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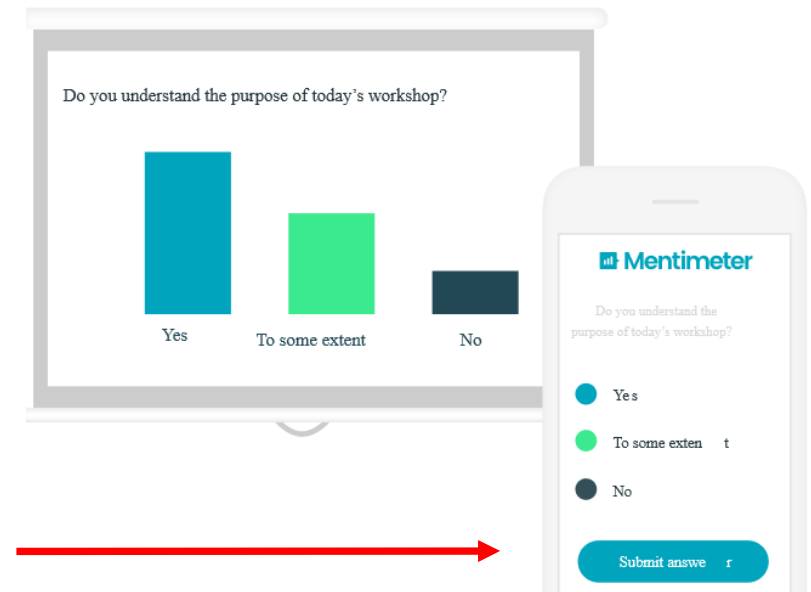
SCIENTIFIC WEBINAR SERIES

Welcome to Phoenix 8.0



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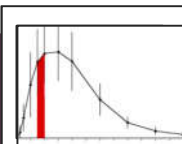


Today's speaker

- Nathan Teuscher
 - Vice President of Pharmacometric Solutions at Certara
 - Leader in the pharmaceutical industry as a scientist, consultant, and teacher
 - Over 20 years experience teaching and training in the pharmaceutical industry



New Features in Phoenix 8



NCA

- ◆ Business rules
- ◆ New parameters
- ◆ User-defined Parameters



NLME

- ◆ Automatic Parallelization on Remote Grids
- ◆ Distributed Delay Function



Validation Suite

- ◆ Integrated into Phoenix
- ◆ Reduced Run Time
- ◆ History stored in Phoenix



Phoenix Framework

- ◆ Lock Workflows
- ◆ Load/save Object settings
- ◆ License Activation within Phoenix

New NCA Features

New NCA Features

- Rules for Lambda z best fit
 - Specify maximum number of points
 - Specify earliest time for slope
 - Not applicable for Drug Effect model
- Lambda z acceptance criteria
 - Flag Output data based on criteria set for
 - R^2 adjusted
 - % Extrapolated AUC (Observed or Predicted)
 - Span (defined as sampling interval / $t_{1/2}$)
- User-defined parameters can be added
 - Computed concentrations at specific time points
 - Arithmetic combinations of any NCA parameter (e.g. $C_{\max}/2$)

Lambda Z Rules for Best Fit – Set Max # Points

- Enforces that the Best-Fit method follows the user's rules
- Lambda Z values can be different from those computed by Best-Fit
- Does NOT apply to Time Range or Drug Effect Model 220

Without Max # of Points set:

Options	User Defined Parameters	Rules
Lambda Z Rules for Best Fit Option		
Max # of Points		
Start Time Not Before		

Form	Subject	N_Samples	Dose (mg)	No_points_lambda_z	Lambda_z (1/min)
1	Capsule	12	10	6	0.016987622
2	Capsule	11	10	3	0.014881624
3	Capsule	14	10	10	0.016266891

After Max # of Points set:

Options	User Defined Parameters	Rules
Lambda Z Rules for Best Fit Option		
Max # of Points	6	
Start Time Not Before		

Form	Subject	N_Samples	Dose (mg)	No_points_lambda_z	Lambda_z (1/min)
1	Capsule	12	10	6	0.016987622
2	Capsule	11	10	3	0.014881624
3	Capsule	14	10	6	0.016342763

