Quick Tour of Phoenix

Using a number of the sample files provided with the Phoenix software, this tutorial introduces the steps to complete the following common tasks:

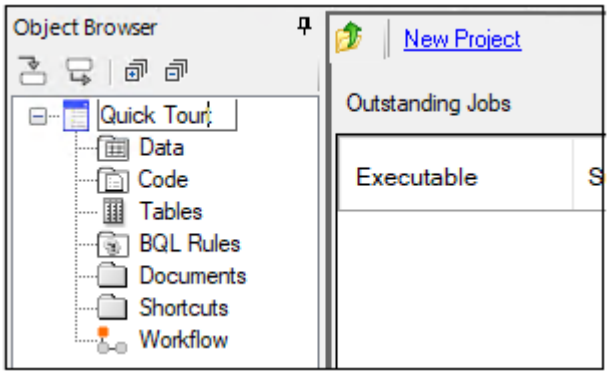
Start Phoenix and create a new project
Import a dataset
Create a plot
Create a table
Execute noncompartmental analysis
Perform pharmacokinetic modeling
Execute a bioequivalence model

Most Phoenix objects require the same basic steps for their use. However, there may be multiple paths to accomplishing a step (e.g., main menu, right-click menu, drag-and-drop, etc.). For simplicity, only one is listed here.

Note: Any object added to a project can be viewed in its own window by selecting the object in the Object Browser and double-clicking it or pressing **ENTER**. All instructions for setting up and executing an object are the same whether the object is viewed in its own window or in Phoenix's viewing.

Start Phoenix and create a new project

1. Double-click the Phoenix icon ( ) on your desktop to start Phoenix.
2. Select **File > New Project** to create a new project.
   A new project is created in the Object Browser and is in edit mode for you to name.
3. Name the new project by typing `Quick Tour`.

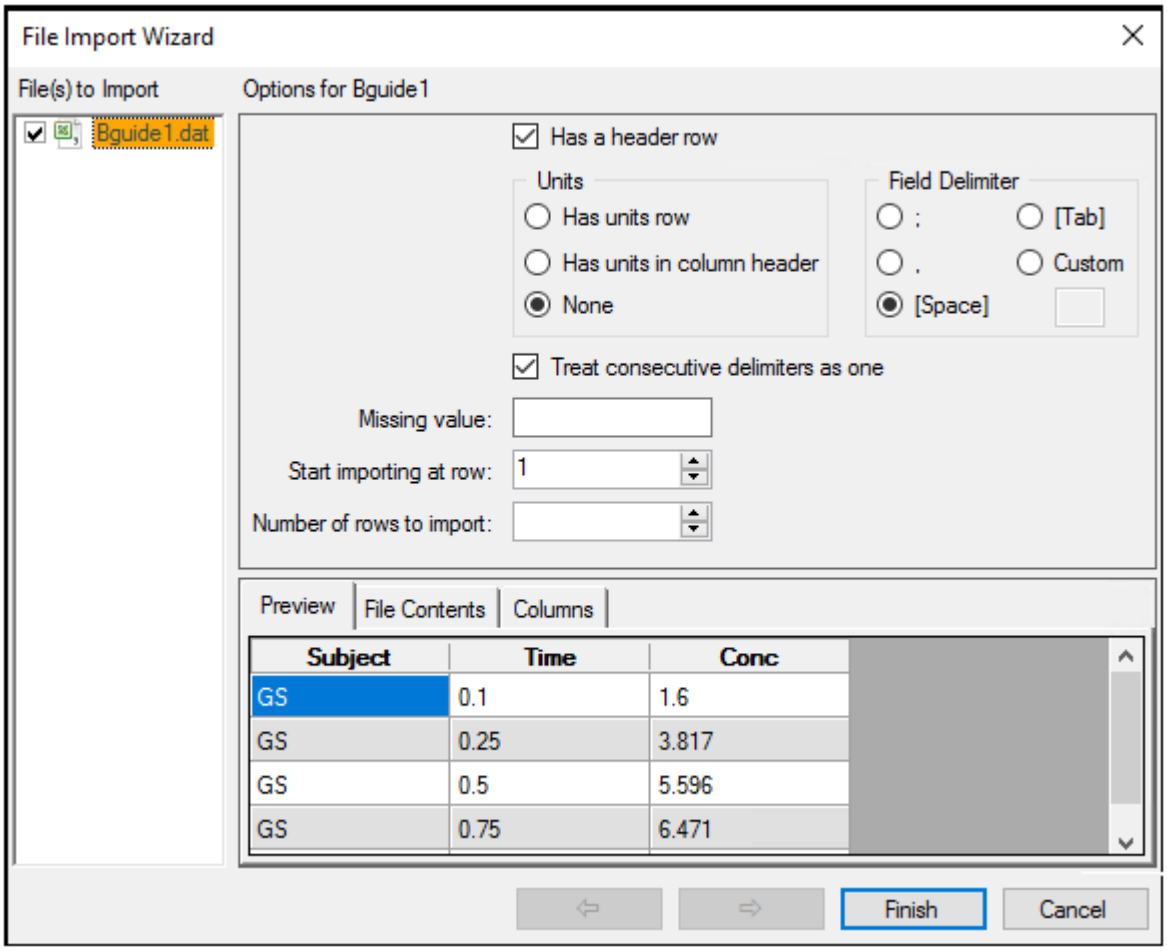


panel's default view is blank, unless one of the project folders or the workflow is selected.

