

PKPlus™ 2.5

'Plug-n-Play' PK Modeling



S+ *SimulationsPlus*
SCIENCE + SOFTWARE = SUCCESS
simulations-plus.com/pkplus

Simulations Plus (NASDAQ: SLP) (total employees ~100)



SimulationsPlus | *Cognigen* | *DILIsym Services*
SCIENCE+SOFTWARE=SUCCESS

- **Simulations Plus, Inc.**

- Incorporated in 1996
- Software development, PBPK modeling & simulation, and QSAR modeling

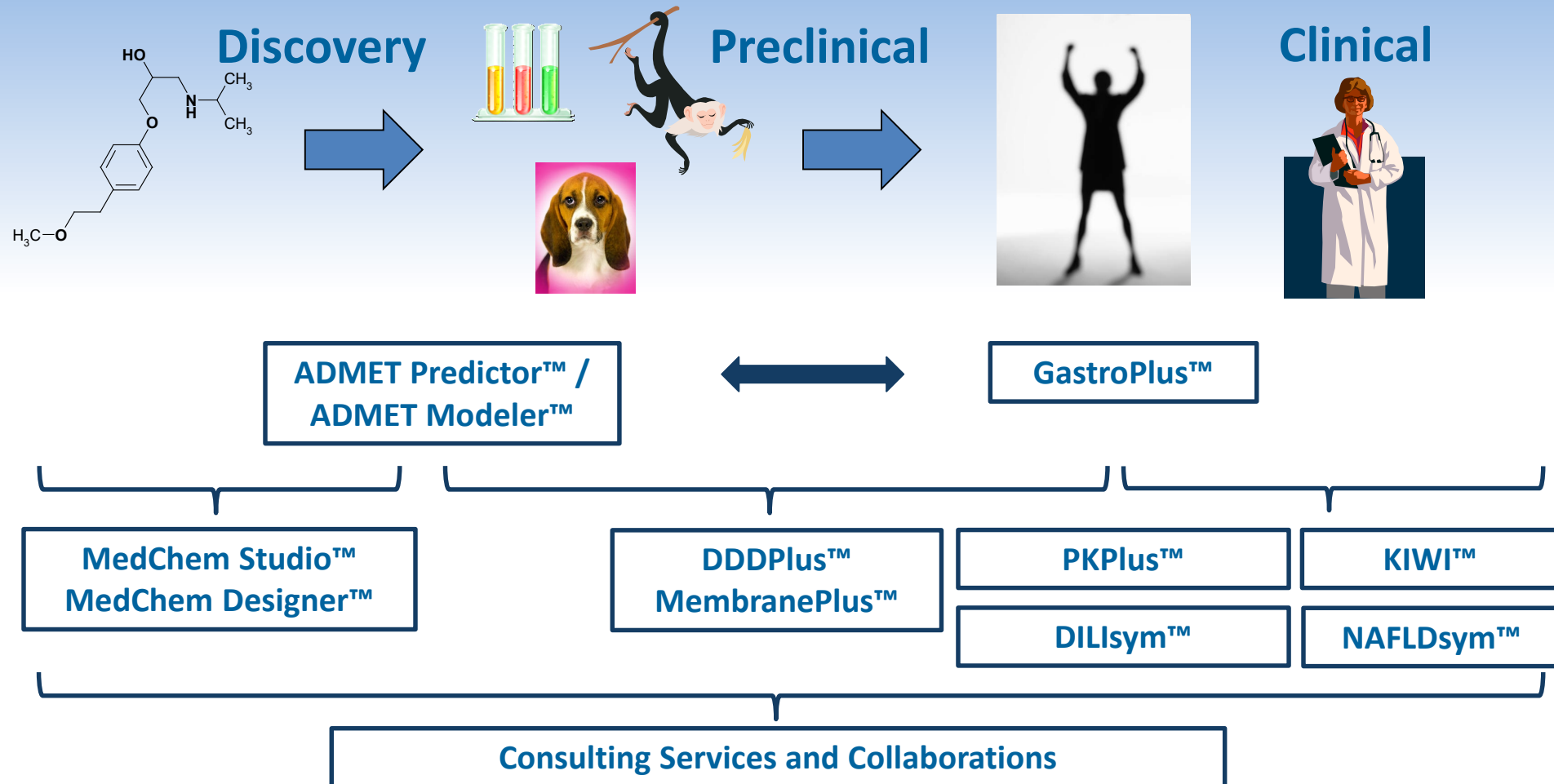
- **Cognigen Corporation, a Simulations Plus company**

- Incorporated in 1992
- Software development, pharmacometric services, and population PK/PD data analyses

- **DILIsym Services, a Simulations Plus company**

- Incorporated in 2015
- Software development, systems pharmacology/toxicology modeling

Simulations Plus: Your end-to-end M&S solutions provider



PKPlus™:

‘Plug-n-Play’ PK Modeling Platform That Combines...

✓ Sophistication

- Powerful NCA options
- Streamlined data visualization and review
- Efficient compartmental analysis routines
- **NEW!** Import of CDISC SEND packages with PC as the source data
- **NEW!** Compatible with 64 bit windows operating systems

✓ Simplicity

- Gives you what is needed for NCA/CA work
- Database file format serves as repository
- Point-and-click interface to minimize errors
- Easy import of common data files
- Smooth Exploratory Data Analysis features
- **NEW!** Improved auto-reporting
- **NEW!** Command line script options

How Does This Benefit You?

