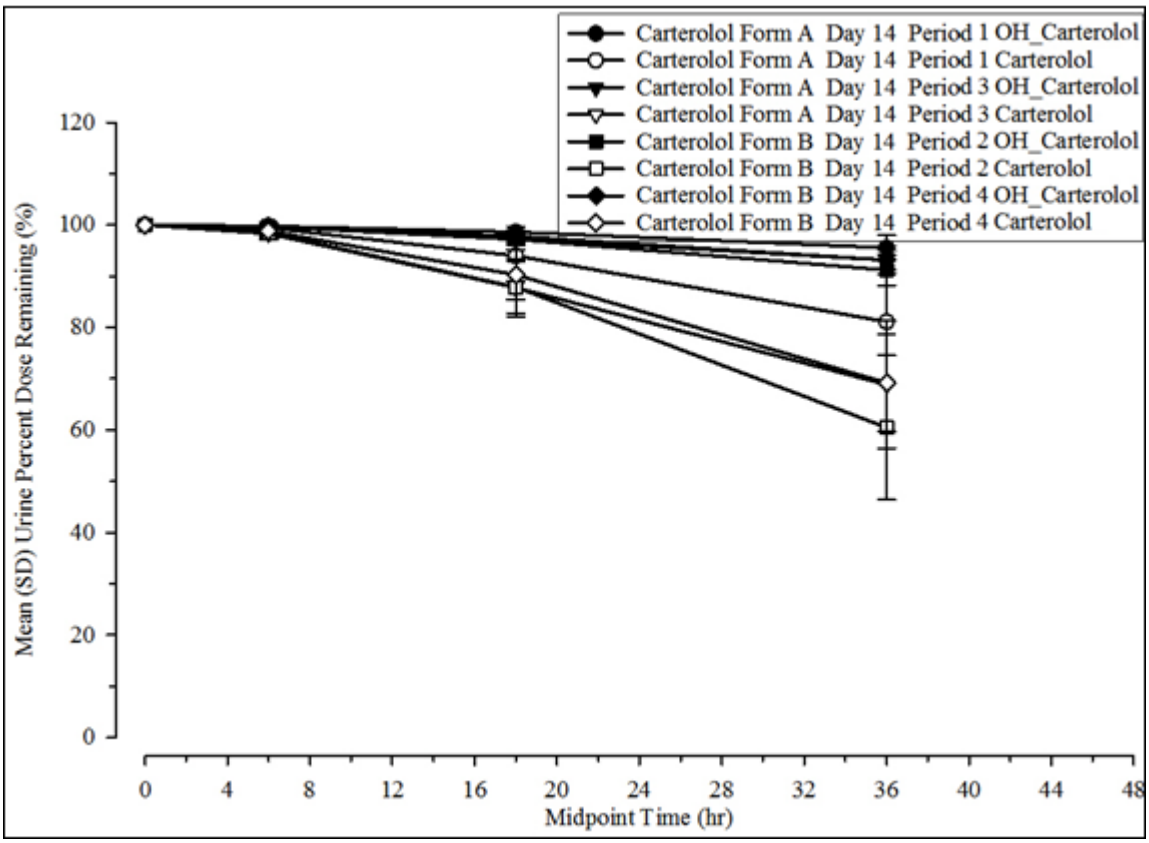


Figure 14-39. Percent dose remaining comp. by subject



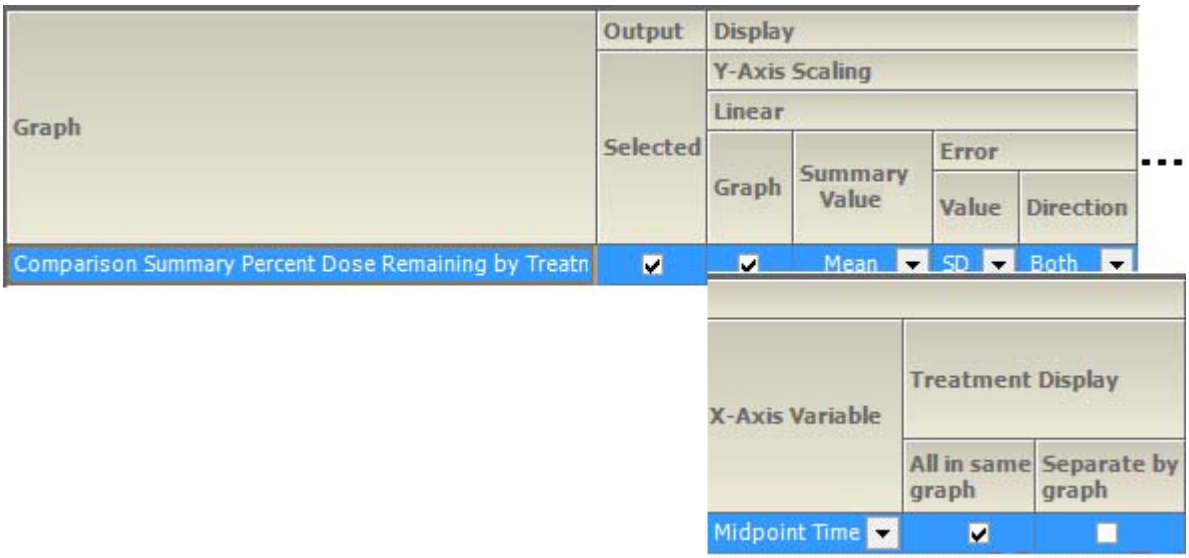
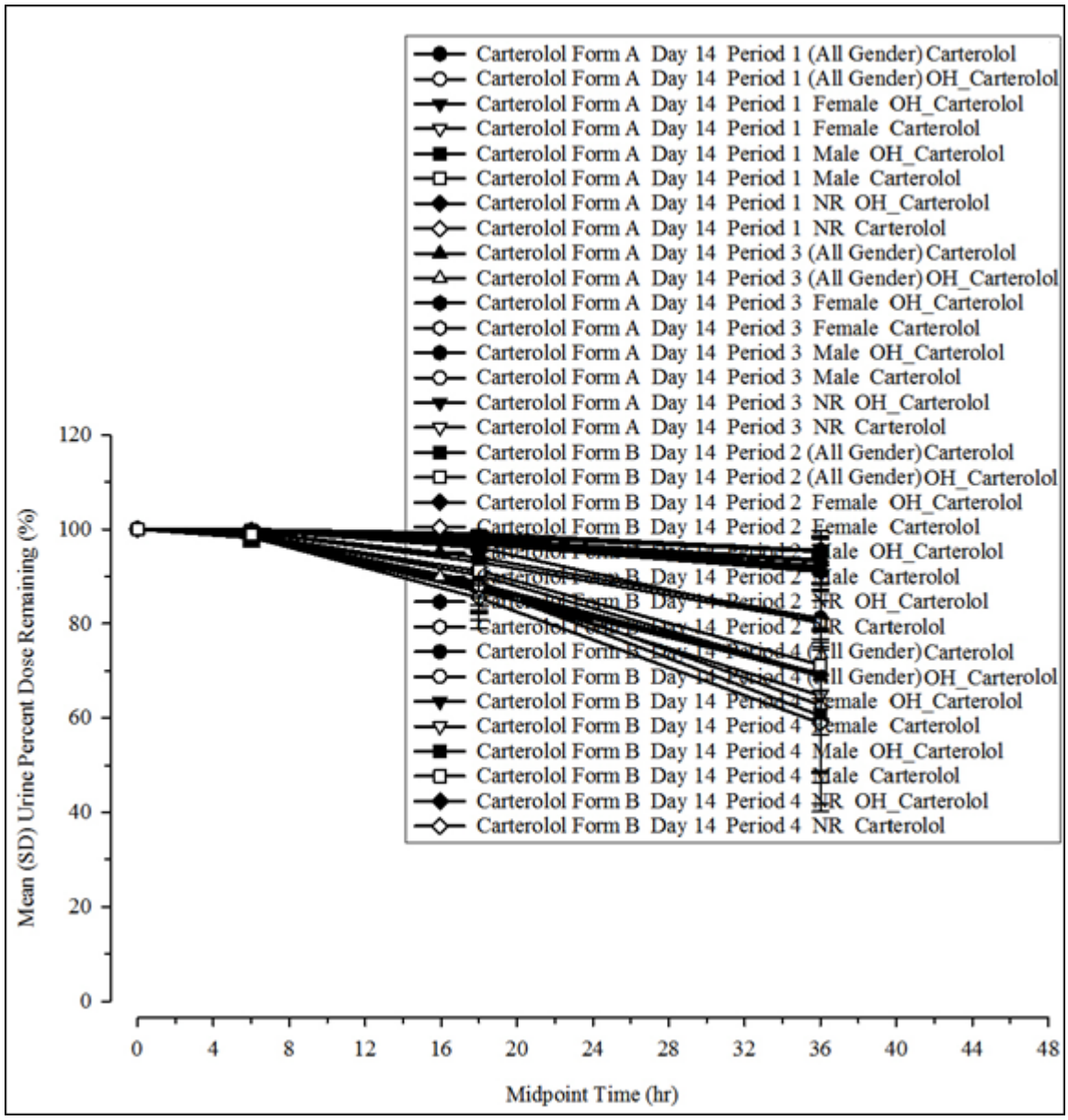


Figure 14-40. Percent dose remaining comp. by treatment


Carterolol Form A Day 14 Period 1 (All Gender) Carterolol
Carterolol Form A Day 14 Period 1 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 1 Female OH_Carterolol
Carterolol Form A Day 14 Period 1 Female Carterolol
Carterolol Form A Day 14 Period 1 Male OH_Carterolol
Carterolol Form A Day 14 Period 1 Male Carterolol
Carterolol Form A Day 14 Period 1 NR OH_Carterolol
Carterolol Form A Day 14 Period 1 NR Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) Carterolol
Carterolol Form A Day 14 Period 3 (All Gender) OH_Carterolol
Carterolol Form A Day 14 Period 3 Female OH_Carterolol
Carterolol Form A Day 14 Period 3 Female Carterolol
Carterolol Form A Day 14 Period 3 Male OH_Carterolol
Carterolol Form A Day 14 Period 3 Male Carterolol
Carterolol Form A Day 14 Period 3 NR OH_Carterolol
Carterolol Form A Day 14 Period 3 NR Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) Carterolol
Carterolol Form B Day 14 Period 2 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 2 Female OH_Carterolol
Carterolol Form B Day 14 Period 2 Female Carterolol
Carterolol Form B Day 14 Period 2 Male OH_Carterolol
Carterolol Form B Day 14 Period 2 Male Carterolol
Carterolol Form B Day 14 Period 2 NR OH_Carterolol
Carterolol Form B Day 14 Period 2 NR Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) Carterolol
Carterolol Form B Day 14 Period 4 (All Gender) OH_Carterolol
Carterolol Form B Day 14 Period 4 Female OH_Carterolol
Carterolol Form B Day 14 Period 4 Female Carterolol
Carterolol Form B Day 14 Period 4 Male OH_Carterolol
Carterolol Form B Day 14 Period 4 Male Carterolol
Carterolol Form B Day 14 Period 4 NR OH_Carterolol
Carterolol Form B Day 14 Period 4 NR Carterolol
Mean (SD) Urine Percent Dose Remaining (%)
120
100
80
60
40
20
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Midpoint Time (hr)

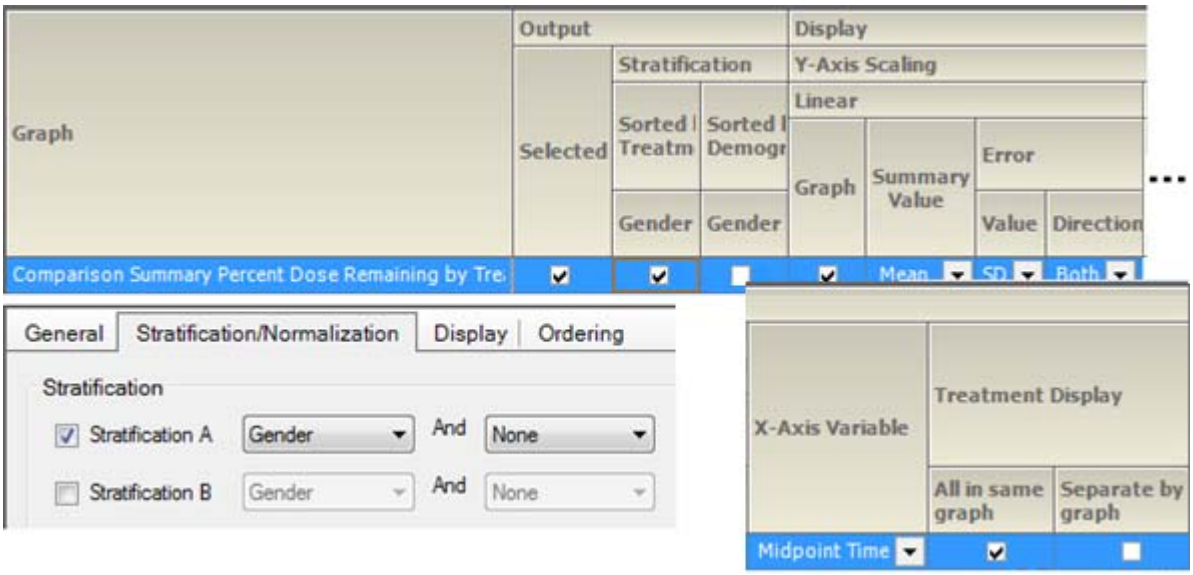
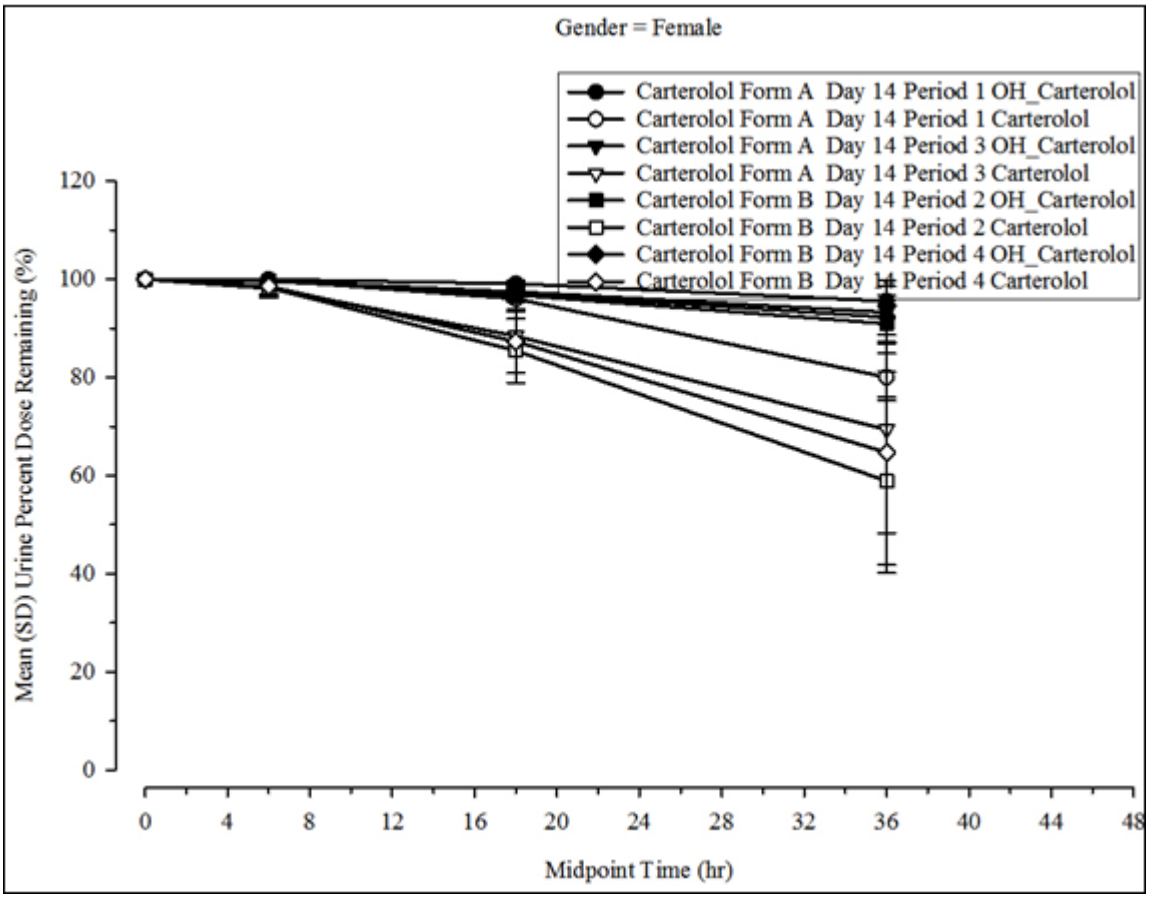


Figure 14-41. Percent dose remaining comp. summary by treatment, sorted by treatment, and strat. by group



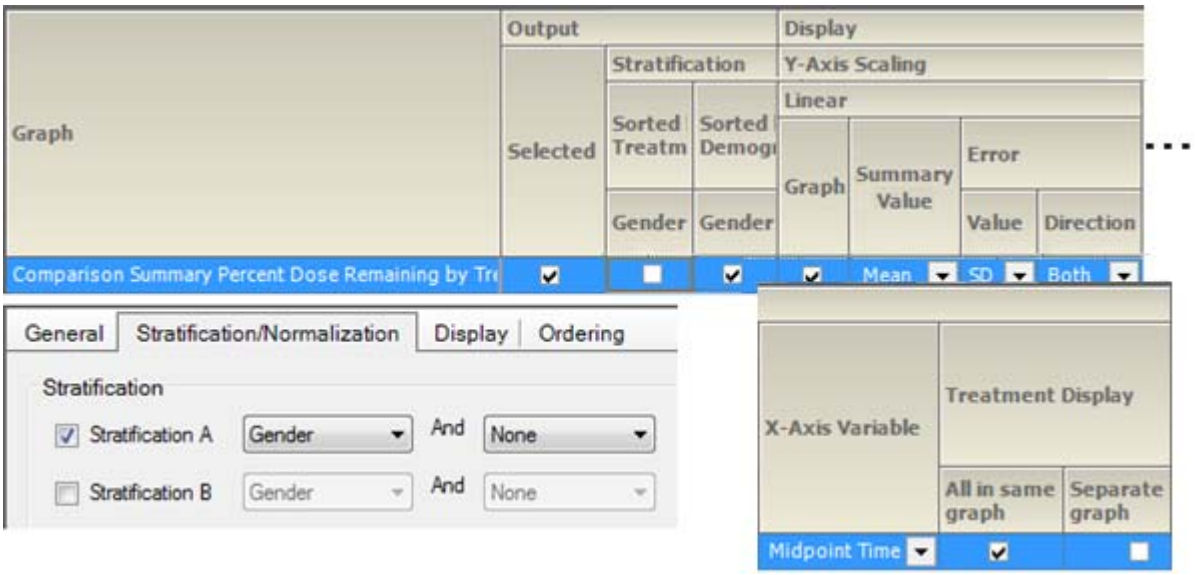
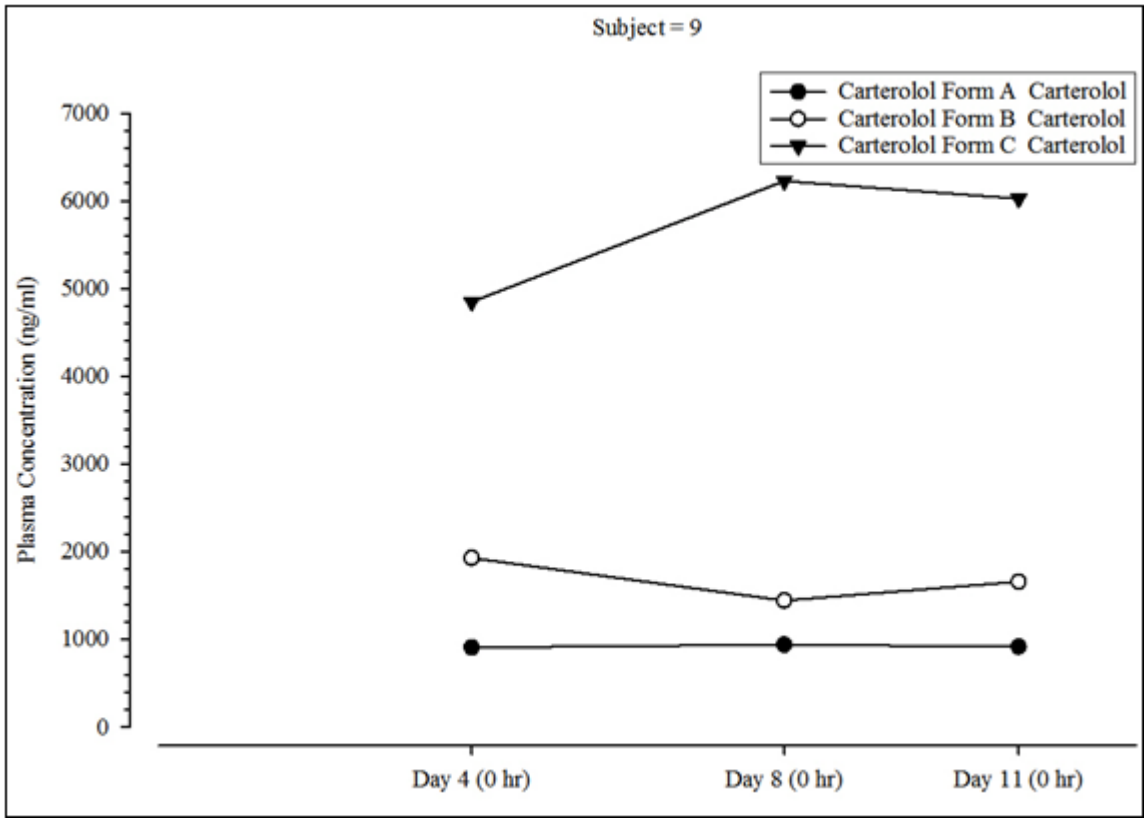


Figure 14-42. Percent dose remaining comp. summary by treatment, sorted and strat. by group

Trough comparison time concentration

Trough concentration comparison by subject
Trough concentration comparison by treatment

Trough conc. comp. summary by treatment, sorted by treatment, and strat. by group
Trough conc. comp. summary by treatment, sorted and strat. by group



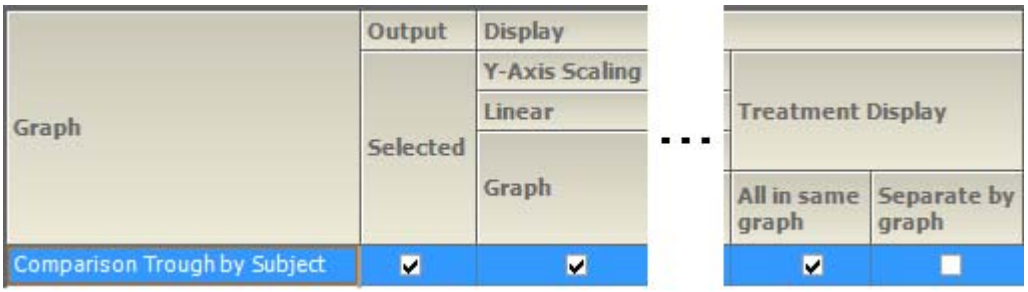
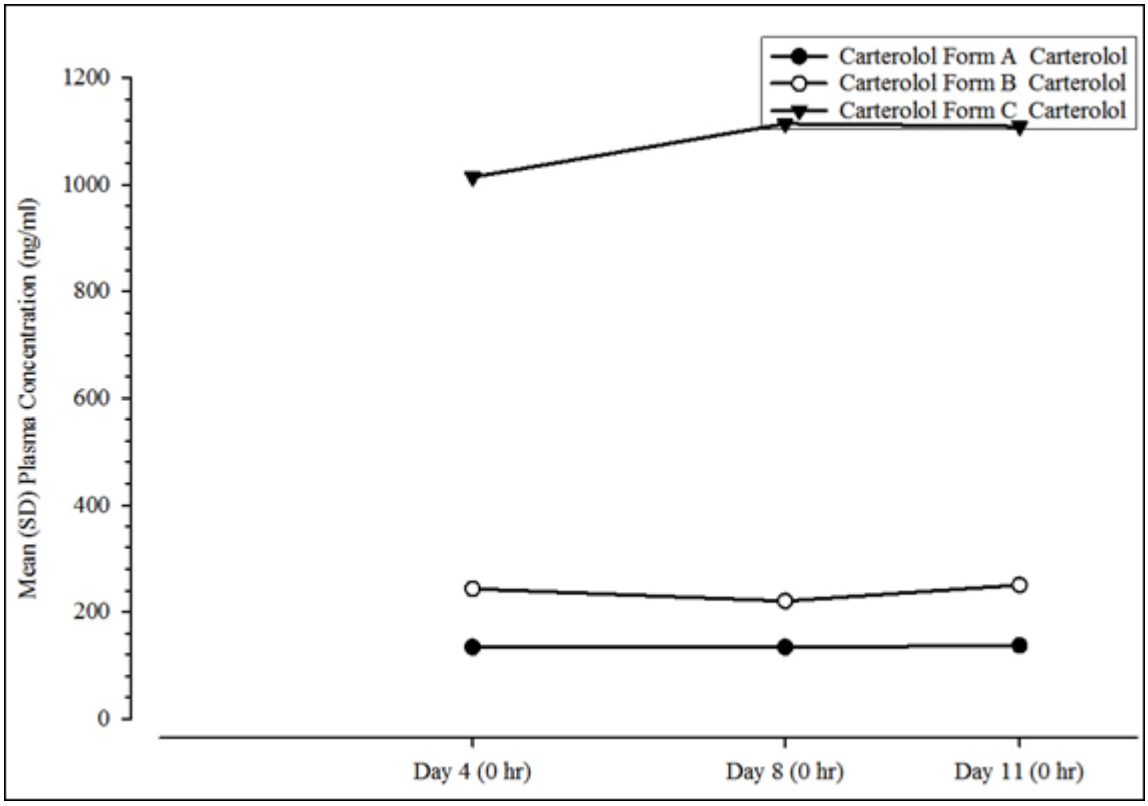


Figure 14-43. Trough concentration comparison by subject



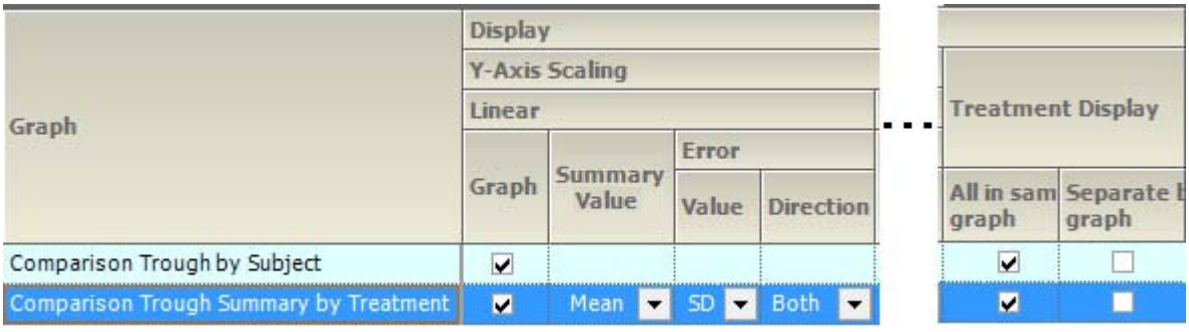
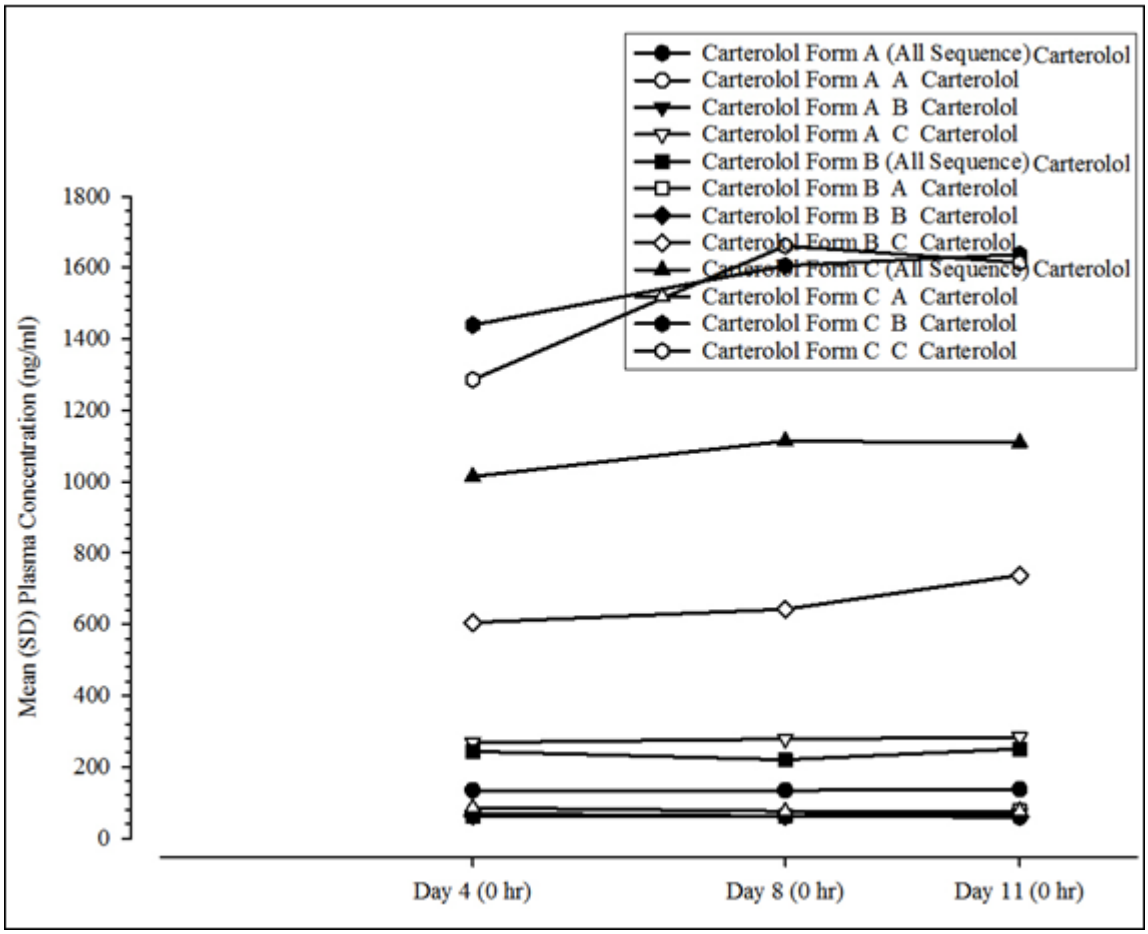


Figure 14-44. Trough concentration comparison by treatment



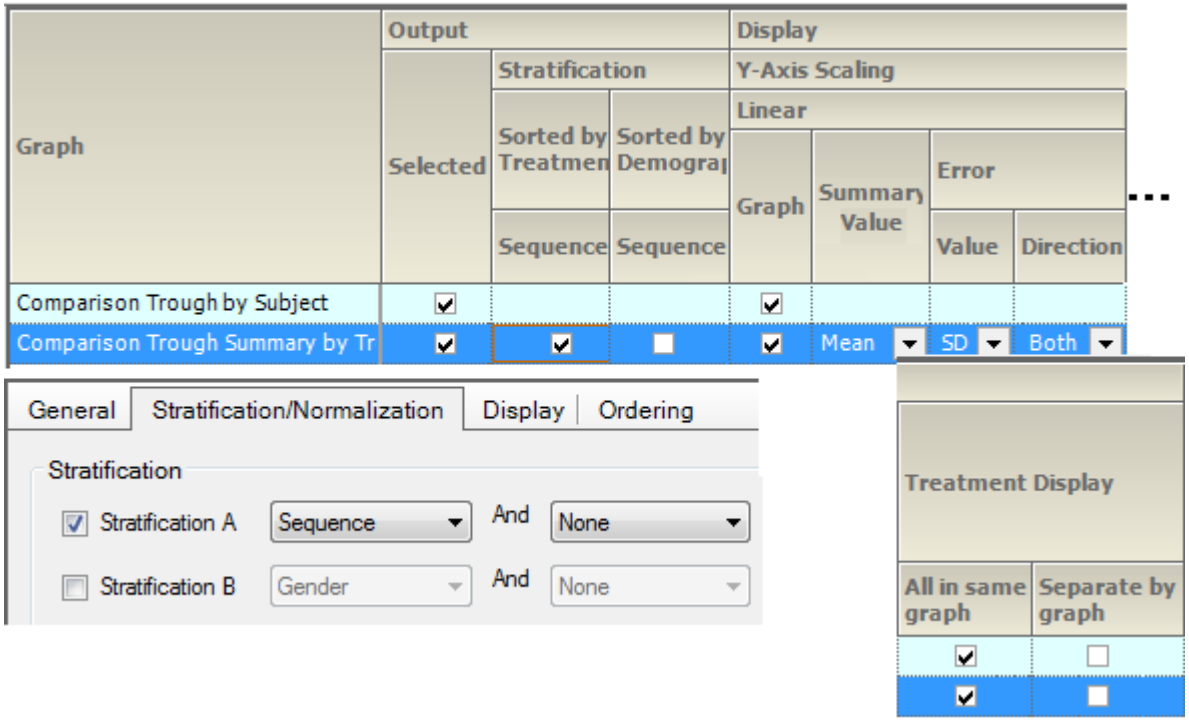
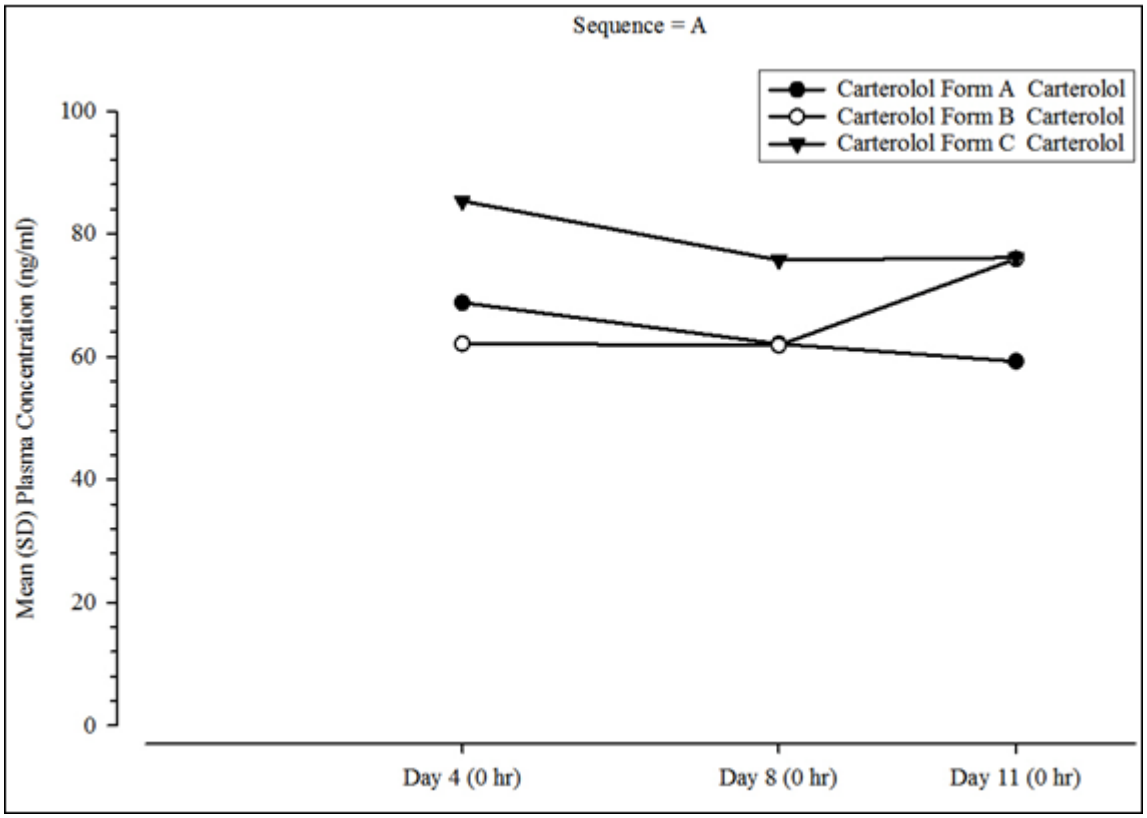


Figure 14-45. Trough conc. comp. summary by treatment, sorted by treatment, and strat. by group