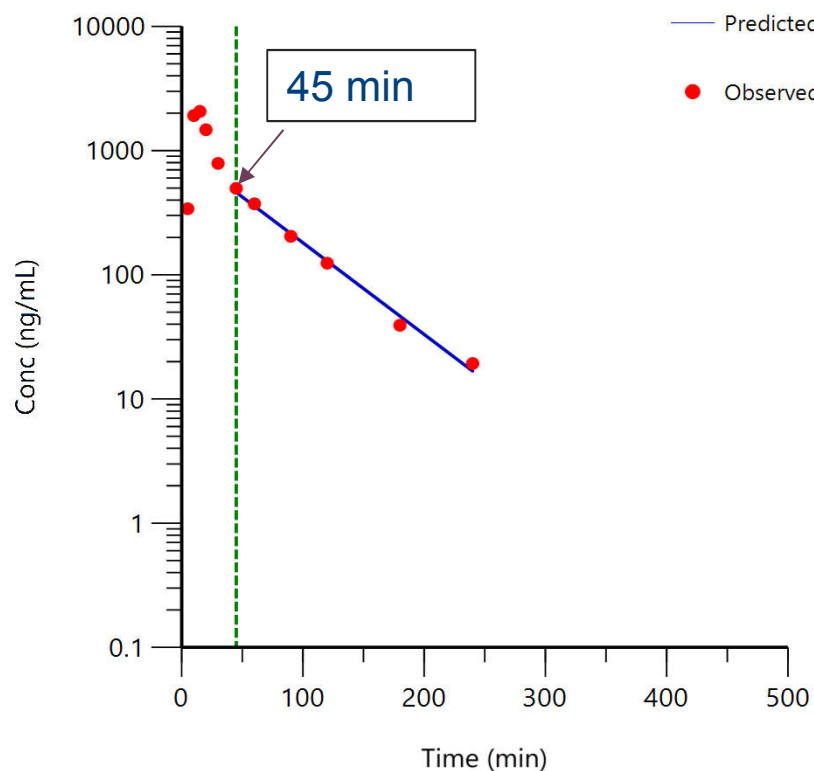
Rules for Lambda Z Best Fit – Set Start Time

Lambda Z Rules for Best Fit Option

Max # of Points

Start Time Not Before

Form=Capsule, Subject=1
Rsqr=0.9927 Rsqr_adjusted=0.9908 HL_Lambda_z=40.8031
6 points used in calculation



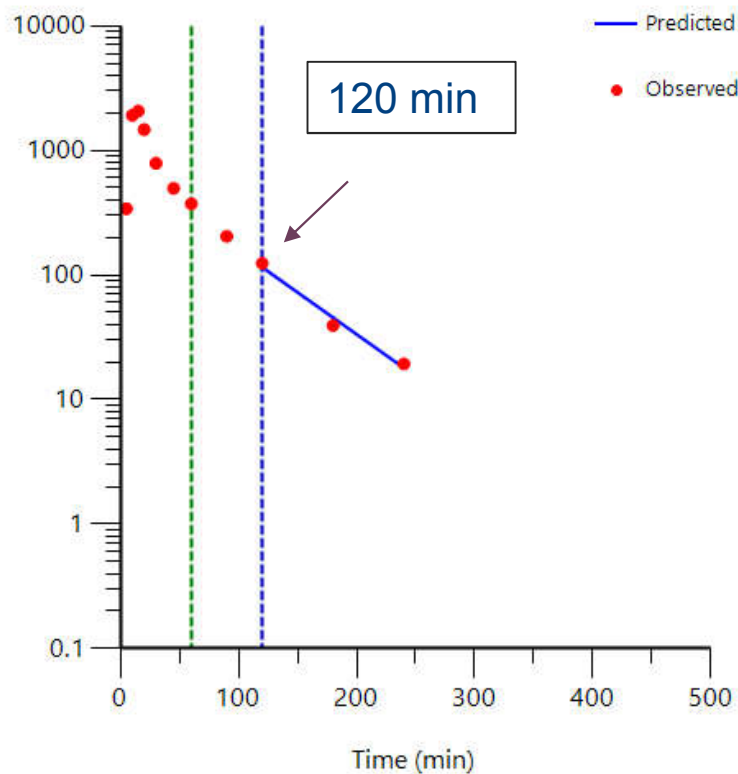
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Lambda Z Rules for Best Fit Option

