

**Experiment Number:** S0643  
**Route:** Gavage, Gavage with IV Challenge  
**Species/Strain:** Mouse/B6C3F1

**Toxicokinetics Data Summary**  
**Test Compound:** 3'-Azido-3'-deoxythymidine/Rifampicin  
**CAS Number:** AZTRIFAMPIN

**Date Report Requested:** 11/09/2016  
**Time Report Requested:** 14:06:02  
**Lab:** Research Triangle Institute

Male									
Treatment Groups (mg/kg)									
	100 a, #, 1	100 a, #, 2	100 b, e, 1	100 b, *, 2	100 b, ~, 2	100 b, *, 3	100 b, ~, 3	100 b, e, 3	100 b, ~, 1
Plasma									
C <sub>max</sub> (mg/L)	37.2	36.8							
T <sub>max</sub> (hour)	0.250	0.083							
Alpha (hour <sup>-1</sup> )									
t <sub>1/2</sub> (Alpha) (hour)									
Beta (hour <sup>-1</sup> )	0.22	1.34							
t <sub>1/2</sub> (Beta) (hour)	3.19	0.52							
k <sub>01</sub> (hour <sup>-1</sup> )									
k <sub>10</sub> (hour <sup>-1</sup> )									
k <sub>12</sub> (hour <sup>-1</sup> )									
k <sub>21</sub> (hour <sup>-1</sup> )									
Cl <sub>1</sub> (L/hr/kg)									
Cl <sub>1(F)</sub> (L/hr/kg)	2.80	3.34							
V <sub>1</sub> (L/kg)									
V <sub>1(F)</sub> (L/kg)	12.9	2.50							
MRT (hour)	3.14	1.42							
AUC <sub>inf</sub> (hr*mg/L)	37.0	30.2	6.46	4.03	0.84	2.34	0.60	0.08	4.17
F (fraction)	0.6	0.5							

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Treatment Groups (mg/kg)

100 b, \*, 1      100 b, °, 2      100 c, #, 3      100 d, #, 2      100 e, #, 3      100 f, #, 1

Plasma

C <sub>max</sub> (mg/L)		119			
T <sub>max</sub> (hour)		0.083			
Alpha (hour <sup>-1</sup> )					2.65 ± 0.56
t <sub>1/2</sub> (Alpha) (hour)					0.262 ± 0.055
Beta (hour <sup>-1</sup> )		3.44			0.14 ± 0.10
t <sub>1/2</sub> (Beta) (hour)		0.20			5.1 ± 3.8
k <sub>01</sub> (hour <sup>-1</sup> )			99.6 ± 4073.6		8.32 ± 2.45
k <sub>10</sub> (hour <sup>-1</sup> )			1.33 ± 0.18	3.09 ± 0.19	1.85 ± 0.42
k <sub>12</sub> (hour <sup>-1</sup> )					0.74 ± 0.32
k <sub>21</sub> (hour <sup>-1</sup> )					0.19 ± 0.13
Cl <sub>1</sub> (L/hr/kg)		2.17			
Cl <sub>1(F)</sub> (L/hr/kg)					
V <sub>1</sub> (L/kg)		0.63		0.62 ± 0.02	
V <sub>1(F)</sub> (L/kg)			2.59 ± 1.32		1.62 ± 0.27
MRT (hour)		0.38			
AUC <sub>inf</sub> (hr*mg/L)	0.83	1.69	44.9		
F (fraction)					

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	100 a, #, 2	100 a, #, 1	100 a, #, 2	100 b, ~, 1	100 b, *, 1	100 b, *, 3	100 b, °, 1
	<b>Plasma</b>						
C <sub>max</sub> (mg/L)	52.2	41.5	52.2				
T <sub>max</sub> (hour)	0.167	0.250	0.167				
Alpha (hour <sup>-1</sup> )							
t <sub>1/2</sub> (Alpha) (hour)							
Beta (hour <sup>-1</sup> )	1.78	0.22	0.19				
t <sub>1/2</sub> (Beta) (hour)	0.39	3.17	3.67				
k <sub>01</sub> (hour <sup>-1</sup> )							
k <sub>10</sub> (hour <sup>-1</sup> )							
k <sub>12</sub> (hour <sup>-1</sup> )							
k <sub>21</sub> (hour <sup>-1</sup> )							
Cl <sub>1</sub> (L/hr/kg)							
Cl <sub>1(F)</sub> (L/hr/kg)	2.29	1.93	2.28				
V <sub>1</sub> (L/kg)							
V <sub>1(F)</sub> (L/kg)	1.28	8.82	12.1				
MRT (hour)	2.10	2.90	1.36				
AUC <sub>inf</sub> (hr*mg/L)	44.2	54.3	44.5	3.24	1.63	0.76	3.33
F (fraction)	0.62	0.73	0.62				