✓ Industry

- **DMPK scientists/preclinical PK study managers:**
 - Generate quick, accurate PK study reports
 - Simulate single/multiple-dose regimens
- **Clinical pharmacologists:**
 - Store large data sets in secure file formats
 - Reuse custom variable/plot settings for quick analyses
- **Modelers:**
 - Easy setup of analysis datasets
 - Automate fitting different compartmental PK models

✓ Academia

- **Students:**
 - Learn fundamentals of PK modeling within intuitive interface
- **Professors:**
 - Teach students PK modeling principles in 'real-world' environment
- **Researchers on government/nonprofit grants:**
 - Perform PK data analyses and generate validated reports

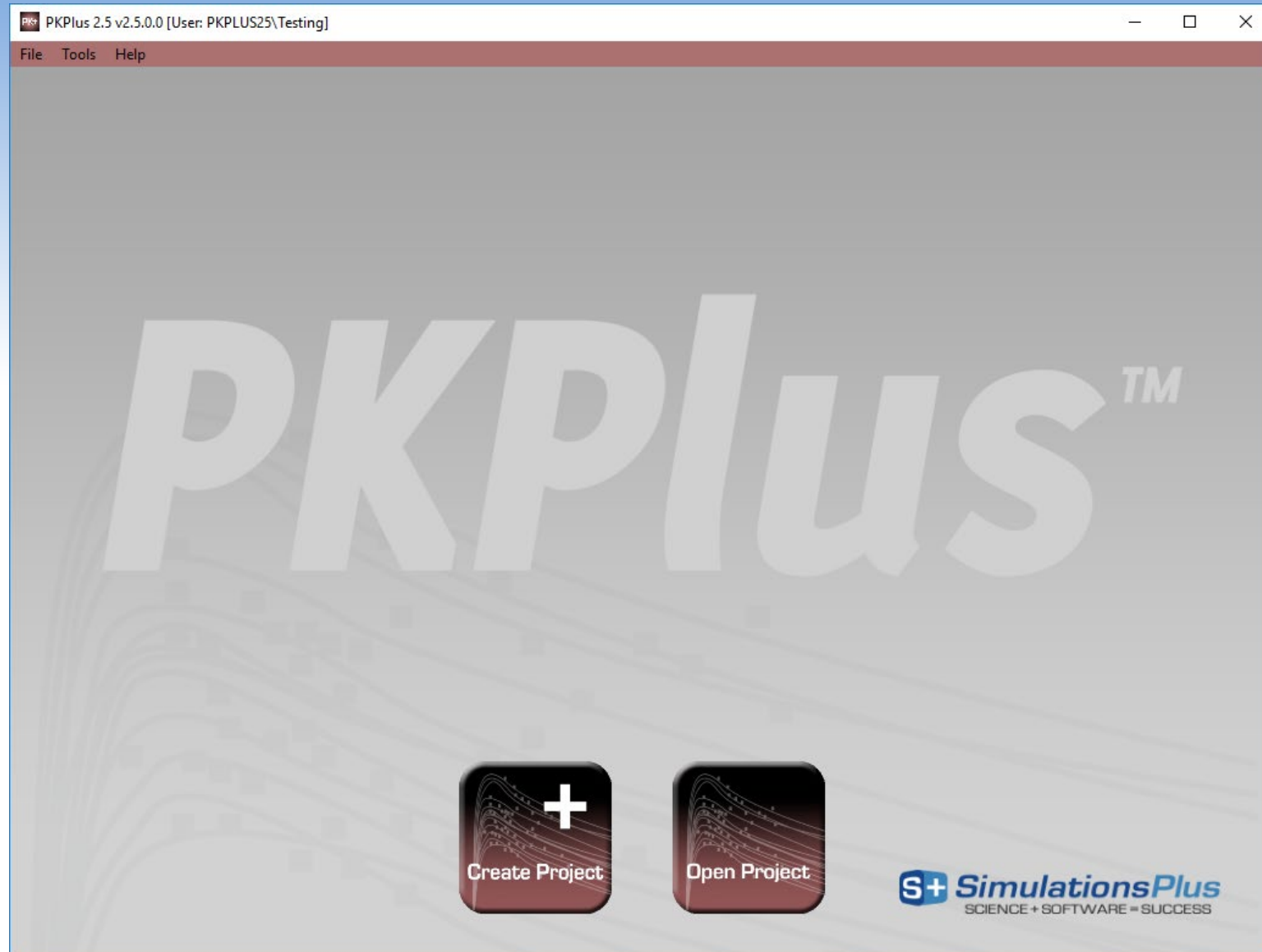
- ✓ **EVERY PKPlus™ user license treated as 'floating seat', able to be shared across/within departments**
- ✓ **NO optional modules**
- ✓ **User licenses cost fraction of competing tools**
- ✓ **Dedicated development team providing rapid support**

PKPLUS™ V2 – A REFRESHER...

PKPlus™ v2 – Features

- **Microsoft® Windows program that provides:**
 - Point-and-click ease of use
 - Eliminate/minimize typing errors
 - Maximize productivity
 - Easy import of common data file formats (.csv, .xpt)
 - Easy **File Mapping** to internal **Display Names**
 - Easy **Data Preview**/Exploratory Data Analysis (EDA)
 - Easy set up of **Analysis Datasets**
 - **Filters**
 - **BLQs**
 - **Exclusions**
 - Easy **NCA** & compartmental analysis (**CA**)
 - Easy report-quality output of **Tables, Figures, and Lists**
 - Easy command line functionality for high throughput analysis

Database Repository



Mapping Raw Data Names to Display Names

File Mapping means connecting the **Raw Data** column headers with the corresponding **Display Names** in PKPlus.