Max # of Points

Start Time Not Before

Form=Capsule, Subject=1
Rsqr=0.9815 Rsqr_adjusted=0.9631 HL_Lambda_z=44.726
3 points used in calculation



Rules - Lambda Z Acceptance Criteria

When Rules are set, Flag columns appear as next column in the outputs to indicate the status of the parameters

- **Accepted:** Criterion was met
- **Not_Accepted:** Criterion was NOT met
- **Insufficient:** Insufficient data
- **Missing:** Not calculated

Options	User Defined Parameters	Rules	Plots
Lambda Z Rules for Best Fit Option			
Max # of Points		<input type="text"/>	
Start Time Not Before		<input type="text"/>	
Lambda Z Acceptance Criteria			
Rsqr_adjusted		≥ 0.98	
AUC_%Extrap_obs		≤ 20	
Span		≥ 3	

Setup	Results	Verification
Filter:		
Output Data		
Dosing Used		
Exclusions		
Final Parameters		
Final Parameters Pivot		
Partial Areas		
Plot Titles		
Slopes Settings		
Summary Table		
Therapeutic Response		
User Defined Comput		
User Defined Paramete		
User Defined Paramete		
Plots		
Observed Y and Predict		

	Form	Subject	N_Samples	Flag_N_Samples	Rsqr_adjusted	Flag_Rsqr_adjusted	Span	Flag_Span	AUC_%Extrap_obs ({%})	Flag_AUC_%Ext
1	Capsule	1	12		0.99084131	Accepted	4.7790519	Accepted	1.5667721	Accepted
2	Capsule	2	11		0.99830568	Accepted	1.9322681	Not_Accepted	4.5425152	Accepted
3	Capsule	3	14		0.98994607	Accepted	10.795355	Accepted	0.045827201	Accepted
4	Capsule	4	12		0.97396481	Not_Accepted	1.357575	Not_Accepted	19.313218	Accepted
5	Capsule	5	13		0.99517799	Accepted	2.1988469	Not_Accepted	2.79903	Accepted
6	Capsule	6	13		0.95238716	Not_Accepted	4.6806009	Accepted	1.2559696	Accepted
7	Tablet	1	1	Insufficient		Missing		Missing		Missing
8	Tablet	2	13		0.99940672	Accepted	5.0199767	Accepted	0.13358334	Accepted
9	Tablet	3	13		0.9752163	Not_Accepted	8.6250895	Accepted	0.09562258	Accepted
10	Tablet	4	13		0.99800676	Accepted	5.1786059	Accepted	1.1223817	Accepted
11	Tablet	5	13		0.98318632	Accepted	4.1813116	Accepted	1.2675492	Accepted
12	Tablet	6	14		0.96603833	Not_Accepted	6.8755816	Accepted	0.83773836	Accepted

Updated Insufficient Data Rules

- Compute all possible final parameters
 - Removes imputation of “missing”
 - “Exclude Profiles with Insufficient Data” checkbox removed
 - Profiles with insufficient data are flagged with N_Samples_Flag
- N_Sample Flag rules:

Available Data Example	N_Samples	N_Samples Flag Column	Output Result
N=1 and Dose point cannot be inserted IV Bolus: T=5 min, Cp= 40.5 PO: T=0, Cp=5.1	1	Insufficient	Cmax, Tmax, Cmin and Tmin etc.
Non-bolus profile with 1 nonmissing datum & Dosepoint can be inserted	1	No Flag	Based on two data points Cmax, AUClast, Tmax etc.

New NCA Features – Parameters

Plasma Matrix

- Swing
- Swing_Tau
- %Fluctuation
- %Fluctuation_Tau
- Clast_pred
- Ctau (obs and pred)
- Span
- AUClast_D
- AUC_Tau_D
- AUC_Tau_%Extrap
- Lambda_z_intercept
- N_Samples
- Dose

Urine Matrix

- Rate_last_pred
- AURC_last_D
- N_Samples
- Dose

Renamed


- TimeBetween
- TimeHigh
- TimeInfBetween
- AUCBetween
- AUCHigh
- AUCInfBetween
- Lambda_z_Intercept

Computed Concentrations

- Allows user to specify Times at which to compute C (or Y) by Imputation
- Times can be separated by comma or seq(start, end, interval)

Options | User Defined Parameters | Rules | Plots

☒ Include with Final Parameters

Compute Concentrations at Times: 