Import a dataset

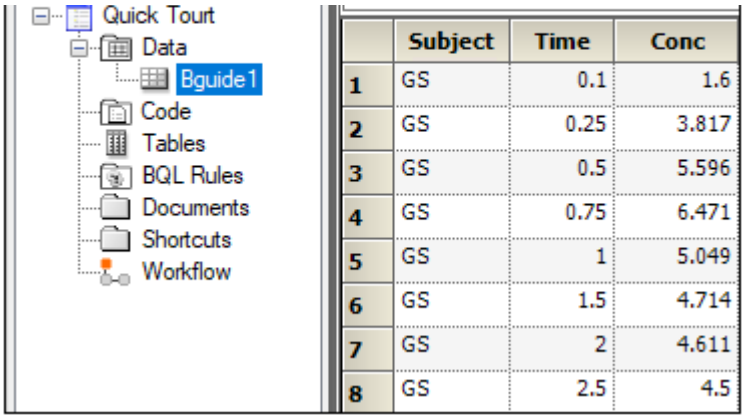
The dataset `Bguide1.dat` will be used to test key Phoenix functions.

1. Select **File > Import** or click (**Import File** icon).
2. Navigate to `<Phoenix_install_dir>\application\Examples\WinNonlin\Supporting files`.
3. Select the file **Bguide1.dat** and click **Open**.
   The *File Import Wizard* is used to assign options for how the data are imported and presented.



   No changes need to be made to the default options for this dataset.
4. Click **Finish**.

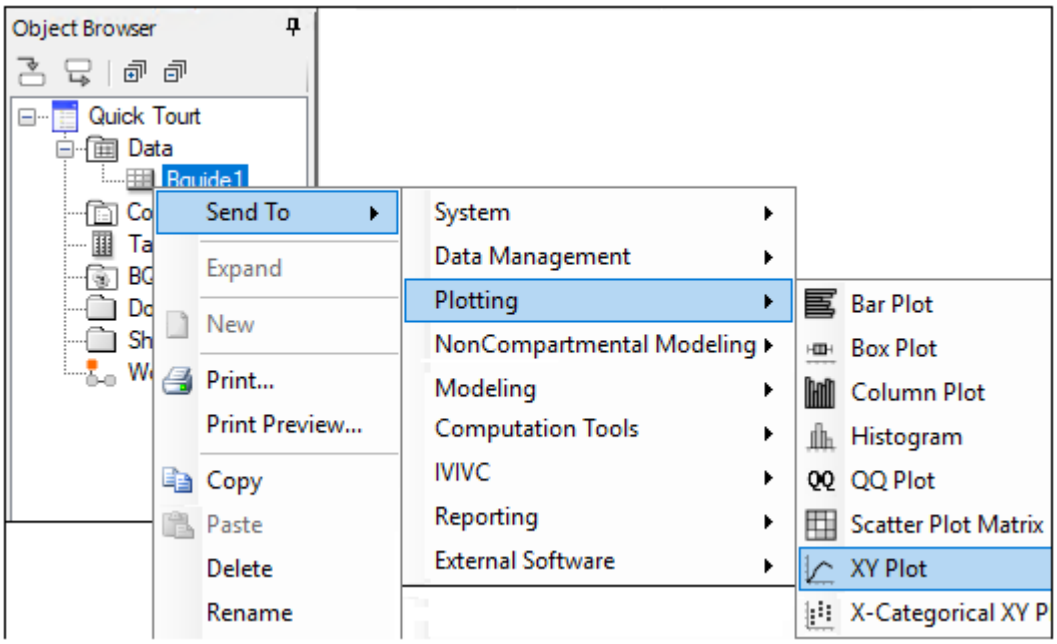
The dataset is added to the project Data folder and the worksheet is displayed in the right viewing panel.



	Subject	Time	Conc
1	GS	0.1	1.6
2	GS	0.25	3.817
3	GS	0.5	5.596
4	GS	0.75	6.471
5	GS	1	5.049
6	GS	1.5	4.714
7	GS	2	4.611
8	GS	2.5	4.5