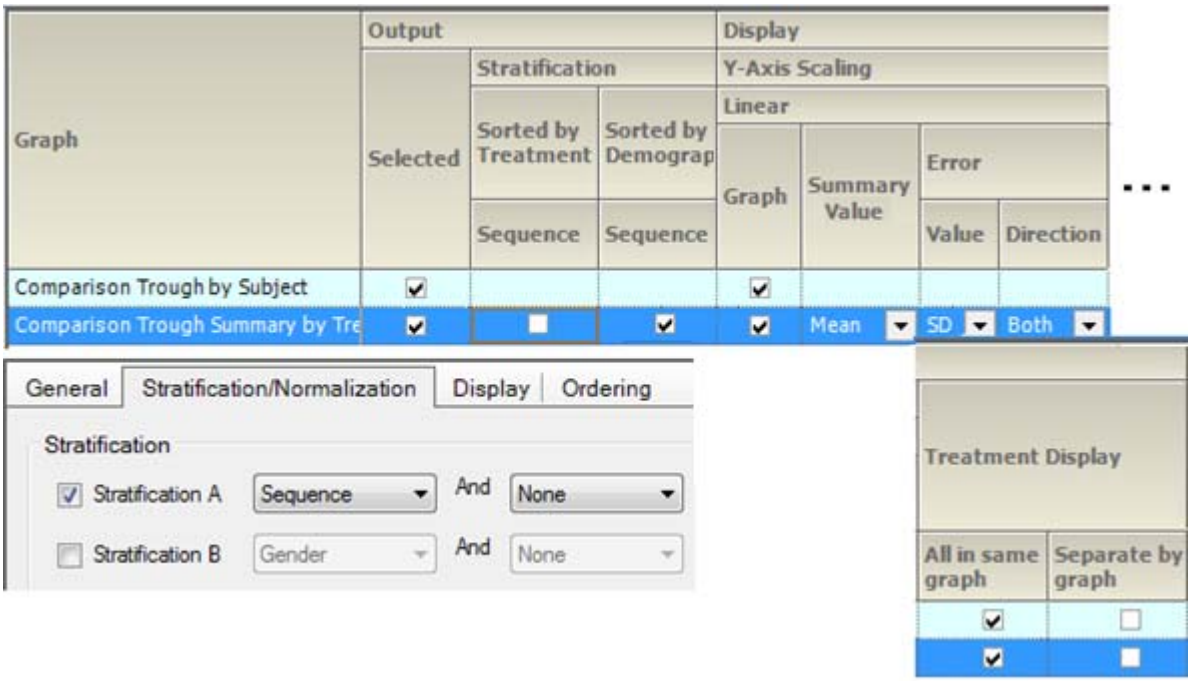


Figure 14-46. Trough conc. comp. summary by treatment, sorted and strat. by group

Plasma and urine comparison categorical standard PK parameter graphs

PK parameter analyte comparison

PK param. analyte comp. by treatment, sorted by treatment, and strat. by group
PK param. analyte comp. by treatment, sorted and strat. by group

PK parameter accumulation comparison

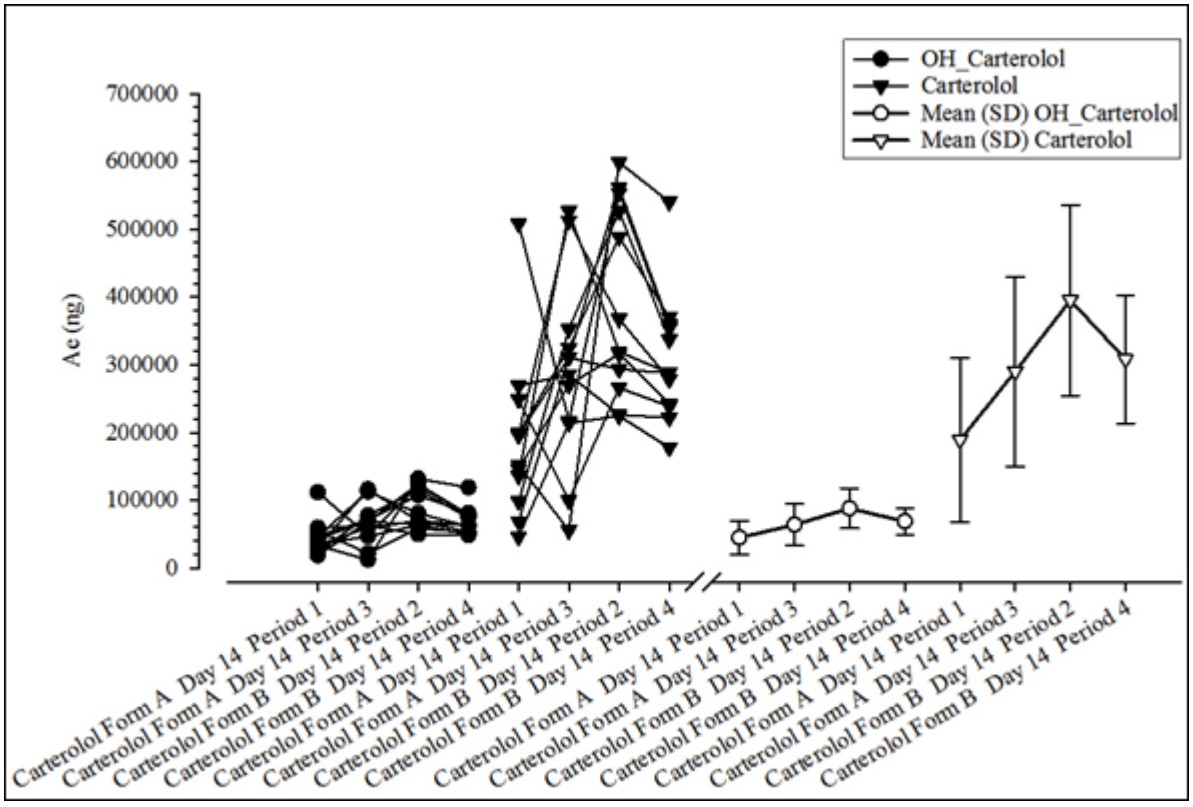
PK param. accum. comp. by treatment, sorted by treatment, and strat. by group
PK param. accum. comp. by treatment, sorted and strat. by group

PK parameter absolute bioavail. comparison

PK param. abs. bioavail. comp. by treatment, sorted by treatment, and strat. by group
PK param. abs. bioavail. comp. by treatment, sorted and strat. by group

PK parameter renal clearance comparison

PK param. renal clearance comp. by treatment, sorted by treatment, and strat. by group
PK param. renal clearance comp. by treatment, sorted and strat. by group



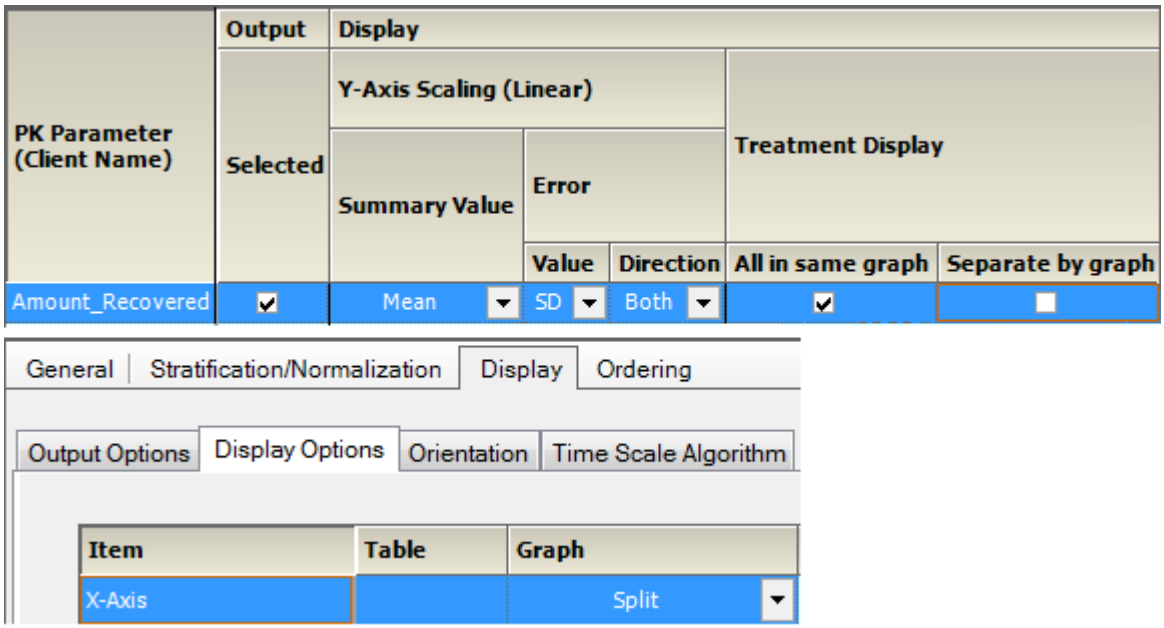
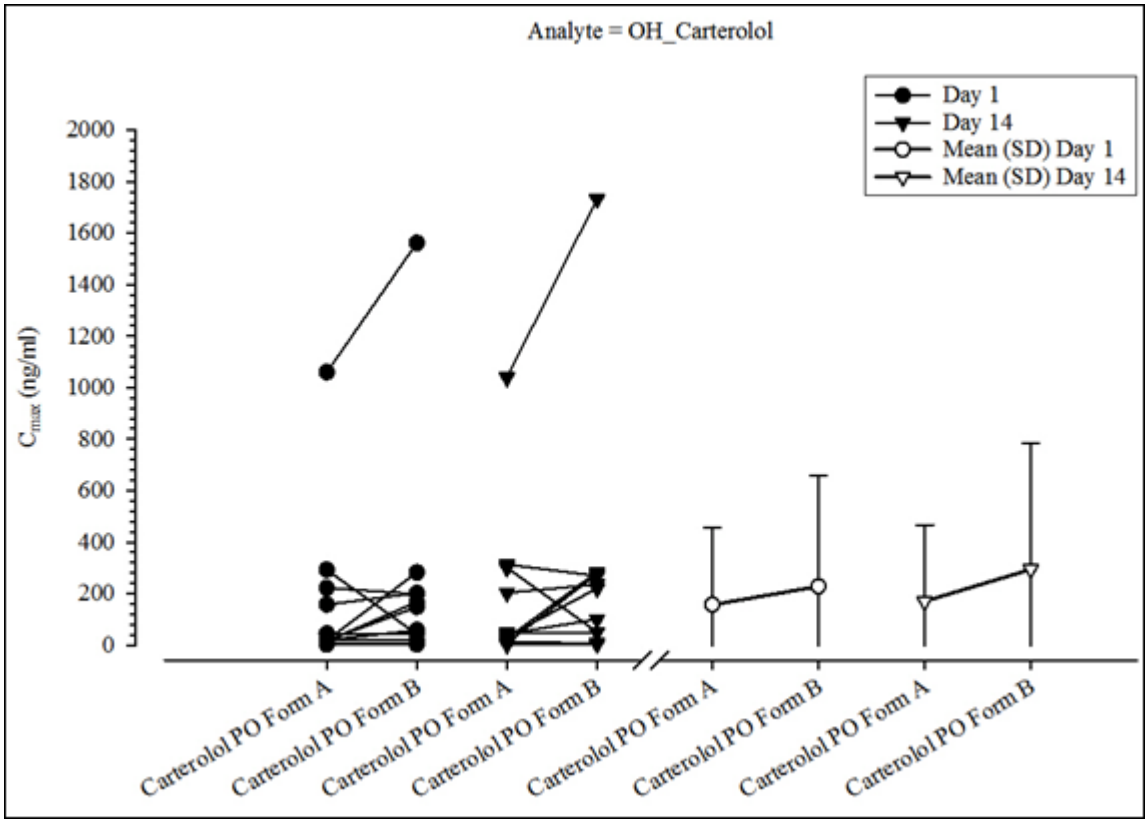


Figure 14-47. PK parameter analyte comparison



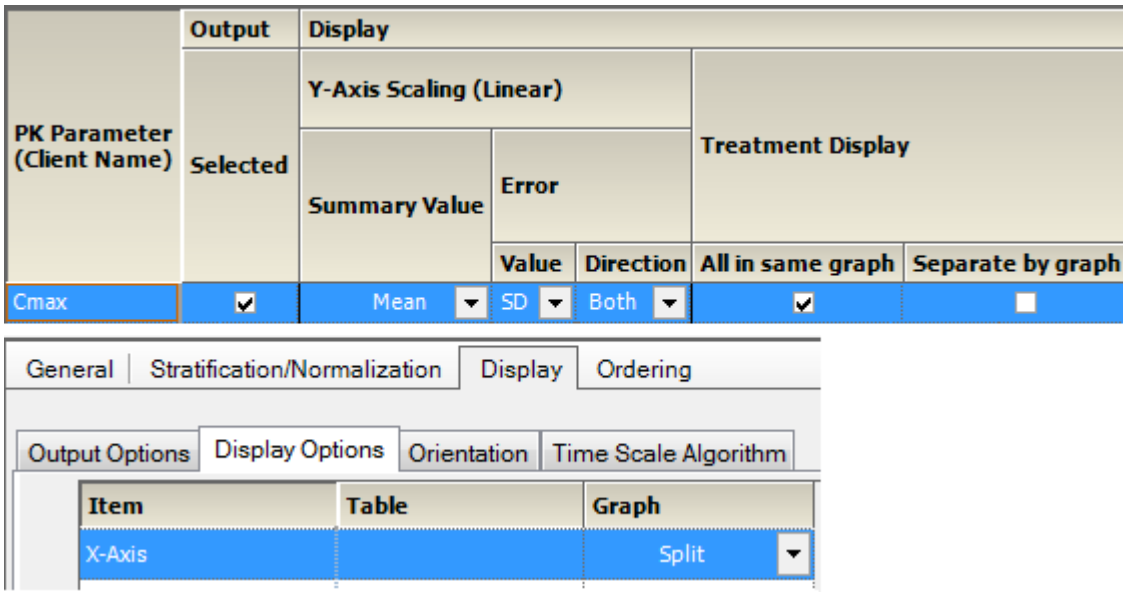
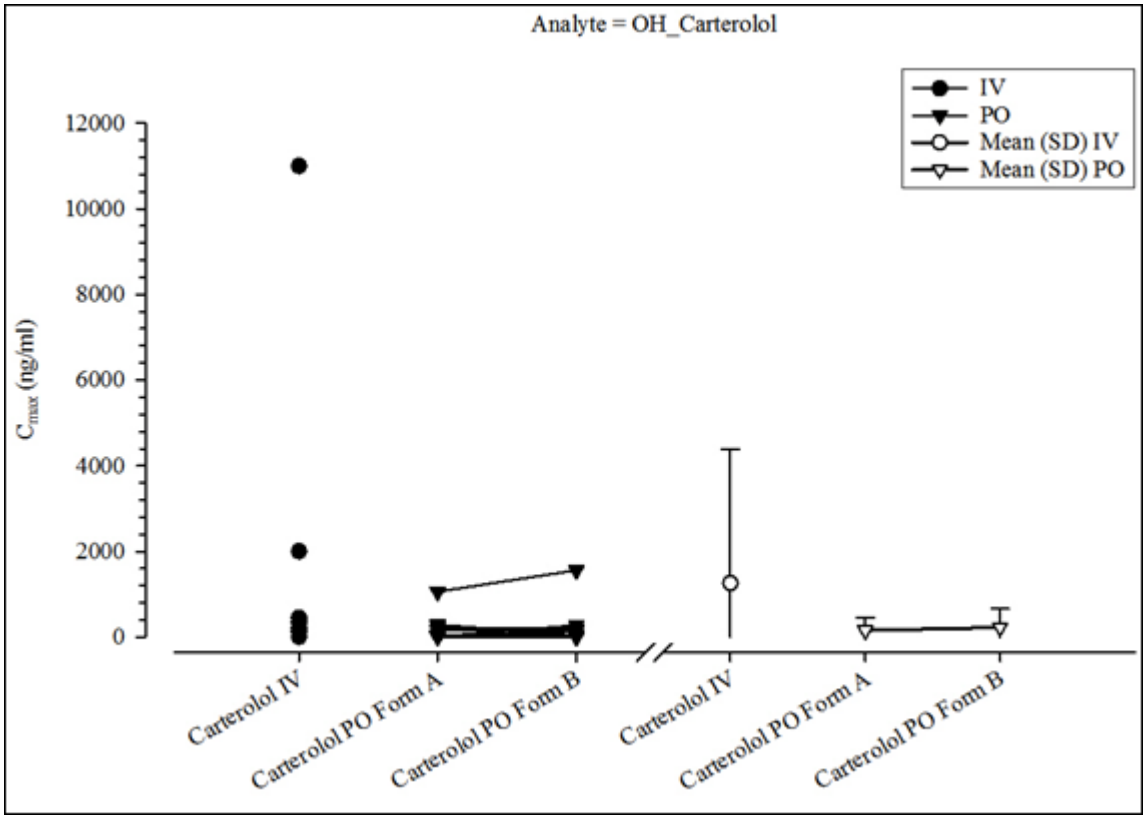


Figure 14-48. PK parameter accumulation comparison



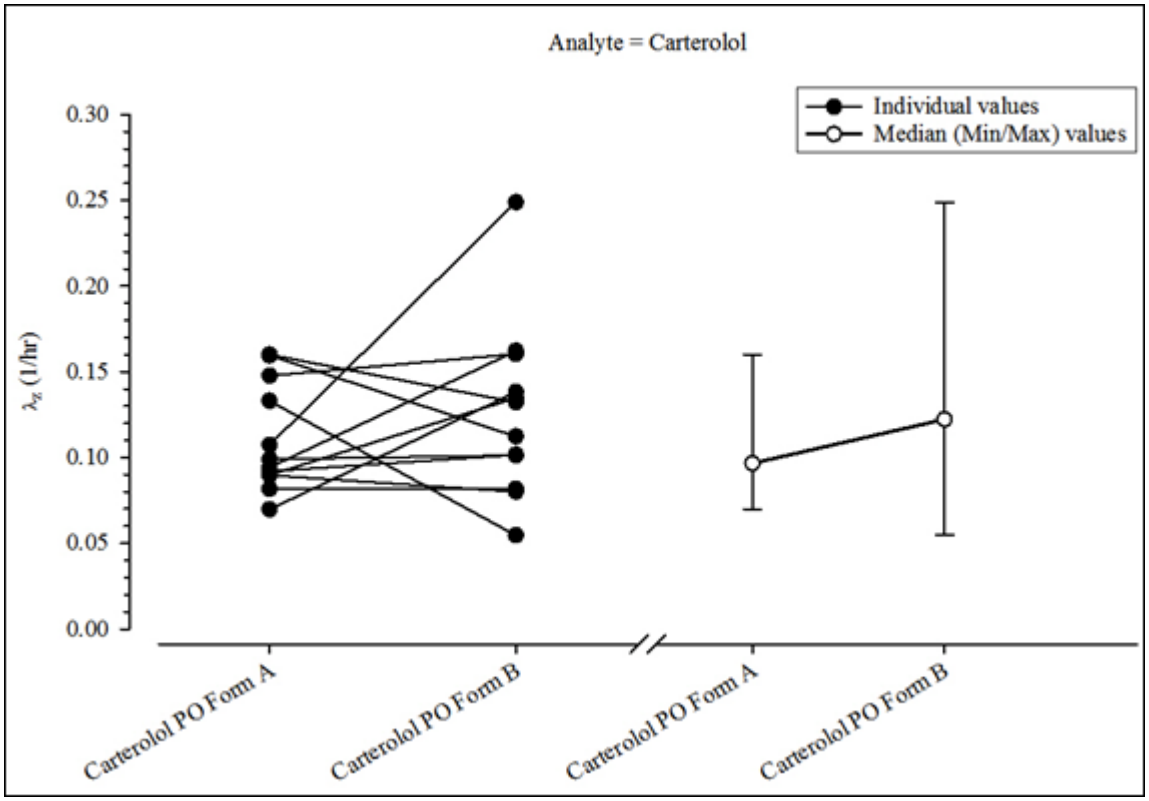
PK Parameter (Client Name)	Output	Display		
	Selected	Y-Axis Scaling (Linear)		
		Summary Value	Error	
			Value	Direction
Cmax	☑	Mean	SD	Both

General | Stratification/Normalization | Display | Ordering

Output Options | Display Options | Orientation | Time Scale Algorithm

Item	Table	Graph
X-Axis		Split

Figure 14-49. PK parameter absolute bioavail. comparison



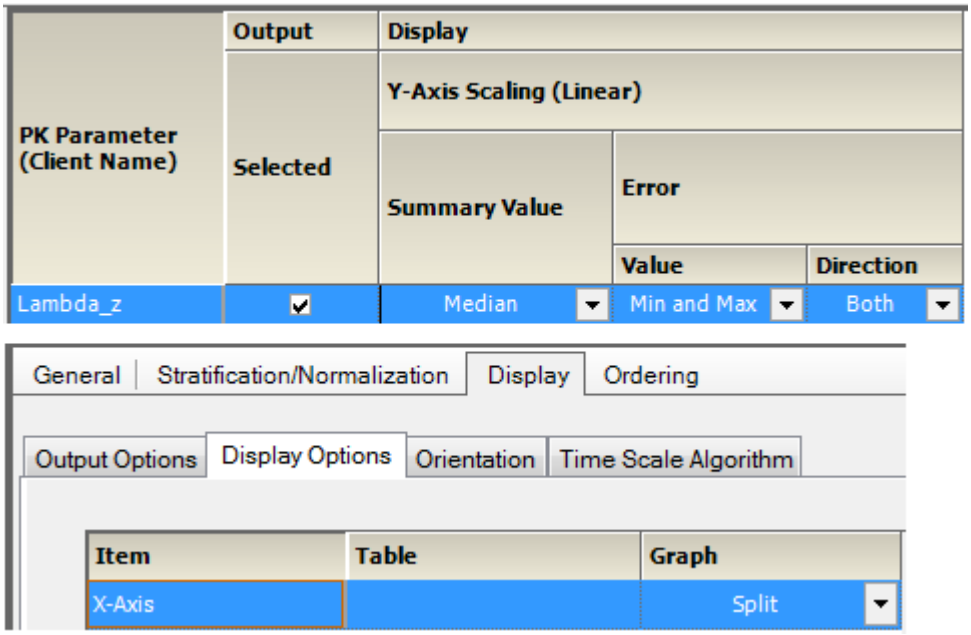
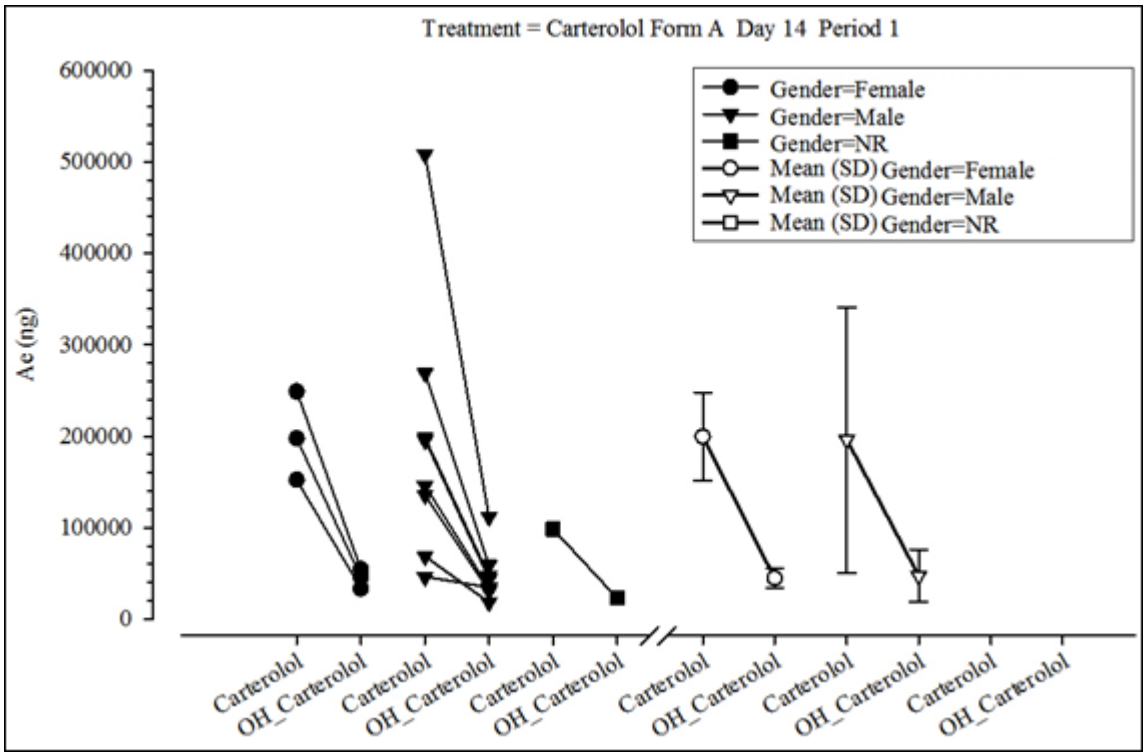


Figure 14-50. PK parameter renal clearance comparison



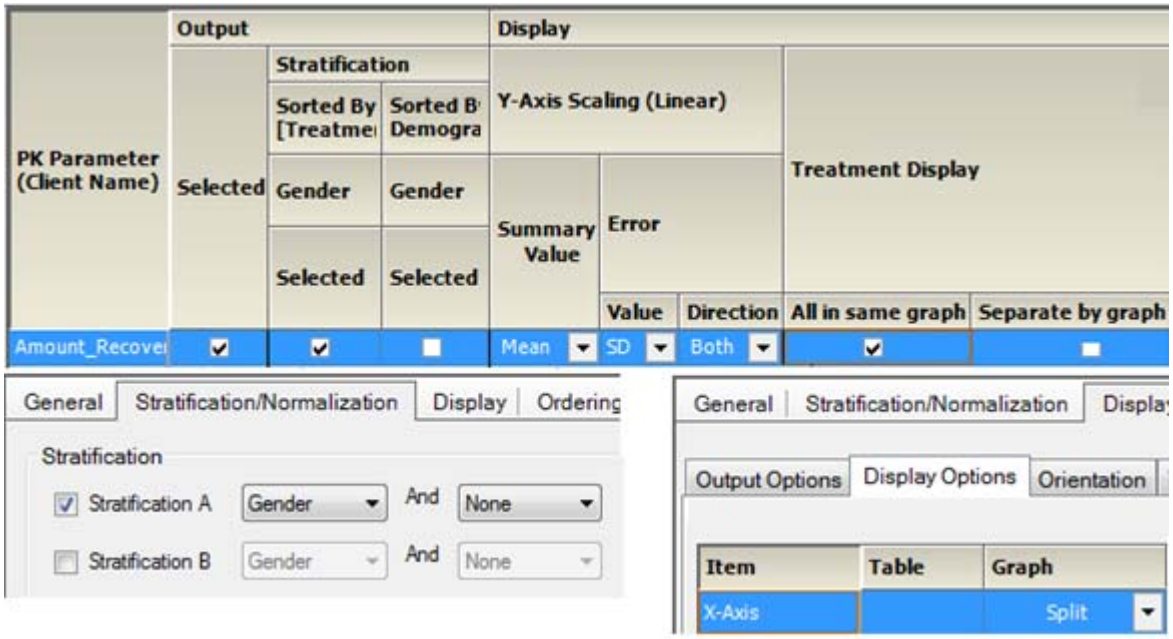
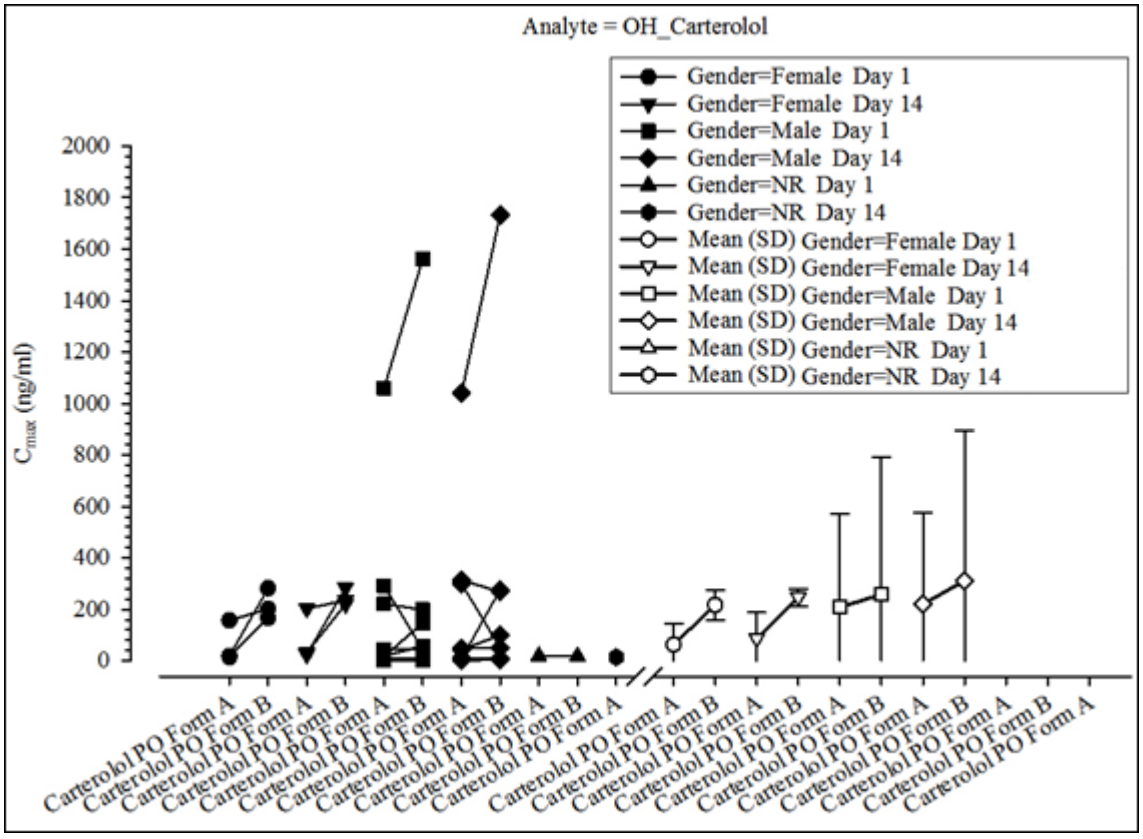


Figure 14-51. PK param. analyte comp. by treatment, sorted by treatment, and strat. by group



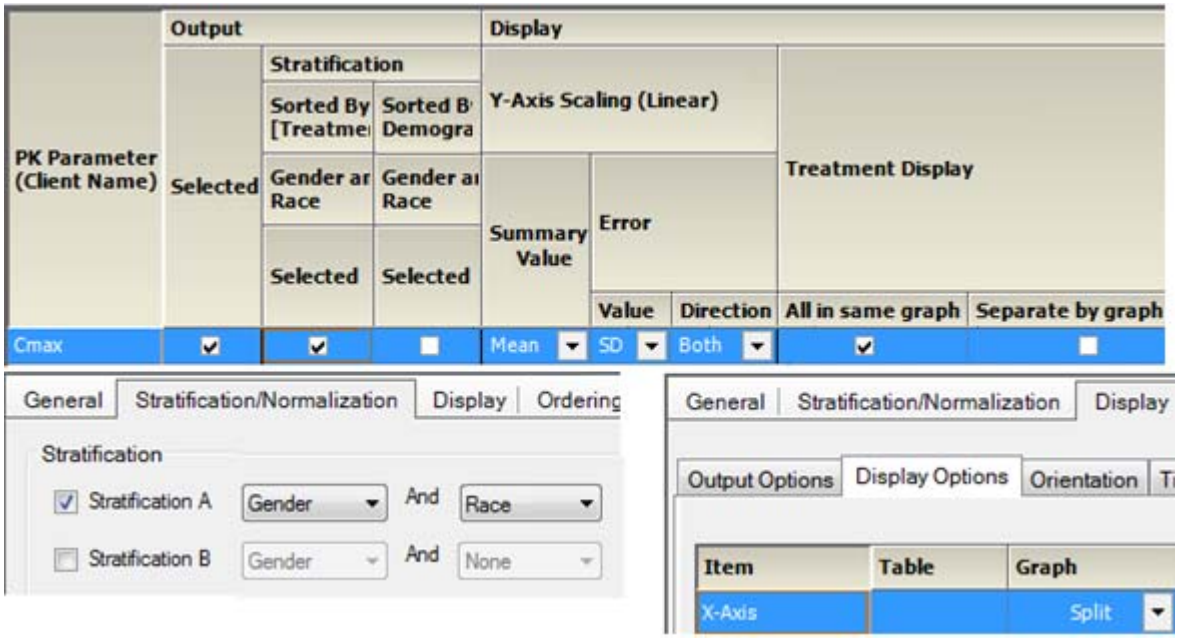
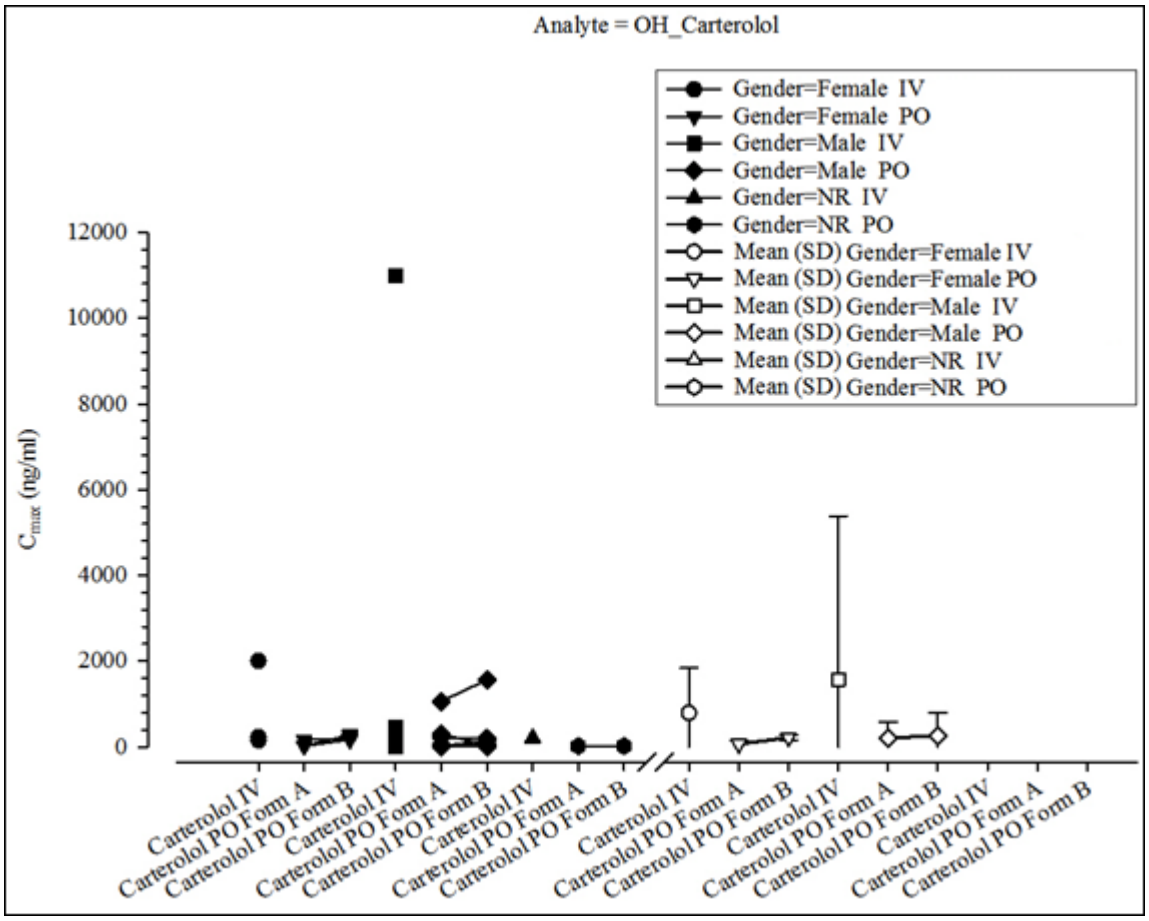


Figure 14-52. PK param. accum. comp. by treatment, sorted by treatment, and strat. by group