Setup | Results | Verification

Filter:

Output Data

- Dosing Used
- Exclusions
- Final Parameters
- Final Parameters Pivoted
- Partial Areas
- Plot Titles
- Slopes Settings
- Summary Table
- Therapeutic Response
- User Defined Computed Y**
- User Defined Parameters
- User Defined Parameters Pivoted

Computed					
	subj	Time (hr)	Computed_Conc (ng/mL)	Type	Wt (kg)
1	1	2	9.66	Observed	79.6
2	1	6	7.915	Computed	79.6
3	1	8	7.18	Computed	79.6
4	1	16	5.0533333	Computed	79.6
5	2	2	8.33	Observed	72.4
6	2	6	5.74	Computed	72.4
7	2	8	4.975	Computed	72.4
8	2	16	2.3066667	Computed	72.4
9	3	2	7.8	Observed	70.5
10	3	6	5.75	Computed	70.5

User Defined Parameters

- Users can define their own parameters as functions of
 - NCA final parameters (default or preferred names)
 - Carry Column, Dose and Tau from External worksheets
- Option to merge with Final Parameters outputs

Options	User Defined Parameters	Rules	Plots	
<input checked="" type="checkbox"/> Include with Final Parameters				
Compute Concentrations at Times: <input type="text" value="2, 6, 8, 16"/>				
Additional NCA Parameters				
<input type="button" value="Add"/>				
Parameter		Definition	Units Label	Errors
Clast_D	=	Clast_pred/Dose	ng/mL/mg	✗
CLss_F_wt	=	Cl_F_obs/Wt	mL/hr/kg	✗

Original parameters

User-defined parameters

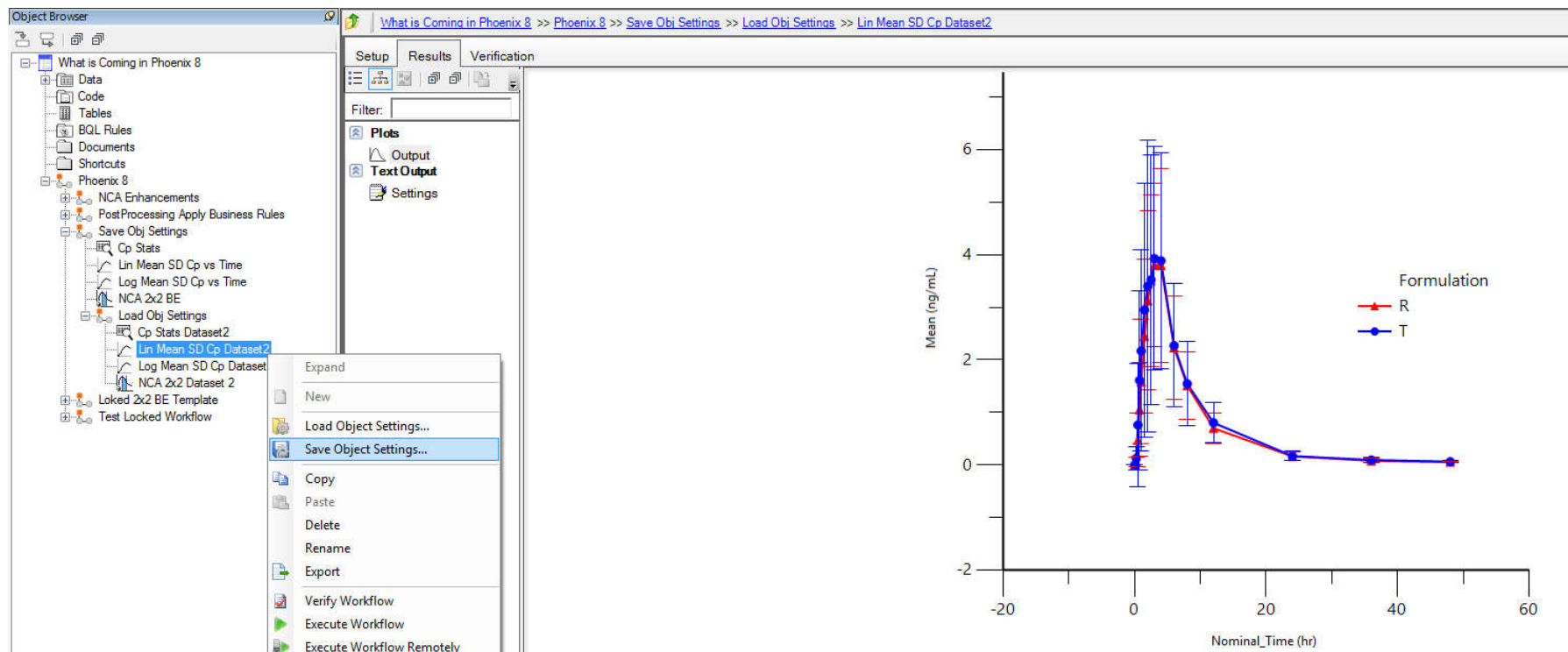
Filter:										
<div>Output Data</div> <div> <div>Dosing Used</div> <div>Exclusions</div> <div>Final Parameters</div> <div>Final Parameters Pivoted</div> <div>Partial Areas</div> <div>Plot Titles</div> <div>Slopes Settings</div> </div>		MRTlast (hr)	MRTINF_obs (hr)	MRTINF_pred (hr)	C2 (ng/	C6 (ng/	C8 (ng/	C16 (ng/mL)	Clast_D (ng/mL/mg)	CLss_F_wt (mL/hr/kg)
	1	9.6400131	20.377609	20.377683	9.66	7.915	7.18	5.0533333	0.32800326	588.71029
	2	7.6425671	9.8419073	9.8201811	8.33	5.74	4.975	2.3066667	0.089028951	1386.78
	3	8.0080512	10.406244	10.413289	7.8	5.75	5.1	2.8166667	0.10534038	1304.339
	4	8.2483914	10.656747	10.673947	8.38	6.33	5.555	3.1766667	0.11590806	1178.0693
	5	8.2837377	11.765752	11.742919	9.33	7.325	6.495	3.4366667	0.15581946	1326.4708
	6	8.2249857	11.588667	11.622849	6.32	4.48	3.74	2.16	0.093068538	1475.9362