	COMPUND	ROUTE	DOSE	DOSEU	SERIES	FEDFAST	DRUGINFO	DRUGID	TIME
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.1
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.25
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.5
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	1
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	3
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	6
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	9
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	12
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	24
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.1
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.25
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.5
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	1
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	3
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	6
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	9
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	12
M	C-ABC123	IV	2	mg	1	Non-Fasted	C-ABC123 (Lot ...	ABC123	24
M	C-ABC123	PO	20	mg	2	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.25
M	C-ABC123	PO	20	mg	2	Non-Fasted	C-ABC123 (Lot ...	ABC123	0.5
M	C-ABC123	PO	20	mg	2	Non-Fasted	C-ABC123 (Lot ...	ABC123	1
M	C-ABC123	PO	20	mg	2	Non-Fasted	C-ABC123 (Lot ...	ABC123	3
M	C-ABC123	PO	20	mg	2	Non-Fasted	C-ABC123 (Lot ...	ABC123	6

Display Name	Source Column	Unit Source	Units
Conc	CONC	Use Default	ng/mL
Dose	DOSE	Use Default	mg
Fedfast	FEDFAST	Use Default	
Route	ROUTE	Use Default	
Series	SERIES	Use Default	
Sex	SEX	Use Default	
Subj	SUBJ	Use Default	
Time	TIME	Use Default	h

Raw Data can contain many different headers (labels) for the columns. For example, subjects might be identified in different ways such as:

Subject #

Name

Initials

Alphanumeric code

File Mapping – Saving to Database

The screenshot shows the PKPlus 2.5 v2.5.0.0 software interface. The window title is "PKPlus 2.5 v2.5.0.0 [User: PKPLUS25\Testing] [Project: v2.5 Webinar]". The menu bar includes "File", "Tools", and "Help". Below the menu bar are tabs for "Files", "Data Preview", "Analysis", and "Results".

The "Files" tab is active, showing the following fields:

- Project Name: v2.5 Webinar
- Description: (empty)
- Source File Name: C:/Users/Testing/Desktop/PKPlus v2.5 Webinar/source_files/v25_webinar.csv

The "File Information" section shows:

- Source File Columns: 14
- Source File Rows: 34
- Mapped Data Columns: 0
- Mapped Data Rows: 0

A "Save Notes" button is located to the right of the File Information section.

Below the file information are tabs for "Raw Data", "File Mapping", and "Mapped Data". The "File Mapping" tab is active, displaying a table with the following data:

Conc	Dose	FedFast	Route	Series	Sex	Subj	Time
2015	2	Non-Fasted	IV	1	M	S-01	0.1
1510	2	Non-Fasted	IV	1	M	S-01	0.25
1320	2	Non-Fasted	IV	1	M	S-01	0.5
600	2	Non-Fasted	IV	1	M	S-01	1
32.7	2	Non-Fasted	IV	1	M	S-01	3
7.12	2	Non-Fasted	IV	1	M	S-01	6
4.25	2	Non-Fasted	IV	1	M	S-01	9
1.62	2	Non-Fasted	IV	1	M	S-01	12
0.35	2	Non-Fasted	IV	1	M	S-01	24
2110	2	Non-Fasted	IV	1	M	S-02	0.1
1795	2	Non-Fasted	IV	1	M	S-02	0.25
1400	2	Non-Fasted	IV	1	M	S-02	0.5
631	2	Non-Fasted	IV	1	M	S-02	1
42.7	2	Non-Fasted	IV	1	M	S-02	3
5.93	2	Non-Fasted	IV	1	M	S-02	6
2.5	2	Non-Fasted	IV	1	M	S-02	9
0.98	2	Non-Fasted	IV	1	M	S-02	12
0	2	Non-Fasted	IV	1	M	S-02	24
3105	20	Non-Fasted	PO	2	M	S-03	0.25
2823	20	Non-Fasted	PO	2	M	S-03	0.5

At the bottom of the interface, there is a "Mapped data summary" section with the text "No issues found". To the right of this section, there are two buttons: "Save Data to Database" (circled in red) and "Reset Database".

Select **Save Data to Database** only after you are sure you have mapped everything the way you want

Data Preview – Preview data by: Subject

PKPlus 2.5 v2.5.0.0 [User: PKPLUS25\Testing] [Project: v2.5 Webinar]

File Tools Help

Files **Data Preview** Analysis Results

Preview data by:

Subject
 Groups

Total Profiles: 4 Total Subjects: 4 Selected Profiles: 2

Series	Subj	FedFast	Route	Dose	Sex	Profile type
1	S-01	Non-Fasted	IV	2	M	SOURCE
3	S-05	Non-Fasted	PO	20	M	SOURCE

Subjects:

Subj	# Profiles
S-01	1
S-02	1
S-03	1
S-04	1

View Selected Subjects

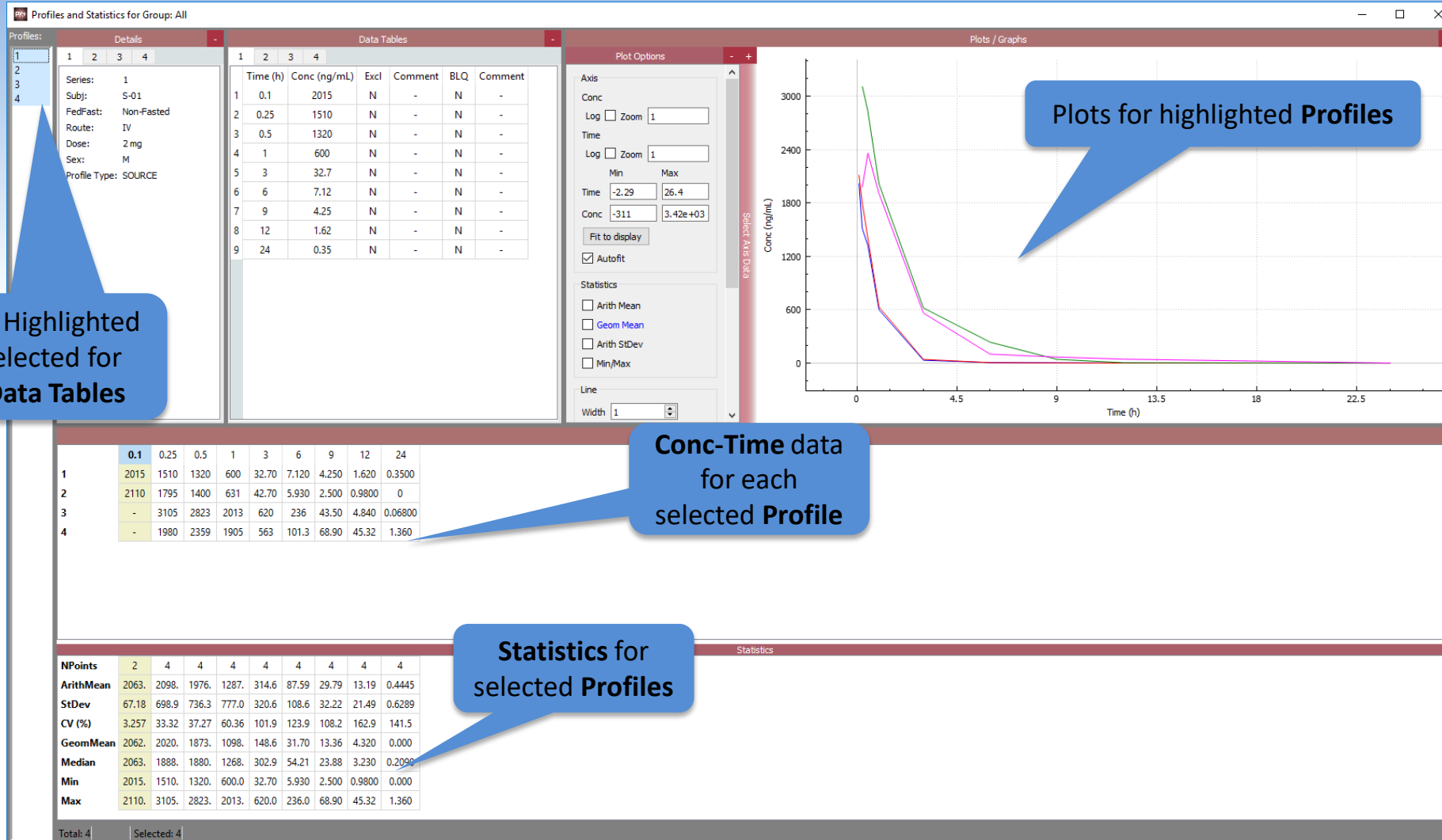
List of Profiles for the Subjects selected at the left

Preview data by selected Subjects or by Groups

Select Subjects you want to view

Click on View Selected Subjects to see their Profiles and Statistics

Data Preview – Profiles and Statistics



Analysis Tab – Analysis Datasets

PKPlus 2.5 v2.5.0.0 [User: PKPLUS25\Testing] [Project: v2.5 Webinar]

File Tools Help

Files Data Preview Analysis Results

Total Profiles: 4 Dataset Profiles: 4 Total Subjects: 4 Dataset Subjects: 4

Filters BLQs Exclusions

Add Filter
Remove Filter

NCA Compartmental

Analysis Settings

AUC Method: Lin & Log
Route: Mapped 0 h
Dose: Mapped mg
Body Weight: Mapped kg
Tau: Single Dose h

Nonparametric Superposition

Interpolation Method: Linear
Half lives to reach steady state: 7
Loading Dose: 100 mg
Maintenance Dose: 100 mg
Interval: 0 h
Number of doses: 7

Output Options

New Dataset Name:

The input cannot be empty.

Return Only Steady-State Profile(s)

Begin Time End Time Begin End
Add Range
Remove Range

Terminal Slopes

Initial Method: None
Num Points: 3 View / Edit Terminal Slope Points

Run NCA Run NPS

Dataset Actions

Add Rename Delete
View Selected Copy to New

Name	Type
All	Source

ID	Name	Type
----	------	------

Profile	Dose	FedFast	Route	Series	Se
1	2	Non-Fasted	IV	1	M
2	2	Non-Fasted	IV	1	M
3	20	Non-Fasted	PO	2	M
4	20	Non-Fasted	PO	2	M

Groups from the **Data Preview** tab can be pushed here as potential **Analysis Datasets**.

Different **Analysis Datasets** can have different treatments for **BLQs** and **Exclusions**.

Adding BLQs: works on Data Preview and Analysis tabs

PKPlus 2.5 v2.5.0.0 [User: PKPLUS25\Testing] [Project: v2.5 Webinar]

File Tools Help

Files Data Preview Analysis Results

Datasets

Name	Type
All	Source

Analyses

ID	Name	Type
----	------	------

Profiles

Profile	Dose	FedFast	Route	Series	Se
1	2	Non-Fasted	IV	1	M
2	2	Non-Fasted	IV	1	M
3	20	Non-Fasted	PO	2	M
4	20	Non-Fasted	PO	2	M

Dataset Actions

Add Rename Delete

View Selected Copy to New

Total Profiles: 4 Dataset Profiles: 4 Total Subjects: 4 Dataset Subjects: 4

Filters BLQs Exclusions

Add BLQ Remove BLQ

PKPlus Add BLQ

Trigger

Alphanumeric: concentration =

Numeric: concentration <

Action

Use imputed value:

Treat as missing

Use actual value

Reason

Application range

Full profile

Before tmax

After tmax

OK Cancel

View / Edit Terminal Slope Points

Run NCA Run NPS

Click here to go to the
BLQs subtab

Click here to add
a BLQ

Select the **Trigger**,
Action, and
Application Range
for the BLQ

BLQs and Exclusions are tied to each **Analysis Dataset**. If you copy a dataset, they are carried along (and then you can modify them for the copy).