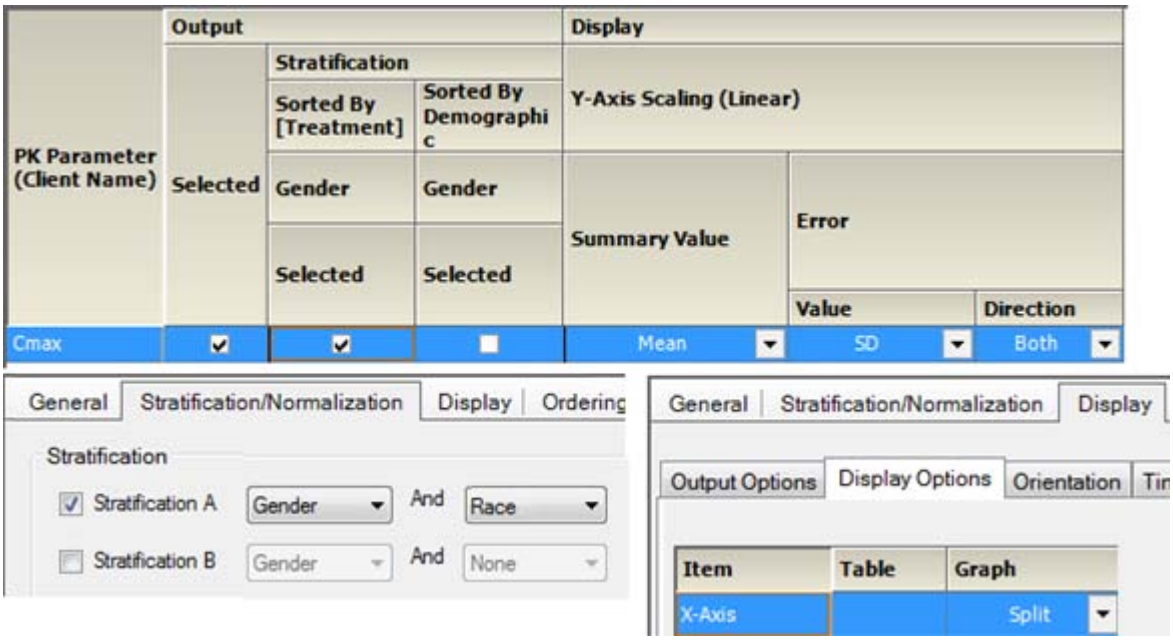
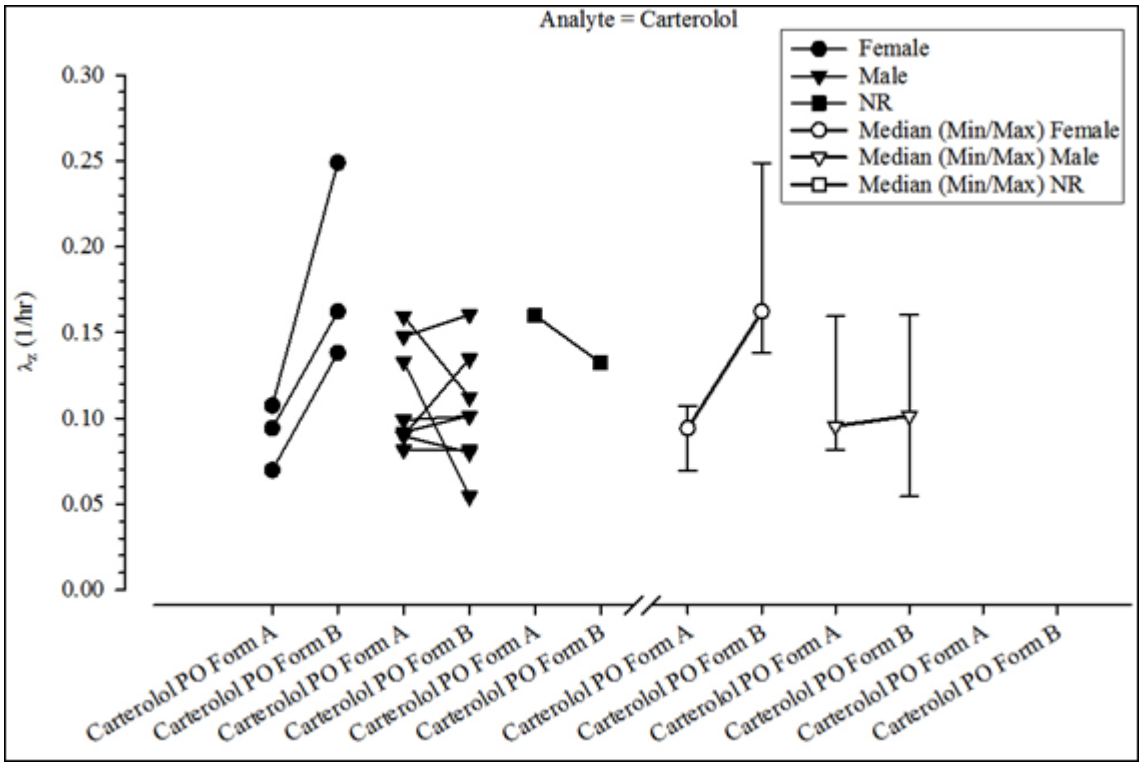


Figure 14-53. PK param. abs. bioavail. comp. by treatment, sorted by treatment, and strat. by group



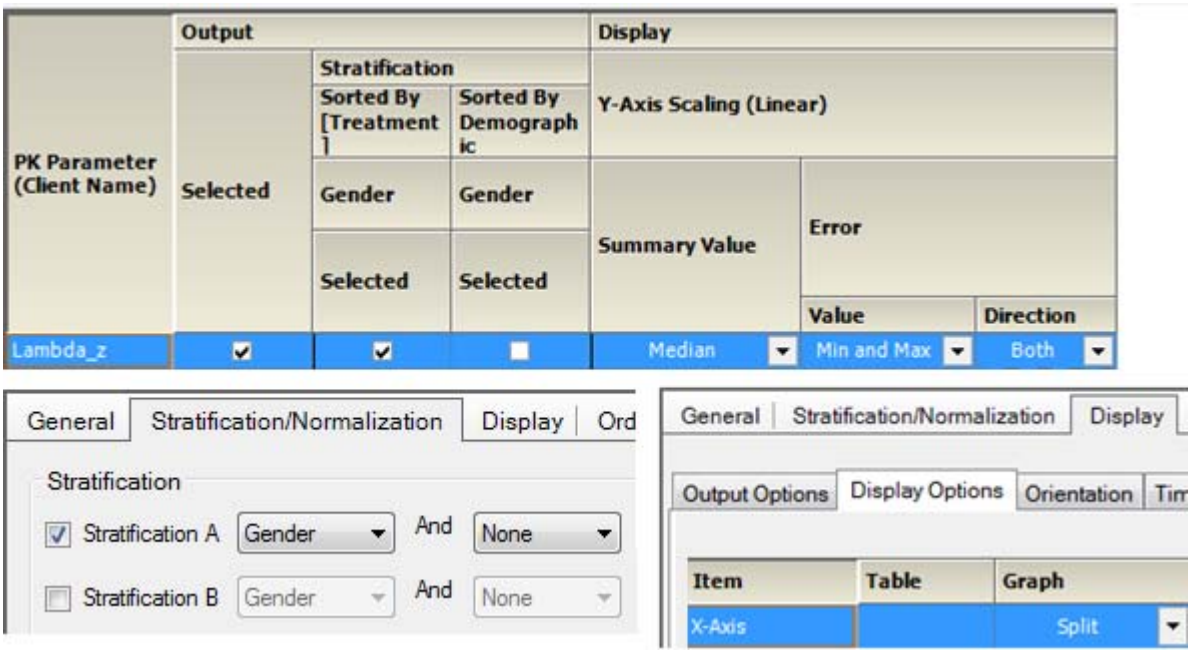
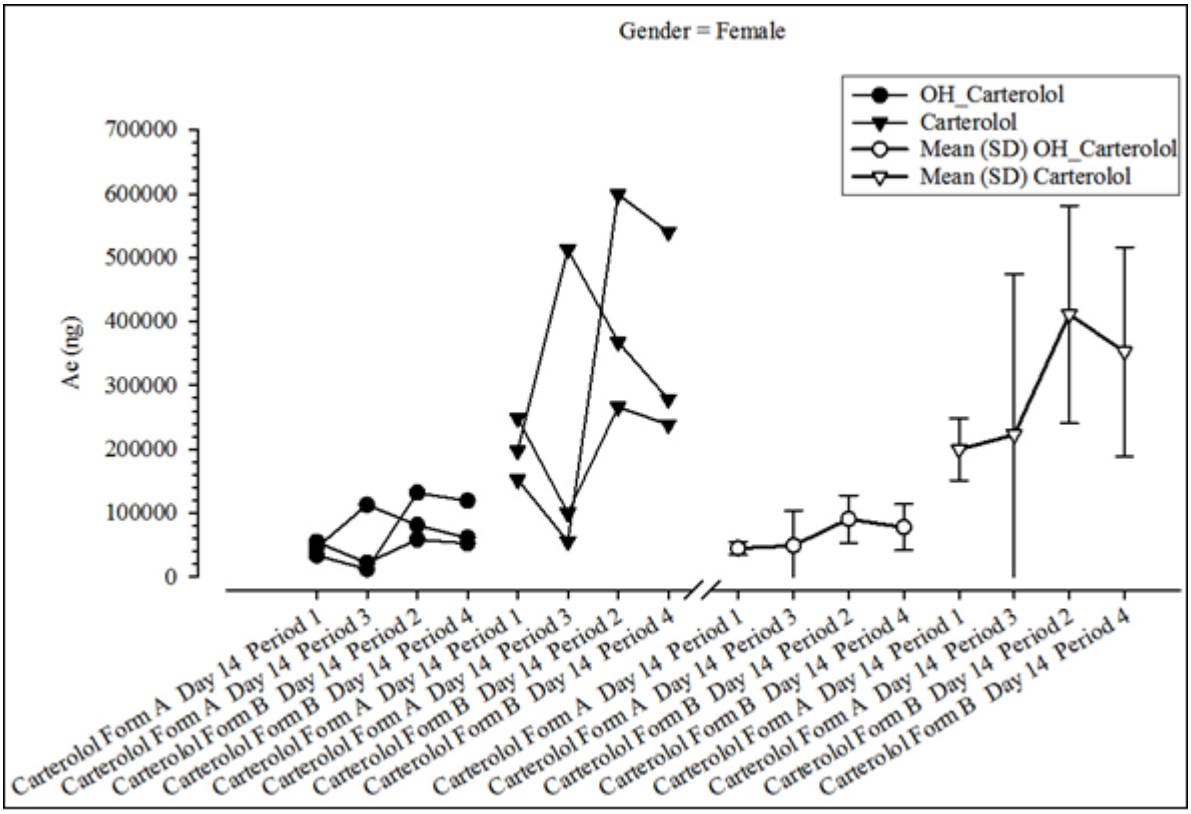


Figure 14-54. PK param. renal clearance comp. by treatment, sorted by treatment, and strat. by group



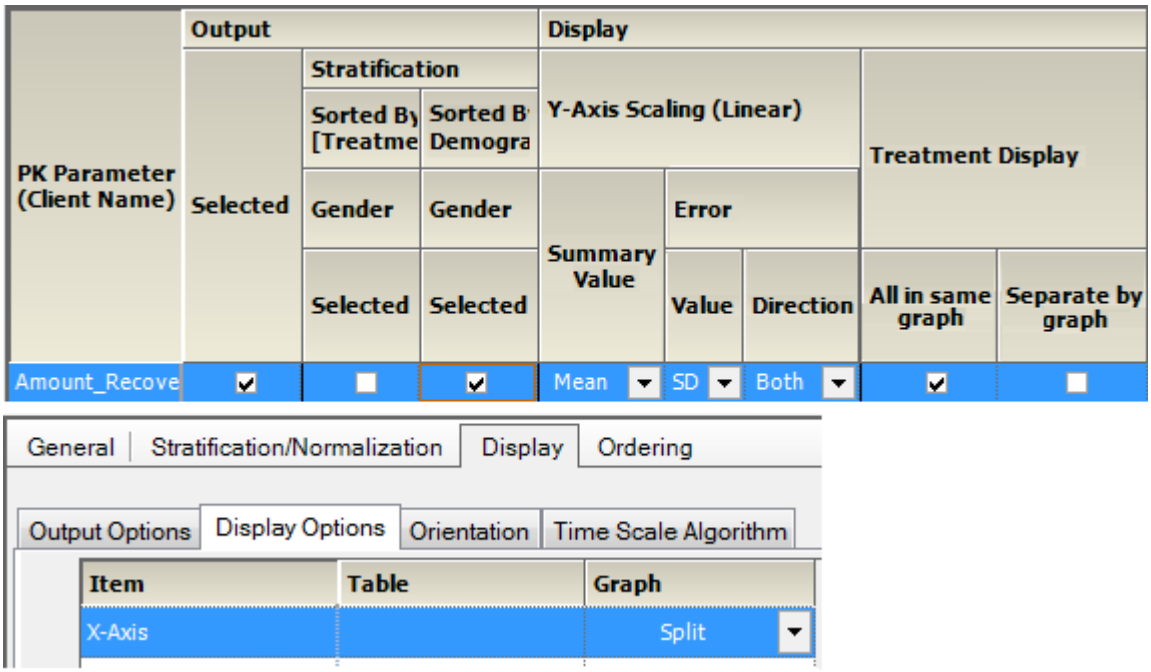
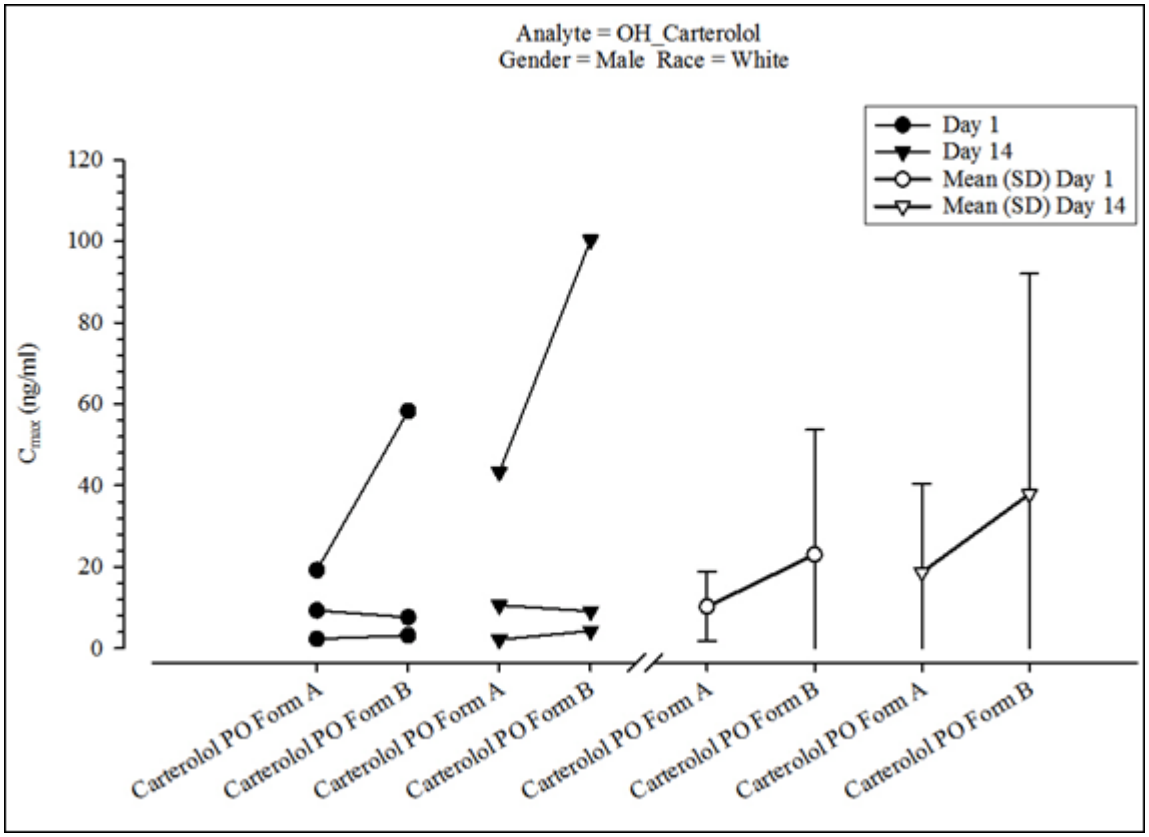


Figure 14-55. PK param. analyte comp. by treatment, sorted and strat. by group



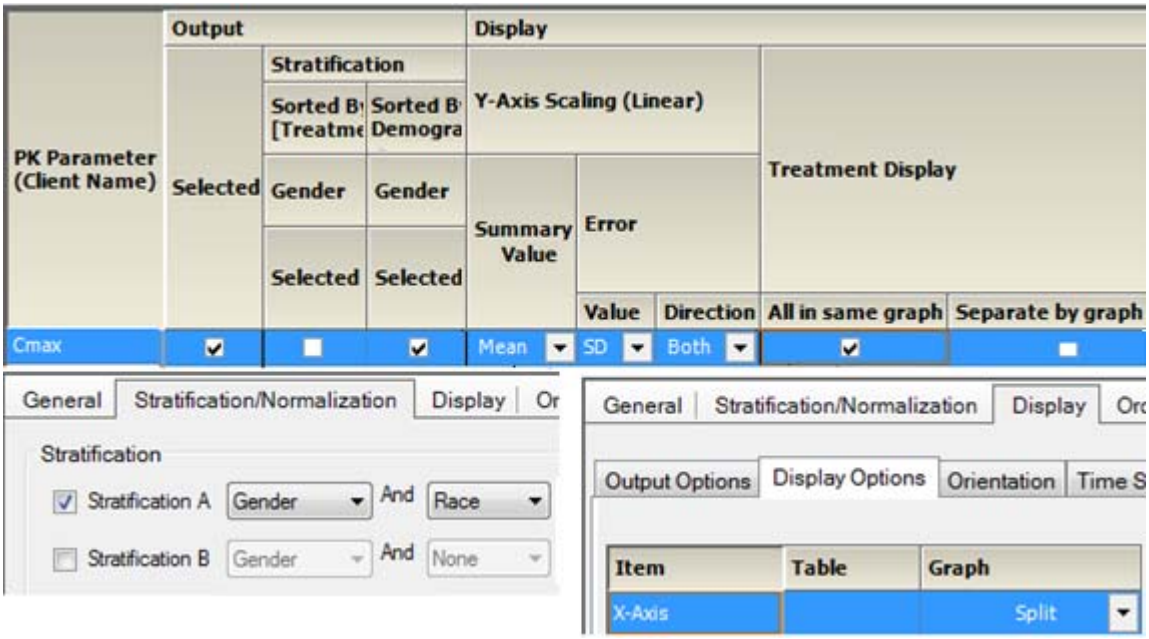
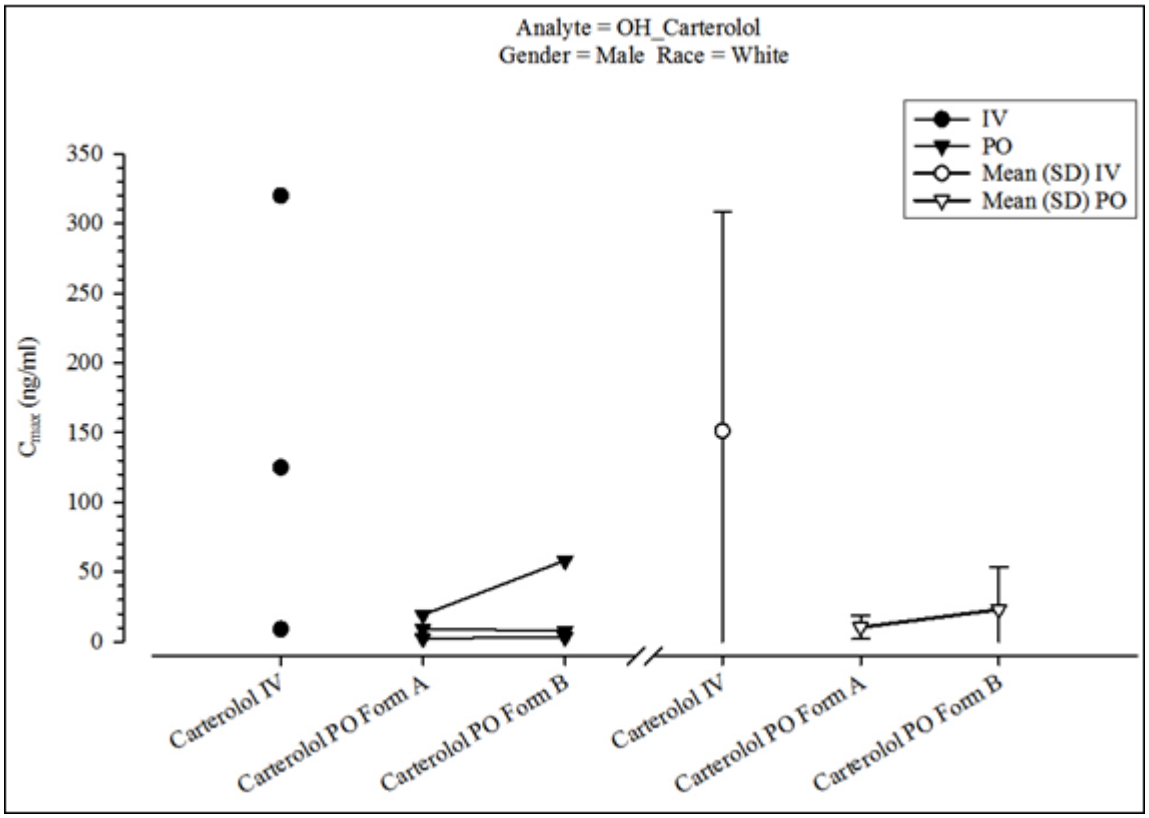


Figure 14-56. PK param. accum. comp. by treatment, sorted and strat. by group



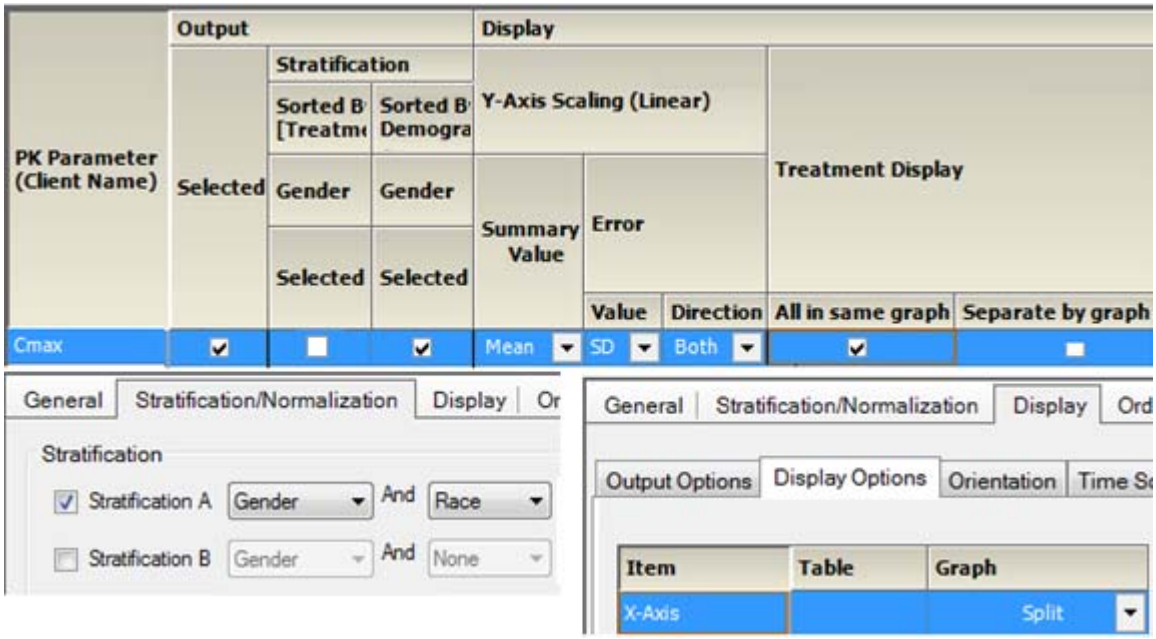
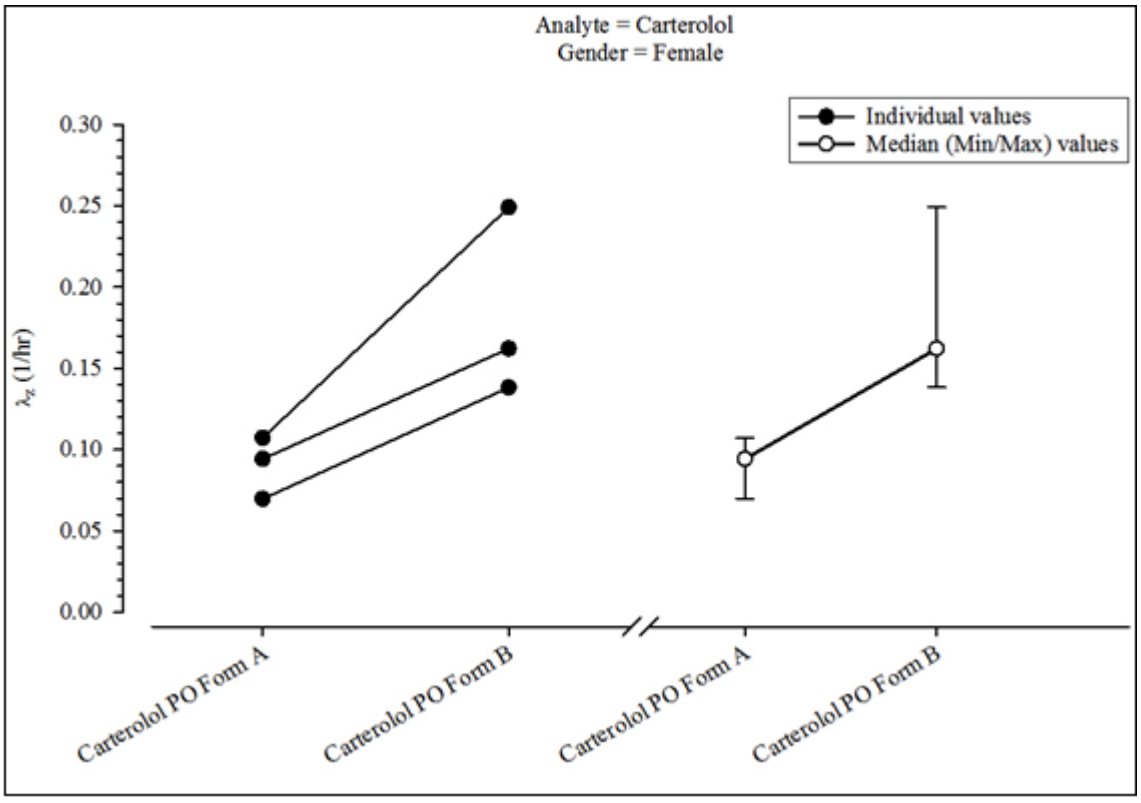


Figure 14-57. PK param. abs. bioavail. comp. by treatment, sorted and strat. by group



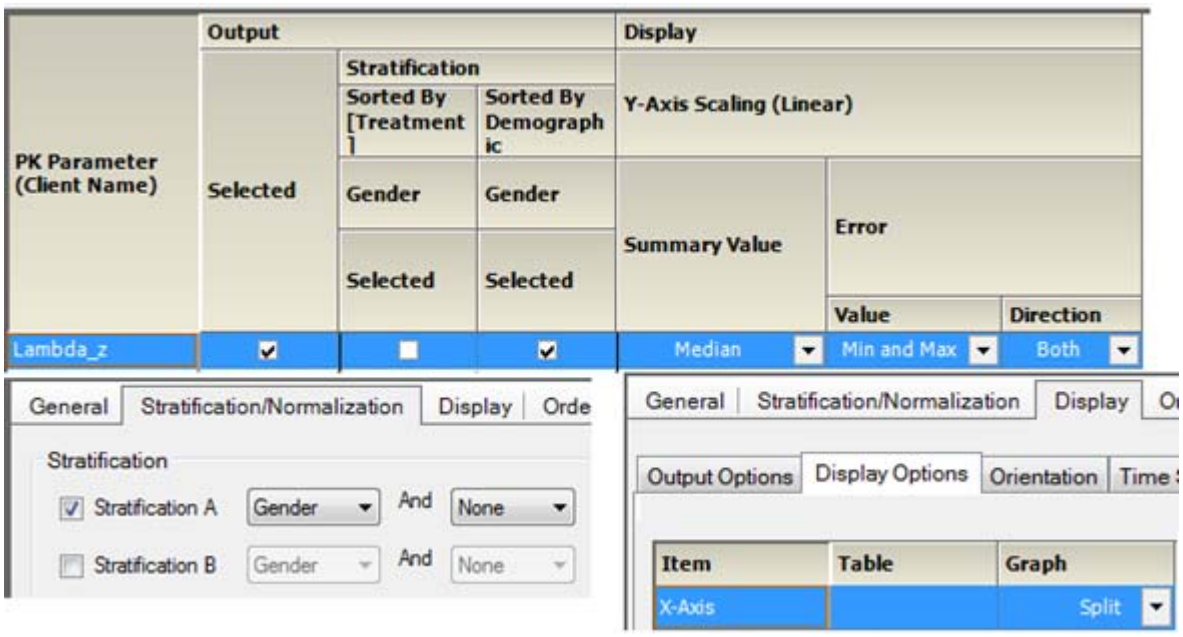
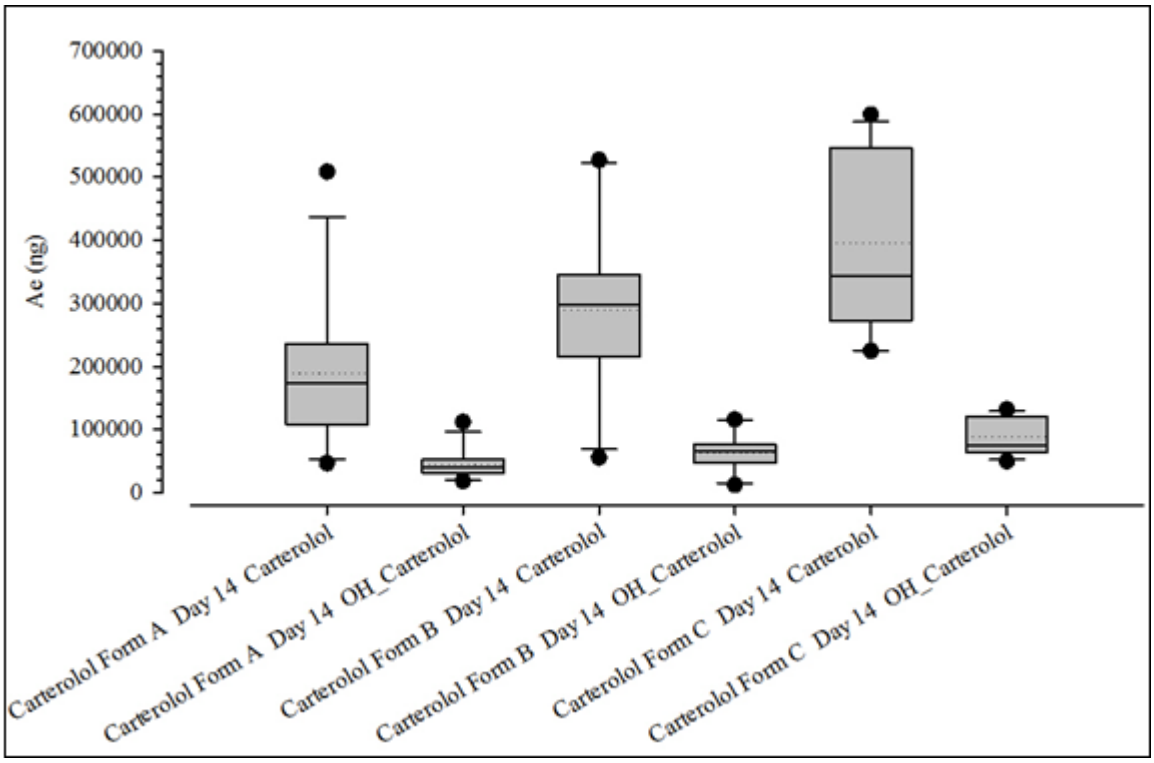


Figure 14-58. PK param. renal clearance comp. by treatment, sorted and strat. by group

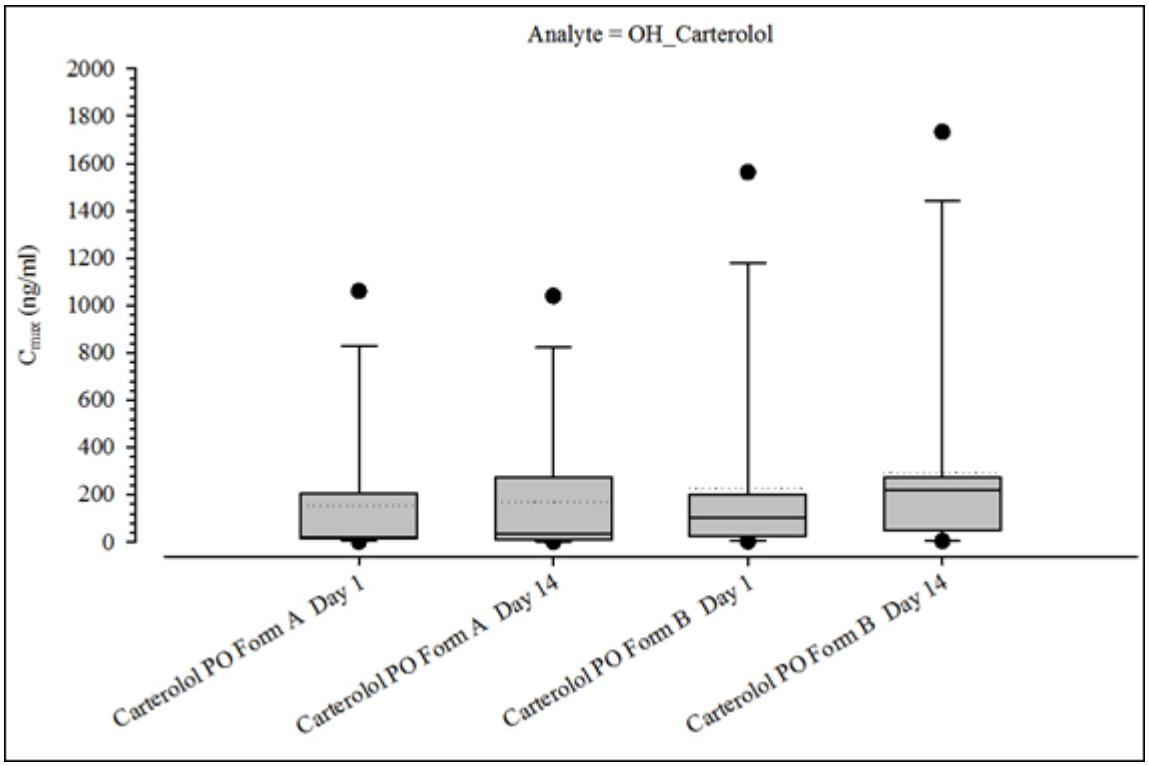
Plasma and urine comparison categorical box and whisker PK parameter graphs

Box and whisker PK param. analyte comparison
Box and whisker PK param. analyte comp. by treatment, sorted by treatment, and strat. by group
Box and whisker PK param. analyte comp. by treatment, sorted and strat. by group
Box and whisker PK param. accum. comparison
Box and whisker PK param. accum. comp. by treatment, sorted by treatment, and strat. by group
Box and whisker PK param. accum. comp. by treatment, sorted and strat. by group
Box and whisker PK param. abs. bioavail. comp.
Box and whisker PK param. abs. bioavail. comp. by treatment, sorted by treatment, and strat. by group
Box and whisker PK param. abs. bioavail. comp. by treatment, sorted and strat. by group
Box and whisker PK param. renal clearance comp.
Box and whisker PK param. renal clearance comp. by treatment, sorted by treatment, and strat. by group
Box and whisker PK param. renal clearance comp. by treatment, sorted and strat. by group



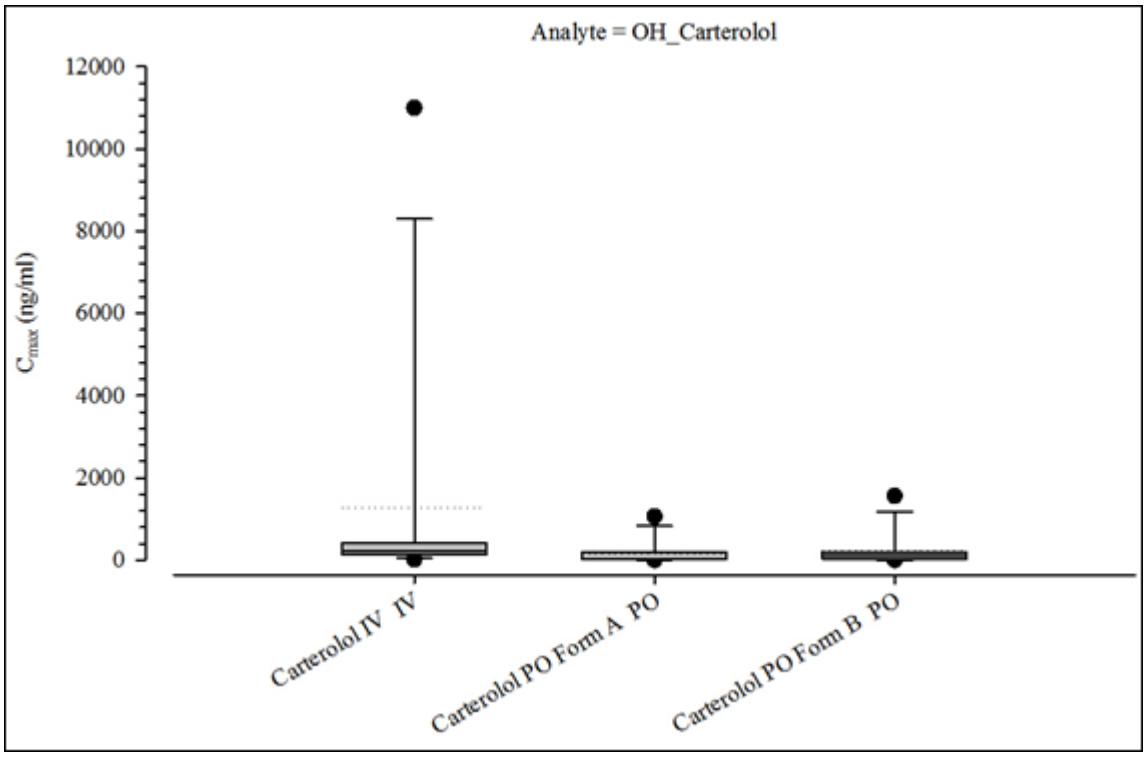
PK Parameter (Client Name)	Output Selected	Treatment Display	
		All in same graph	Separate by graph
Amount_Recovered	☑	☑	☐

Figure 14-59. Box and whisker PK param. analyte comparison



PK Parameter (Client Name)	Output	Treatment Display	
	Selected	All in same graph	Separate by graph
Cmax	☑	☑	☐

Figure 14-60. Box and whisker PK param. accum. comparison



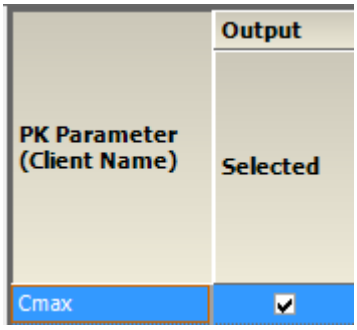
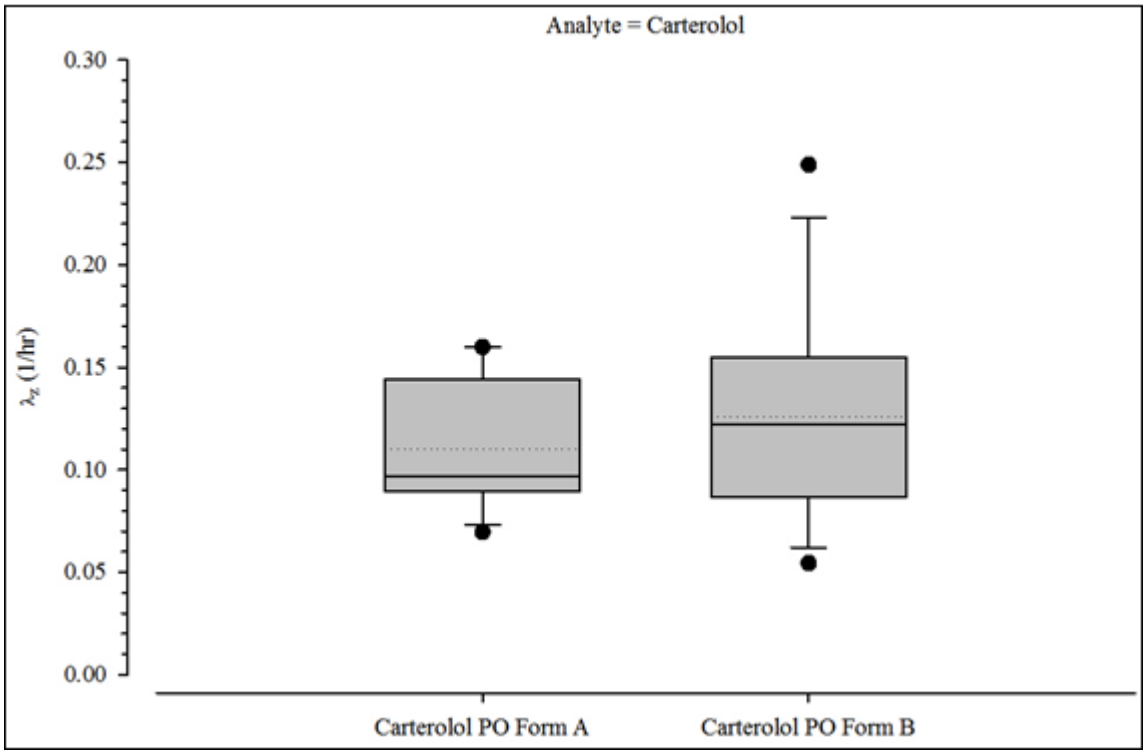


Figure 14-61. Box and whisker PK param. abs. bioavail. comp.