Demonstration of New NCA Features

New Phoenix Framework Features

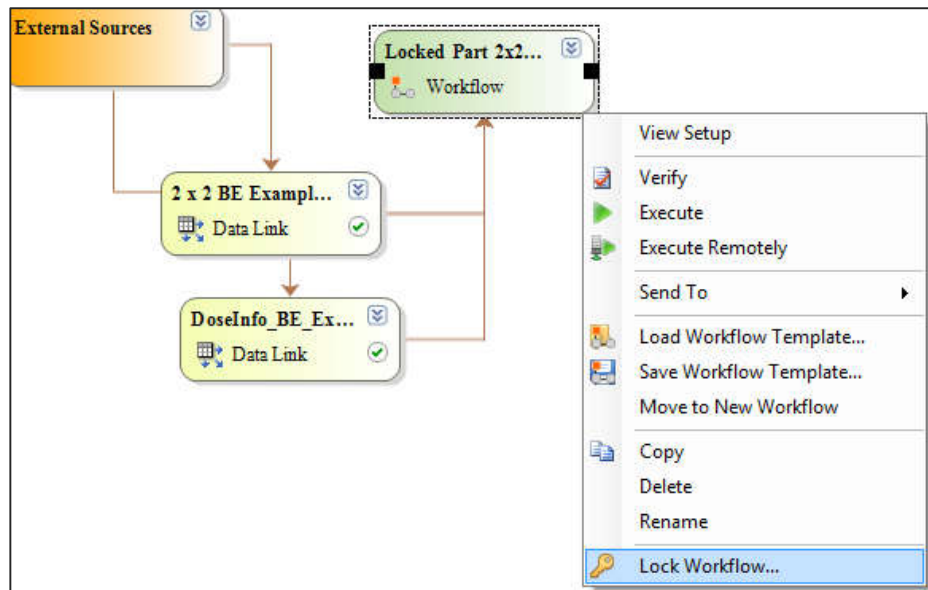
New Phoenix Framework Features

- Flexibility to work with Object settings
 - One Click Load/Save settings
 - Ability to manage (add, remove, rename) saved settings
 - Single-click modification of all settings
 - Create library of settings for each operational object



New Phoenix Framework Features

- Ability to lock workflows to prevent changes
 - Password protected Workflow Objects
 - Locked workflows can be executed, but not modified
 - Simplifies QC/QA efforts for Phoenix templates



The 'Lock Workflow' dialog box is shown, featuring a warning message: 'Please note that passwords cannot be recovered.' It contains three input fields: 'Name:' with the value 'Local User', 'Password:' with masked characters, and 'Confirm Password:' with masked characters. 'Lock' and 'Cancel' buttons are at the bottom right.