If you create a **new dataset**, you **must set** the BLQs and Exclusions for it.

Excluding Data Points...

Profiles and Statistics for Dataset: All

Profiles:

1
2
3
4

Details

Series: 2
Subj: S-03
FedFast: Non-Fasted
Route: PO
Dose: 20 mg
Sex: M
Profile Type: SOURCE

Data Tables

	1	2	3	4
Time (h)	0.25	0.5	1	3
Conc (ng/mL)	3105	2823	2013	620
Excl	N	N	N	N
Comment	-	-	-	-
BLQ	N	N	N	N
Comment	-	-	-	-

Plot Options

Axis

Conc
Log Zoom 1

Time
Log Zoom 1

Min Max
Time -2.29 25.4
Conc -292 3.43e+03

Autofit

Statistics

Arith Mean
 Geom Mean
 Arith StDev
 Min/Max

Line
Width 1

Plots / Graphs

Data summary

	0.1	0.25	0.5	1	3	6	9	12	24
1	2015	1510	1320	600	32.70	7.120	4.250	1.620	0.3500
2	2110	1795	1400	631	42.70	5.930	2.500	0.9800	0
3	-	3105	2823	2013	620	236	43.50	4.840	0.06800
4	-	1980	2359	1905	563	101.3	68.90	45.32	1.360

Statistics

	2	4	4	4	4	4	4	4	
NPoints	2063.	2098.	1976.	1287.	314.6	87.59	29.79	13.19	0.4445
ArithMean	67.18	698.9	736.3	777.0	320.6	108.6	32.22	21.49	0.6289
StDev	3.257	33.32	37.27	60.36	101.9	123.9	108.2	162.9	141.5
GeomMean	2062.	2020.	1873.	1098.	148.6	31.70	13.36	4.320	0.000
Median	2063.	1888.	1880.	1268.	302.9	54.21	23.88	3.230	0.2090
Min	2015.	1510.	1320.	600.0	32.70	5.930	2.500	0.9800	0.000
Max	2110.	3105.	2823.	2013.	620.0	236.0	68.90	45.32	1.360

Total: 4 Selected: 4

Analysis Tab – NCA Model Settings

PKPlus 2.5 v2.5.0.0 [User: PKPLUS25\Testing] [Project: v2.5 Webinar]

File Tools Help

Files Data Preview Analysis Results

Total Profiles: 4 Dataset Profiles: 4 Total Subjects: 4 Dataset Subjects: 4

Filters BLQs Exclusions

Datasets

Name	Type
All	Source

Analyses

ID	Name	Type
----	------	------

Profiles

Profile	Dose	FedFast	Route	Series	Se
1	2	Non-Fasted	IV	1	M
2	2	Non-Fasted	IV	1	M
3	20	Non-Fasted	PO	2	M
4	20	Non-Fasted	PO	2	M

Dataset Actions

Add Rename Delete

View Selected Copy to New

Analysis Settings

AUC Method: Lin & Log

Route: Mapped 0 h

Dose: Mapped mg

Body Weight: Mapped kg

Tau: Single Dose h

Begin Time: Begin End

Begin: h

End: h

Add Range Remove Range

Terminal Slopes

Initial Method: None

Num Points: 3 View / Edit Terminal Slope Points

Run NCA

Nonparametric Superposition

Interpolation Method: Linear

Half lives to reach steady state: 7

Loading Dose: 100 mg

Maintenance Dose: 100 mg

Interval: 0 h

Number of doses: 7

Output Options

New Dataset Name:

The input cannot be empty.

Return Only Steady-State Profile(s)