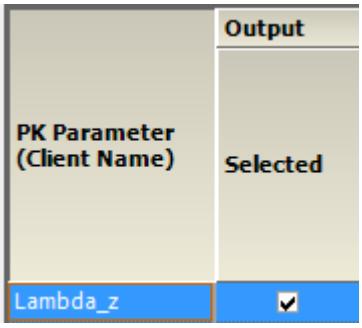
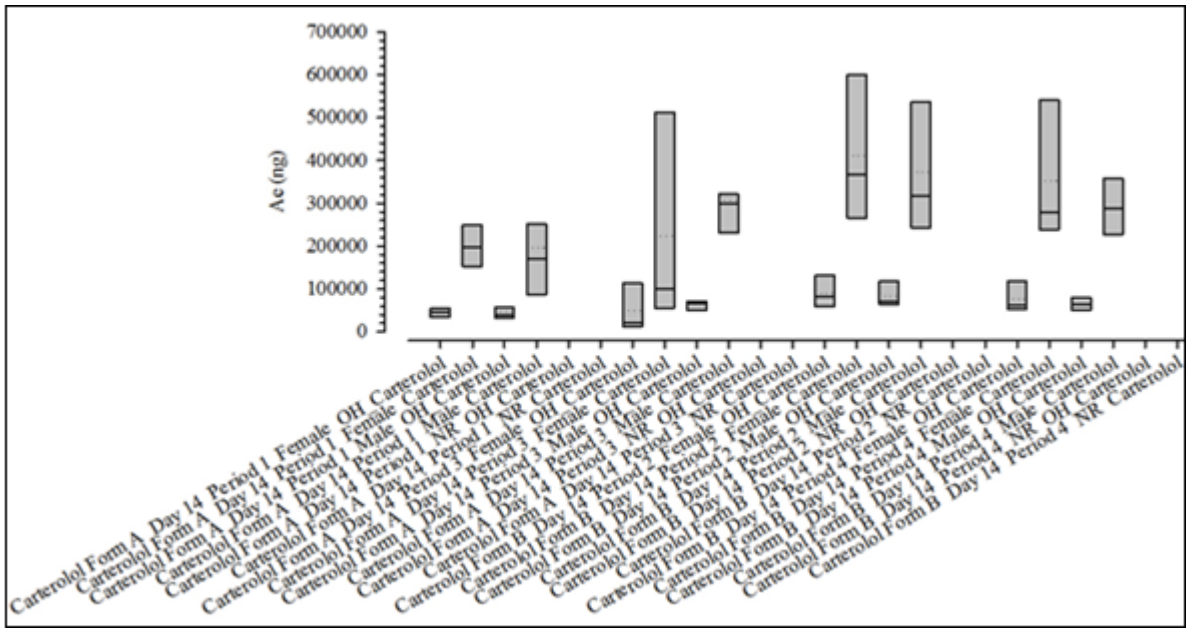


Figure 14-62. Box and whisker PK param. renal clearance comp.



PK Parameter (Client Name)	Output			Treatment Display	
	Selected	Stratification			
		Sorted By [Treatment]	Sorted By Demographic		
		Gender	Gender		
		Selected	Selected		
				All in same graph	Separate by graph
Amount_Recovered	☑	☑	☐	☑	☐

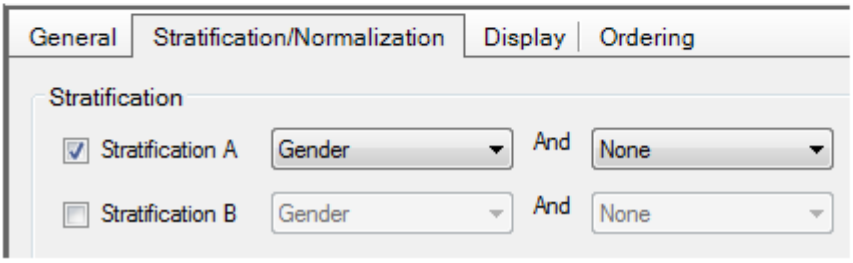
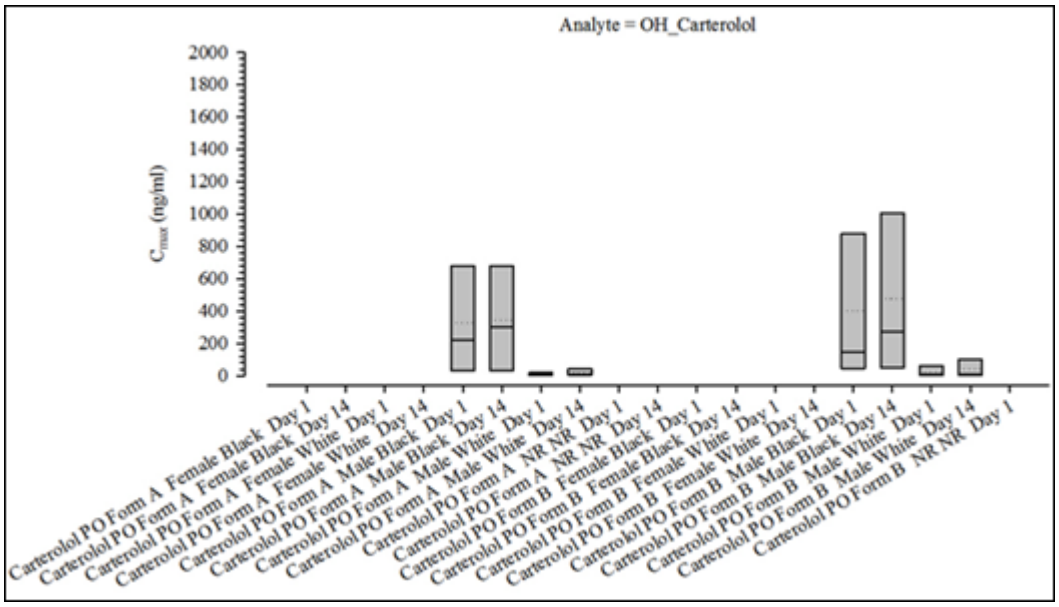


Figure 14-63. Box and whisker PK param. analyte comp. by treatment, sorted by treatment, and strat. by group



PK Parameter (Client Name)	Output			Treatment Display	
	Selected	Stratification			
		Sorted By [Treatment]	Sorted By Demographic		
		Gender and Race	Gender and Race		
		Selected	Selected		
				All in same graph	Separate by graph
Cmax	☑	☑	☐	☑	☐

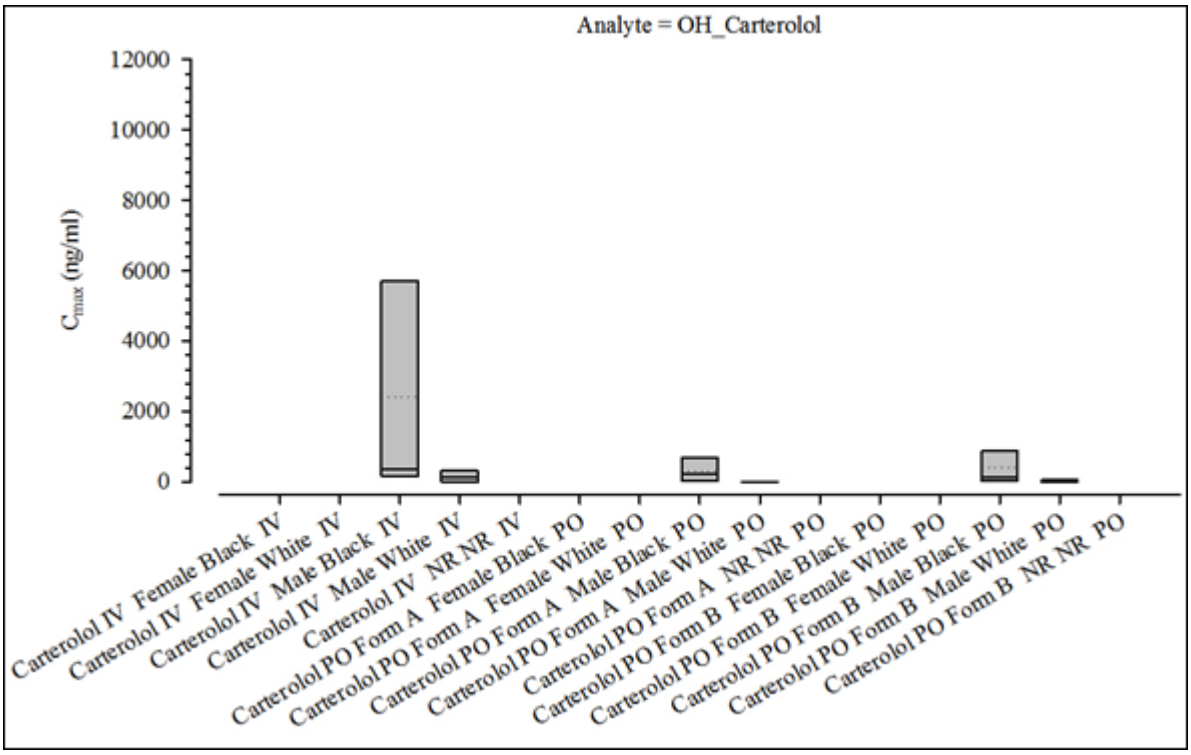
General | Stratification/Normalization | Display | Ordering

Stratification

☑ Stratification A — Gender — And — Race

☐ Stratification B — Gender — And — None

Figure 14-64. Box and whisker PK param. accum. comp. by treatment, sorted by treatment, and strat. by group



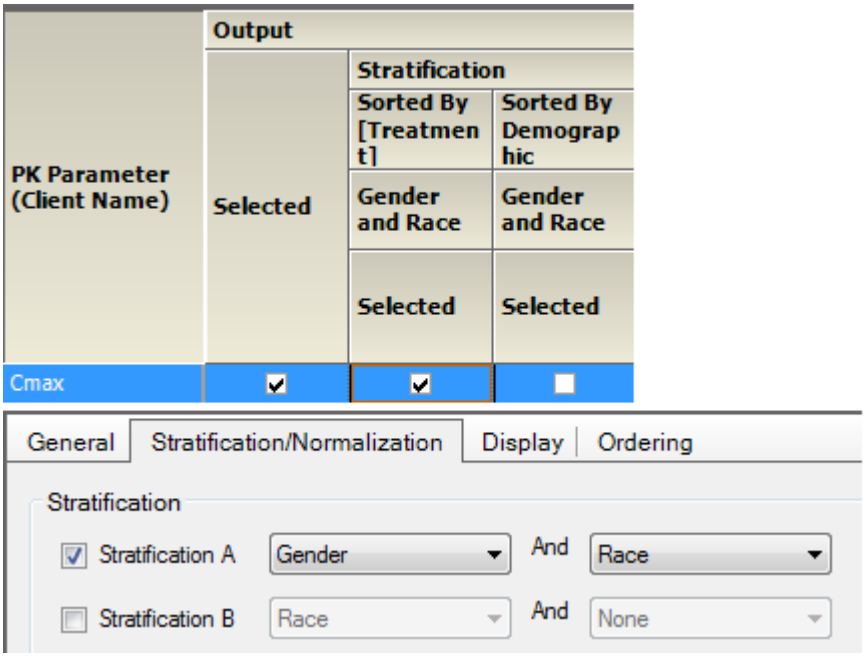
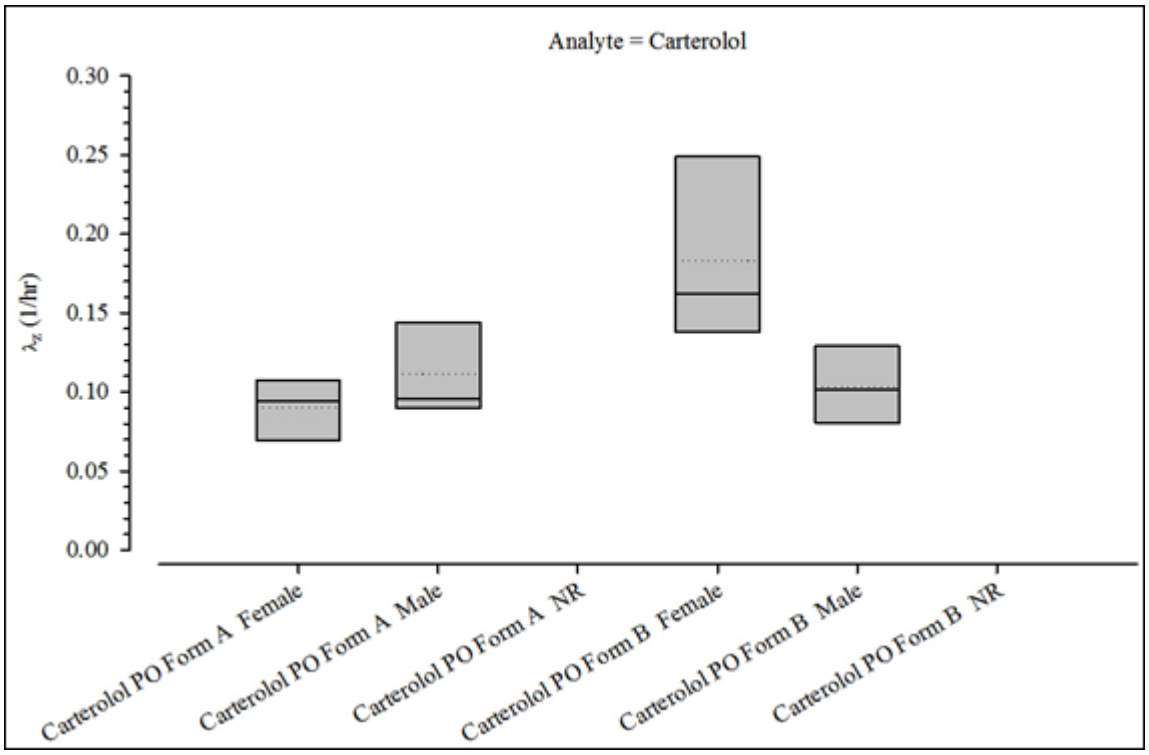


Figure 14-65. Box and whisker PK param. abs. bioavail. comp. by treatment, sorted by treatment, and strat. by group



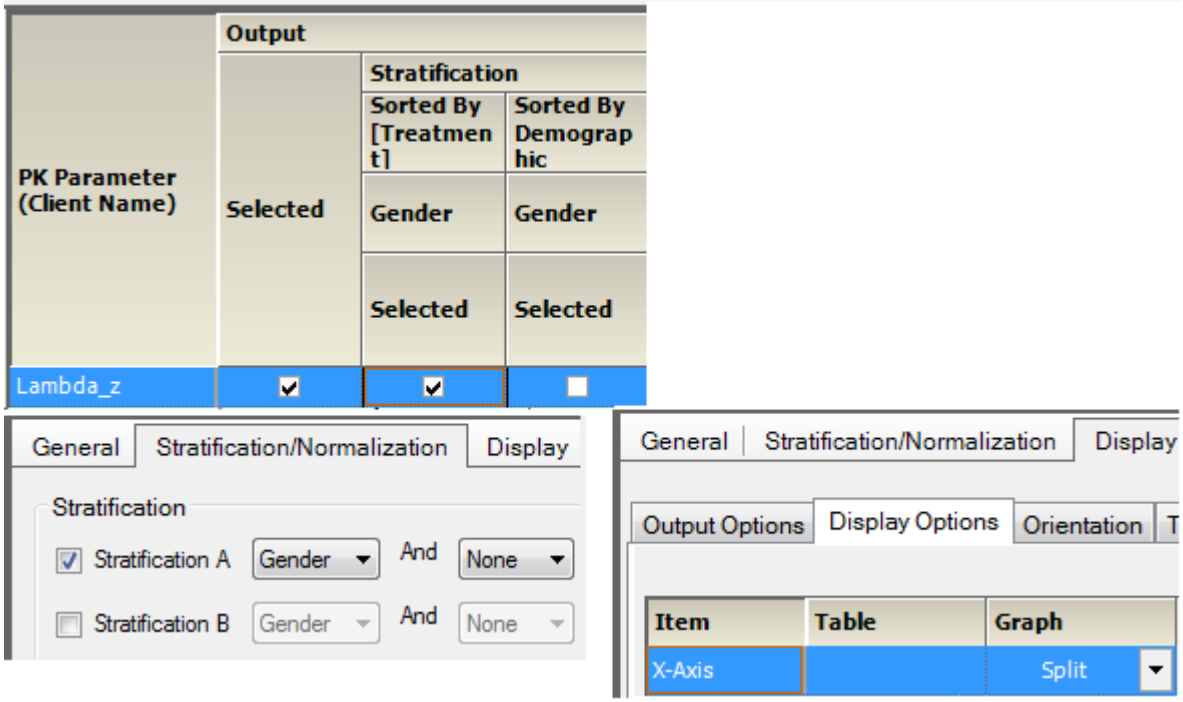
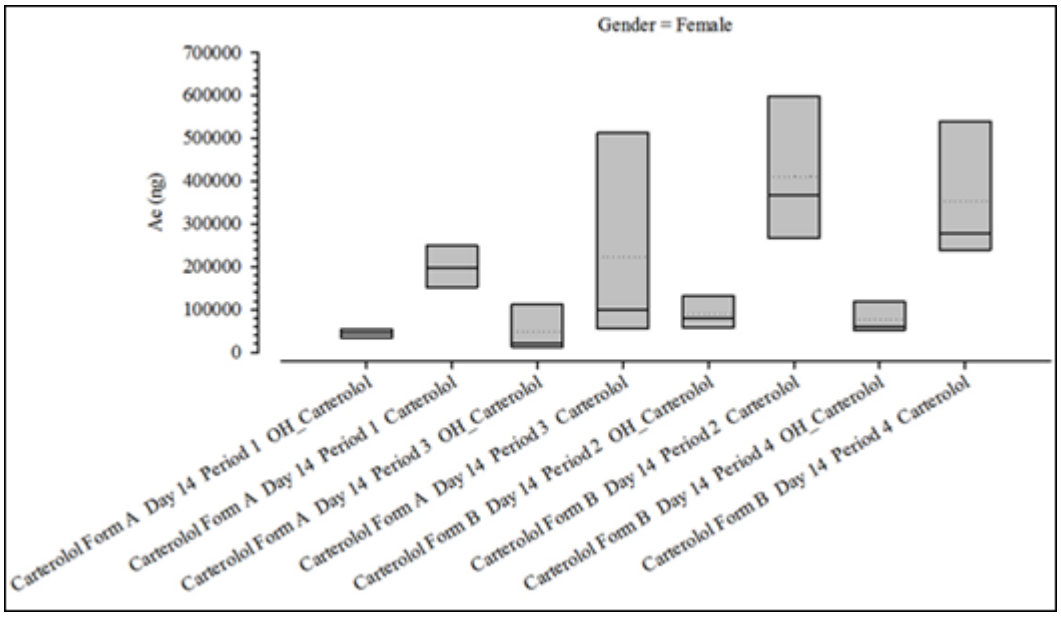


Figure 14-66. Box and whisker PK param. renal clearance comp. by treatment, sorted by treatment, and strat. by group



PK Parameter (Client Name)	Output			Treatment Display	
	Selected	Stratification			
		Sorted By [Treatment]	Sorted By Demographic		
		Gender	Gender		
		Selected	Selected		
				All in same graph	Separate by graph
Amount_Recovered	☑	☐	☑	☑	☐

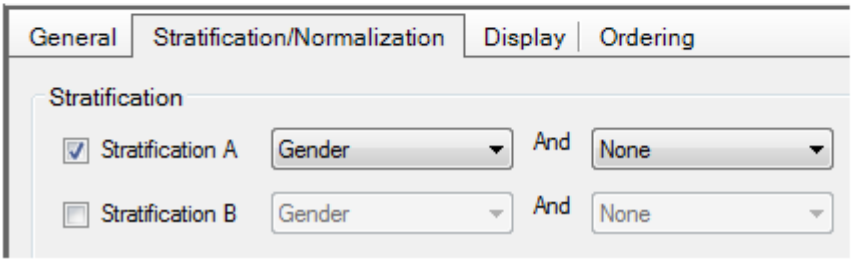
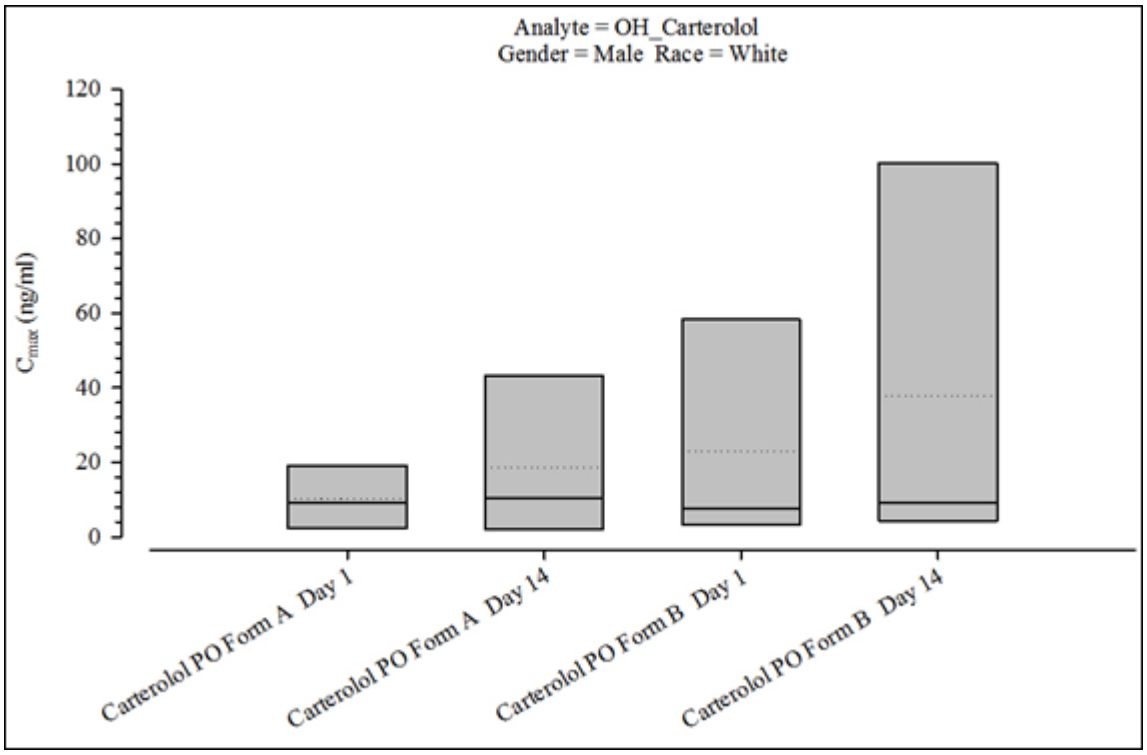


Figure 14-67. Box and whisker PK param. analyte comp. by treatment, sorted and strat. by group



PK Parameter (Client Name)	Output			Treatment Display	
	Selected	Stratification			
		Sorted By [Treatment]	Sorted By Demographic		
		Gender and Race	Gender and Race		
		Selected	Selected		
				All in same graph	Separate by graph
Cmax	☑	☐	☑	☑	☐

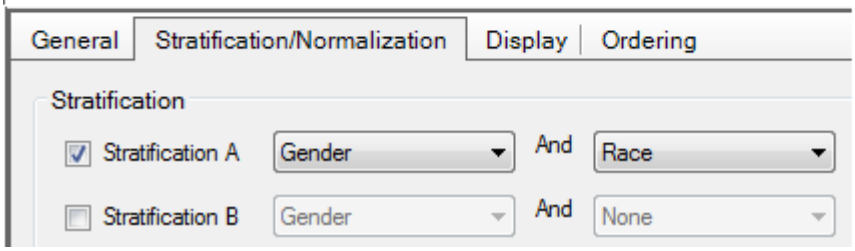
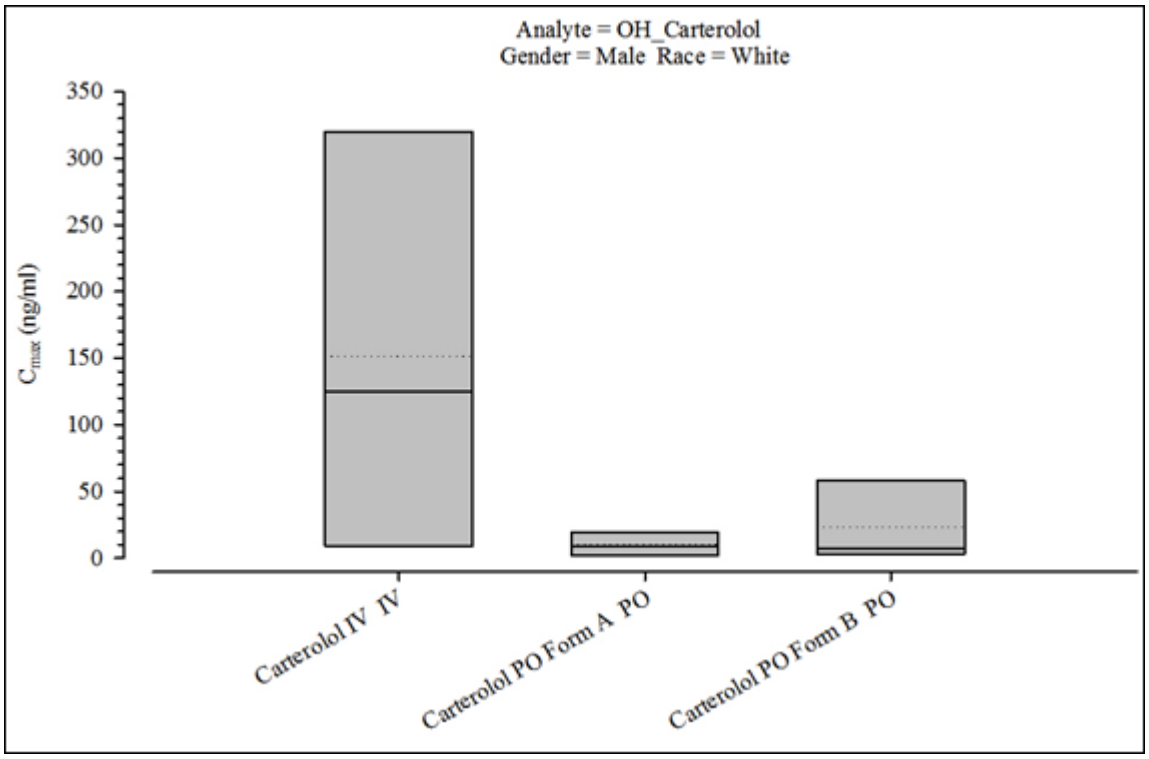


Figure 14-68. Box and whisker PK param. accum. comp. by treatment, sorted and strat. by group



PK Parameter (Client Name)	Output		
	Selected	Stratification	
		Sorted By [Treatment]	Sorted By Demographic
		Gender and Race	Gender and Race
		Selected	Selected
Cmax	☑	☐	☑

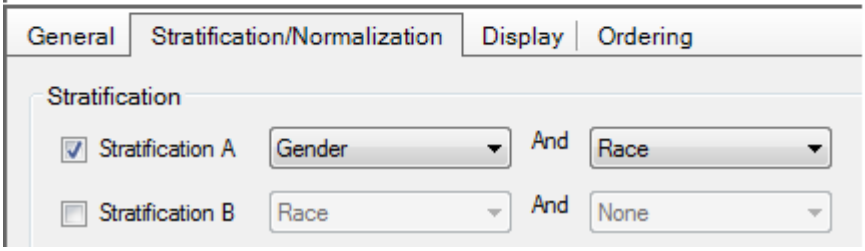
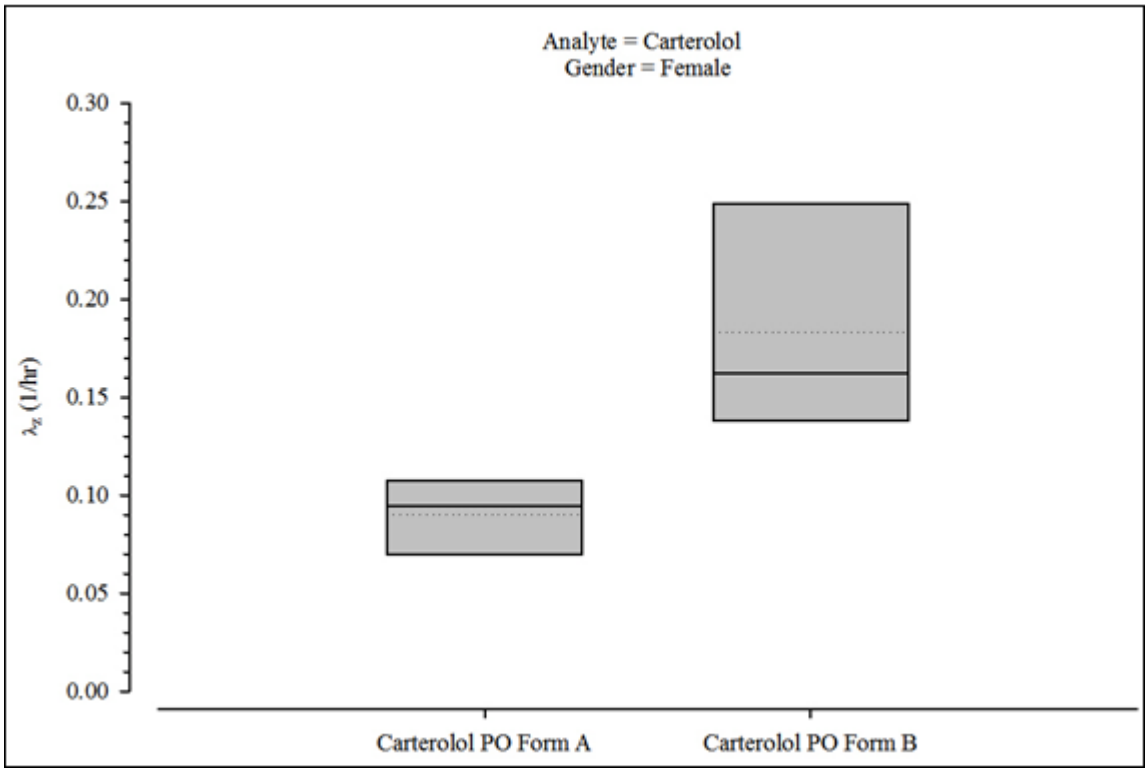


Figure 14-69. Box and whisker PK param. abs. bioavail. comp. by treatment, sorted and strat. by group