Create a plot

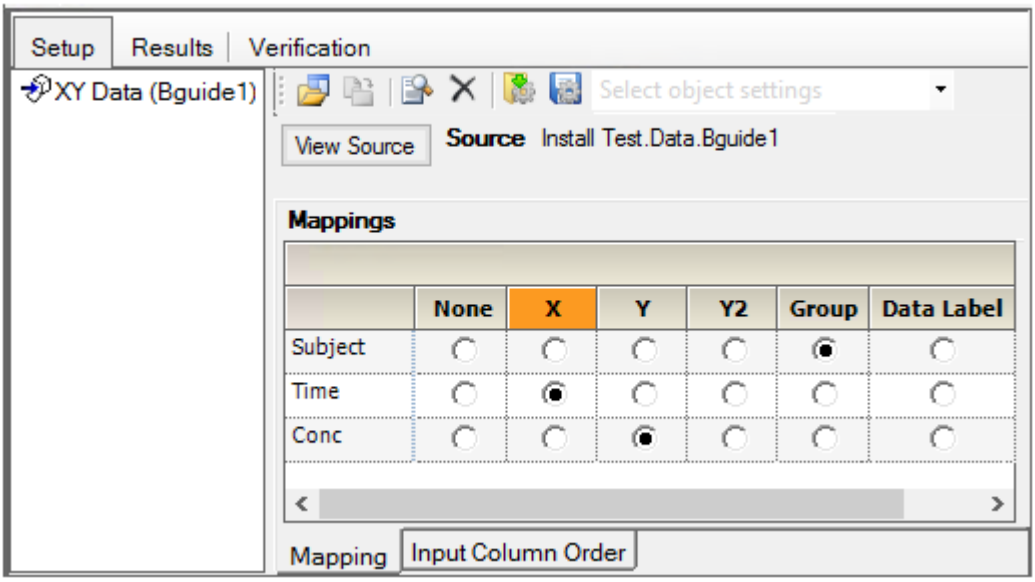
1. Right-click **Bguide1** in the Data folder and select **Send To > Plotting > XY Plot** from the menu.



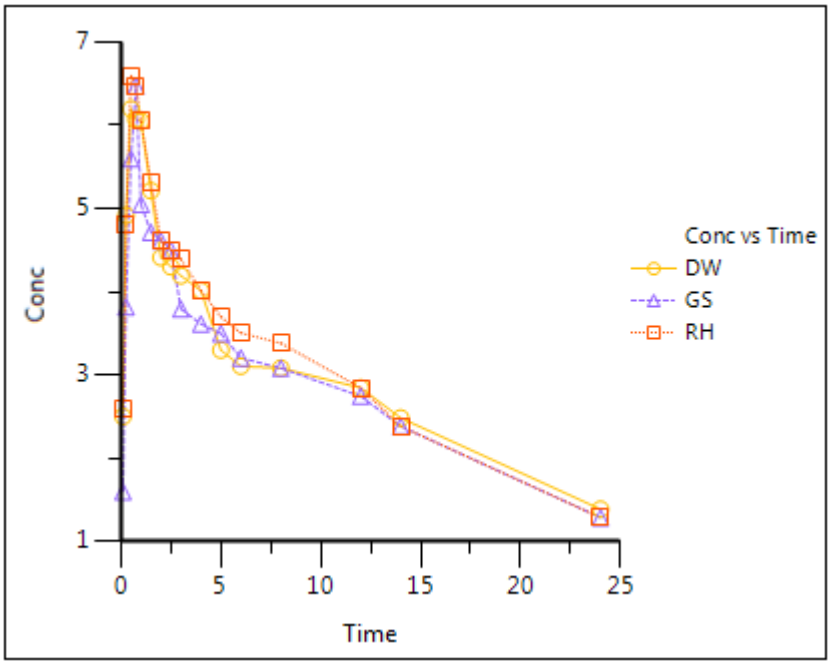
An XY Plot object can also be added to a Workflow by selecting the Workflow object in the Object Browser and then selecting **Insert > Plotting > XY Plot**. Or by right-clicking the Workflow object, selecting **New > Plotting > XY Plot**, and then using the pointer to drag the **Bguide1** worksheet from the Data folder to the XY Data Mappings panel.

The default view of an object is the Setup tab, which contains all the steps necessary to set up an object.

2. Use the option buttons in the XY Data Mappings panel to map the data types to the contexts as follows:
Map **Subject** to the **Group** context.



3. Click (**Execute** icon) to execute the workflow.



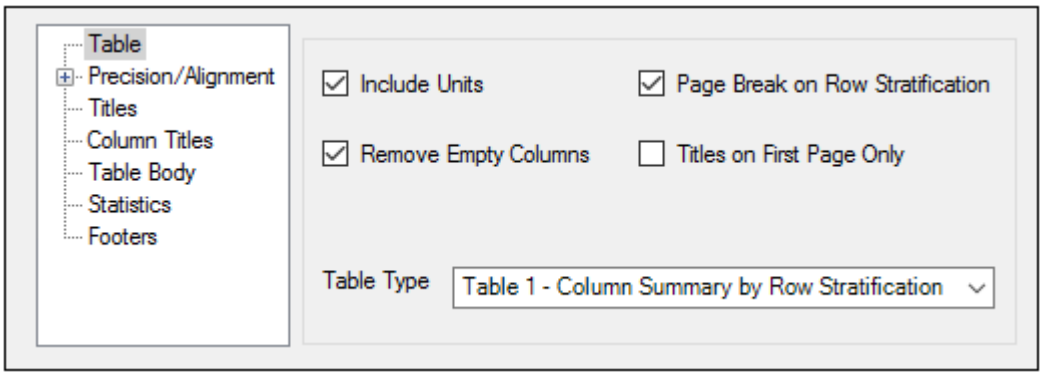
Now use the Bguide1 dataset to test the Table object and its summary statistics function.