Demonstration of New Phoenix Framework Features

New NLME Features

New NLME Features – Parallelization Remote Grids

- Automatic parallelization on remote computational grids
 - Easy to set up
 - No user intervention required
 - All scenarios are executed in parallel across maximum possible cores
 - Supports all NLME run modes except Sim/Predictive Check
- Simple run (no sort variable)
 - Smaller number of (1) number of cores and (2) number of subjects divided by 3
 - Example: 360 cores, 300 subjects:



New NLME Features – Parallelization Remote Grids

- Simple run with sort variable
 - Smaller number of (1) number of cores divided by number of unique sort keys and (2) number of subjects per unique sort key divided by 3
 - Example: 360 cores, 3 sort keys, 400 subjects per sort key



- Covariate Search Shotgun
 - Total number of covariate models is 2^p , where p is the number of covariate-parameter relationships
 - Smaller number of (1) number of cores divided by 2^p and (2) number of subjects divided by 3
 - Example: 360 cores, 6 covariate-parameter relationships, 300 subjects: (64 models, 5 cores each)

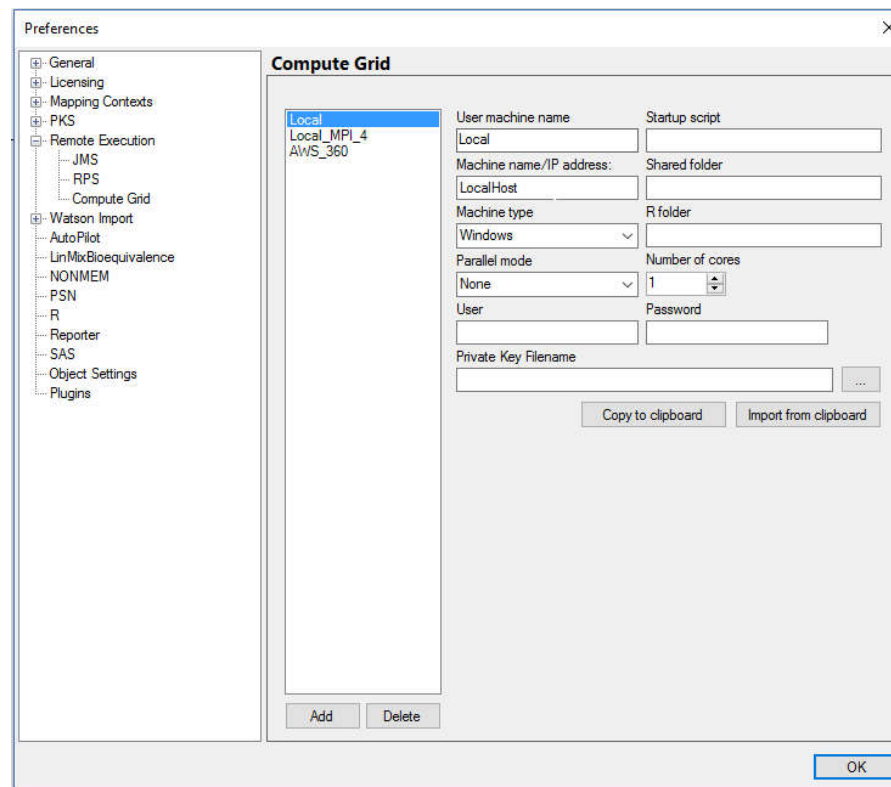


New NLME Features – Parallelization Remote Grids

Run Mode	No of Subjects	No of Models	No of Cores	Utilization of Cores
Simple, No Sort	300	-	360	1 x 100 Cores (300 / 3)
Simple	400 / Sort	3 Unique Sorts	360	120 Core/Sort (360 / 3)
Scenarios, No Sort	300 / Scenario	6 Scenarios	360	60 Core/Scenario (360 / 6)
Scenarios with 3 Sort Keys	200 / Sort / Scenario	18 (6 Scenarios & 3 Sort Keys)	360	20 Cores/Sort/Scenario (360 / (3 * 6))
Covariate Search – Forward addition	300	Round 1 -> 9 (Base + 8 Covariates)	360	40 Cores/Covariate (360 / 9)
Covariate Search – Backward deletion	300	3 Covariates (From Final model)	360	100 Cores/Covariate (300 / 3)
Covariate Search – Shot Gun	300	6 Covariate/ Parameter relationships	360	5 Cores / model (360 / 2^6)
Boot-Strap	200	500 Replicates	360	66 Cores First Run, 1 Core / Replicate