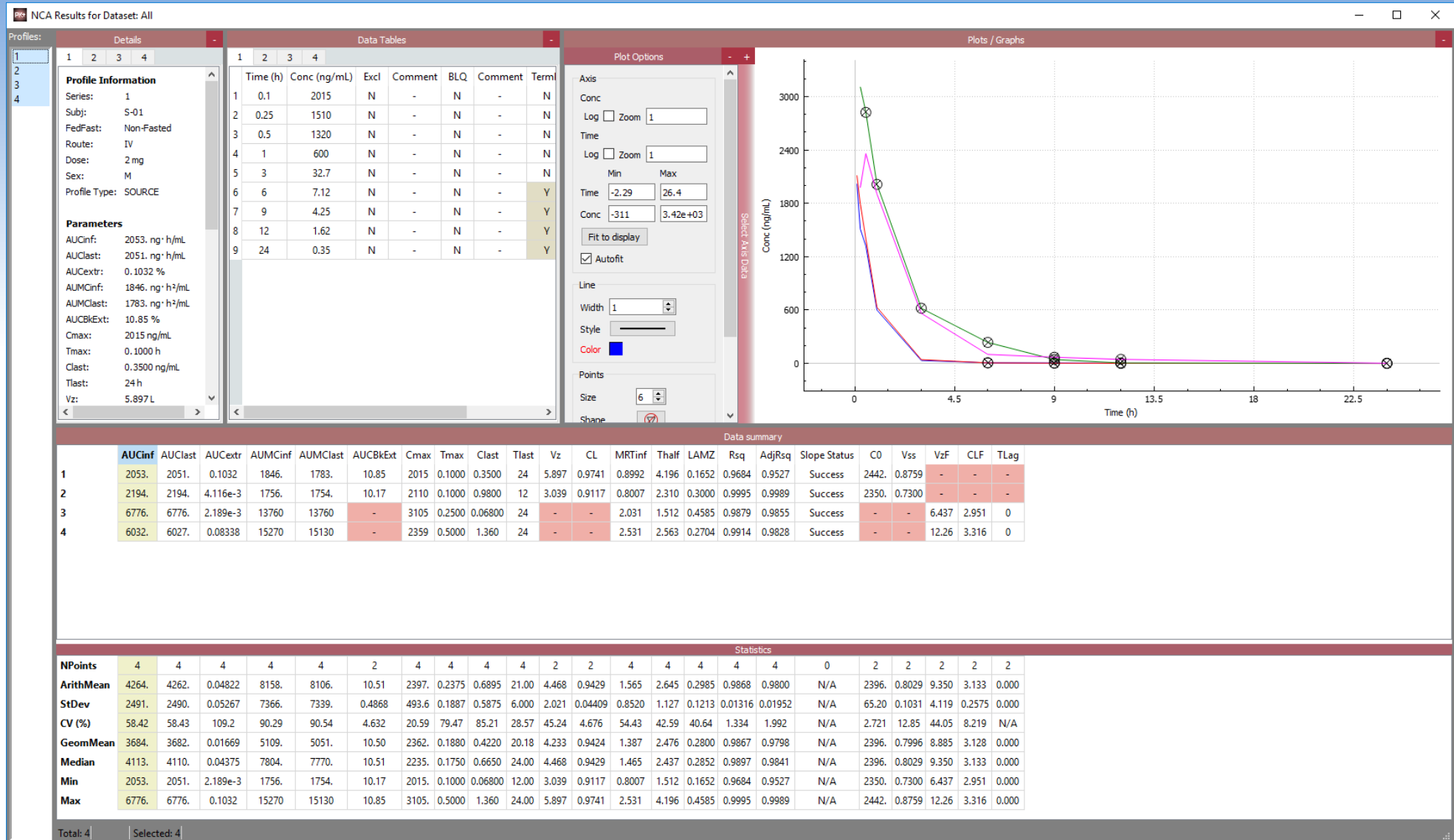
Run NPS

To run an **NCA**:

- (1) Select the **Analysis Dataset**
- (2) Set terminal slopes
- (3) Select the **NCA Model Settings**
- (4) Click on **Run NCA**

When the **NCA** is complete, the **NCA Results** window will appear.

NCA Results Window



Compartmental PK Analysis

PKPlus 2.5 v2.5.0.0 [User: PKPLUS25\Testing] [Project: v2.5 Webinar]

File Tools Help

Files Data Preview Analysis Results

Datasets

Name	Type
All	Source

Analyses

ID	Name	Type
----	------	------

Profiles

Profile	Dose	FedFast	Route	Series	Se
1	2	Non-Fasted	IV	1	M
2	2	Non-Fasted	IV	1	M
3	20	Non-Fasted	PO	2	M
4	20	Non-Fasted	PO	2	M

Compartment

One Two Three

Dataset Actions

Add Rename Delete

View Selected Copy to New

Total Profiles: 4 Dataset Profiles: 4 Total Subjects: 4 Dataset Subjects: 4

Filters BLQs Exclusions

CA model settings

Add BLO Remove BLO

NCA Compartmental

Analysis Settings

Models: All

Fit Profiles: Across profiles

Fit Lag Time: No

Clearance: Linear

Route: Mapped

Infusion Time: h

Dose: Mapped

Dose: mg

Body Weight: Mapped

Body Weight: kg

Obj Fcn Weighting: $1/\text{Yhat}^2$

Initial Values: NCA of each profile

Results

Initial Values

V_c L CL L/h

k_{12} 1/h k_{21} 1/h

k_{13} 1/h k_{31} 1/h

V_{max} mg/h k_a 1/h

K_m mg/L F 100 %

Lag h

Multiple Dose Simulation

Total Simulation Time 1 h Points per Profile 3

New Dataset Name:

The input cannot be empty.

Dose Regimen

Route	Amount (mg)	Start (h)	Interval (h)	Inf Time (h)	Count
-------	-------------	-----------	--------------	--------------	-------