Create a table

1. Right-click **Bguide1** in the Data folder and select **Send To > Reporting > Table**.

2. In the Main Mappings panel, map the data types as follows:
   Map **Subject** to the **Stratification Row** context.
   Leave **Time** mapped to **None**.
   Map **Conc** to the **Data** context.

4. Check the **Page Break on Row Stratification** box.



5. Select the **Statistics** tab, which is also located below the Setup tab.

6. Click **Select All** to select all output statistics.

7. Execute the object.

The results are presented as three HTML tables in the Results tab. Compare the table for the DW subject in the Results tab to the table pictured below.

Subject		Conc
DW	N	16
	NMiss	0
	NObs	16
	Mean	4.004
	SD	1.432
	SE	0.358
	Variance	2.051
	CV%	35.8
	Min	1.39
	Median	4.10
	Max	6.20
	Range	4.81
	Mean Log	1.3179
	SD Log	0.4039
	Geometric Mean	3.736
	Geometric SD	1.498
	Geometric CV%	42.10
	CI 95% Lower	0.95
	CI 95% Upper	7.06
	CI 95% Lower Mean	3.24
	CI 95% Upper Mean	4.77
	CI 95% Lower Var	1.12
	CI 95% Upper Var	4.91
	CI GEO 95% Lower	1.58
	CI GEO 95% Upper	8.84

CI 95% Lower GEO Mean	3.01
CI 95% Upper GEO Mean	4.63
Lower 1SD	2.572
Upper 1SD	5.436
GEO Lower 1SD	2.494
GEO Upper 1SD	5.595
1%	1.39
2.5%	1.39
5%	1.39
10%	2.15
25%	2.90
50%	4.10
75%	5.14
90%	6.11
95%	6.20
97.5%	6.20
99%	6.20
IQR	2.24
Sum	64.06
Harmonic Mean	3.434
Skewness	0.0595
Skewness Pop	0.0537
Kurtosis	-0.8084
Kurtosis Pop	-0.9299
Pseudo SD	1.7578
KS PValue	0.96

Execute noncompartmental analysis

1. Select **File > Load Project**.

3. Select **Multiple_Profiles.phxproj** and click **Open**.

   This project contains:
   – A dataset worksheet (profiles)
   – A worksheet of dosing information (Dosing published from NCA)
   – An XY Plot object
   – An NCA model object
   – A Descriptive Statistics object
   – A Data Wizard object
   – An X-Categorical XY Plot object

4. Expand the workflow node.

5. Select the **NCA** model object in the Object Browser.

6. Select items in the Setup tab list to explore the data mappings and option settings.

7. Execute the object.

Text output

The **Core output** contains the model settings and the same data as the worksheets, but presented in plain ASCII text. If there were errors in the model they would be listed here. Below is part of a Core output text file.

```
…
Model: Plasma Data, Extravascular Administration
Number of nonmissing observations:   12
Dose time:      0.00
Dose amount:      100.00
Calculation method: Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression
Compute Concentrations at: 75

Summary Table
-------------
 Time  Conc.  Pred. Residual    AUC         AUMC      Weight
 min   ng/ml  ng/ml  ng/ml   min*ng/ml  min*min*ng/ml
-------------------------------------------------------------
  0.0000 0.0000                  0.0000       0.0000
  5.000  340.3                    850.8        4254.
  10.00  1914.                    6487.    5.636e+04
  15.00  2069.                  1.644e+04    1.818e+05   1.000
  20.00  1471.                  2.529e+04    3.329e+05   1.000
  30.00  788.8                  3.659e+04    5.983e+05   1.000
```

```
90.00* 204.3  214.6 -10.33   6.141e+04    1.890e+06    1.000
120.0* 124.1  128.9 -4.852   6.633e+04    2.389e+06    1.000
180.0* 39.25  46.52 -7.266   7.123e+04    3.048e+06    1.000
240.0* 19.32  16.79  2.531   7.299e+04    3.389e+06    1.000
```

The **Settings** file lists all the settings used to specify the noncompartmental analysis. Below is part of a Settings text file.

```
…
  Sort: Subject, Form
  Time: Time [min]
  Concentration: Conc [ng/mL]
  Carry:
Dosing: (Internal)
Slopes: (Internal)
Partial Areas: (Internal)
Therapeutic Response: <None>
Units: (Internal)
Parameter Names: <None>
…
Plasma Model
Title=Processing Multiple Profiles with Model 200
Linear Trapezoidal Linear Interpolation
Sparse=False
Weighting=Uniform Weighting; 0
Dose Type=Extravascular
Dose Unit=ng
Dose Normalization=None
Compute Concentrations at: 75
```

Output data

The NCA object creates several results worksheets including: Dosing Used, Exclusions, Final Parameters, Final Parameters Pivoted, Partial Areas, Plot Titles, Slopes Settings, and Summary Table. Selections from the Final Parameters and Summary Table worksheets are shown below.