New NLME Features - Remote Computational Grid setup

- Three options for adding remote platforms
 - Text file in installation directory: ..\Phoenix\application\ (admin privileges required)
 - Text file in user app directory: %appdata%\..\Phoenix
 - Edit | Preferences | Remote Execution | Compute Grid



New NLME Features – Delay Function

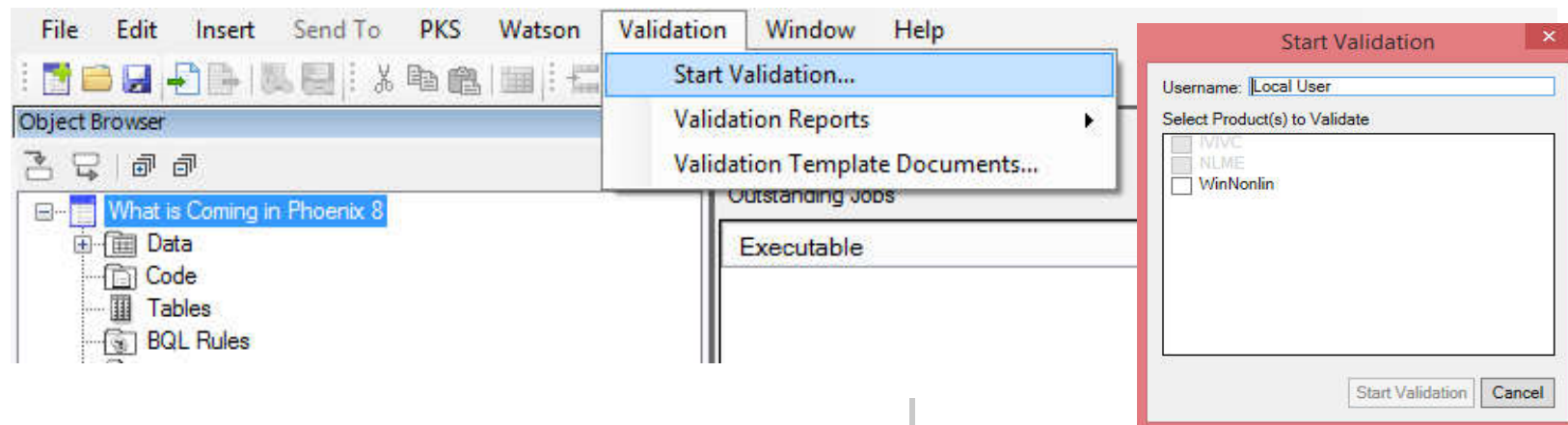
- Distributed delay added to PML
 - To simplify coding model delays in PK/PD models with
 - transit compartments
 - dual absorption models
 - effect compartment models
 - indirect response
 - Shape parameter added to “delay” function
 - New function “delayInfCpt” to accommodate absorption delays

Demonstration of New NLME Features

New Validation Suite Features

New Validation Suite Within Phoenix

- Validation Suite integrated into the Phoenix application
 - No separate installation
 - Simultaneous release along with Phoenix WNL
- Significantly reduced run-time
 - Reduced average run-time from about two days to less than 30 mins!
- Validation results saved within Phoenix
- Users can continue using other applications during validation
- Results verified with 3rd party tools



Demonstration of New Validation Suite Features

Questions?



Upcoming webinars

Best Practices in Clinical Pharmacology Gap Analysis

Presented by: Julie Bullock

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What's New in the Simcyp Simulator v17?

Presented by:
Nikunj Kumar Patel, Matthew Harwood,
Oliver Hatley

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How to Perform Level C IVIVC in Phoenix

Presented by: Jean-Michel Cardot

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Using Model-based Meta-analysis to Inform Drug Development for Autoimmune Diseases

Presented by: Mark Lovern

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