Add New Dose Remove Dose

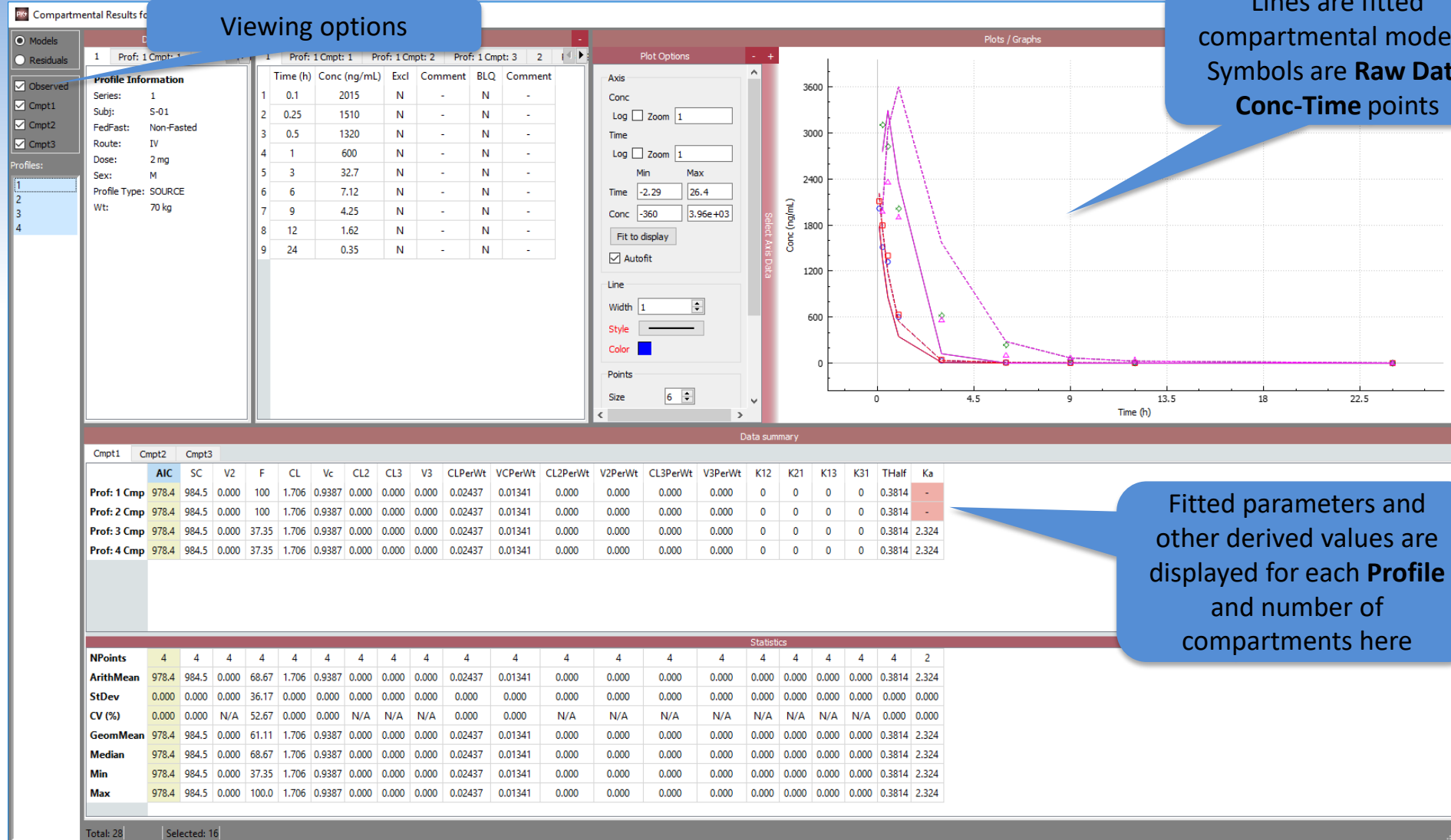
Run Compartmental Simulate

To run a **CA** on any **Analysis Dataset**:

- (1) Select the dataset
- (2) Set the **CA** settings
- (3) Click on **Run Compartmental**

When the **CA** is complete, the **CA Results** window will appear

Compartmental PK Results Window



Results Tab

Analysis ID	Analysis	Dataset	Notes
1	nca	all	NCA analysis for the all dataset

Setting	Value
1 AUC	Lin/Lin
2 AUC	0.000 - 12.00
3 Dose	Mapped
4 Route	Mapped
5 Infusion Time	Mapped
6 Single Dose	
7 Slope	Auto

Tables, Figures, and Lists

- List of Individual PK Concentrations and Times
- List of Individual PK Parameters
- Summary Table of PK Concentrations
- Summary Table of PK Parameters
- Individual PK Plots
- Mean PK Plots

Double-click on an analysis to bring up the **NCA Results** or **CA Results** window to view the results of the analysis

Select from the list of available templates for Auto Reports

After selecting an analysis and the reports you want, click on **Auto** or **Custom Reports** to produce TFLs

Example – Table of Individual PK Parameters (.docx file)

List of Individual PK Parameters

Dataset: All

Username: Walt

Run date: 2016-04-29 04:00:45

Project: Example for manual

AUC Method	Slope Method	Dose	Route	Analysis ID	Slope Status												
Linear & Log Interpolation	Manually selected points	Mapped	Mapped	1	SUCCESS												
Profile ID	AUCinf	AUClast	AUMCinf	AUMClast	Num. Points	Cmax	LAMZ	MRTinf	Tmax	VzF	AUCextr	CLF	Clas	Tlast	Thalf	Rsq	AdjRsq
9	1.138	1.093	8.585	7.177	14	0.1546	0.1359	7.543	1.500	905.3	3.945	123.0	6.100e-3	24.00	5.101	0.9993	0.9991
10	0.8355	0.8237	4.684	4.332	14	0.1571	0.1734	5.606	1.500	966.5	1.415	167.6	2.050e-3	24.00	3.998	1.0000	0.9999
11	0.7076	0.7071	2.470	2.456	14	0.1961	0.3003	3.490	1.000	658.9	0.07059	197.9	1.500e-4	24.00	2.308	0.9999	0.9999
12	1.094	1.065	7.718	6.859	14	0.1484	0.1586	7.056	1.500	806.8	2.593	128.0	4.500e-3	24.00	4.369	0.9994	0.9987
13	0.6053	0.6016	3.160	3.055	14	0.1087	0.2184	5.221	1.500	1.059e+3	0.6052	231.3	8.000e-4	24.00	3.174	1.0000	0.9999
14	0.9283	0.9131	5.796	5.347	14	0.1388	0.1779	6.244	2.000	847.7	1.635	150.8	2.700e-3	24.00	3.896	0.9994	0.9993
15	0.9414	0.8979	7.687	6.309	14	0.1092	0.1308	8.166	1.500	1.137e+3	4.628	148.7	5.700e-3	24.00	5.298	0.9998	0.9998
16	0.7466	0.7321	4.762	4.327	14	0.1137	0.1657	6.378	2.000	1.132e+3	1.940	187.5	2.400e-3	24.00	4.183	0.9993	0.9991
17	0.8697	0.8475	5.902	5.226	14	0.1288	0.1535	6.787	1.500	1.049e+3	2.547	161.0	3.400e-3	24.00	4.516	0.9999	0.9997
18	0.7774	0.7706	4.344	4.147	14	0.1317	0.2056	5.587	1.500	876.0	0.8760	180.1	1.400e-3	24.00	3.372	1.0000	0.9999
19	1.242	1.215	8.312	7.477	14	0.1731	0.1594	6.691	2.000	706.9	2.222	112.7	4.400e-3	24.00	4.348	0.9996	0.9994
20	0.9334	0.9304	3.889	3.804	14	0.2200	0.2326	4.167	1.000	644.8	0.3224	150.0	7.000e-4	24.00	2.980	0.9998	0.9997
21	1.204	1.132	10.67	8.360	14	0.1383	0.1218	8.865	2.000	954.5	5.966	116.3	8.750e-3	24.00	5.690	1.0000	1.0000
22	0.5786	0.5757	2.861	2.778	14	0.1107	0.2227	4.945	1.500	1.087e+3	0.5045	242.0	6.500e-4	24.00	3.113	0.9999	0.9998