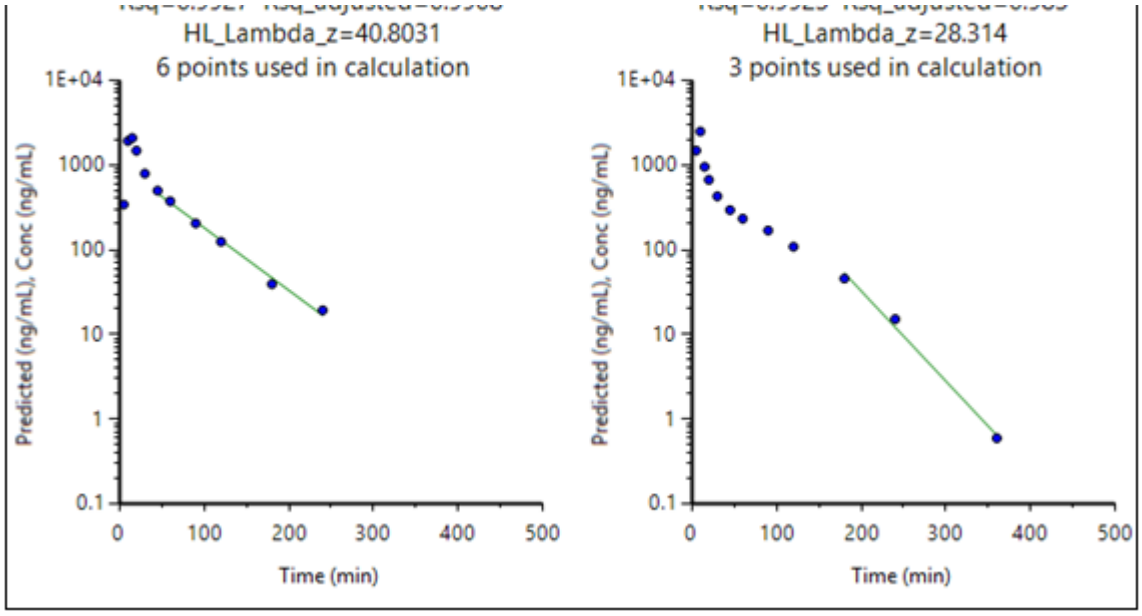
2	1	Capsule	Dose	ng	100
3	1	Capsule	Rsq		0.99267305
4	1	Capsule	Rsq_adjusted		0.99084131
5	1	Capsule	Corr_XY		-0.99632979
6	1	Capsule	No_points_lambda_z		6
7	1	Capsule	Lambda_z	1/min	0.016987622
8	1	Capsule	Lambda_z_intercept		6.8975665
9	1	Capsule	Lambda_z_lower	min	45
10	1	Capsule	Lambda_z_upper	min	240
11	1	Capsule	HL_Lambda_z	min	40.803072
12	1	Capsule	Span		4.7790519
13	1	Capsule	Tlag	min	0
14	1	Capsule	Tmax	min	15

Part of the Final Parameters worksheet

	Sub	Form	Time (min)	lam	Conc (ng/mL)	Predicted (ng/mL)	Residual (ng/mL)	AUC (min*ng/mL)	AUMC (min*min*ng/mL)	Weighting
1	1	Capsule	0		0			0	0	0
2	1	Capsule	5		340.3167			850.79175	4253.9588	0
3	1	Capsule	10		1914			6486.5835	56357.918	0
4	1	Capsule	15		2069.167			16444.501	181801.68	0
5	1	Capsule	20		1470.917			25294.711	332941.29	0
6	1	Capsule	30		788.75			36593.046	598345.49	0
7	1	Capsule	45	*	496.4167	460.87344	35.543259	46231.796	943354.88	1
8	1	Capsule	60	*	372.8333	357.20475	15.628553	52751.171	1278670.5	1
9	1	Capsule	90	*	204.25	214.57954	-10.329536	61407.421	1889958	1
10	1	Capsule	120	*	124.05	128.90192	-4.8519188	66331.921	2388985.5	1
11	1	Capsule	180	*	39.25	46.515912	-7.2659123	71230.921	3047515.5	1
12	1	Capsule	240	*	19.31667	16.785864	2.5308059	72987.921	3398545.5	1
13	1	Tablet	0		0			0	0	0

Part of the Summary Table worksheet

A total of 12 pages of plots are generated; one for each of two formulations, for each of the six subjects. The first two charts for subject one are shown below.



Plots for subject one, capsule and tablet formulation

Perform pharmacokinetic modeling

1. Select **File > Load Project**.
2. In the dialog, navigate to `<Phoenix_install_dir>\application\Examples\WinNonlin`.
3. Select **PK_Model.phxproj** and click **Open**.

   This project contains:
   – A dataset worksheet (study1)
   – An XY Plot object
   – A PK model object
4. Expand the workflow node.
5. Select the **PK** object in the Object Browser.
6. Select items in the Setup tab list to explore the model's data mappings and option settings.

   The imported PK Model object uses PK Model 3, which is a one-compartment model with 1st order absorption.
7. Execute the object.