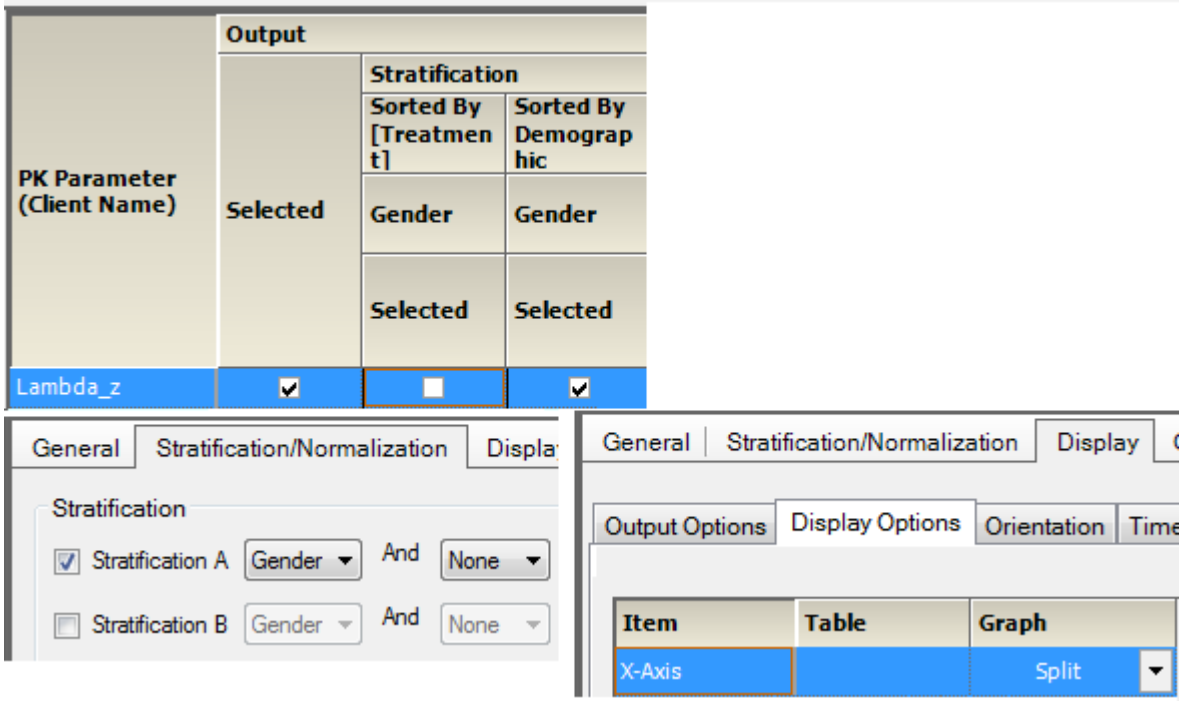
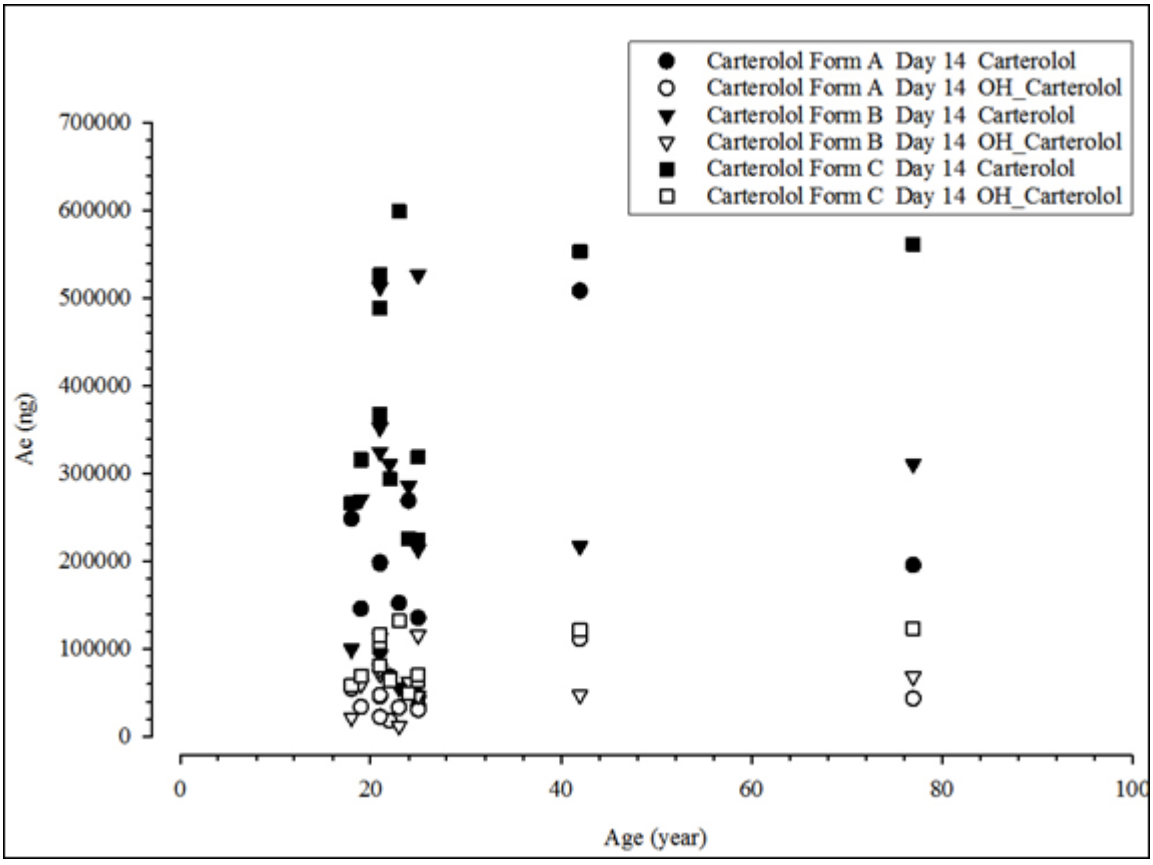


Figure 14-70. Box and whisker PK param. renal clearance comp. by treatment, sorted and strat. by group

Comparison continuous demographic PK parameter graphs

PK param. vs continuous demographic analyte comp.
PK param. vs continuous demographic analyte comp. by treatment, sorted by treatment, and strat. by group

PK param. vs continuous demographic analyte comp. by treatment, sorted and strat. by group
PK param. vs continuous demographic accum. comp.
PK param. vs continuous demographic accum. comp. by treatment, sorted by treatment, and strat. by group
PK param. vs continuous demographic accum. comp. by treatment, sorted and strat. by group
PK param. vs continuous demographic abs. bioavail. comp.
PK param. vs continuous demographic abs. bioavail. comp. by treatment, sorted by treatment, and strat. by group
PK param. vs continuous demographic renal clearance comp.
PK param. vs continuous demographic renal clearance comp. by treatment, sorted by treatment, and strat. by group



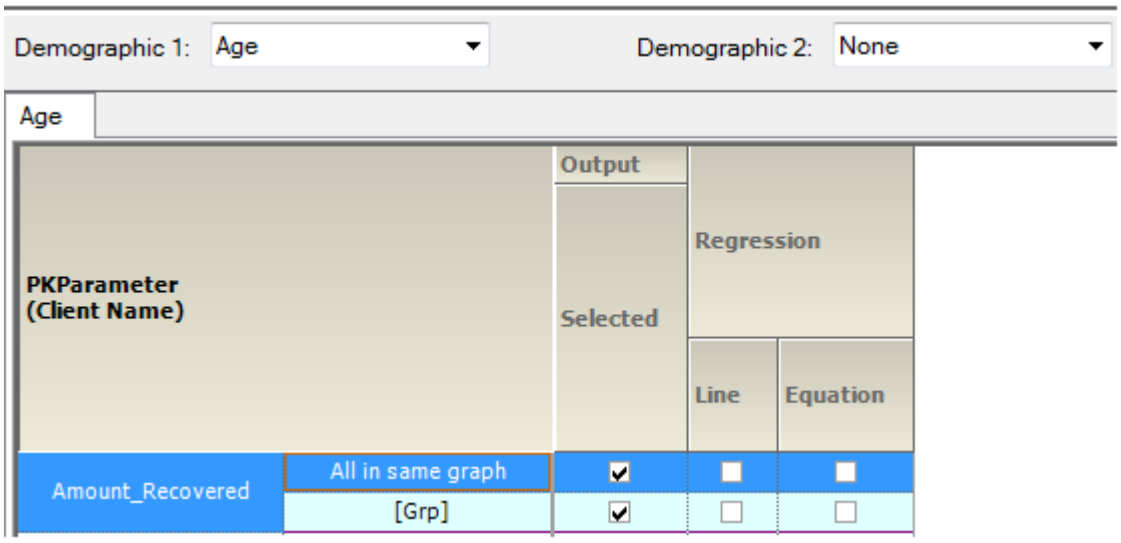
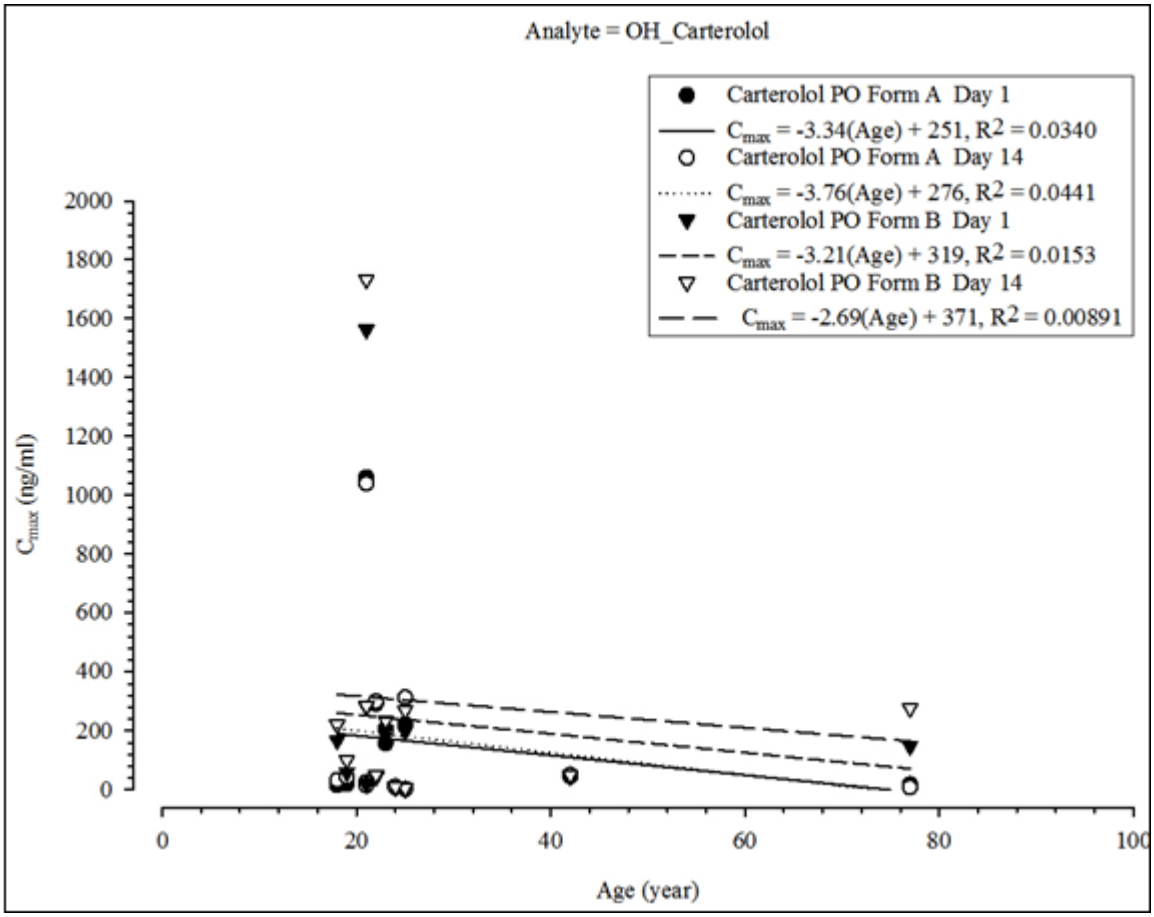


Figure 14-71. PK param. vs continuous demographic analyte comp.



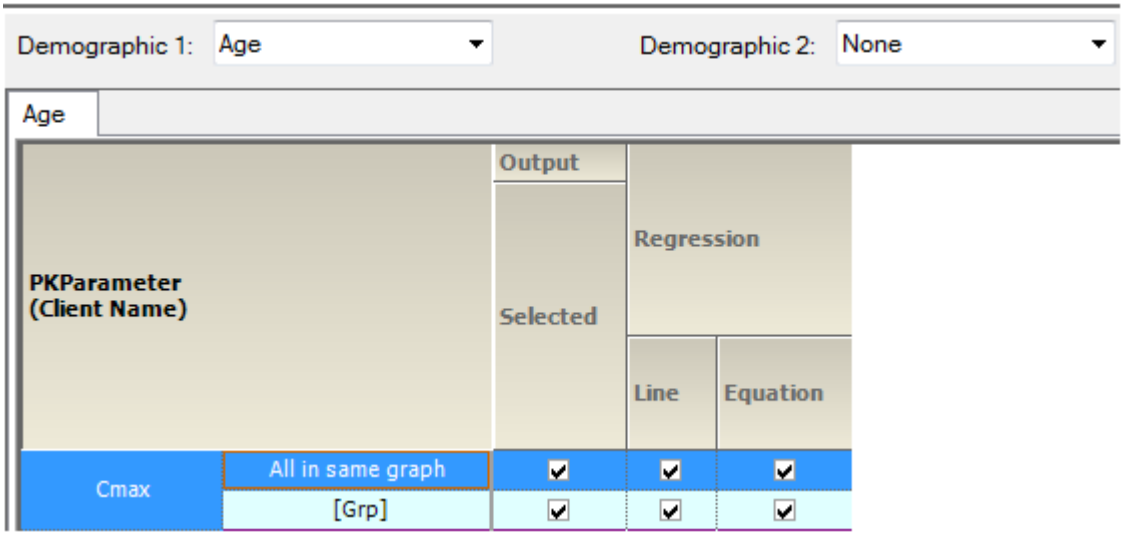
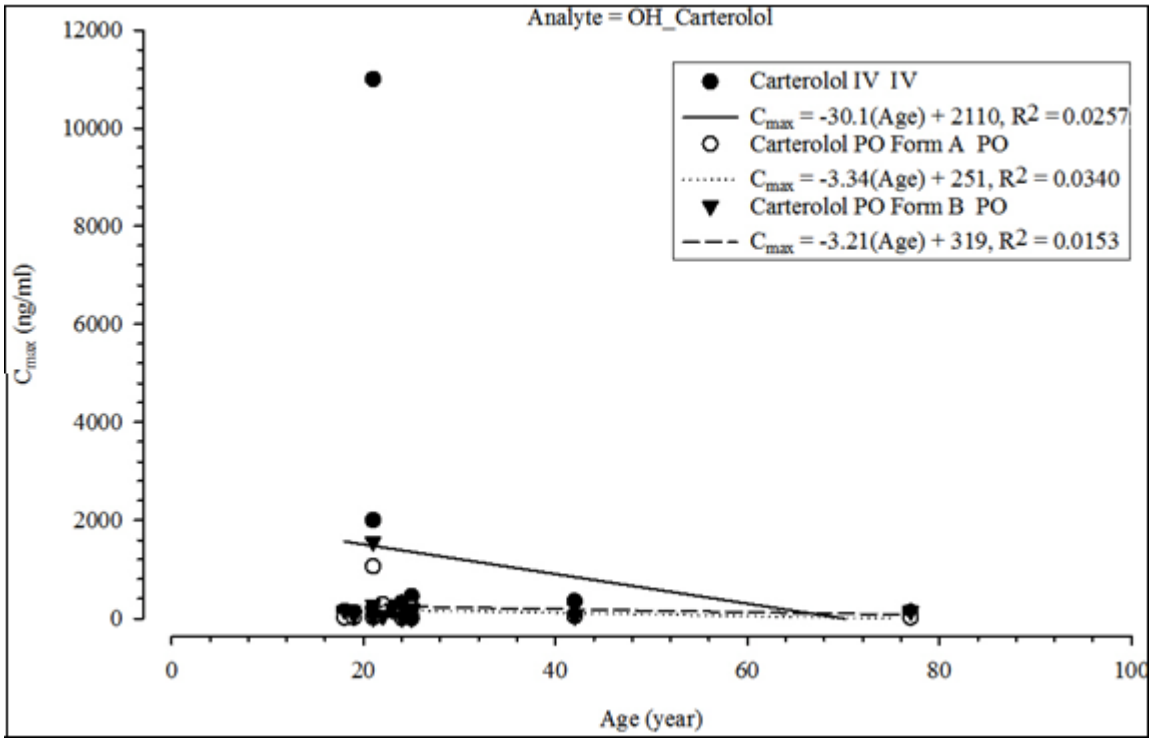


Figure 14-72. PK param. vs continuous demographic accum. comp.



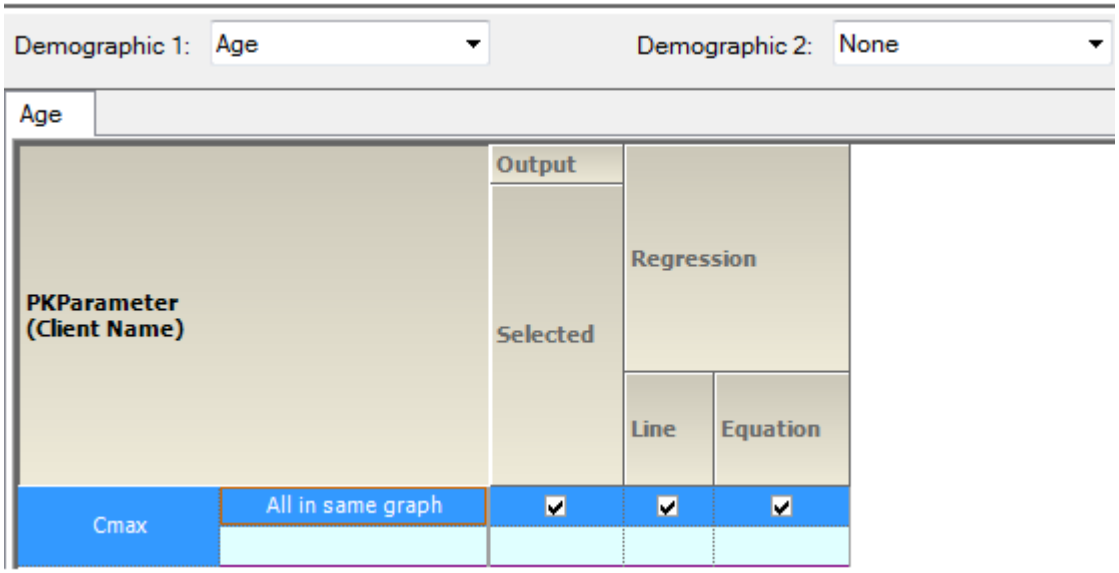
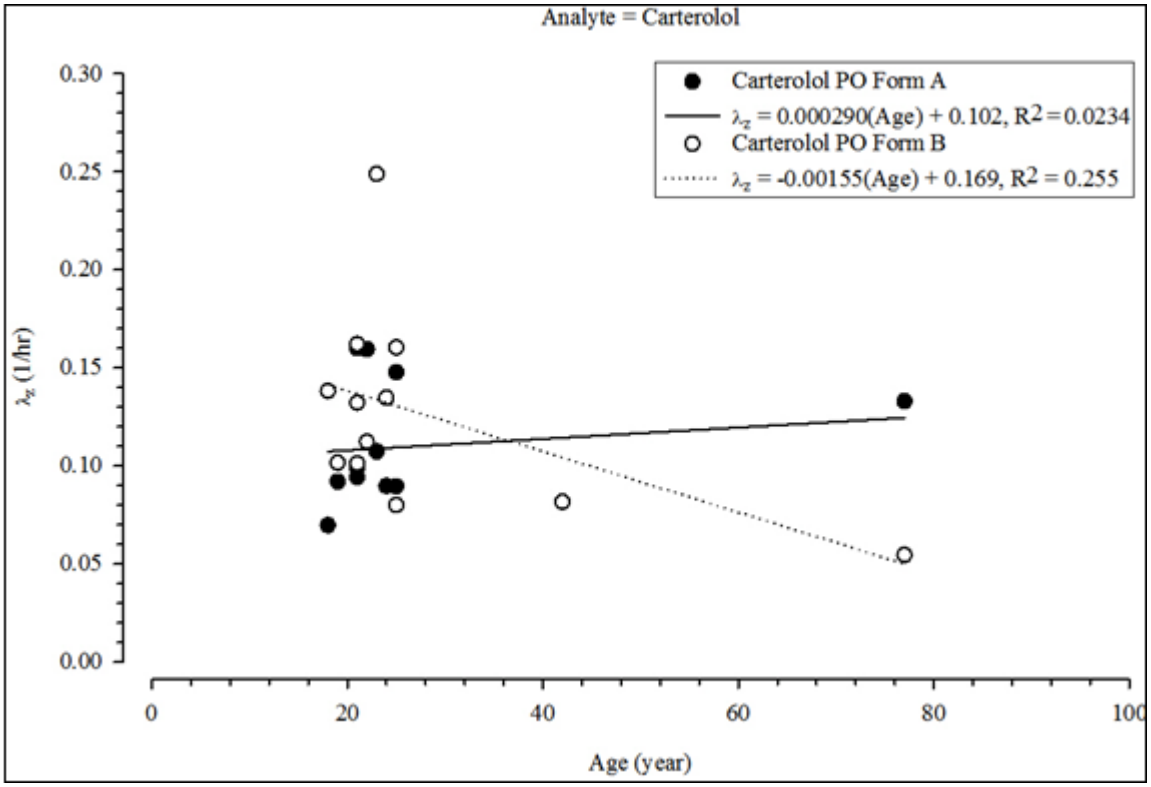


Figure 14-73. PK param. vs continuous demographic abs. bioavail. comp.



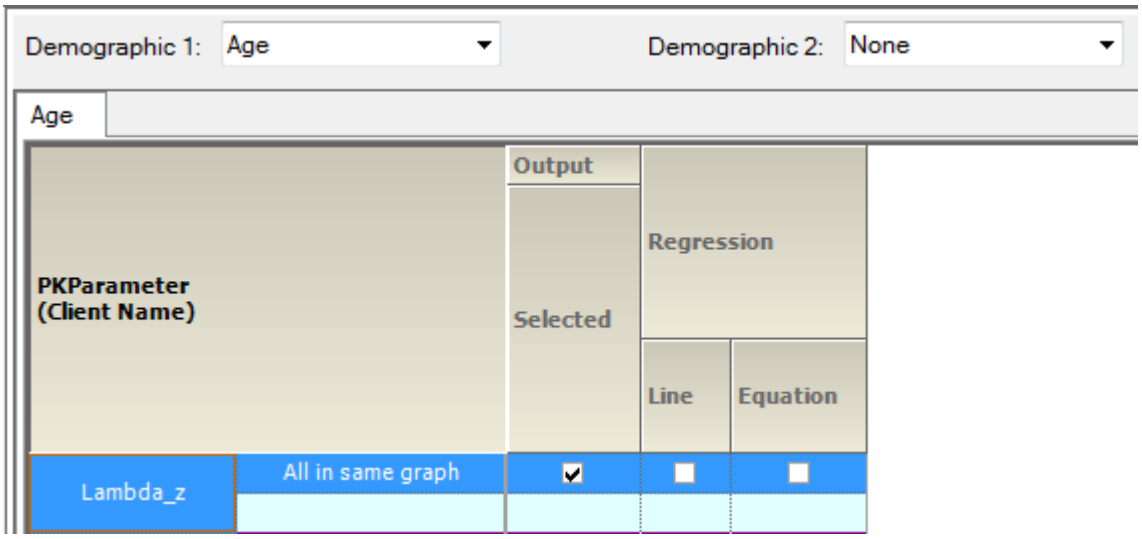
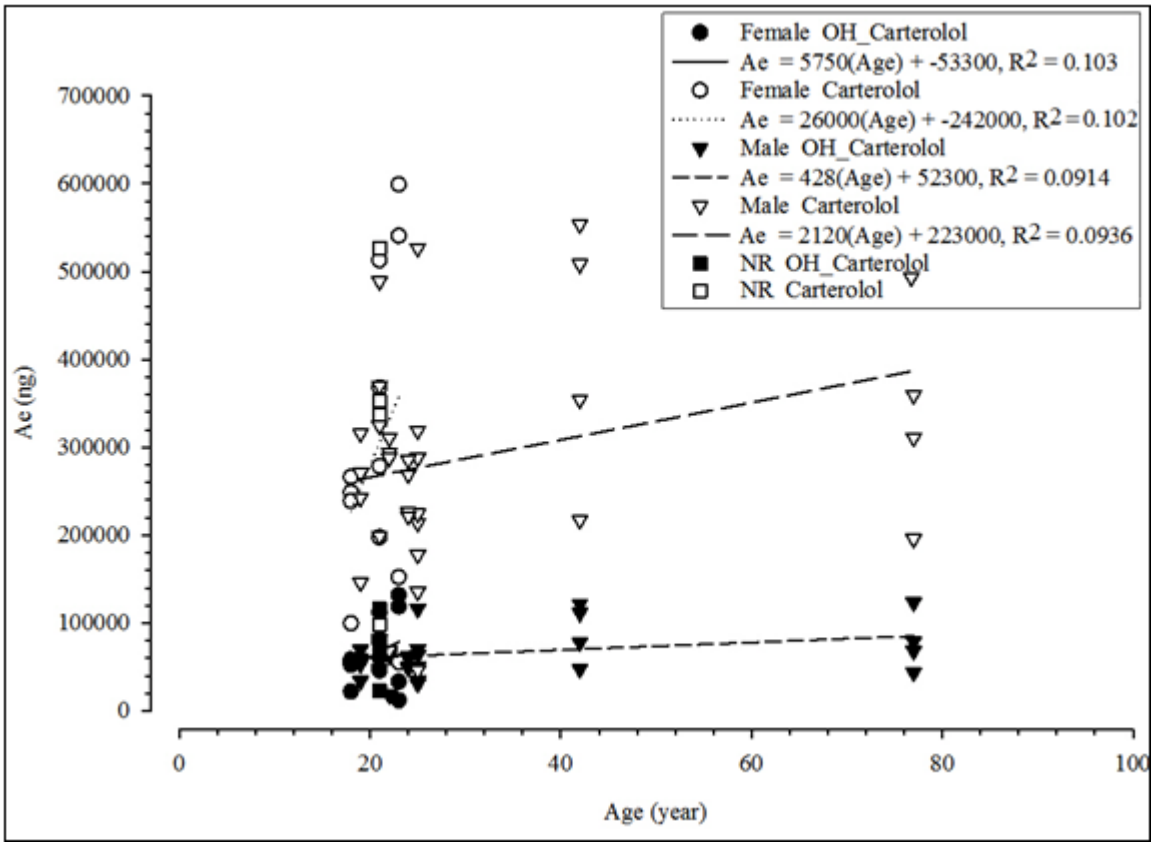


Figure 14-74. PK param. vs continuous demographic renal clearance comp.



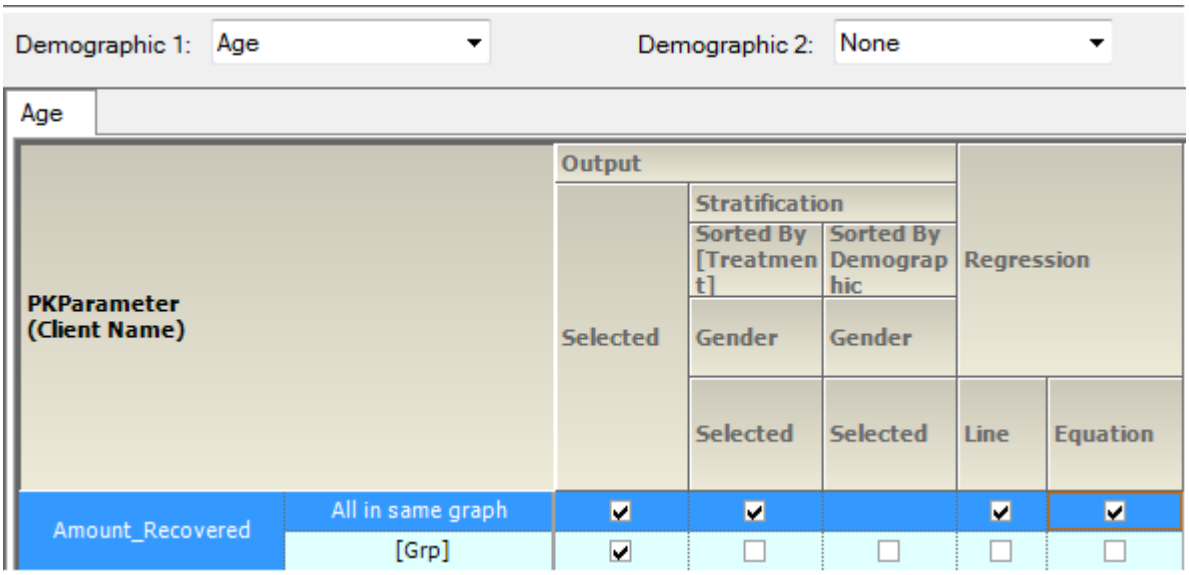
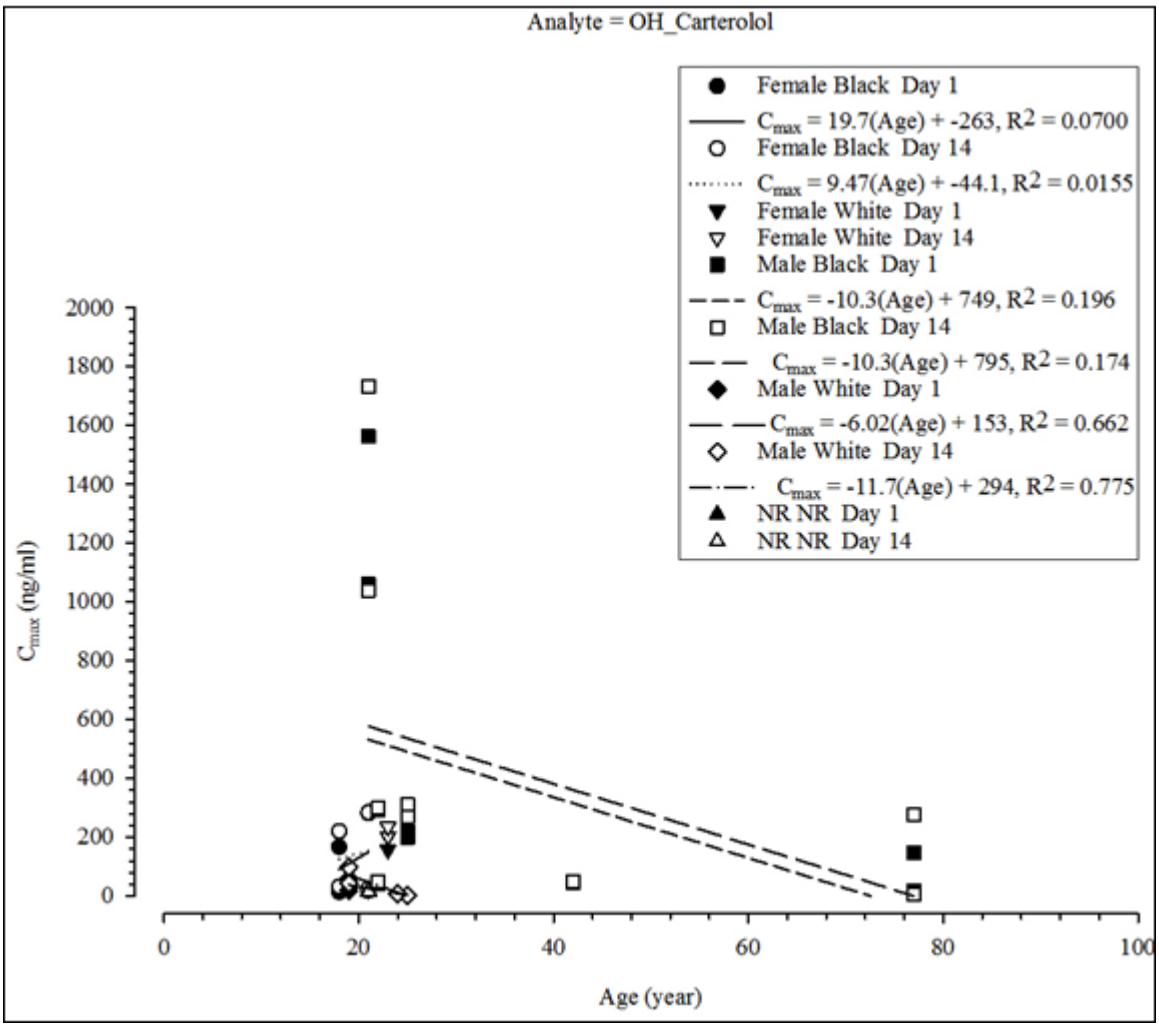


Figure 14-75. PK param. vs continuous demographic analyte comp. by treatment, sorted by treatment, and strat. by group



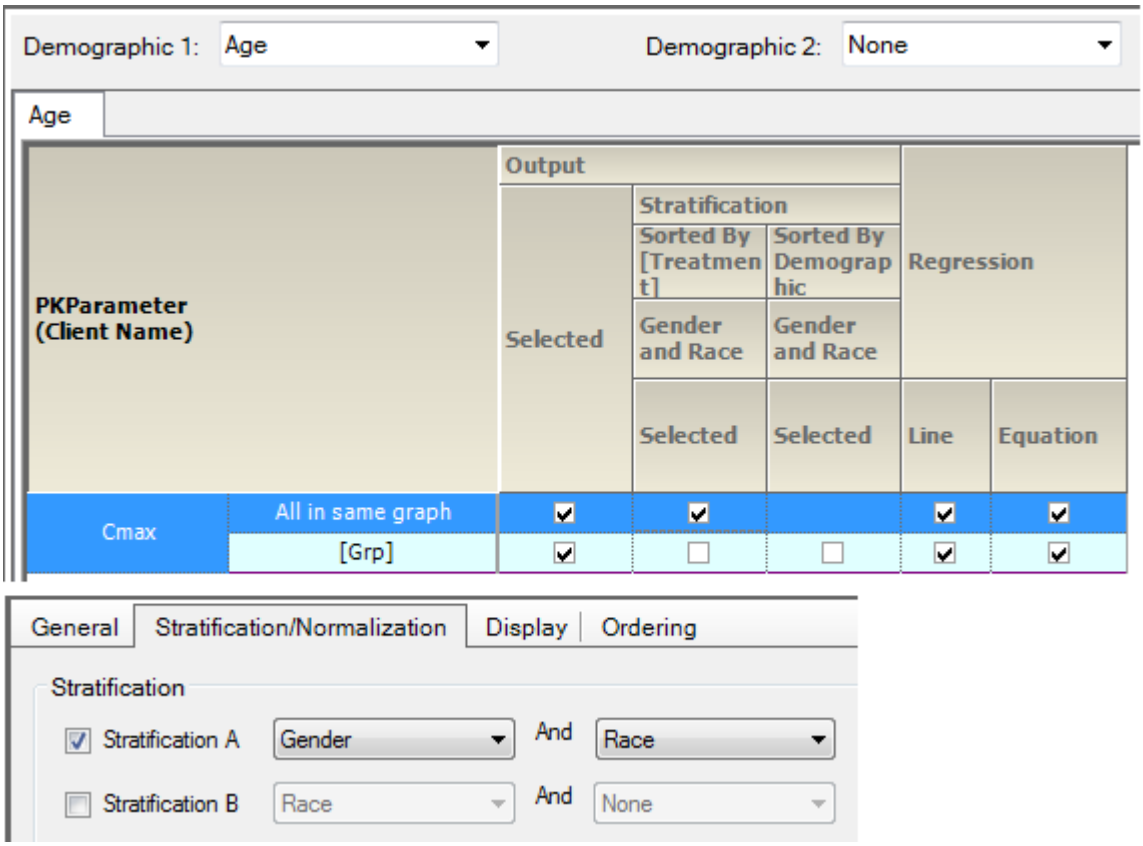
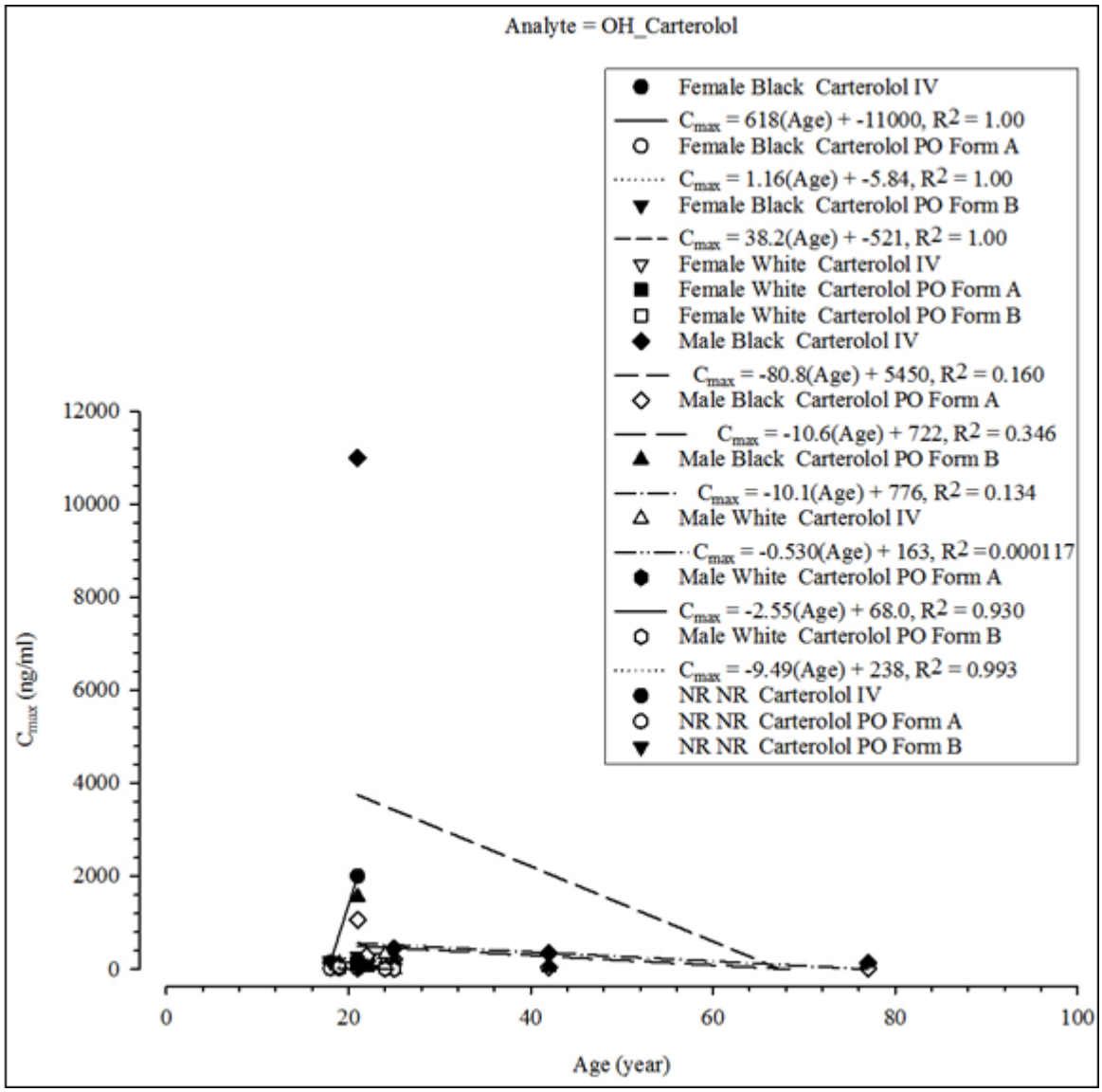