Example – Mean PK Plots (.docx file)

Mean PK Plots

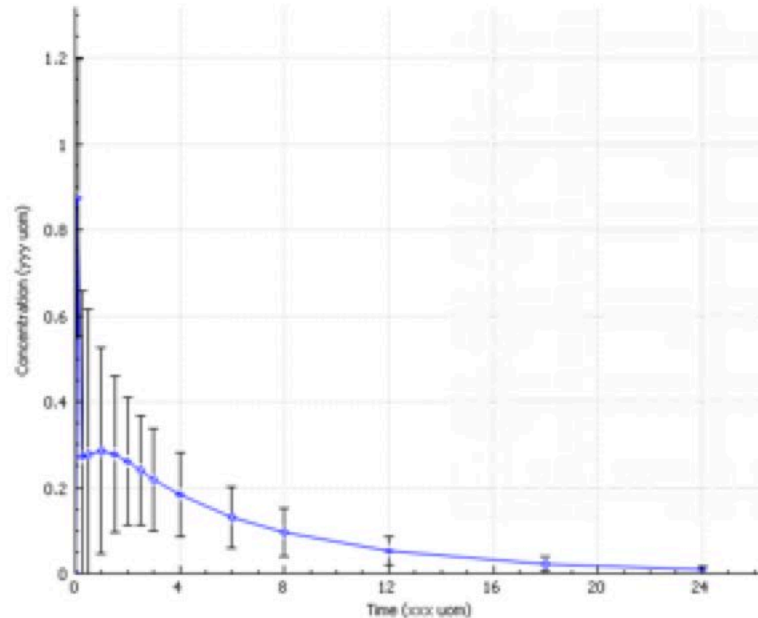
Dataset: All

Username: Walt

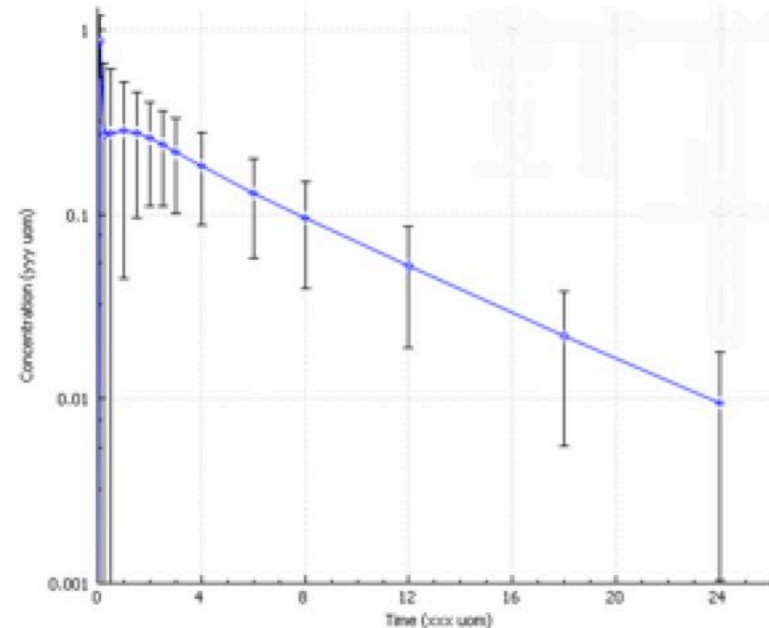
Run date: 2016-04-29 04:00:45

Project: Example for manual

Linear View



Semilogarithmic View



WHAT'S NEW IN PKPLUS™ V2.5?

NEW Additions in PKPlus™ v2.5 – Highlights

- **Now compatible with 64 bit windows operating systems**
- **Import of CDISC SEND packages with PC as the source file data**
- **Improvements to auto-reporting**
- **Improvements to command line processing**
- **Bug fixes**

PRODUCT DEMONSTRATION

SUMMARY

PKPlus™ v2.5 Adds...

- Now compatible with 64 bit windows operating systems
- Import of CDISC SEND packages with PC as the source file data
- Improvements to auto-reporting
- Improvements to command line processing

PKPlus™ offers all necessary PK modeling & simulation functionality!

Final Questions to Ask Yourself...

- **Competing tools offer more capabilities with:**
 - Higher prices
 - Restrictive licensing (e.g., standalone only)
- **Ask yourself these questions about competing tools:**
 - Is it easy to perform the basic PK operations I need?
 - How much of the functionality do I really use?
 - What am I paying for?
- **Honest answers will lead you to PKPlus™**



SimulationsPlus | *Cognigen* | *DILsym Services*

SCIENCE+SOFTWARE=SUCCESS

For More Information on PKPlus™, Visit:

www.simulations-plus.com/software/pkplus

For Company News & Events, Visit:

www.simulations-plus.com