Worksheet results

The PK Model object's output worksheets partially include Condition Numbers, Diagnostics, Dosing Used, Final Parameters, Initial Estimates, Secondary Parameters,

	Sub	Param	Units	Estimate	StdError	CV%	UnivarCI_	UnivarCI_(	PlanarCI_L	PlanarCI_(
1	1	V_F	mL	301.28617	5.4850738	1.8205528	289.3352	313.23713	283.22832	319.34401
2	1	K01	1/hr	2.1586326	0.090628388	4.1984166	1.96117	2.3560951	1.8602676	2.4569975
3	1	K10	1/hr	0.21483403	0.007340839	3.4169816	0.1988397	0.23082837	0.19066667	0.2390014

Final Parameters worksheet

	Subject	Parameter	Units	Estimate	StdError	CV%
1	1	AUC	hr*ng/mL	30.899234	0.63214664	2.0458327
2	1	K01_HL	hr	0.32110476	0.013467848	4.1942224
3	1	K10_HL	hr	3.226431	0.11013642	3.413568
4	1	CL_F	mL/hr	64.726523	1.3255206	2.0478785
5	1	Tmax	hr	1.1870389	0.026332083	2.2182999
6	1	Cmax	ng/mL	5.1439722	0.046900364	0.91175384

Secondary Parameters worksheet

	Sub	Time_ob (hr)	Conc_ob (ng/mL)	Time (hr)	Conc (ng/mL)	Predicted (ng/mL)	Residual (ng/mL)	We	SE_Yhat	Standard_Re
1	1	0.1	1.29	0.1	1.29	1.2745998	0.015400175	1	0.033025914	0.15795305
2	1	0.25	2.81	0.25	2.81	2.6889731	0.12102695	1	0.055940643	1.4005554
3	1	0.5	4.16	0.5	4.16	4.1158923	0.044107747	1	0.058589906	0.52112365
4	1	0.75	4.6	0.75	4.6	4.8144531	-0.21445309	1	0.049693255	-2.3788162
5	1	1	5.13	1	5.13	5.0953875	0.034612464	1	0.045856544	0.37556116
6	1	1.5	5.03	1.5	5.03	5.051743	-0.021742964	1	0.050117469	-0.24181407
7	1	2	4.78	2	4.78	4.6987536	0.081246401	1	0.050279037	0.90448852
8	1	2.5	4.39	2.5	4.39	4.2750813	0.11491872	1	0.045791316	1.2464824
9	1	3	3.68	3	3.68	3.8583222	-0.17832217	1	0.041419535	-1.8922238
10	1	4	3.2	4	3.2	3.1202607	0.079739284	1	0.040325291	0.84190556
11	1	5	2.55	5	2.55	2.5179435	0.03205647	1	0.044871579	0.34601201
12	1	6	2.03	6	2.03	2.0312675	-0.001267533	1	0.048709632	-0.013977098
13	1	8	1.28	8	1.28	1.3218078	-0.041807823	1	0.049677892	-0.46370881
14	1	12	0.552	12	0.552	0.5597105	-0.007710497	1	0.037020818	-0.080273645
15	1	14	0.321	14	0.321	0.36421764	-0.043217644	1	0.029360941	-0.43802838

Summary Table worksheet

Text output

The **Core output** text results include all model settings and iterations, including the output from the worksheets. Any model errors would be listed here. Below is part of the Core output text file.

```
…
Listing of input commands
 MODEL 3
```

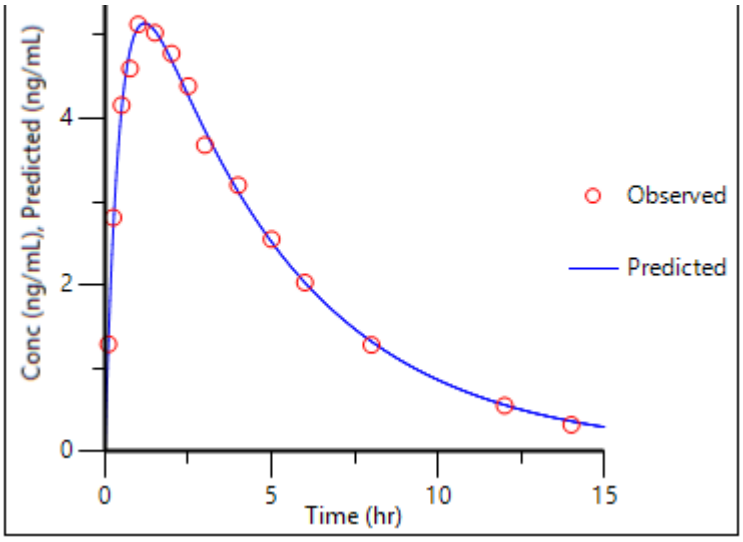
```
 XNUM 2
 YNUM 3
 NCON 3
 CONS 1,2,0
METH 2'Gauss-Newton (Levenberg and Hartley)
 ITER 50
 INIT 0.25,1.81,0.23
 MISS '.'
 DATA 'WINNLIN.DAT'
 BEGIN
```

The **Settings** file lists all the settings used to specify the noncompartmental analysis. Below is part of the Settings text file.