Figure 14-76. PK param. vs continuous demographic accum. comp. by treatment, sorted by treatment, and strat. by group


Analyte = OH_Carterolol
Female Black Carterolol IV
C_{max} = 618(Age) + -11000, R^2 = 1.00
Female Black Carterolol PO Form A
C_{max} = 1.16(Age) + -5.84, R^2 = 1.00
Female Black Carterolol PO Form B
C_{max} = 38.2(Age) + -521, R^2 = 1.00
Female White Carterolol IV
Female White Carterolol PO Form A
Female White Carterolol PO Form B
Male Black Carterolol IV
C_{max} = -80.8(Age) + 5450, R^2 = 0.160
Male Black Carterolol PO Form A
C_{max} = -10.6(Age) + 722, R^2 = 0.346
Male Black Carterolol PO Form B
C_{max} = -10.1(Age) + 776, R^2 = 0.134
Male White Carterolol IV
C_{max} = -0.530(Age) + 163, R^2 =0.000117
Male White Carterolol PO Form A
C_{max} = -2.55(Age) + 68.0, R^2 = 0.930
Male White Carterolol PO Form B
C_{max} = -9.49(Age) + 238, R^2 = 0.993
NR NR Carterolol IV
NR NR Carterolol PO Form A
NR NR Carterolol PO Form B
C_{max} (ng/ml)
12000
10000
8000
6000
4000
2000
0
0
20
40
60
80
100
Age (year)

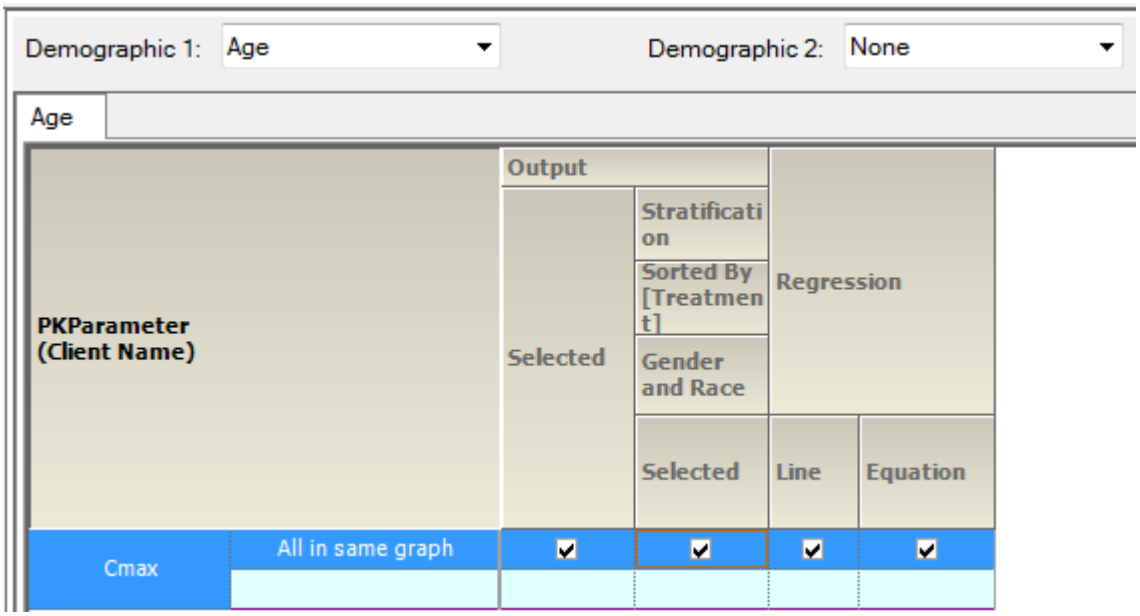
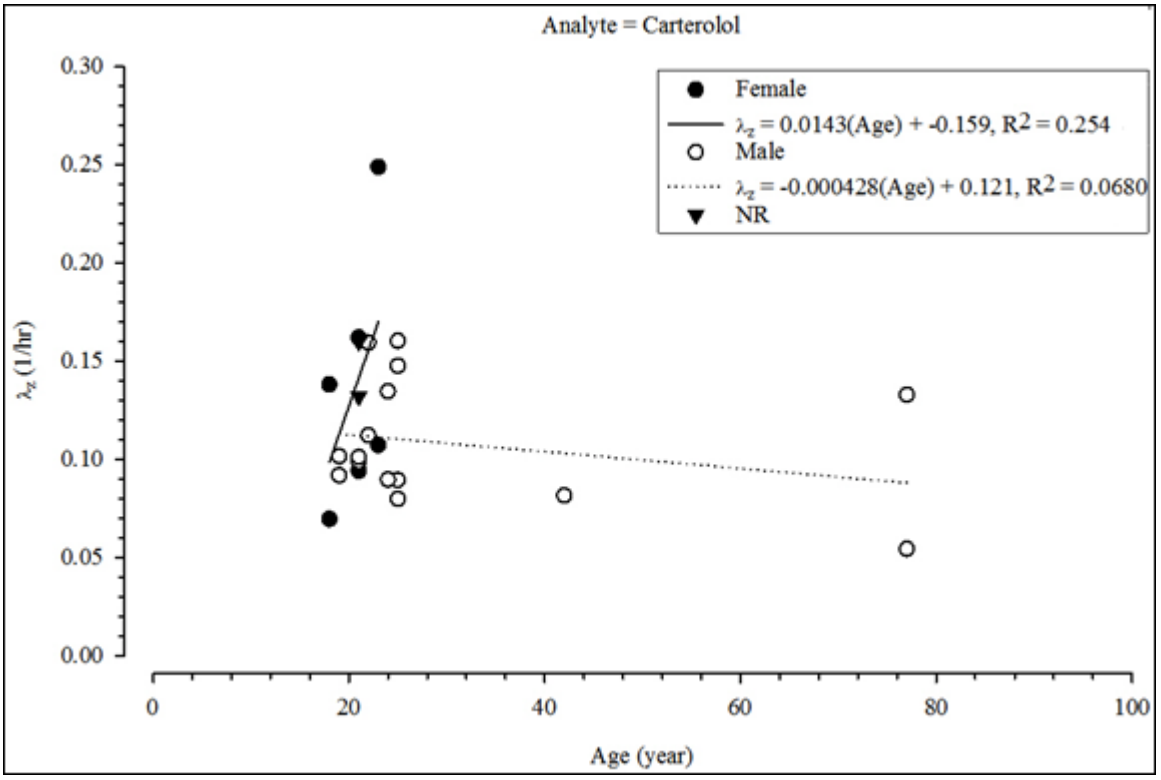


Figure 14-77. PK param. vs continuous demographic abs. bioavail. comp. by treatment, sorted by treatment, and strat. by group



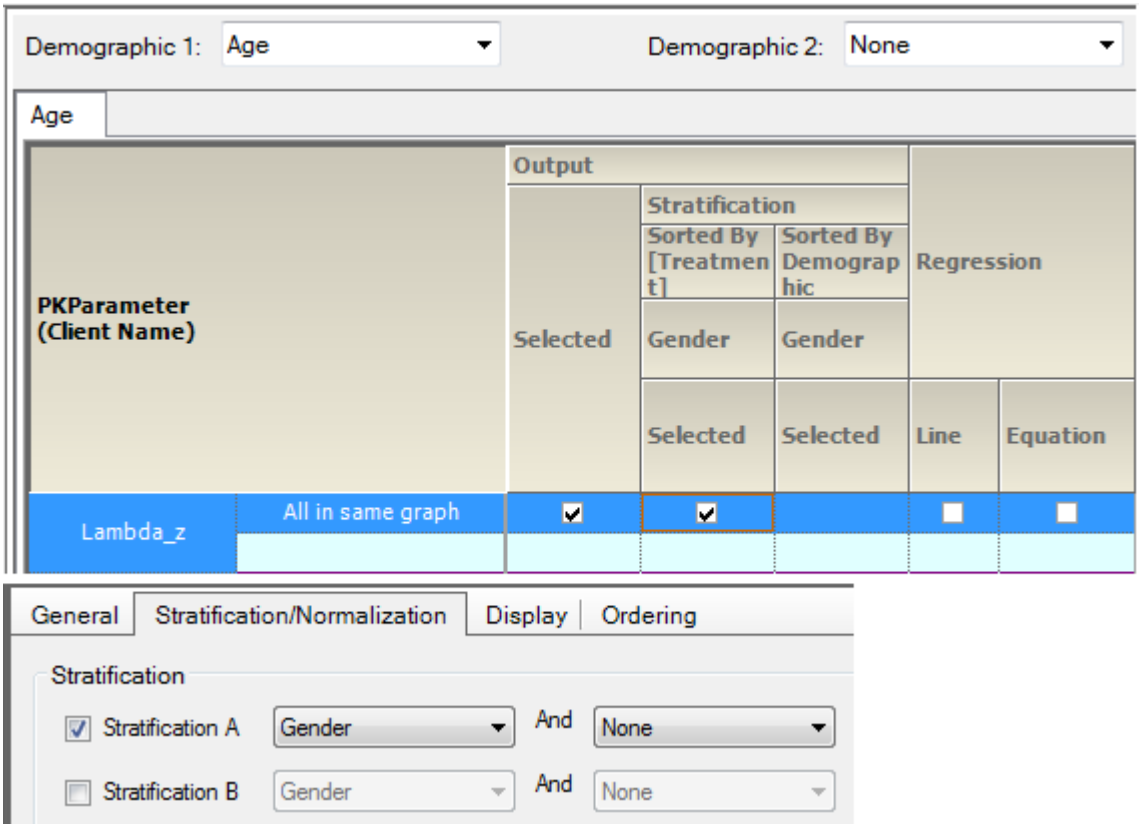
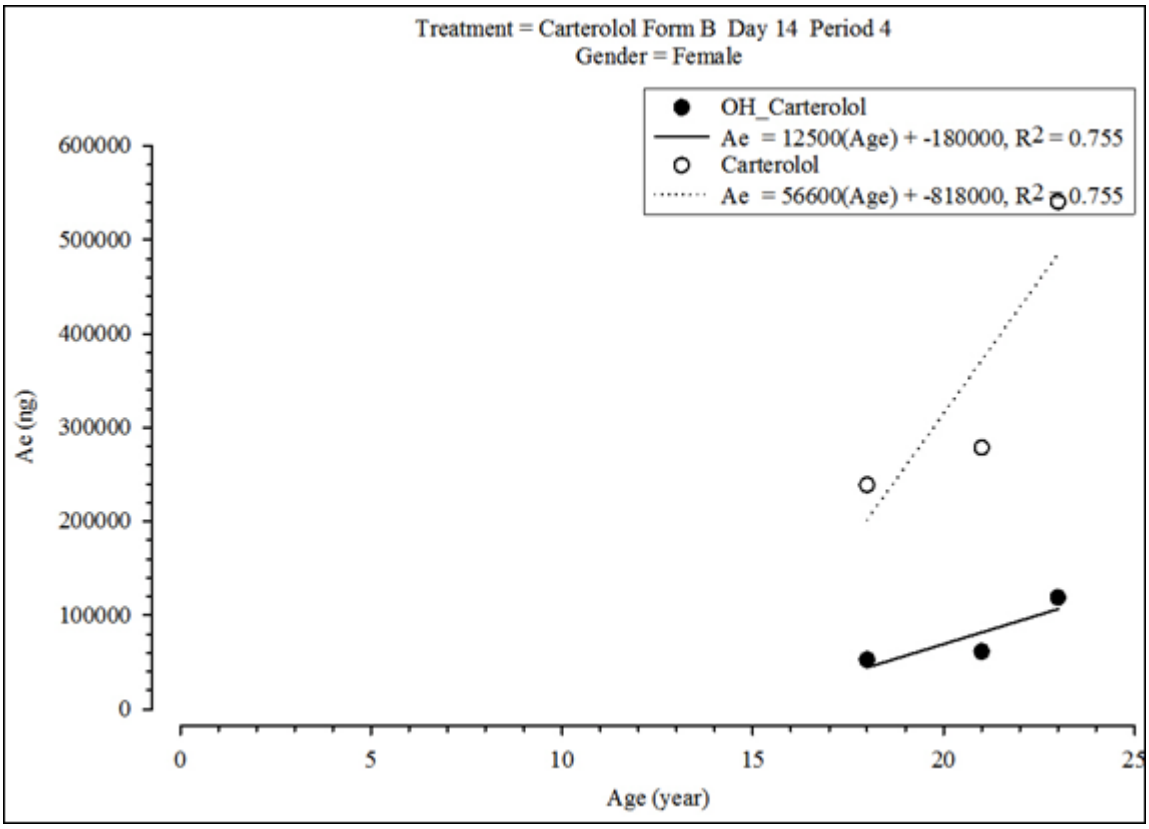


Figure 14-78. PK param. vs continuous demographic renal clearance comp. by treatment, sorted by treatment, and strat. by group



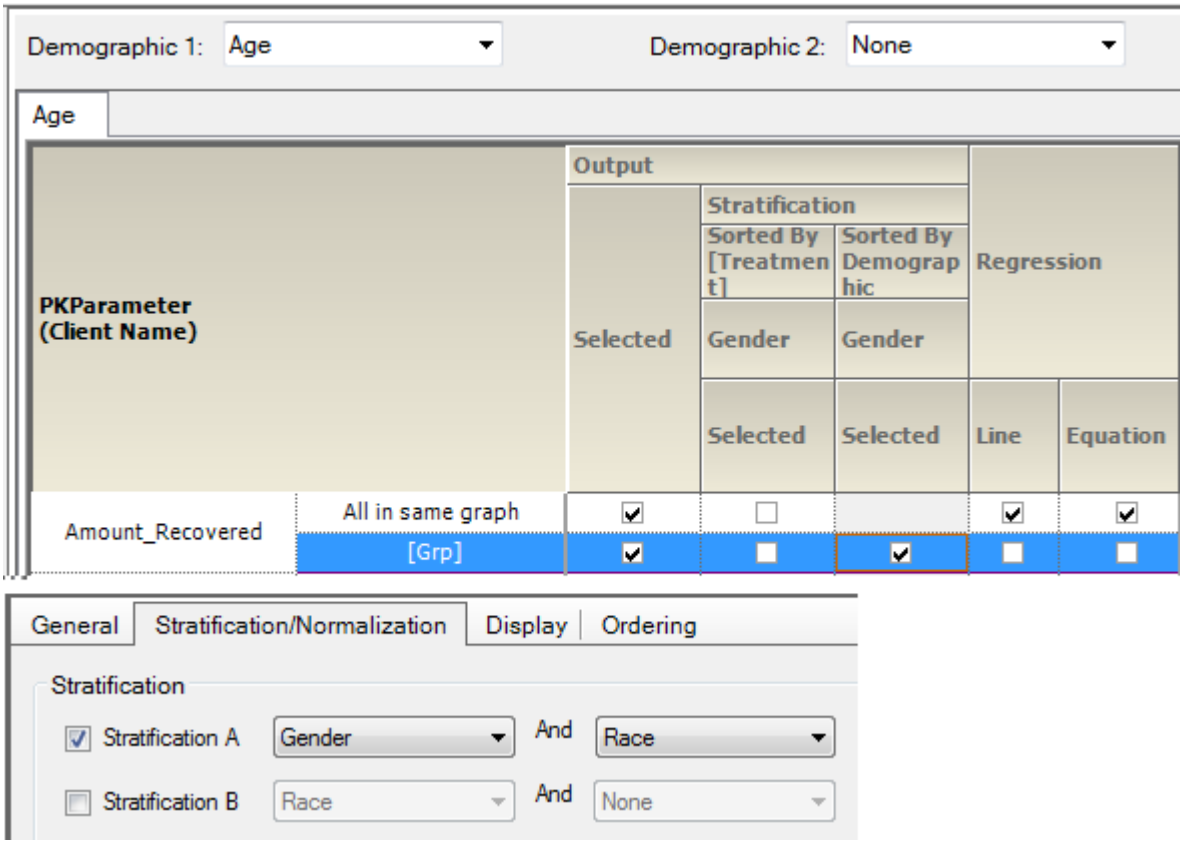
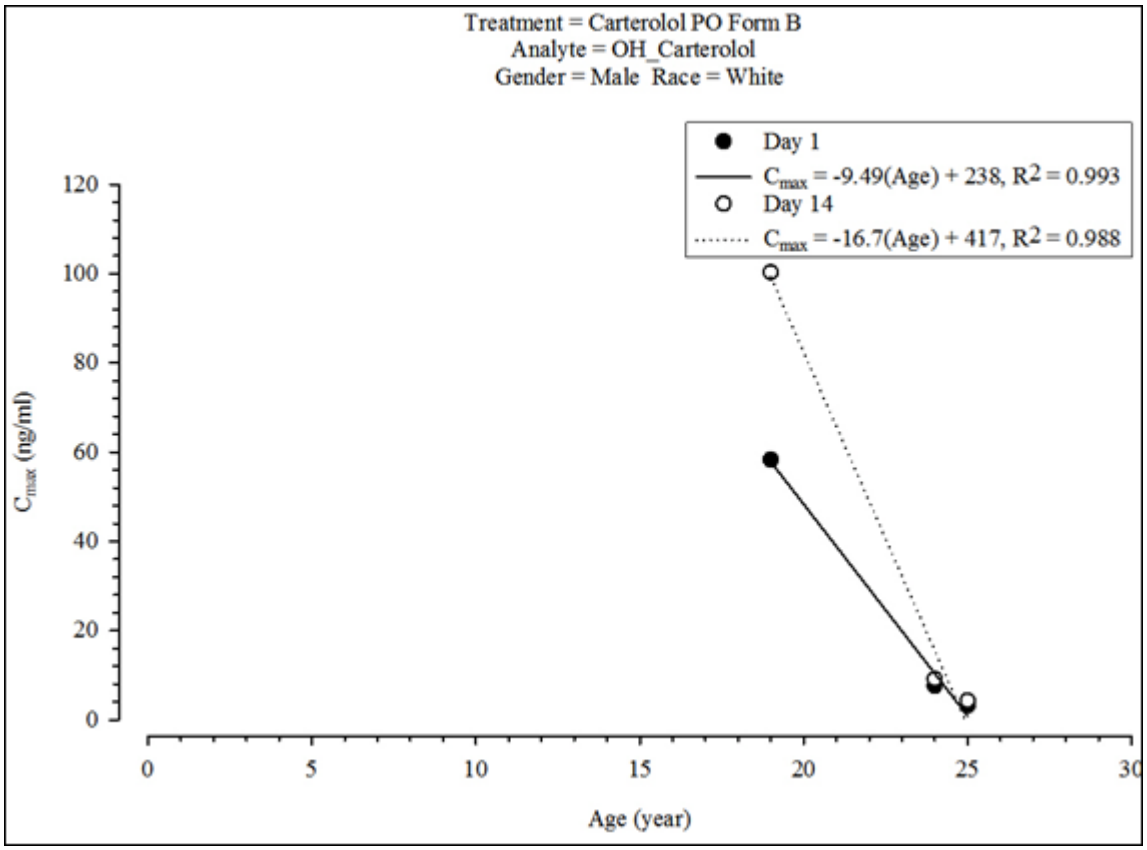


Figure 14-79. PK param. vs continuous demographic analyte comp. by treatment, sorted and strat. by group



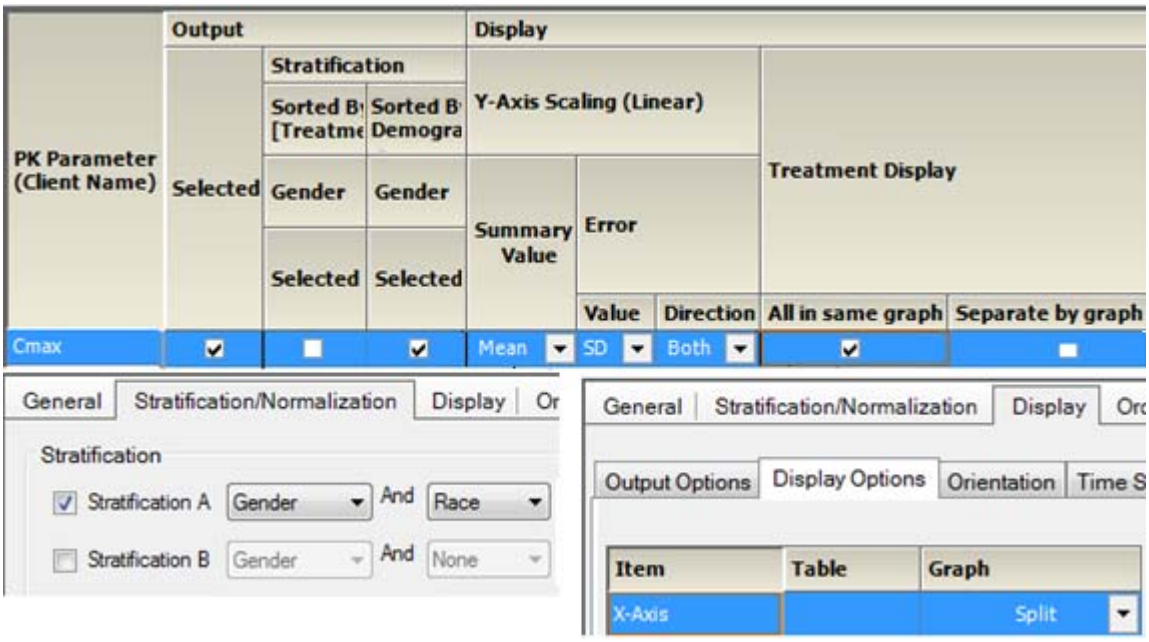


Figure 14-80. PK param. vs continuous demographic accum. comp. by treatment, sorted and strat. by group

Administration Module

Users can open the Administrator Module to configure AutoPilot Toolkit business rules and system settings for analyses, and output, including formatting. Settings made in the Administrator Module override the p shipped defaults and provide the default settings in the AutoPilot Toolkit User Module. The administrator settings are saved to an XML file, which can be shared among systems and users to standardize AutoPilot Toolkit configuration across your organization.

See “Study data variables” for a list of user- and administrator-configurable settings.

For all PK_Parameter graphs the [PK_Param] part of the filename can be changed by the administrator. The resulting filename can include only allowed characters for the Windows operating system.

To open the Admin Module

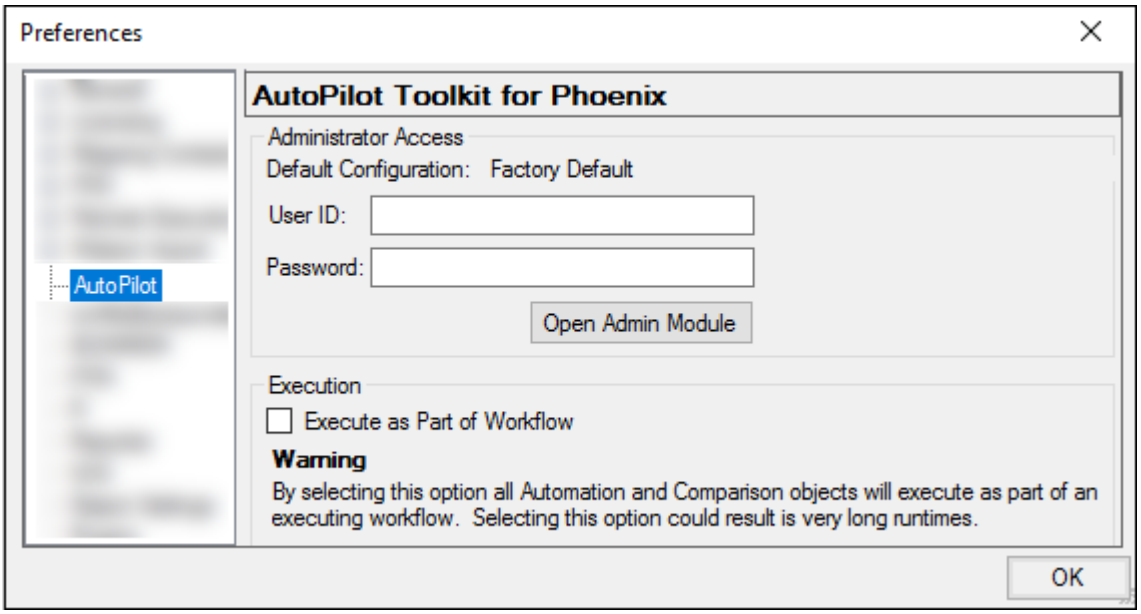


Figure 15-1. AutoPilot Toolkit administrator access

- In the **Edit** menu, select **Preferences**.
- In the list, select **AutoPilot**.
- Enter administrator user credentials in the **User ID** and **Password** fields.

  `admin` is the default user name and `Admin` is the default password. The password is case-sensitive.
- Click **Open Admin Module**.

AutoPilot Toolkit’s default system files directory is located at `C:\Users\<user name>\My Documents\APSystem\<user name>`.

This section contains the following topics:

Administrator and user settings

Some attributes in AutoPilot Toolkit are user configurable, while others are only configurable by an administrator. Configurable options range from PK parameter selection to chart and table output formats.

Strikeout effect not supported: Users can edit table and graph s for automation and comparison projects. The *Font* dialog displays a **Strikeout** effect option. The **Strikeout** effect is not supported in AutoPilot Toolkit output, so this option is not applied if it is selected.

The following lists show AutoPilot Toolkit configurable features and describe the modifications that administrators and users can make.

Input settings

Study data column nomenclature configuration (column mapping)

Admin can configure the mapping of study input column headers to system names in AutoPilot Toolkit and has ability to create new demographic variables (e.g. phenotype) and define the data type (e.g. discrete). Also can define the concentration column header potentially for matrix and analyte per the concentration variable template.
User cannot modify these settings.

Selection of study data and output location to use in an Automation or Comparison run

Only applicable with the PKS Edition of AutoPilot Toolkit, the ability to decide if PKS can be used as an input and output location.
User can select the input (load study) and output (save AutoPilot Toolkit objects created) to PKS and/or non-PKS (local) destinations through a standard browsing feature.

Analysis settings

Selection of study design

Admin – Not applicable
User can select study design type and subtype (e.g., Crossover, Randomized).

Normalizations

Admin – Not applicable
User can select PK Parameters to be normalized by continuous demographics (e.g., weight) located in the study data. The user can select up to two normalization schemes per run.

Stratifications

Admin – Not applicable
User can select output to be stratified (summarized) by discrete demographics (e.g., gender) located in the study data. The user can select up to two stratification schemes and for each scheme they can define one or two stratification variables (e.g., Gender, Gender and Smoking) per run.

Statistical analysis

Admin – Not applicable
User can select to run inferential statistics on PK Parameters during PK automation of crossover studies, using WinNonlin's LinMix BE tool.

Business rules: settings affecting all outputs

AUC % Extrapolation

Admin can configure rule regarding the display of a flag or a replacement value and associated footnote for PK parameters selected by the Admin where the AUC % extrapolation exceeds the threshold set by the user on an individual run. The Admin can also specify which parameters are affected and if the values that exceed the threshold are used for summary statistics calculations.
User can select whether to use the settings if the rule is activated by Admin and can also set the threshold value (e.g., 30%).

Display of source data

Admin can set the default to display information in the form of a footnote regarding the source data (study file) in tables or graphs.
User can decide to apply the source data footnotes per tables and graphs independently per run and what parts of the source information are displayed (location, path, time and date).

Exclusion

Admin can allow for exclusions and set how exclusions are displayed in final tables and figures, including corresponding footnotes.
If Admin enables exclusions, **User** can define the exclusion on a profile-by-profile basis. User can also define if corresponding graphs and tables created reflect the excluded profiles.

Display order

Admin – Not applicable
User can decide the order of the treatment identifiers (e.g. treatment, day, etc.) that are displayed in intext tables (top to bottom) and X-axis for categorical graphs (left to right).

Matrix mapping

Admin can configure through addition or deletion matrix abbreviations and map to the concentration column headers to encompass full matrix names into the final tables and graphs. For example, PLS in the concentration column would equate to 'Plasma' in the final output.
User cannot modify these settings.

Concentration variable used for concentration final output

Admin can set the default of which concentration column in the study data to use in the creation of the concentration tables and graphs independently.
User can select which concentration column in the study data to use in creation of the concentration tables and graphs independently.

Business rules: table settings

Table splitting

Allows splitting of tables if they won't fit on one page per page type and in margins set in the Administration module. **Admin** can enable or disable the table splitting feature for Users.
If Admin enables table splitting, **User** can activate/deactivate it per run.

Context-sensitive footnotes-display-calculation of non-numeric values for descriptive statistics

Allows definition/modification via addition or deletion of the default list of non-numeric values (e.g., NS) and associated footnotes (NS: No Sample). In addition, **Admin** can configure how

these non-numeric values are handled during descriptive statistics calculations (missing or zero).
User cannot modify these settings.

Intext table template

Admin can configure the style, including number of descriptive statistics and define if PK parameters are time-dependent. Also, can default the specific descriptive statistics.
User can modify the selection of summary statistics (Mean, SD, etc.), but cannot modify the style nor PK parameters assigned to time-dependent.

Display of different sample sizes in intext tables

Admin can configure a rule that displays if there are differences in sample size used to calculate summary statistics for PK parameters via flags and corresponding footnotes.
User cannot modify these settings.

Calculation/display of summary statistics for small sample sizes

Admin can configure rule that allows the values of summary statistics involved with small sample sizes (1–3) to be overwritten by text values and apply corresponding footnotes (e.g., NC – Not calculated, sample size is too small).
User cannot modify these settings.

Significance level is displayed in statistics tables

Admin can configure a threshold for the display of p-values (e.g., 0.05), along with a corresponding footnote to be displayed or replaced by non-numeric text if the value is lower than the threshold.
User cannot modify these settings.

Summary statistics based on % threshold

Admin can configure a rule to set a minimum percentage of values relative to total sample size that must exist in a profile before calculations are performed.
User cannot modify these settings.

Individual values of zero treated as "missing"

Admin can configure a rule that allows values of 0 to be treated as Missing prior to any summary statistic calculation.
User cannot modify these settings.

LOQ replacement and display

Admin can configure a rule that allows replacement of numerical values with text values and corresponding footnotes if value is less than the threshold set by the user per run (value of 0.01 is replaced with BQL). Also can configure which PK parameters are governed by this rule.
User can decide whether to use the rule and set the replacement threshold that is used.

Time deviations calculation, flags, and footnotes

Allows **Admin** to select how the time deviation is calculated and how time deviation is displayed (threshold, footnote, and footnote flag)
User cannot modify these settings.

Display of missing references

Admin can configure the display, including value and corresponding footnote, for 'missing' values for the following table types, time-concentration, demographics, all others.
User cannot modify these settings.

Relative nominal time replacement

Admin can apply the rule and configure the associated footnote that if relative nominal times are used instead of relative actual times, each concentration value is flagged in the time-concentration tables and has an associated footnote assigned.
User cannot modify these settings.

Display analyte, matrix, and day

Admin can independently select as a default for the Matrix (e.g., Plasma), Analyte (e.g. Parent), and Day (e.g., Day 1) to be displayed in the final table as headers.
User can independently select for the Matrix (e.g., Plasma), Analyte (e.g., Parent), and Day (e.g., Day 1) to be displayed in the final table as headers.

Formatted output: table settings

Selection of tables

Admin can determine which tables are available for the user and from this list initially create the default list of available tables.
From the list of available tables as set by Admin, **User** can determine which of these tables are actually generated per run, i.e., User can modify the default list set by Admin.

Selection of variables for tables

For each table, **Admin** can determine which variables are available for inclusion, along with their order. From the list of available variables, Admin determines which variables are actually included and their default ordering in the generated table.
From the list of available table variables based on the Admin settings, **User** can determine which of these variables are actually included in the table and their order per run, i.e., User can change the defaults that were set by Admin.

Summary statistics

Admin can determine which summary statistics are available to be included in the table along with their order. From the list of available statistics, Admin determines which statistics are actually included and their default ordering in the generated tables.
From the list of available summary statistics based on the Admin settings, **User** can determine which of these summary statistics are actually included in the table and their order per run, i.e., User can change the defaults that were set by Admin.

Precision

Admin can set the defaults for the precision of variables and summary statistic values.
User can modify the Admin defaults for precision per variable. Precision choices include number of decimal places, significant figures, or special significant figures.

If **SpecialSignificant** is selected and the number of digits before the decimal is more than or equal to the number of significant digits specified, the result is the value before the decimal. Otherwise, the traditional significant rule is applied to the value.

Formatting

Tables are considered to be constructed from basic elements such as Header, Body, Footnotes, Variable Names, Variable Values, etc. **Admin** can set the font, font style, font size, alignment, and underline/no underline for these elements. In addition the thickness of separation lines (e.g., between the header and body of a table) can be set and grid lines can be switched on and off. Output settings such as paper size (US Letter vs. A4) and orientation (portrait vs. landscape) can be configured and set as defaults per table type.
User cannot modify most of the formatting options for tables. The exceptions are the settings for output setting, which can be user-modified for a specific run.

Business rules: graph settings

Time-Scale factors set on a per time scale range basis

Admin can configure time scale factors independently for each time scale range, to define the number of major ticks based on minutes, hours, days, and weeks for time-concentration graphs. Admin can also configure if all concentration graphs have the same scaling and ticks independently for the X- and Y-axis.
User can make changes for individual runs.

Display analyte, matrix, and day

Admin can default to have independently the Matrix (e.g., Plasma), Analyte (e.g., Parent), and Day (e.g., Day 1) be displayed in the final graph as labels.
User can independently have the Matrix (e.g., Plasma), Analyte (e.g., Parent), and Day (e.g., Day 1) be displayed in the final graph as labels.

X-Axis format for categorical graphs

Admin can default if categorical graphs have split or offset display for the X-axis.
User can select if categorical graphs in a run have split or offset display for the X-axis.

Axis starting points

Admin can default independently to either force the X-axis and/or Y-axis to start from zero or not.
User cannot modify these settings.

Formatted output: settings affecting all output

Variable and PK parameter nomenclature (mapping)

Admin can configure the display name to be used in the final output created by AutoPilot Toolkit for variables (e.g., gender) and PK parameters (e.g., AUCinf). Also, Admin can configure the name of the PK parameter graph filenames.
User cannot modify these settings.

PK parameter selection

The configuration settings file does not retain the PK Parameter settings that are changed by the Administrator.
User cannot modify which PK parameters are available, but can assign per table which PK parameters are displayed in the output.

Descriptive statistics selection

Admin can configure which descriptive statistics are available to the user for the overall system.
User cannot modify which descriptive statistics are available, but can assign per table which PK parameters are displayed in the output.

Precision selection

Admin can configure the precision per variable for the overall system.
User can modify these precision per output and run.

Formatted output: graph settings

Selection of graphs

Admin can determine which graphs are available and from this list initially create the default list of available graphs.
From the list of available graphs as determined by Admin, **User** can determine which of these graphs are actually generated per run, i.e., User can modify Admin default for generated graphs.

Output details

Admin can determine default values for output details on the graphs that are generated. Depending on graph type, these details can include:
Creation of lin and/or log Y-axis
Display of a summary value such as mean or median
Display of an error value such as Standard Deviation or Standard Error
Display of up and/or down error bars
Display of regression line (for PK Parameters)
Display of LOQ lines (for PK Parameters)

User can modify all of the output details on a per-run basis.

Formatting

Admin can determine the following formatting options for graphs:
Print options such as orientation, paper size and margins
Text elements of a graph such as title, legend, and labels can be activated or deactivated, the format (font, font style, font size)
Legend position (note that center or left alignment may not work for a legend, in which case the default of upper-right is used)
Line elements of a graph such as error bars, axis line, tick lines, etc.

Grid lines and line thickness have not yet been implemented.
On occasion, the individual plot of the first subject may not display the same font as what is set here, whereas the remaining plots use the specified font.

User cannot modify most of the options for the formatting of graphs. An exception is the print orientation (portrait vs. landscape).

Formatted output: text and appendix settings

Selection

Admin can determine which text items are available for the user and from this list initially create the default of available text items.
From the list of available text items as determined by admin, **User** can determine which items are actually generated per run, i.e., User can modify the Admin default for generated text output.

Formatting

Admin can set the defaults for orientation, paper size, and margins and select the order and layout options for the graphs that are included in the text document that incorporates all the individual time-concentration, excretion rate, and percent dose remaining graphs.
User can modify all of the Admin formatting settings on a per-run basis.