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	100 b, ~, 3	100 b, ~, 2	100 b, *, 2	100 c, #, 3	100 d, #, 2	100 e, #, 3	100 f, #, 1
<b>Plasma</b>							
C <sub>max</sub> (mg/L)				130			
T <sub>max</sub> (hour)				0.083			
Alpha (hour <sup>-1</sup> )						2.44 ± 0.98	
t <sub>1/2</sub> (Alpha) (hour)						0.285 ± 0.114	
Beta (hour <sup>-1</sup> )				2.92		0.21 ± 0.17	
t <sub>1/2</sub> (Beta) (hour)				0.24		3.2 ± 2.6	
k <sub>01</sub> (hour <sup>-1</sup> )					11.3 ± 1.4	7.03 ± 3.27	
k <sub>10</sub> (hour <sup>-1</sup> )					2.10 ± 0.19	2.56 ± 0.05	1.60 ± 0.54
k <sub>12</sub> (hour <sup>-1</sup> )						0.73 ± 0.46	
k <sub>21</sub> (hour <sup>-1</sup> )						0.33 ± 0.26	
Cl <sub>1</sub> (L/hr/kg)				1.71			
Cl <sub>1(F)</sub> (L/hr/kg)							
V <sub>1</sub> (L/kg)				0.59		0.62 ± 0.01	
V <sub>1(F)</sub> (L/kg)					1.34 ± 0.08		1.35 ± 0.39
MRT (hour)				0.41			
AUC <sub>inf</sub> (hr*mg/L)	0.95	1.26	0.83	57.9			
F (fraction)							

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## LEGEND

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Data are displayed as mean  $\pm$  SEM

### MODELING METHOD & BEST FIT MODEL

- <sup>a</sup> WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA; non-compartmental analysis (NCA) Model 200 Uniform weighting
- <sup>b</sup> WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA; non-compartmental analysis (NCA) Model 200 Uniform weighting, curve stripping disabled
- <sup>c</sup> WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA; non-compartmental analysis (NCA) Model 201 Uniform weighting
- <sup>d</sup> WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA; one-compartmental PK Model 3 with uniform weighting
- <sup>e</sup> WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA; one-compartmental for intravenous dose PK Model 1 with uniform weighting, time points for which mean AZT concentrations were below ELOQ were excluded from the data sets.
- <sup>f</sup> WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA; two-compartment PK Model 11 a weighting scheme of 1/Y was used where Y is the observed AZT plasma concentration.

### ANALYTE

- # 3'-Azido-3'-deoxythymidine
- \* 3'-Azido-3'-deoxy-5'-beta-D-glucopyranosylthymidine
- ~ 3'-Amino-3'-deoxythymidine
- ° 3'-Amino-3'-deoxythymidine glucuronide

### DOSING

- <sup>1</sup> AZT at 100 mg/kg and RIF at 100 mg/kg were orally coadministered twice daily for 7 days with one final oral dose of AZT and RIF on Day 8
- <sup>2</sup> AZT at 100 mg/kg and RIF at 100 mg/kg were orally coadministered twice daily for 7 days with one final oral dose of AZT only on Day 8
- <sup>3</sup> AZT at 100 mg/kg and RIF at 100 mg/kg were orally coadministered twice daily for 7 days with one final intravenous dose of AZT only (5mL/kg) on Day 8

### TK PARAMETERS

- $C_{max}$  = Observed or Predicted Maximum plasma (or tissue) concentration
- $T_{max}$  = Time at which  $C_{max}$  predicted or observed occurs
- Alpha = Hybrid rate constant of the alpha phase
- $t_{1/2(\alpha)}$  = Half-life for the alpha phase
- Beta = Hybrid rate constant of the beta phase
- $t_{1/2(\beta)}$  = Half-life for the beta phase
- $k_{01}$  = Absorption rate constant,  $k_a$
- $k_{10}$  = Elimination rate constant from the central compartment also  $k_e$  or  $k_{elim}$
- $k_{12}$  = Distribution rate constant from first to second compartment etc.
- $k_{21}$  = Distribution rate constant from second to first compartment etc.
- $Cl_1$  = Clearance of central compartment,  $Cl_{app}$  or apparent clearance for intravenous groups
- $Cl_{1(F)}$  = Apparent clearance of the central compartment, also  $Cl_{(F)}$  for gavage groups in non-compartmental model

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### TK PARAMETERS

$V_1$  = Volume of distribution of the central compartment, includes  $V_d$  and  $V_{\text{volume}}$  of distribution,  $V_z$  apparent volume of distribution NCA,  $V_{\text{app}}$  apparent volume of distribution for intravenous studies

$V_{1(F)}$  = Apparent volume of distribution for the central compartment includes  $V_{d(F)}$ ,  $V_{(F)}$  for oral groups, and  $V_{c(F)}$

MRT = Mean residence time

$AUC_{\text{inf}}$  = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

**\*\* END OF REPORT \*\***