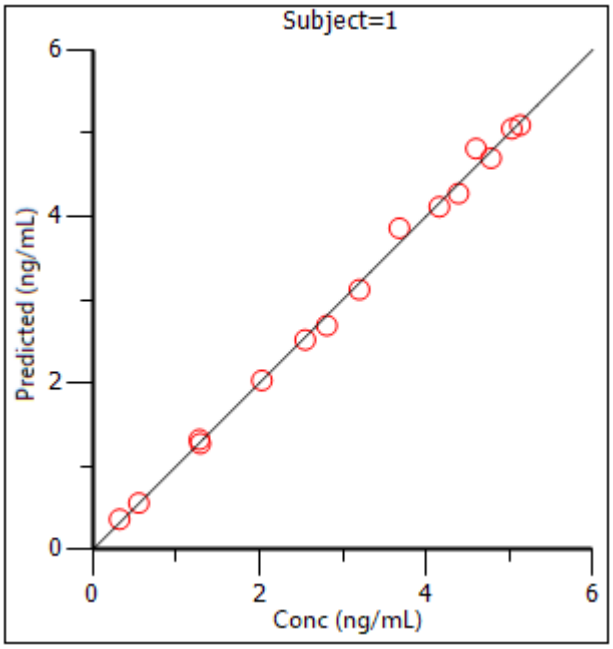
```
…
Main: PK Model.Data.study1
  Sort: Subject
  Time: Time [hr]
  Concentration: Conc [ng/mL]
  Carry:
Dosing: (Internal)
Initial Estimates: (Internal)
Units: (Internal)
***** Other Parameters *****
…
PK 3-[PK]
Gauss-Newton (Levenberg and Hartley)
Convergence criteria of 0.0001 used during minimization process
50 maximum iterations allowed during minimization process
```

Plots

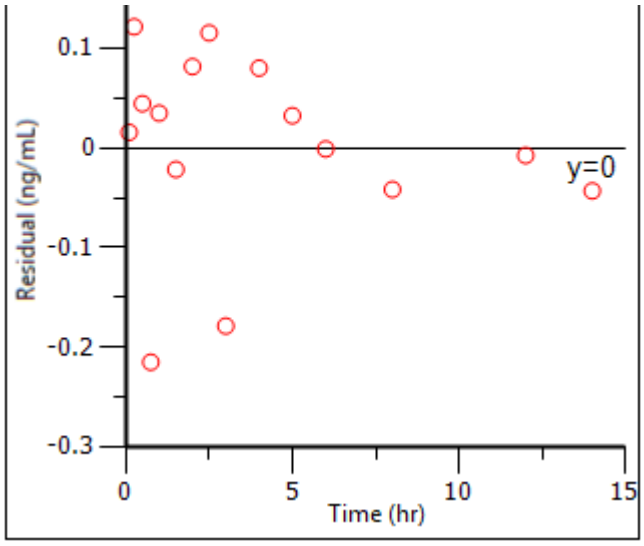
The plot results include Observed Y and Predicted Y vs X, Partial Derivatives Plot, Predicted Y vs Observed Y, Predicted Y vs X, Residual Y vs Predicted Y, and Residual Y vs X. Some plot results are shown below.