General settings

The following options are available under the General Settings node. You can override any parameters set under this node for individual tables or graphs found under the applicable node, such as PK Automation or PK Comparison. For example, the administrator can select to allow the user access to specific parameters for specific types of studies. For a specific example, see “Selecting content for generated output”.

PK parameters

On the Available to User tab, the administrator determines which PK parameters are available to the user for inclusion in generated output on a model-specific basis. If you clear a parameter checkbox on

this page, then it is also unavailable for individual selection under the PK Automation node, when selecting details on tabular and graphical output.

	PK Parameters	Model 200 Extravascular		Model 201 IV Bolus		Model 202 IV Infusion		Model 210-212 Urine	Compar
		SD	MD	SD	MD	SD	MD		
1	Rsq	☑	☑	☑	☑	☑	☑		
2	Rsq_adjusted	☑	☑	☑	☑	☑	☑		
3	Corr_XY	☑	☑	☑	☑	☑	☑		
4	No_points_lambda_z	☑	☑	☑	☑	☑	☑		
5	Lambda_z	☑	☑	☑	☑	☑	☑		
6	Lambda_z_lower	☑	☑	☑	☑	☑	☑		
7	Lambda_z_upper	☑	☑	☑	☑	☑	☑		
8	HL_Lambda_z	☑	☑	☑	☑	☑	☑		
9	Tlag	☑	☑						

Figure 15-2. Available to User tab

On the User Default Selection tab, the administrator determines whether a PK parameter is included in all of the generated output by default. The user can then choose to not include a given parameter on a per-run basis.

Variable data

An administrator can configure variables and their associated descriptive statistics and precision.

Variables tab

Using the Variables tabs, an administrator can determine which demographic and data collection points (DCP) are available to users and which are selected by default in the AP Automation object. An administrator can define discrete demographics which are used in stratifications, continuous demographics, which are used in normalizations, or sample collection points.

- With the Category set to **Discrete Demographics** or **Continuous Demographics**, click **Edit Master List** to add or remove custom demographic variables.

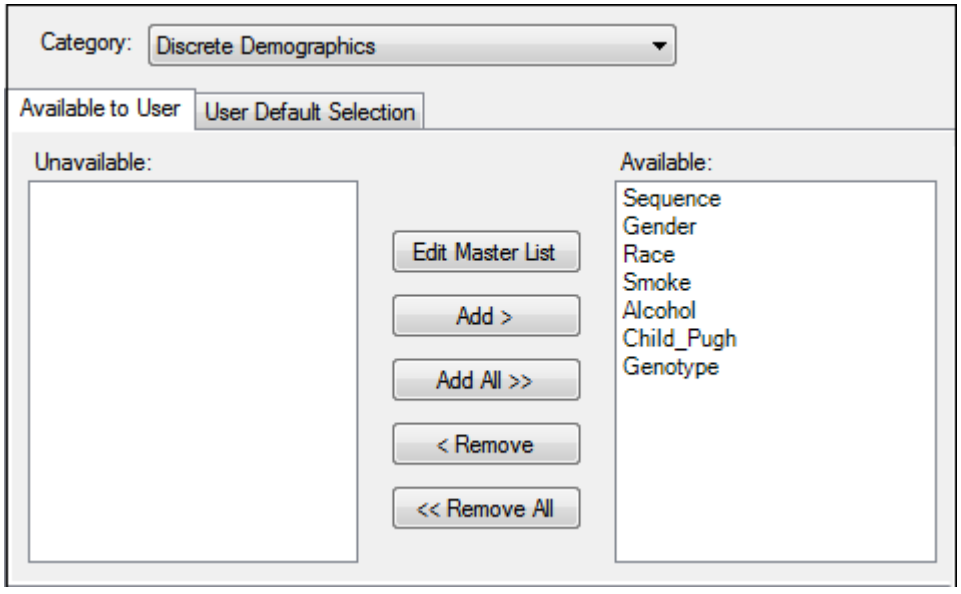


Figure 15-3. Variables tab

- In the dialog, click **Add** to add custom System and Client Name variables.

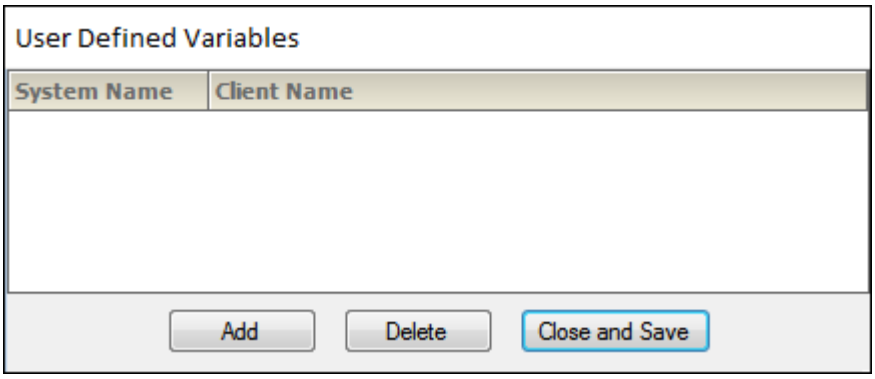


Figure 15-4. User Defined Variables dialog

- Click **Delete** to remove a demographic variable, and click **Close and Save** to add the new demographic variable.

Statistics tab

Using the Statistics tabs, an administrator can determine which statistical variables along with their order of display in worksheet output are available to the user and which are included by default. Statistical variables are available for all study variables and PK parameters.

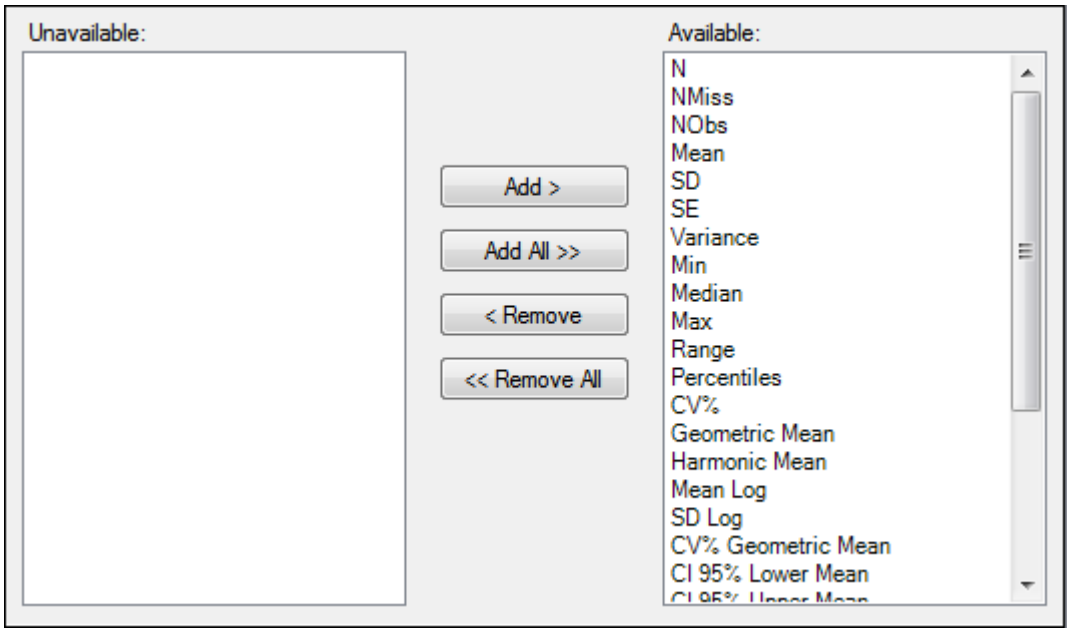
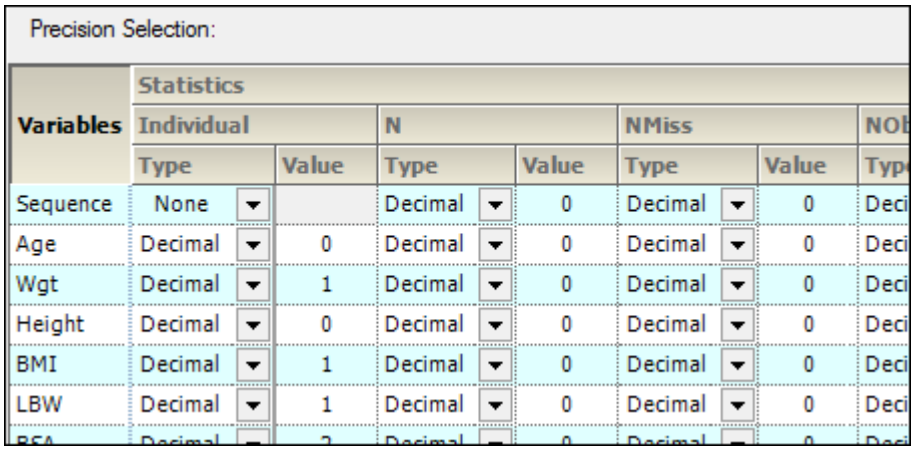


Figure 15-5. Statistics tab

Precision tab

Using the Precision tab, an administrator can set the precision type, decimal or significant digits, and the corresponding value for each variable and statistic combination.


Precision Selection:

Variables	Statistics						
	Individual		N		NMiss		NOE
	Type	Value	Type	Value	Type	Value	Type
Sequence	None		Decimal	0	Decimal	0	Deci
Age	Decimal	0	Decimal	0	Decimal	0	Deci
Wgt	Decimal	1	Decimal	0	Decimal	0	Deci
Height	Decimal	0	Decimal	0	Decimal	0	Deci
BMI	Decimal	1	Decimal	0	Decimal	0	Deci
LBW	Decimal	1	Decimal	0	Decimal	0	Deci
BSA	Decimal	2	Decimal	0	Decimal	0	Deci

Figure 15-6. Precision tab

Column mapping

An administrator can use column mapping to apply an organization's settings regarding input or study data and output nomenclature for PK parameters by using the Study Variables tab, PK Parameters tab, Concentration Variable Template Selection tab, and Time Variables tab.

Study Variables tab

In the Study Variables tab, an administrator can change the default names in AutoPilot Toolkit, which are called System names, to match what is used in the study data, or the Client name. The Plasma and Urine Display Names show how the variables are displayed in the AP Automation output. The Display names are independent of both System names and Client names and can be changed at any time. To support stacked datasets a new column called Analyte is included in the Study Variables tab.

Note: The Plasma and Urine Display Names for Treatment_Description cannot be changed because they are not used in the output. The Display Names for Treatment_Display are used instead.

Treatment_Description and Treatment_Display

AutoPilot Toolkit's default behavior requires the use of a Treatment_Description column in datasets as a sort variable for crossover studies. Treatment_Description in AutoPilot Toolkit can be mapped to whatever column in a dataset that contains treatment information.

Some datasets use a treatment information column that solely contains alphanumeric values (1, 2, A, or B, for example) that are used as sort variables in a model, and a treatment display column that is used to display meaningful treatment information in table and graph output.

AutoPilot Toolkit provides a study variable, **Treatment_Display**, that allows for meaningful treatment descriptions in table and graph output instead of simply 1, 2, A, or B.

The treatment display order is displayed in the Treatments tab in the AP Automation object's Ordering tab. The Treatment Description values are matched to the corresponding Treatment Display values. There must be a one to one correspondence between the Treatment_Description and Treatment_Display values.

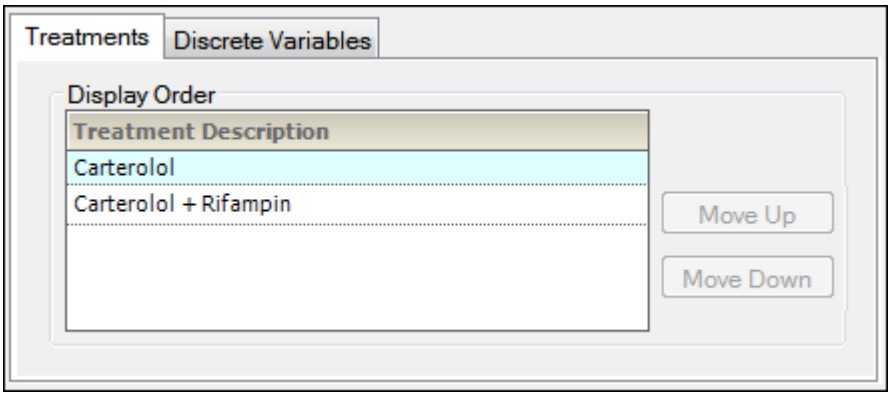


Figure 15-7. Default treatment order

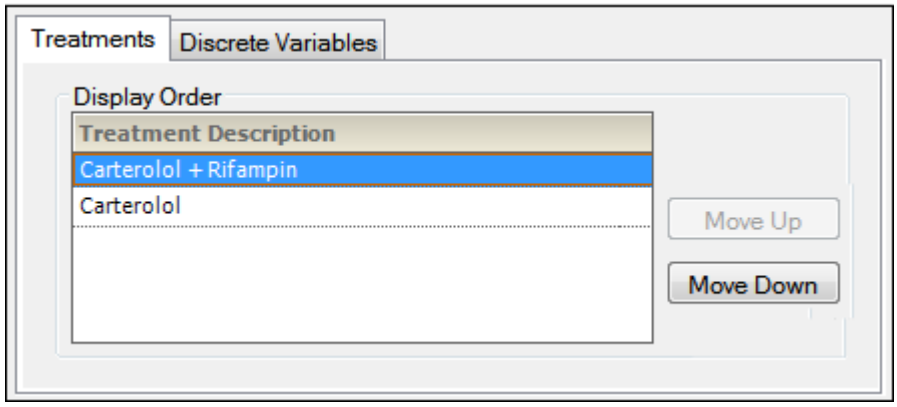


Figure 15-8. Custom treatment order

If a user wants to use a custom treatment display, an administrator must change the treatment sort variable from its default setting to a custom setting. If a dataset contains Treatment and Treatment_-Description columns, and a user wants to set Treatment as the NCA model's sort variable and include Treatment_Description in the output, an administrator must make the following changes:

- Open the Admin Module.
- In the Admin Module menu, select **Config > General > Column Mapping**.
- Select the **Treatment_Description Client Name** field. Change the Client Name to `Treatment`.

  The System Name Treatment_Display is mapped to Treatment_Description by default.
- If needed, change the default mapping by selecting the **Treatment_Display Client Name** field. Change the Client Name to the treatment description variable in the input dataset.

Note: Treatment_Display can be mapped to any column in a dataset.

- Click  to save the custom System Config file.

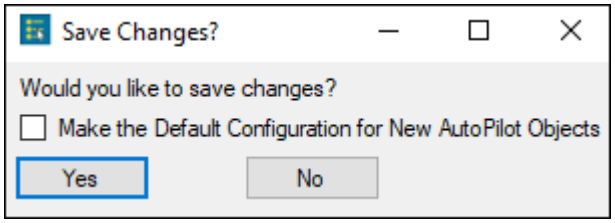


Figure 15-9. Save Changes? dialog

- To make this configuration the default one, select the **Make Default Configuration** checkbox in the *Save Changes?* dialog.
- Click **Yes** to save the system configuration file.

To load a custom configuration file in the Admin Module

- Open the Admin Module.
- Click  to select a custom configuration file.

Users can only load a custom configuration file before mapping an input dataset to the AP Automation object.

- Select the **Use Custom Configuration** option button in the General tab.
- Click the **[…]** button to browse to the custom system configuration file.
- Select the file in the *Select System Configuration* dialog and click **Open**.
- Click **Set as Default** to set the custom configuration as the default configuration.

	System Name	Client Name	Plasma Display Name	Urine Display Name
15	Gender	Gender	Gender	Gender
16	Sequence	Sequence	Sequence	Sequence
17	Dose	Dose	Dose	Dose
18	Treatment_Description	TreatmentDescription	Treatment	Treatment
19	Period	Period	Period	Period
20	Day	Day	Day	Day
21	Treatment_Display	Treatment_Description	Treatment	Treatment
22	Analyte	Analyte	Analyte	Analyte
23	LOQ	LOQ	LOQ	LOQ
24	Relative_Nominal_Time	*Relative_Nominal_Time*	Nominal Time	Nominal Time

Figure 15-10. Default study variables

Study Variables | PK Parameters | Concentration Variable Template Selection | Time Variables

	System Name	Client Name	Plasma Display Name	Urine Display Name
15	Gender	Gender	Gender	Gender
16	Sequence	Sequence	Sequence	Sequence
17	Dose	Dose	Dose	Dose
18	Treatment_Description	TreatmentDescription	Treatment	Treatment
19	Period	Period	Period	Period
20	Day	Day	Day	Day
21	Treatment_Display	Treatment_Display	Treatment	Treatment
22	Analyte	Analyte	Analyte	Analyte
23	LOQ	LOQ	LOQ	LOQ
24	Relative_Nominal_Time	*Relative_Nominal_Time*	Nominal Time	Nominal Time

Figure 15-11. Custom study variables

Note: If Treatment_Display is not in the dataset, AutoPilot Toolkit displays a warning and defaults to the Client Name that Treatment_Description is mapped to. Users can either fix the problem or proceed with the project.

Note: If the Treatment and Treatment_Display columns do not match with unique values, AutoPilot Toolkit gives an error message and does not allow the user to proceed with the project until the problem is fixed.

LOQ study variable

While LOQ numbers can be set on a run-by-run basis, AutoPilot Toolkit can also be configured to read LOQ values from a data column by mapping the LOQ system name to the correct column.

For wide data, a cell in the LOQ column can be empty or contain a value. However, the LOQ value must be the same for all concentration variables that use the column. For example, wide data can contain an LOQ column with empty cells and cells with a value of 0.05.

For data stacked by analyte, a different LOQ value can be set for each analyte. The value for LOQ must be the same across a single analyte. For example, the following table depicts data stacked by analyte for three analytes.

Analyte	Time	LOQ
Alpha	0	
Alpha	2	
Alpha	4	
Alpha	8	
Alpha	16	
Beta	0	0.05
Beta	2	0.05
Beta	4	
Beta	8	
Beta	16	
Gamma	0	0.05
Gamma	2	
Gamma	4	0.08
Gamma	8	
Gamma	16	

Figure 15-12. Example of data stacked by analyte

In this case, the Alpha analyte will have no LOQ, the Beta analyte will have an LOQ of 0.05, and the Gamma analyte will have no LOQ: if different LOQ values are entered for the same analyte, they are all ignored.

- To use LOQ values from the data columns, select the Output Options tab in the AP Automation object.

For more information see “Display tabs”.

PK Parameters tab

In the PK Parameters tab, an administrator can set the display name, which is used in the final generated output, and the file name, which determines the root name of the graph output file for a specific parameter (`AUClast.jpg`, for example). The display name can have superscripts, subscripts, and some symbols.

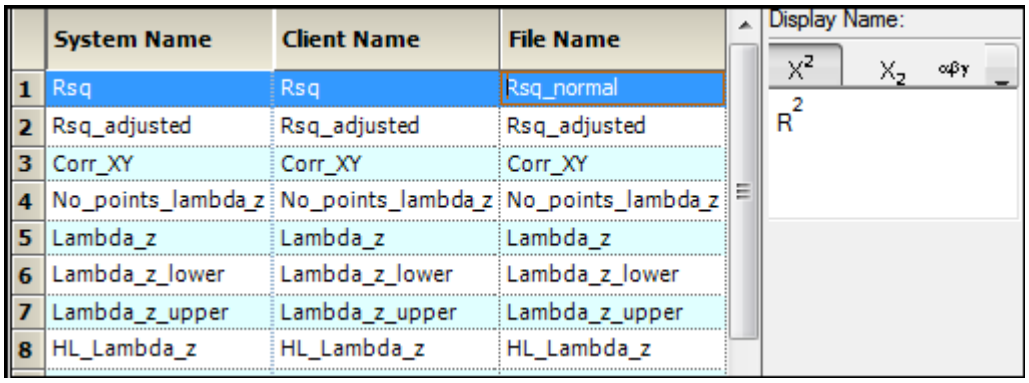


Figure 15-13. PK Parameters tab

To set the file name

- Select a parameter in the File Name column.
- Change the file name.

To set the display name

- Select a PK Parameter.

  The parameter is displayed in the Display Name area.
- Modify the parameter display name by clicking the **Superscript** or **Subscript** button.
- Add a symbol to the parameter display name by selecting one in the **Symbols** menu.

Concentration Variable Template Selection tab

On the Concentration Variable Template Selection tab, administrators can set the mapping for the Concentration Variable column by using the pointer to drag the matrix [M], analyte [A], route [R], and asterisk [*] symbols from the Palette to the Template, or by typing a base name in the Base Name field.

Note: In order to support a greater variety of concentration columns, the concentration variable template now contains an asterisk [*] as a wildcard field.

As shown below, no route is selected and the base name is Conc, so the column name is defined by the template [Matrix]_[Analyte]_*Conc*.

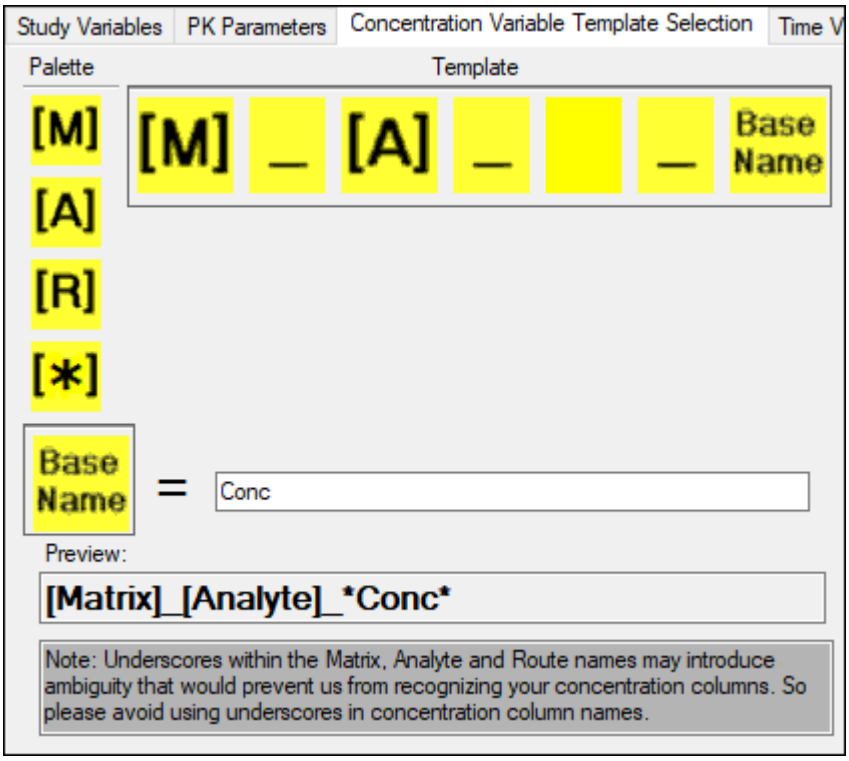


Figure 15-14. Default Concentration Variable Template Selection tab

Concentration variable template using an asterisk

Some concentration column names in datasets that must be supported by AutoPilot Toolkit have components set off by underscores that are neither analytes, matrices, routes, or base names. For example, Concentration_1, Concentration_2, and Concentration_3. or the name of the compound being tested. To handle a greater variety of concentration columns, the concentration variable template recognizes a wildcard field with an asterisk [*].

For example, if the concentration column name is PLS_XYZ_PKConc, use the following steps to change the concentration variable template:

- Use the pointer to drag [A] (analyte) from the Template to the Palette.
- Use the pointer to drag [*] (asterisk) from the Palette to the Template to allow AutoPilot Toolkit to bypass the XYZ part of the name.

The column name PLS_XYZ_PKConc is defined by the template [Matrix]_[*]_*Conc*.

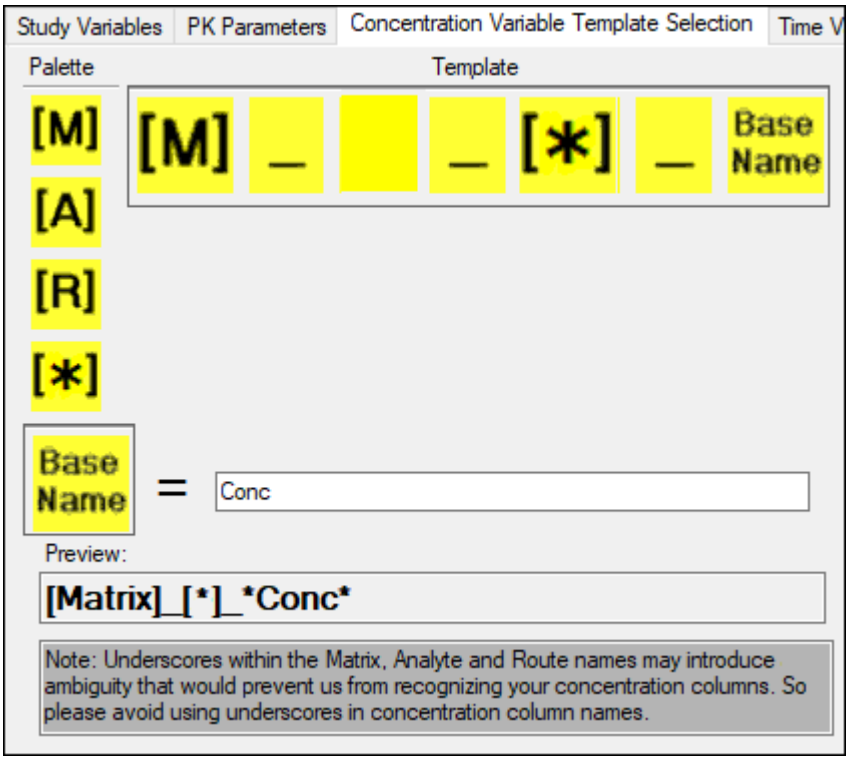


Figure 15-15. Concentration Variable Template using asterisk

Concentration variable template selection for stacked data

To use stacked data, use the pointer to drag [A] (analyte) to the Pallet. The column name is defined by the template [Matrix]_ *Conc*.

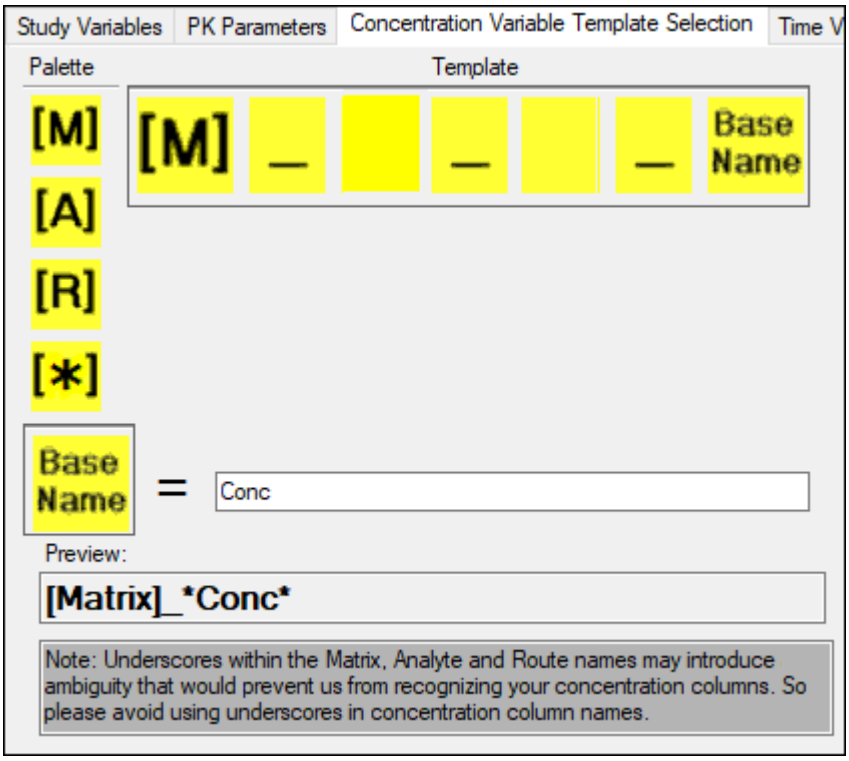


Figure 15-16. Concentration Variable Template used for stacked data

The AutoPilot Toolkit project `AutoPilot Comparison Demo - Stacked Data.phxproj` is located in …`\Examples\AutoPilot`. This project file can be used to run a comparison project using stacked data. Users can compare the output from a stacked data comparison project with the output from a wide data comparison project.

Missing analyte columns

An analyte must be present in a data column in order for AutoPilot Toolkit to recognize a stacked data-set. If an analyte column is not present, the data is analyzed as if it was wide data.

Time Variables tab

The Time Variables tab is used to set the default time variables and to map the Relative and Nominal start and end times to the correct column names in the dataset. Users can select the time variable to map, and enter the input data variable name in the Identifying Text field.

In the screen shot below, Time is entered as the identifying text for Relative Nominal End Time. This means that AutoPilot Toolkit will select all columns with Time in the name.

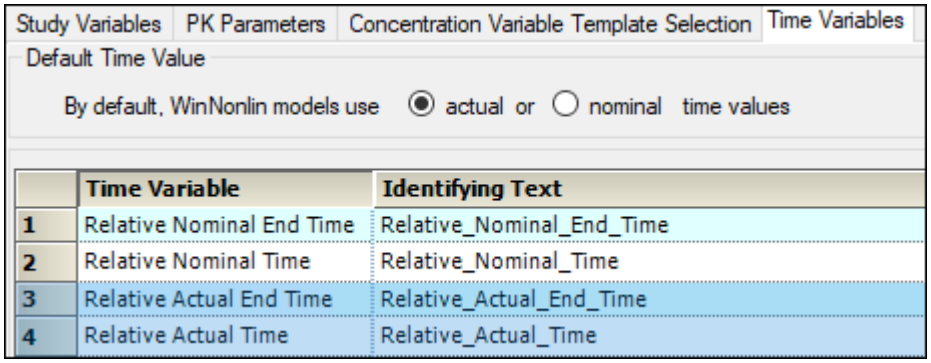


Figure 15-17. Time Variables tab

When an AP Automation object is created, users have the option to select which column to use. See “Display tabs”.

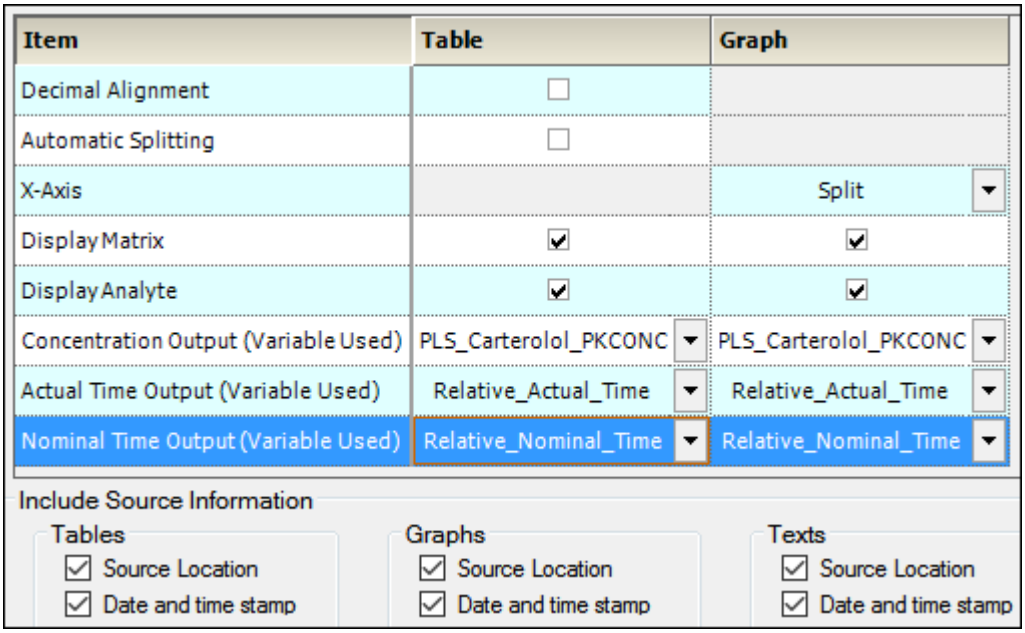


Figure 15-18. Time variable column selection

AutoPilot Toolkit business rules

The following table summarizes the business rules that set formats and options for calculations and output in AutoPilot Toolkit. For each rule the table indicates whether the rule is approved for worksheet and graph output and whether the user can activate/deactivate or modify the rule on a run-by-run basis. For details see the descriptions for each rule listed after the AutoPilot Toolkit Business Rules table.

Business rules

Rule and page number for details	Tables	Graphs	Run-specific	Enable/Disable; default selection
General				
Context-sensitive footnotes	Y	Y	N	Y; disabled
Managing footnotes	Y	Y	N	
PK parameter percent-extrapolated threshold				Y; enabled
– Calculation of summary values	Y	Y	N	
– Footnote	Y	N	N	
PK parameter Rsq adjusted threshold				Yes; enabled
– Calculation of summary values	Y	Y	N	
– Footnote	Y	N	N	
LOQ replacement				Y; some enabled
– Calculation of summary values	Y	Y	N	
– Footnote	Y	N	N	
Matrix mapping	Y	Y	N	Y; enabled
Summary statistics display for small sample sizes (Summary stat calculation criteria)	Y	Y	N	N; admin can set defaults
Summary statistics based on % threshold (Summary stat calculation criteria)	Y	Y	N	N; admin can set defaults
Individual values of zero treated as missing (Summary stat calculation criteria)	Y	Y	N	N; admin can set defaults
Exclusions	Y	Y	Y	Y; enabled
Tables				
General business rules	Y	N	Y; tables only; all footnotes on each split	N
Missing references in WinNonlin	Y	N	N	Y; enabled
Intext Table Template tab	Y	N	N	N
Display of different sample sizes in intext tables	Y	N	N	Y; enabled
Significance level display in statistical tables	Y	N	N	Y; enabled
Footnote about model time	Y	N	N	Y; enabled
RNT predose replacement	Y	Y	Y; set LOQ value only	Y; disabled

Business rules

Rule and page number for details	Tables	Graphs	Run-specific	Enable/Disable; default selection
Display analyte and matrix information	Y	Y	Y	
Time deviations	Y	N	N	N
Multiple analyte handling	Y	Y		
Graphs				
Time scale algorithm	N	Y	N	Y; enabled
Categorical PK parameter graph X-axis split/offset	N	Y	Y	N
Display analyte and matrix information	Y	Y	Y	N; admin can set defaults
Axis starting points				N
– Display negative scale for X-axis/Y-axis	N	Y	N	
– Force X-axis/Y-axis to start at zero	N	Y	N	
Multiple analyte handling	Y	Y		
Suppression of summary values below LOQ	N	Y	Y	

General business rules

Context-sensitive footnotes
Managing footnotes
PK parameter percent-extrapolated threshold
PK parameter Rsq adjusted threshold
LOQ replacement
Matrix mapping
Summary stat calculation criteria
Exclusions

Context-sensitive footnotes

The Context Sensitive Footnotes tab under General business rules contains a list of non-numeric default values. For example, NRC and EM are assigned the corresponding strings “No Sample Received” and “Extensive Metabolizer” (respectively), which serve as footnotes for worksheet output.

The **Enabled** checkbox controls whether or not the context-sensitive footnote rules are applied.

In the Context Sensitive Footnotes tab, administrators can add footnotes to or remove footnotes from this list by clicking **Add** and **Remove**. Administrators can also set Key and Footnote values and configure whether matching values are set equal to zero when calculating summary statistics or if the data should not be included (missing), which decreases the n-value.

In addition, administrators can configure which of the non-numeric values and corresponding footnotes are associated with the LOQ rule set. See “LOQ replacement”. The default settings for footnotes are shown in the following table.

Key	Footnote	Summary Stat Calculation	LOQ GUI Overwrite
LOQ	LOQ: Lower limit of quantification.	Zero	No

Key	Footnote	Summary Stat Calculation	LOQ GUI Overwrite
BQL	BQL: Below limit of quantification.	Zero	No
HEM	HEM: No sample, hemolyzed.	Missing	No
NRC	NRC: No sample received.	Missing	No
INS	INS: Insufficient volume to analyze.	Missing	No
PLC	PLC: Placebo, not analyzed.	Missing	No
BLK	BLK: Blank, not analyzed.	Missing	No
NBC	NBC: No barcode, not analyzed.	Missing	No
NRI	NRI: Assay interference, not analyzed.	Missing	No
EM	EM: Extensive Metabolizer	Missing	No
PM	PM: Poor Metabolizer	Missing	No

More on the LOQ GUI Overwrite option

- If the LOQ GUI Overwrite is set to **No** or if an LOQ value is ***not*** entered in an AP Automation object, then the Context Sensitive Footnote rules for calculation of summary statistics applies.
- If the LOQ GUI Overwrite is set to **Yes** and an LOQ value is entered in an AP Automation object, then the Context Sensitive Footnote Rules for the calculation of summary statistics is disabled, and the LOQ Replacement rules apply.

The LOQ GUI Overwrite feature associated with these rules and the context-sensitive footnotes work as illustrated in the following table. Note that the settings in the third case potentially create two different footnotes for the same entry in the concentration table and should be avoided by the administrator.

