Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Amino-3'-deoxythimidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[a,h]	**100 AZT/100 RIF Gavage Plasma[a,h]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[a,h]**
AUCinf_pred (hr*mg/L)	4.17	0.84	0.60

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Amino-3'-deoxythimidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Female

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[a,h]	**100 AZT/100 RIF Gavage Plasma[a,h]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[a,h]**
AUCinf_pred (hr*mg/L)	3.24	1.26	0.95

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Amino-3'-deoxythimidine glucuronide
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[a,i]	**100 AZT/100 RIF Gavage Plasma[a,i]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[a,i]**
AUCinf_pred (hr*mg/L)	6.46	1.69	0.08

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Amino-3'-deoxythimidine glucuronide
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Female

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[a,i]	**100 AZT/100 RIF Gavage Plasma[b,j]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[b,j]**
		NO DATA RECORDED	**NO DATA RECORDED**
AUCinf_pred (hr*mg/L)	3.33		

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Azido-3'-deoxythimidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[c,o]	**100 AZT/100 RIF Gavage Plasma[c,p]**	**100 AZT/100 RIF Gavage Plasma[d]**
Cmax_pred (mg/L)	37.2	36.8	
Tmax_pred (hour)	0.250	0.083	
Alpha ($hour^{-1}$)			2.65 ± 0.56
Alpha Half-life (hour)			0.262 ± 0.055
Beta ($hour^{-1}$)	0.22	1.34	0.14 ± 0.10
Beta Half-life (hour)	3.19	0.52	5.1 ± 3.8
k01 ($hour^{-1}$)			8.32 ± 2.45
k10 ($hour^{-1}$)			1.85 ± 0.42
k12 ($hour^{-1}$)			0.74 ± 0.32
k21 ($hour^{-1}$)			0.19 ± 0.13
Cl1_F (L/hr/kg)	2.80	3.34	
V1_F (L/kg)	12.9	2.50	1.62 ± 0.27
MRT (hour)	3.14	1.42	
AUCinf_pred (hr*mg/L)	37.0	30.2	
F	0.6	0.5	

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Azido-3'-deoxythimidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[e]	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[f,q]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[g]**
Cmax_pred (mg/L)		119	
Tmax_pred (hour)		0.083	
Beta ($hour^{-1}$)		3.44	
Beta half-life (hour)		0.20	
k01 ($hour^{-1}$)	99.6 ± 4073.6		
k10 ($hour^{-1}$)	1.33 ± 0.18		3.09 ± 0.19
Cl1 (L/hr/kg)	2.17		
V1 (L/kg)		0.63	0.62 ± 0.02
V1_F (L/kg)	2.59 ± 1.32		
MRT (hour)		0.38	
AUCinf_pred (hr*mg/L)		44.9	

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-Deoxythymidine/Rifampicin
Analyte: 3'-Azido-3'-deoxythimidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Female

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[c,k]	**100 AZT/100 RIF Gavage Plasma[c,l]**	**100 AZT/100 RIF Gavage Plasma[c,m]**
Cmax_pred (mg/L)	41.5	52.2	52.2
Tmax_pred (hour)	0.250	0.167	0.167
Beta ($hour^{-1}$)	0.22	0.19	1.78
Beta Half-life (hour)	3.17	3.67	0.39
Cl1_F (L/hr/kg)	1.93	2.28	2.29
V1_F (L/kg)	8.82	12.1	1.28
MRT (hour)	2.90	1.36	2.10
AUCinf_pred (hr*mg/L)	54.3	44.5	44.2
F	0.73	0.62	0.62

Female

	Treatment Group (mg/kg)	
	100 AZT/100 RIF Gavage Plasma[d]	**100 AZT/100 RIF Gavage Plasma[e]**
Alpha ($hour^{-1}$)	2.44 ± 0.98	
Alpha Half-life (hour)	0.285 ± 0.114	
Beta ($hour^{-1}$)	0.21 ± 0.17	
Beta Half-life (hour)	3.2 ± 2.6	
k01 ($hour^{-1}$)	7 ± 3.27	11 ± 1.4
k10 ($hour^{-1}$)	1.60 ± 0.54	2.10 ± 0.19
k12 ($hour^{-1}$)	0.73 ± 0.46	
k21 ($hour^{-1}$)	0.33 ± 0.26	
V1_F (L/kg)	1.35 ± 0.39	1.34 ± 0.08

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Azido-3'-deoxythimidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Female

	Treatment Group (mg/kg)	
	100 AZT/100 RIF Gavage Plasma w/ IV Challenge[f,n]	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[g]**
Cmax_pred (mg/L)	130	
Tmax_pred (hour)	0.083	
Beta ($hour^{-1}$)	2.92	
Beta half-life (hour)	0.24	
k10 ($hour^{-1}$)		2.6 ± 0.05
Cl1 (L/hr/kg)	1.71	
V1 (L/kg)	0.59	0.62 ± 0.01
MRT (hour)	0.41	
AUCinf_pred (hr*mg/L)	57.9	