Observed Y and Predicted Y vs X



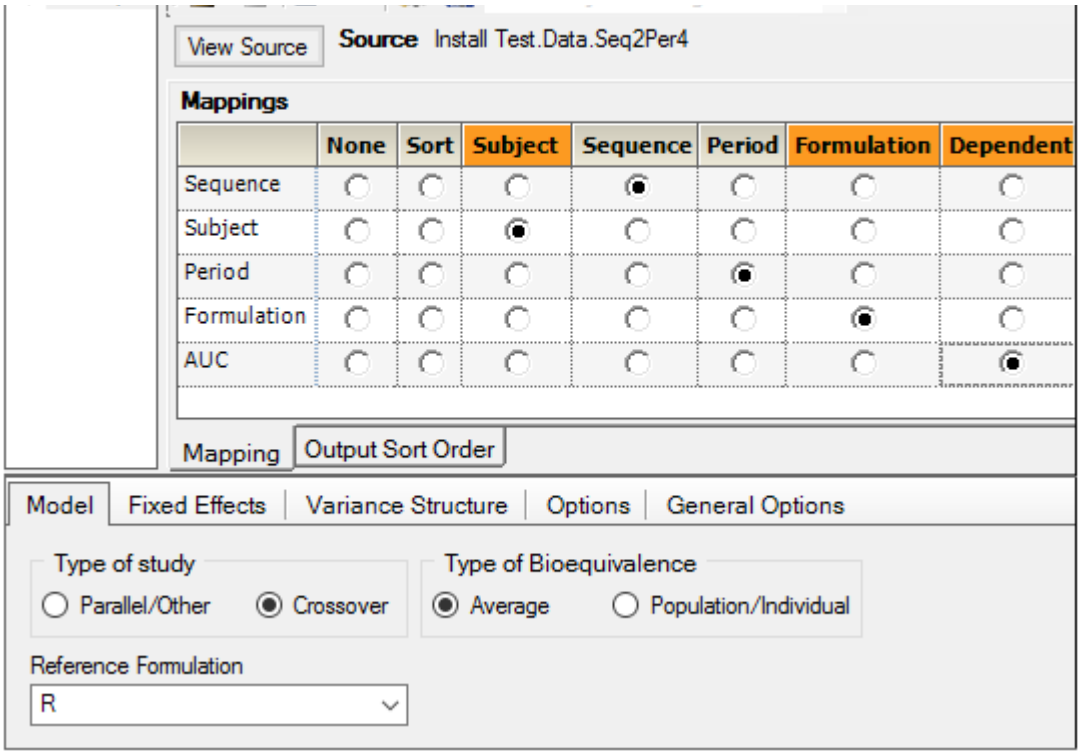
Predicted Y vs Observed Y



Residual Y vs X

Execute a bioequivalence model

1. Select the **Quick Tour** project in the Object Browser.
2. Select **File > Import**.
3. In the dialog, navigate to `<Phoenix_install_dir>\application\Examples\WinNonlin\Supporting files`.
4. Select the file `Seq2Per4.csv` and click **Open**.
   In the *File Import Wizard* dialog, click **Finish**. The dataset is added to the project Data folder.
5. Right-click the **Seq2Per4** worksheet in the Data folder and select **Send To > Computation Tools > Bioequivalence**.
   The **Bioequivalence** object is added to the workflow in the Object Browser and the following data types are automatically mapped to contexts.
   – **Sequence** to the **Sequence** context
   – **Subject** to the **Subject** context
   – **Period** to the **Period** context
   – **Formulation** to the **Formulation** context
6. In the Main Mappings panel, map **AUC** to the **Dependent** context.
7. In the Model tab (located below the Setup tab), ensure the following:
   – **Crossover** is selected as the **Type** of study
   – **Average** is selected as the **Type of Bioequivalence**
   – **R** is selected as the **Reference Formulation**



8. Select the **Fixed Effects** tab, which is located below the Setup tab.

9. **Ln(x)** is automatically selected in the **Dependent Variables Transformation** menu. Do not change this setting.

10. Execute the object.

Output data

The bioequivalence model worksheet output partially includes Average Bioequivalence, Diagnostics, Final Fixed Parameters, Final and Initial Variance Parameters, Least Squares Means, and Sequential Tests. The Diagnostics, Final Variance Parameters, and Sequential Tests worksheets are shown below.

	Depend	Units	FormVar	FormR	RefLSM	RefLSM_S	RefGeoL	Test	TestLSM	TestLSM_
1	Ln(AUC)		Formulation	R	5.5537097	0.10472836	258.1936	T	5.7481984	0.1196125

TestGeoLSM	Difference	Diff_SE	Diff_DF	Ratio_%Ref_	CI_80_Lower	CI_80_Upper
313.62513	0.19448871	0.09348619	24.829354	121.46898	107.40168	137.37878

CI_90_Lower	CI_90_Upper	CI_95_Lower	CI_95_Upper	t1_TOST	t2_TOST	Prob_80_00
103.53701	142.50665	100.1885	147.26953	4.4673151	-0.30651416	7.514E-05

Prob_125_00	MaxProb	TotalProb	Power_TOST	AHpval	Power_80_20	Prob_Eq_Var
0.38088443	0.38088443	0.38095957	0.08554966	0.38080929	0.7482755	

Average Bioequivalence worksheet

2	Ln(AUC)		Observations Us	48
3	Ln(AUC)		Obs. Missing Mo	0
4	Ln(AUC)		Residual SS	0
5	Ln(AUC)		Residual df	0
6	Ln(AUC)		Convergence	Achieved
7	Ln(AUC)		REML log(likelih	-19.238555
8	Ln(AUC)		-2 * REML log(li	38.477111
9	Ln(AUC)		Akaike's Inform	60.477111
10	Ln(AUC)		Schwarz's Bayes	79.591476
11	Ln(AUC)		Hessian eigenva	855.2051
12	Ln(AUC)		Hessian eigenva	715.32814
13	Ln(AUC)		Hessian eigenva	158.63358
14	Ln(AUC)		Hessian eigenva	63.03212
15	Ln(AUC)		Hessian eigenva	21.604278

Diagnostics worksheet

	Dependent	Units	Parameter	Estimate
1	Ln(AUC)		lambda(1,1)_11	0.27893988
2	Ln(AUC)		lambda(1,2)_11	0.35567907
3	Ln(AUC)		lambda(2,2)_11	-1.97E-13
4	Ln(AUC)		Var(Period*For	0.10761781
5	Ln(AUC)		Var(Period*For	0.09035641

Final Variance Parameters worksheet

	Dependent	Units	Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
1	Ln(AUC)		int	1	10.008139	3055.0348	8.9E-14
2	Ln(AUC)		Sequence	1	10.008139	0.095274924	0.7639047
3	Ln(AUC)		Formulation	1	24.829354	4.328066	0.047965077
4	Ln(AUC)		Period	3	28.392036	2.1673487	0.11384356

Sequential Tests worksheet

This concludes the Quick Tour of Phoenix.

Last modified date:7/9/20

CERTARA