LOQ GUI overwrite and context-sensitive footnotes settings

Data Values	Context Sensitive Footnote	LOQ GUI Overwrite	LOQ Replacement Setting	Resulting Display in Table (values, footnote)
BQL 0.4 10.0	BQL: CSF footnote	***No***	Value: 0.5 Replacement: ***LLOQ*** Footnote: LLOQ: LOQ footnote	BQL LLOQ 10.0 Footnotes BQL: CSF footnote LLOQ: LOQ footnote
BQL 0.4 10.0	BQL: CSF footnote	***Yes***	Value: 0.5 Replacement: ***LLOQ*** Footnote: LLOQ: LOQ footnote	LLOQ LLOQ 10.0 Footnotes LLOQ: LOQ footnote
BQL 0.4 10.0	BQL: CSF footnote	***No***	Value: 0.5 Replacement: ***BQL*** Footnote: LLOQ: LOQ footnote	BQL BQL 10.0 Footnotes BQL: CSF footnote BQL: LOQ footnote

LOQ GUI overwrite and context-sensitive footnotes settings

Data Values	Context Sensitive Footnote	LOQ GUI Overwrite	LOQ Replacement Setting	Resulting Display in Table (values, footnote)
BQL 0.4 10.0	BQL: CSF footnote	***Yes***	Value: 0.5 Replacement: ***BQL*** Footnote: BQL: LOQ footnote	BQL BQL 10.0 Footnotes BQL: LOQ footnote

For non-analyte comparisons, each automation run applies its own LOQ and AUC%Extrap rules. However, ***only*** the rule for the reference study gets footnoted in the output. For plasma analyte comparisons, if there is a LOQ value set in the reference study, those same settings are used in the comparison.

Managing footnotes

Footnotes for graphs and/or tables can be selected and cleared in the Footnotes tab. An administrator can manage footnotes in the Tables and Texts and Graphs areas. When the **Provide source footnotes** checkbox for graphs is selected, the checkboxes in the Include Source Information (Integral) areas are selected. checkboxes for each footnote can then be selected or cleared. Clearing the **Provide source footnotes** checkbox disables all footnotes. When a table or graph footnote is disabled, the area is made unavailable.

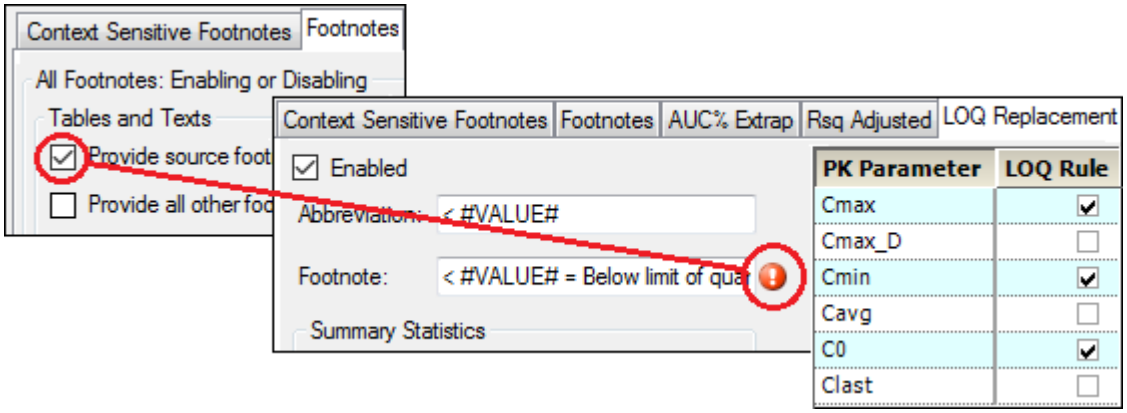


Figure 15-19. Footnote disabled for LOQ replacement

Multiple footnotes can be managed in the Footnotes tab. Settings made in the tab override any local settings, although the local settings can still be edited.

PK parameter percent-extrapolated threshold

PK parameters that rely on the regression can be altered in the final presentation of graphs and worksheets. Administrators can choose to apply the rules by turning on the **Enabled** checkbox.

The display rules can be configured as follows:

- Specify whether the extrapolated value is to be based on **Observed** or **Predicted** data (pred or obs).
- Define a flag or replacement value for these PK values, with a corresponding footnote.

The default is to flag the value with an asterisk when the value is greater than a value set in the User Module and to provide a corresponding footnote: "* - Extrapolation exceeds #VALUE#%", where #VALUE#% is the user-defined value.

If the individual values are flagged, they are still displayed in the graphs. However, if individual values are replaced with non-numerical values, they are not displayed in the graphs. The summary values are displayed the same for both graphs and tables.

- Specify whether or not values that exceed the threshold are to be included in summary statistics and derived parameter calculations.

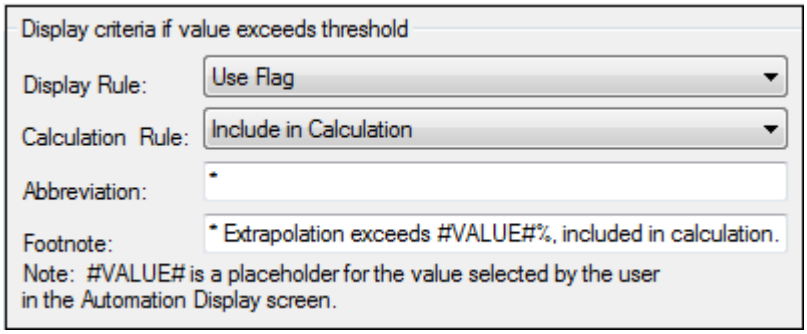


Figure 15-20. Default display settings for parameter values exceeding the threshold

- Administrators can configure which, if any, PK parameters are affected by this rule by turning on the corresponding checkbox in the table. This selection applies to both graphs and tables. Default parameters include any PK Parameter that uses the regression fit as part of its computation, including Volume, Clearance, any 'infinity' and 'tau' parameters, Half-Life, Lambda z, and Partial AUCs.

PK parameter Rsq adjusted threshold

PK parameters that rely on the regression can be altered in the final presentation of graphs and worksheets. Administrators can choose to apply the rules by turning on the **Enabled** checkbox.

The display rules can be configured as follows:

- Define a flag or replacement value for these PK values, with a corresponding footnote.

  The default is to flag the value with a hash sign when the value is greater than a value set in the User Module and to provide a corresponding footnote: "# - Rsq Adjusted lower than #VALUE#, included in calculation", where #VALUE# is the user-defined value.

  If the individual values are flagged, they are still displayed in the graphs. However, if individual values are replaced with non-numerical values, they are not displayed in the graphs. The summary values are displayed the same for both graphs and tables.

- Specify whether or not values that exceed the threshold are to be included in summary statistics and derived parameter calculations.

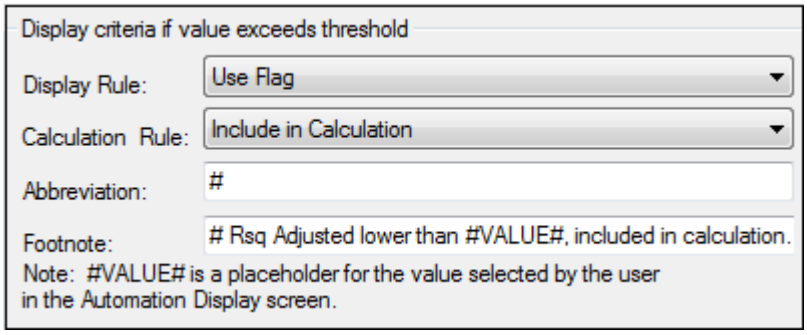


Figure 15-21. Default display settings for parameter values exceeding the threshold

- Administrators can configure which, if any, PK parameters are affected by this rule. This selection applies to both graphs and tables. Default parameters include any PK Parameter that uses the regression fit as part of its computation, including Volume, Clearance, any 'infinity' and 'tau' parameters, Half-Life, Lambda z, and Partial AUCs.

LOQ replacement

Limit of quantification (LOQ) replacement affects both tables and graphs for NCA models 200–202 and Trough only. It applies only if the automation user enters a value in the LOQ field of the *Display - Output Options* tab of the AP Automation object (see the "Output Options tab" section). If a user enters an LOQ value, values in the Concentration tables that are less than the LOQ and affected individual PK parameters (Cmax, for example) are replaced with a text value, such as <#VALUE#, where #VALUE# is the LOQ. Since they are replaced with text values, LOQ values are not displayed in graphs.

All Concentration graphs and some PK parameter graphs include a horizontal line at the value of the LOQ and a legend item identifying this line.

The display rules can be configured as follows:

- Use the **Enabled** checkbox to apply the rules.
- Define a replacement value for these PK values, with a corresponding footnote.

  The default is to replace the original value with < #VALUE# when it is less than a value set in the User Module and to provide a corresponding footnote: "< #VALUE# = Below limit of quantification (#UNITS#)", where #VALUE# is the user-defined value and #UNITS# are the units of the column used in the y-variable of the model (ng/mL, for example).
- Specify if values below the threshold are to be included in summary statistics and derived parameter calculations as **Zero**, **Missing**, or a certain fraction of the specified LOQ value (**Derivation**).
- Indicate whether multiple footnotes are to be identified using letters or numbers.
- Administrators can configure which, if any, PK parameters are affected by this rule, in addition to concentration tables. The complete list of PK parameters is Cmax, Cmax_D, Cmin, Cavg, C0, Clast. By default, the rule is applied to Cmax, Cmin, and C0.

Matrix mapping

The Matrix Mapping tab allows administrators to specify matrix names in graph and table output. The matrix names used in the input study data are listed in the Study Data Column Header Matrix Value column.

Administrators can choose to apply the rules by turning on the **Enabled** checkbox.

Complete names can be entered for the study data matrices in the Full Text Displayed In Output column. For example, PLS in the concentration column is displayed as Plasma in AutoPilot Toolkit output.

The Type of Matrix Value column allows administrators to specify whether the matrix is Non-urine or Urine.

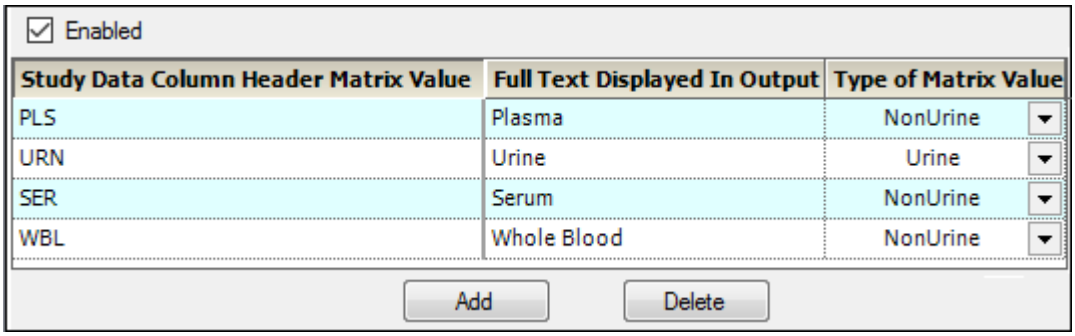


Figure 15-22. Matrix Mapping tab

Administrators can add matrix names to or remove matrix names from this list by clicking **Add** and **Delete**.

Summary stat calculation criteria

Administrators can choose to apply the rules by turning on the **Enabled** checkbox.

Values of summary statistics with small sample sizes can be overwritten by text values with corresponding footnotes. Administrators can set the following options:

- The text value and footnote applied for the overwritten statistics. This setting applies to all summary statistics. The user can set the footnotes based on output type. The default value is "NC" with footnote: "NC = Not Calculated" for both of the output types. Depending on the output type (Time Concentration/PK Parameter) the corresponding value is displayed in the tables. If a value is changed to non-numeric (e.g., NC) in the tables, this value is not displayed in the graphs.
- The text value and footnote applied for the overwritten statistics when the number of samples is less than the specified minimum. The user can set the footnotes to appear in tables and/or graphs. The default is to apply the value (a solid circle) and footnote ("Small sample size rule applied to calculation of summary variable") to tables and graphs. In graphs, a single footnote is displayed at the bottom of the graph. In worksheets, the footnote is displayed on a statistic by statistic basis.
- The text value and footnote applied when a value of zero is set to be treated as a missing value. The user can set the footnotes to appear in tables and/or graphs. The default is to apply the value (an empty circle) and footnote ("Zero treated as missing for calculation of statistics") to tables and graphs.

There are two business rules that can be used to set minimum sample size:

- the absolute number of values required
- the minimum percentage

If both of these business rules are used in conjunction with one another, both minimum sample size business rule conditions must be met before the summary statistics are calculated and displayed in the tables.

- Turn on the **Apply Zero as missing only under Small Sample Size** checkbox to set zero values as missing only when the Small Sample Size rule is not met.

- Turn on the **Do Not Overwrite LOQ Summary Statistics Replacements** to retain the LOQ summary statistics values.
- Turn on the **Do Not Use Raw Data for Small Sample Size** checkbox to prevent small sample size from using raw values of data.
- Administrators can configure which, if any, PK parameters are affected by the rules. Turn on the **Select** checkbox to apply the rule to the parameter. For the minimum sample size, select the value from the pull-down menu. For the sample percentage, enter the minimum percentage, relative to the total sample size, that must exist in a profile before summary statistic calculations are performed. (This percentage is calculated as the number of non-missing, non-alphanumeric values divided by the total number of samples.)

  By default, the minimum sample size of two rule is applied to all PK parameters.
- Turn on the **Treat zero as missing** checkbox for a summary statistic to allow values of zero to be treated as though they were missing during the calculation.

Note: When loading a saved system XML file in which the small sample size is set to a value other than the default, you may have to reset that value. There are situations that can cause the small sample size for certain summary statistics to become frozen at a value of 1, so the value in a saved system XML file may be ignored.

Exclusions

The general exclusion display rules can be configured as follows:

- Turn on the **Enabled** checkbox to apply the rules.
- Define a replacement value for excluded values in tables, with a corresponding footnote.

  The default is to replace the excluded value with an asterisk and to provide a corresponding footnote: “Excluded from the calculation of descriptive statistics”.
- Turn on the **Apply as Default Time Point Exclusion to Concentration Tables** checkbox to have the **Apply Time Point Exclusion to Concentration Tables** option in the User mode checked by default.
- Define a replacement value for excluded values in graphs.

  The default is to replace the excluded value with a cross hair symbol (+).

Table business rules

Missing references in WinNonlin
Intext Table Template tab
Table data display using decimal alignment
Table splitting
Display of different sample sizes in intext tables
Significance level display in statistical tables
Footnote about model time
RNT predose replacement
Display analyte and matrix information
Time deviations
Multiple analyte handling

Missing references in WinNonlin

In the Missing References in WinNonlin tab under Table business rules, administrators can specify how missing or non-existing data points are handled.

Turn on the **Enabled** checkbox to apply the corresponding rule.

Missing values

For existing WinNonlin missing values of '.', '-', 'missing,' or 'blank' in study data, values are replaced with the string listed in the **Value Replacement** field. A footnote is also added below the table.

Footnote defaults for specific table types

Table Type	Body of Table	Statistical Block	Footnote
Time Concentration	NS	NA	NS=No Sample
Demographic	NR	NA	NR=Not Recorded
PK Parameter	NC	NA	NC=Not Calculated

As shown in the table above, missing values summary statistics use NA in two different ways, NR, and NC with corresponding footnotes. Footnotes associated with other business rules such as LOQ are discussed separately under each of the rules.

Note: The wildcard character for context-sensitive footnotes is * (asterisk).

Non-existent values

For non-existent time points, administrators can choose a replacement value and a footnote instead of leaving the cell blank. For example, if a study design indicates that concentration readings are taken every 15 minutes for three subjects, and only every hour for one subject. The single subject will have three missing values for each hour. In this type of situation, users can replace the empty data field with the text string listed in **Value Replacement**.

Missing descriptive statistic values

For missing descriptive statistic values of '.', '-', 'missing,' or 'blank', values are replaced with the string listed in the **Value Replacement** field, 'NA' by default.

Intext Table Template tab

The Admin Module allows users to configure the intext tables to display values using one of the templates below and sets which PK parameters, if any, are considered time dependent. A list of possible time-dependent PK parameters is displayed with the following selected as defaults: Tmax, Tlag, Tmin, Tlast, Tmax_Rate, and Mid_Pt_last.

Intext template

Template	Subgroup 1A (not time-dependent)	Subgroup 1B (time-dependent)
Template 1	A ± B	A (B – C)
Template 2	A (B)	A (B, C)

Intext template

Template	Subgroup 1A (not time-dependent)	Subgroup 1B (time-dependent)
Template 3	A B	A (B – C) A (B, C)
Template 4	A ± B (C)	A (B – C)
Template 5	A (B) [C]	A (B,C)
Template 6	A ± B (C) [D]	A (B – C)
Template 7	A (B) (C) [D]	A (B,C)
Template 8	A (B – C)	A (B, C)
Template 9	A (B, C)	A (B – C)

In the table above, A, B, C, and D in the Template 1A column and A, B, and C in the Template 1B column represent unique summary statistics, e.g., A ± B could represent Mean ± SD in Template 1A and A (B – C) could represent Median (Min – Max) in Template 1B. Select the summary statistic for each variable using the pull-down menus beneath the template equation. Use the **Location in Output** option to define where the template information is to be displayed.

Additional rules

Table data display using decimal alignment

This rule allows all tables to be created with decimal alignment. Admins can set this rule as a default, or allow the user to select it on a run-by-run basis. This selection is made to alter the horizontal alignment of numerical values in tables such that all values in a given column are aligned around their decimal points.

The exceptions to this rule are:

- Values that have an associated footnote are not decimal aligned
- Negative values are not decimal aligned

Table splitting

In some cases, all information within a specific table might not fit within the standard margins of a single page due to a large number of subjects, treatments, and others. In such cases, admins can allow tables to be split across multiple pages. If splitting is allowed, the user sets whether to split tables for each automation or comparison run. This selection affects all tables in a run and appends a split segment to table file names for that run. All tables can be split except for PK_Stats.

During a run, AutoPilot Toolkit determines whether splitting is warranted for each table and determines the splits needed to conform to the appropriate page margins using the following rules:

- Table headers are carried over to each file in a split table.
- Data columns that are underneath a set of merged cells can be separated across split table files with the exception of the Intext tables. Columns that are underneath a set of merged cells within

an Intext table are considered a group. These groups cannot be split; the entire group is moved to the next split table file when needed.

- Splitting across rows within the summary statistics section is not allowed.
- Identical footnotes are displayed at the bottom of each split table, independent of whether the associated value is contained in that specific split table. For example, a table containing the footnote "BQL - Below quantification limit" is split into four smaller tables. Each of these split tables has the identical footnote "BQL - Below quantification limit" even if the BQL value is not present in each of the smaller split tables.
- The split table file names indicate the position of each file in the whole table following the scheme mapped out below. Two numbers are appended to each the end of each file name. The first number identifies the split table's position by row; the second, by column, as follows:

  1_1 1_2

  2_1 2_2

Examples of file names with table splitting

Original (Un-split) Table File Name	**Table Splitting Selected in User Module**	**Total Number of Files after Splitting and Description**	**Final (Split) File Names**
Concentration_Trt1	No	1; no splitting allowed	Concentration_Trt1
Concentration_Trt1	Yes	1; no splitting needed	Concentration_Trt1_1_1
Concentration_Trt1	Yes	2; original table too wide	Concentration_Trt1_1_1 Concentration_Trt1_1_2
Concentration_Trt1	Yes	2; original table too long	Concentration_Trt1_1_1 Concentration_Trt1_2_1
Concentration_Trt1	Yes	4; original table too long and too wide	Concentration_Trt1_1_1 Concentration_Trt1_1_2 Concentration_Trt1_2_1 Concentration_Trt1_2_2

Display of different sample sizes in intext tables

For intext tables, summary statistics on PK parameters might have different sample sizes within the same treatment. The representative sample size for each treatment, presented in a row at the top of the intext table, is based on the number of subjects with Cmax values for each treatment. PK parameter summaries that are based on a different sample size are footnoted. Administrators can set the following options:

- Whether or not to enable this rule. The default is **Enabled**.
- If this rule is used, then administrators can choose to flag footnotes using letters or numbers. The default is letters.

Significance level display in statistical tables

P-values below a certain threshold can be overwritten by a configurable text string. Administrators can configure the following:

- Whether to implement this rule. The default is **Enabled**.
- A global threshold value below which p-values are overwritten. The default is to replace values less than 0.05.
- The text value with which to replace the p-values. The default is “< 0.05”.

Footnote about model time

Values that are based on Relative Nominal Time rather than the default, Relative Actual Time, can be automatically flagged and footnoted. All tables except demographics are displayed with a footnote indicating that Nominal Times were used instead of Actual times. Administrator configurations include the following:

- Turn on the **Enabled** checkbox in the Footnote about Model Time area to set this rule. The default is enabled.
- In the **NCA model time footnote** field, users can enter a new footnote. The default footnote is “Nominal Times used as time variable for NCA”.

RNT predose replacement

RNT values that are less than zero can be replaced with a text value indicating predose values. This option is enabled by default to replace all RNT values less than zero with the text value Predose. Administrators can choose to replace values that are less than or equal to zero, and can edit the replacement text value. To use negative RNT values, the **Enabled** checkbox must be cleared.

Display analyte and matrix information

Matrix and analyte information can be included in the column headers of output tables by turning on the Matrix and/or Analyte checkbox below the desired table types. Administrators can use the Column Mapping tab to map the matrix abbreviation for concentration columns in the study data to a full name, which is displayed in the final output. The concentration column headers follow the nomenclature of [Matrix]_(AnalyteID)_CONC, where the [Matrix] defines the sample matrix. The [Matrix] information can be abbreviated in the column header; with the aid of the mapping, the entire text can be displayed in the output. For tables, the display is in the form of an additional header.

Administrators can make this functionality available as user options by turning on the **Available to user** checkbox.

Time deviations

Administrators can configure settings to calculate and flag deviations from planned time as follows:

- Choose a formula for the calculation of the Time Deviations parameter
- Set a threshold for flagging values
- The abbreviation (flag) and footnote to use are set in the corresponding fields

The default is to use the formula: ((Relative Actual Time – Relative Nominal Time)/Relative Nominal Time)*100, with a threshold of 15. Time deviations are then flagged with an asterisk and the footnote “Actual sampling time exceeds +/-#VALUE#% of nominal sampling time threshold”.

Multiple analyte handling

Administrators can select whether or not to produce separate tables for each analyte. They can also select whether or not to group table columns by treatment and then by analyte.

Graph business rules

Time scale algorithm

The Time Scale algorithm, which is applicable to graphs with a continuous time-based X-axis (for example, time or midpoint), is enabled by default in the Admin Module. If it is disabled, graphs use SigmaPlot's internal algorithm for applying X- and Y-axis scales and for minor and major ticks. Administrators can both enable and configure the settings for this rule, and also choose whether to make the settings configurable by the user during automation and comparison runs.

Note: Any settings selected in the Admin Module can be overridden by the user if the **Available to user** checkbox is selected.

This rule has two parts:

- Force all graphs to have the same X-axis and/or Y-axis scales.
- Force graphs to have consistent ticks and labels for time-related x-variables.

Part 1: Force all graphs that have a continuous time-based X-axis (time, midpoint, etc.) to have the same X-axis scale and ticks and/or the same Y-axis scale and ticks. The following configurations are available:

- Y-axis scaling (choose one option in the user interface):
  - Uniform automatic across all graphs: Based on the maximum value of the dependent variable associated with all data points from the entire dataset. This option is the default.
  - On a graph by graph basis: Based on the maximum value of the dependent variable associated with all data points for a given graph.
  - Uniform for linear and on a graph by graph basis for log graphs: Combination of the first two options, the first is applied to linear graphs and the second to log graphs.
  - On a graph by graph basis for linear and uniform for log graphs: Combination of the first two options, the first is applied to log graphs and the second to linear graphs.
- X-axis scaling (choose one option in the user interface):
  - Uniform across all graphs: Based on the maximum time point associated with all data points from the entire dataset. This option is the default.
  - On a graph by graph basis: Based on the maximum time point associated with all data points for a given graph.

Part 2: Force all graphs that have a continuous time-based X-axis (time, midpoint, etc.) to have consistent ticks and labels for time-related x-variables.

The Major ticks time scale table in the Admin Module and user interface is shown in the screen shot below. If the maximum time point value in a dataset (or a subset of the dataset if the On a graph by

graph basis option is selected) is within the range specified by the lower and upper bounds, that row in the table is used to establish the associated major tick frequency, tick units, and the maximum time scale. The range is always interpreted in hours regardless of the original dataset study units.

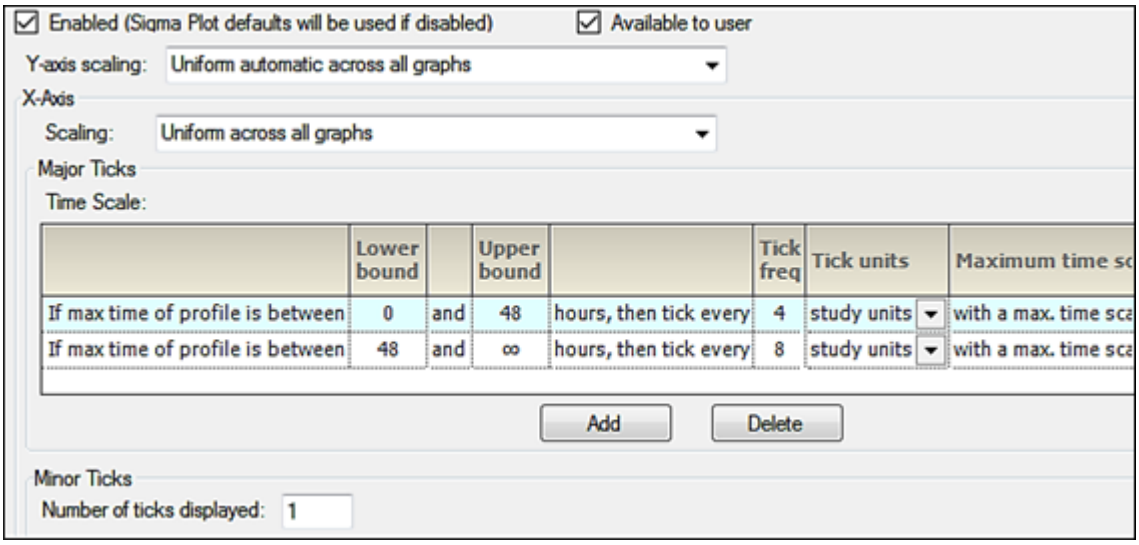


Figure 15-23. Time Scale Algorithm tab

For example, for a Concentration by Treatment graph, users might have two treatments, where the last observation of Trt A is at 24 hours and last observation of Trt A is at 240 hours. If the default selection of Uniform across all graphs is specified for the X-axis scaling, using the screenshot below as an example, only the second row in the table applies to both treatments. However, if the X-axis scaling is changed to On a graph by graph basis, then users can see that for Trt A the first row in the table would apply, but for Trt B, the second would apply.

The second row in the table overrides the study units and that the graphs are generated with time units of days. In the screen shot below, because the Tick unit column was changed from the default Study units to Days, an administrator made the applicable calculation and changed the value in the Tick frequency column to reflect the tick frequency.

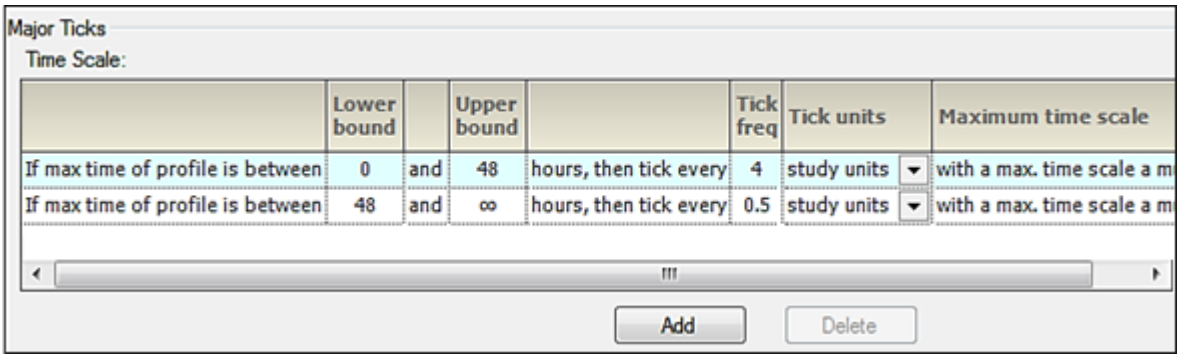


Figure 15-24. Major Ticks Time Scale table

The user interface is similar to the screen shots above, with the exception of the Enabled or Available to user checkboxes, which are not shown, and the time units displayed in the Tick units column are in the units for the current study loaded. These settings only apply to the JNB, JPG, EMF, and WMF files that are created by AutoPilot Toolkit. The settings do not apply to the WinNonlin charts that are created in the Summary_PK_Text document.

Additional rules

Categorical PK parameter graph X-axis split/offset

PK parameter graphs can have a **Split** X-axis based on individual and summary values or **Offset**. Administrators can make this functionality available as user options by turning on the **Available to user** checkbox.

Display analyte and matrix information

Matrix and analyte information can be included in the axes labels of graphs by turning on the Matrix and/or Analyte checkbox below the desired graph types. Administrators can use the Column Mapping tab to map the matrix abbreviation for concentration columns in the study data to a full name, which is displayed in the final output. The concentration column headers follow the nomenclature of [Matrix]_(AnalyteID)_CONC, where the [Matrix] defines the sample matrix. The [Matrix] information can be abbreviated in the column header; with the aid of the mapping, the entire text can be displayed in the output. For graphs, the display is included at the beginning of the y-label. Note that the Analyte name only displays in the y-label for wide (non-stacked) data.

Administrators can make this functionality available as user options by turning on the **Available to user** checkbox.

Axis starting points

Administrators can set the starting points for the X-axis and Y-axis independently. The options include:

- Force the X-axis and/or Y-axis to start from zero (ignoring negative values)
- Force the X-axis and/or Y-axis to start from zero if all values in the set are positive values (if negative values are present, use the data values to determine the scale of the axis)
- Use the data values to determine the scale of the axis

Multiple analyte handling

Administrators can select whether or not to produce separate tables for each analyte. They can also select whether or not to group table columns by treatment and then by analyte.

Suppression of summary values below LOQ

In AP Automation objects, administrators can prevent summary data values such as mean, median, etc., that fall below the LOQ from appearing in any of the following types of graphs by turning on the corresponding **Suppress** checkbox.

- Plasma Time Concentration by Treatment
- Plasma Summary Time Concentration by Treatment
- Trough Time Concentration by Treatment
- Trough Summary Time Concentration by Treatment

This business rule is invoked on a run-by-run basis by setting LOQ output options in the Display tab in the AP Automation object.

Selecting content for generated output

Administrators can use the options located under the PK Automation and PK Comparison nodes to select which content is generated by default and which content the user can select to be generated

when an automation or comparison run is performed. These options can be applied to tables, graphs, and text.

- ***Table data***: An administrator can select which tables are available to the user and which are selected by default by category under PK Automation and PK Comparison. In the Format section, administrators can specify the orientation and page size, and margins. Administrators can also specify alignment, font, font size, and font style and border elements. Text elements can be assigned by table category and section of table.
- ***Graph data***: An administrator can select which graphs are available to the user and which are selected by default by category under PK Automation and PK Comparison.In the Format section, the administrator can specify the orientation and page size, margins, and the graph presentation order and number of graphs per page. In the Output Detail section, the administrator can select graph summaries to include by selecting the **Create Graph** checkbox.

Note: The **Create Graph** checkbox only affects the summary portion of the graph. Clearing the checkbox DOES NOT prevent the creation of the graph, only the summary information.

- ***Appendix data***: Administrators can specify which appendix types are available for users and which types are selected by default for the output. In the Format section, an administrator can specify the orientation and page size, margins, and the graph presentation order and number of graphs per page. The format options apply to individual appendices only.
- ***Crossover/Parallel***: Administrators can use this node to select which studies are available to the user and which are generated by default.

Example

In the **General > PK Parameters** menu, administrators can select a PK parameter, such as AUCall, and make it available to users for a given type of study. For example, a single-dose extravascular model. Administrators can further refine the selection by limiting the PK parameters that are available to the user for an automation or a comparison run.

- Select **PK Automation > Table Data > Tables** in the **Admin Module** menu.
- Select **PK Parameter** in the **Category** menu.

  The Available to User tab is displayed.
- Select **PK Parameter B** in the Available: list and click **Remove**.

PK Automation and PK Comparison intext table formatting

Intext table formatting options can be set in the Table Data Format sections in the Admin Module.

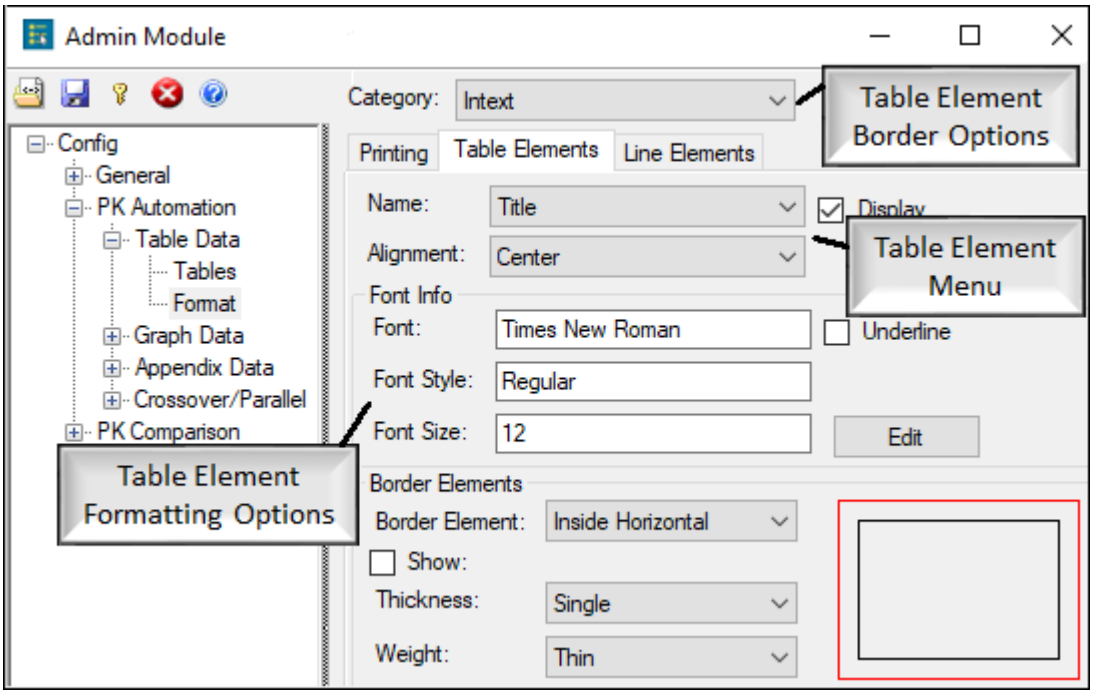


Figure 15-25. Formatting options for the PK Automation Intext table

- In the Admin Module, select **Config > PK Automation > Table Data > Format** or **Config > PK Comparison > Table Data > Format**.
- In the **Category** menu, select **Intext** or **Comparison Intext**.
- Select the **Table Elements** tab.
- In the **Name** menu, select a table element.
- Clear the **Display** checkbox to remove a table element from the table output.

  For example, select **Footnotes** in the **Name** menu and clear the **Display** checkbox to not include footnotes in the Intext table output.
- Click **Edit** to edit a table element's font and style.

Note: For Intext tables, Body formatting settings always override the Summary Statistic Value Settings.

- In the **Border Element** menu, select a border section.

  Available border sections include Inside Horizontal, Inside Vertical, Outline Bottom, Outline Left, Outline Right, and Outline Top.
- Borders can be removed from the output by selecting a border element and clearing the **Show** checkbox.
- Use the **Thickness** and **Weight** menus to define border shape and size.

  Border formatting can be overwritten by other border formats. For example, the bottom border of Title field overwrites the top border in the Header field.

The following graphic shows where table elements are displayed in the Intext table.

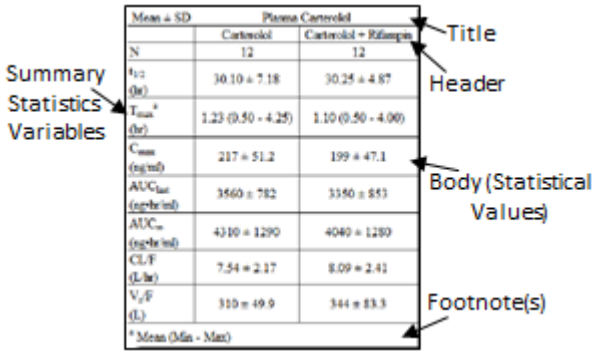


Figure 15-26. Example intext table

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