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[a,r]	**100 AZT/100 RIF Gavage Plasma[a,r]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[a,r]**
AUCinf_pred (hr*mg/L)	0.83	4.03	2.34

Experiment Number: S0643
Route: Gavage, Gavage w/IV
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: 3’-Azido-3’-Deoxythymidine/Rifampicin
Analyte: 3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine
CAS Number: AZTRIFAMPIN

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Female

	Treatment Group (mg/kg)		
	100 AZT/100 RIF Gavage Plasma[a,r]	**100 AZT/100 RIF Gavage Plasma[a,r]**	**100 AZT/100 RIF Gavage Plasma w/ IV Challenge[a,r]**
AUCinf_pred (hr*mg/L)	1.63	0.83	0.76

LEGEND

MODELING SOFTWARE

WinNonlin, Version 1.5A

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, non-compartmental analysis (NCA) Model 200 Uniform weighting, curve stripping disabled

[b]WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, All mean concentration values were zero, hence AUCall = 0. No noncompartmental analysis was conducted.

[c]WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, non-compartmental analysis (NCA) Model 200 Uniform weighting

[d]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

[e]WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, one-compartmental PK Model 3 with uniform weighting

[f]WinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, non-compartmental analysis (NCA) Model 201 Uniform weighting

[g]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.

EXCEPTIONS

[h]AMT

[i]GAMT

[j]GAMT was not detected in any plasma samples from Studies F and H

[k]beta range 2-12 hours, Clapp is Cl/F for oral dose studies (Studies A-F). Vapp is V_F for oral dose studies (Studies A-F). Bioavailability was about 60-75 percent in Studies A, B, C, and D.

[l]beta range 1.5-5 hours, Clapp is Cl/F for oral dose studies (Studies A-F). Vapp is V_F for oral dose studies (Studies A-F)

[m]For Study F, the noncompartmental analysis was also run with the elimination phase ending at t = 2 hours. beta range 0.25-2 hours, Clapp is Cl/F for oral dose studies (Studies A-F). Vapp is V_F for oral dose studies (Studies A-F).

[n]beta range 0.083-2

EXCEPTIONS (cont’d)

[o]beta range 1.5-12 hours, Clapp is Cl/F for oral dose studies (Studies A-F). Vapp is V_F for oral dose studies (Studies A-F). Bioavailability was about 60-75 percent in Studies A, B, C, and D.

[p]beta range 1.5-3 hours, Clapp is Cl/F for oral dose studies (Studies A-F). Vapp is V_F for oral dose studies (Studies A-F)

[q]beta range 0.083-1.5

[r]GAZT

ANALYTE

3'-Amino-3'-deoxythimidine

3'-amino-3'-deoxythymidine glucuronide

3’-Azido-3’-Deoxythymidine

3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_pred = Time at which Cmax predicted or observed occurs
Alpha = Hybrid rate constant of the alpha phase
Alpha Half-life = Half-life for the alpha phase
Beta = Hybrid rate constant of the beta phase
Beta Half-life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k10 = Elimination rate constant from the central compartment also ke or kelim
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl1 = Clearance, includes total clearance
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model

TK PARAMETERS (cont’d)

V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
MRT = Mean residence time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

On Day 8 blood was obtained from 3 (Studies A-H) mice/dose regimen/sex before the dose (T0 samples) and at 15 to 17 time points post-dosing. Plasma was analyzed by high performance liquid chromatography (HPLC) with a UV detector for AZT and three metabolites (GAZT, AMT, and GAMT). Metabolite 1 is 3'-azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine (GAZT), metabolite 2 is 3'-Amino-3'-deoxythimidine (AMT), and metabolite 3 is 3'-amino-3'-deoxythymidine glucuronide (GAMT). Respectively, the LOD, LOQ, and ELOQ for AZT were 0.014, 0.045, and 0.200 mg/L. For AMT, 0.058, 0.19, and 0.200 mg/L. For GAZT, 0.015, 0.050, and 0.200 mg/L. For GAMT, 0.10, 0.33, and 0.200 mg/L. Both non-compartmental and compartmental analysis was performed for AZT but only non-compartmental analysis for the metabolites.

TK_GAVAGE PLASMA

<u>100 mg/kg Male and Female All Analytes</u>

Oral administration twice daily for 7 days (14 gavage doses). Studies A and B were dosed with AZT only twice daily, for 7 days orally, and one oral dose on Day 8. Studies C-H were orally dosed with both AZT and Rifampicin (RIF) twice daily for 7 days, with one final oral dose of AZT and RIF on Day 8 (C and D), one final oral dose of AZT only on Day 8 (E and F), one final intravenous dose of AZT only on Day 8 (G and H). Dose amounts were nominally 100 mg/kg AZT and !00 mg/kg RIF. Shown are Day 7 values for body weight mean and range for all mice in the study.