Experiment Number: K88072
Route: Gavage
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-deoxythimidine/ **Analyte:** AZT HPLC
CAS Number: 30516-87-1

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

Male

	Treatment Group (mg/kg)		
	125 Gavage Plasma[a]	**250 Gavage Plasma[a]**	**500 Gavage Plasma[a]**
Alpha Half-life (hour)	.	.	.
Beta Half-life (hour)	0.75	0.96	1.34
Cl (mL/hr*kg)	1360	1000	868
AUC_0-T (ug*hr/mL)	92.2	250	576

Experiment Number: K88072
Route: Gavage
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-deoxythimidine/ **Analyte:** AZT HPLC
CAS Number: 30516-87-1

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

Male

	Treatment Group (mg/kg)	
	1000 Gavage Plasma[a]	**2000 Gavage Plasma[b]**
Alpha Half-life (hour)	.	0.36
Beta Half-life (hour)	3.38	3.67
Cl (mL/hr*kg)	633	654
AUC_0-T (ug*hr/mL)	1580	3060

Experiment Number: K88072
Route: Gavage
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-deoxythimidine/**Analyte:** AZT RIA
CAS Number: 30516-87-1

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

Male

	Treatment Group (mg/kg)		
	125 Gavage Plasma[a]	**250 Gavage Plasma[b]**	**500 Gavage Plasma[b]**
Alpha Half-life (hour)	.	0.35	0.45
Beta Half-life (hour)	1.37	0.53	0.93
Cl (mL/hr*kg)	977	1110	691
AUC_0-T (ug*hr/mL)	128	225	724

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Male

	Treatment Group (mg/kg)	
	1000 Gavage Plasma[b]	**2000 Gavage Plasma[b]**
Alpha Half-life (hour)	0.22	0.32
Beta Half-life (hour)	3.07	3.56
Cl (mL/hr*kg)	781	690
AUC_0-T (ug*hr/mL)	1280	2900

Experiment Number: K88072
Route: Gavage
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-deoxythimidine
Analyte: AZT HPLC & RIA Average
CAS Number: 30516-87-1

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

Male

	Treatment Group (mg/kg)		
	125 Gavage Plasma[a]	**250 Gavage Plasma[c]**	**500 Gavage Plasma[c]**
Alpha Half-life (hour)	.	NC	NC
Beta Half-life (hour)	1.06	0.75	1.14
Cl (mL/hr*kg)	1170	1055	780
AUC_0-T (ug*hr/mL)	110	238	650

Experiment Number: K88072
Route: Gavage
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: 3'-Azido-3'-deoxythimidine
Analyte: AZT HPLC & RIA Average
CAS Number: 30516-87-1

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

Male

Treatment Group (mg/kg)

	1000 Gavage Plasma[c]	2000 Gavage Plasma[b]
Alpha Half-life (hour)	NC	0.34
Beta Half-life (hour)	3.23	3.62
Cl (mL/hr*kg)	707	672
AUC_0-T (ug*hr/mL)	1430	2980

LEGEND

MODELING SOFTWARE

NONLIN

MODELING METHOD & BEST FIT MODEL

[a]NONLIN (no version given; analysis performed in 1989) Individual animal data available to calculate Cmax, A period means not discernable. Elimination phase only

[b]NONLIN (no version given; analysis performed in 1989) Individual animal data available to calculate Cmax, absorption plus elimination phase

[c]NONLIN (no version given; analysis performed in 1989) Individual animal data available to calculate Cmax, NC = not calculated

ANALYTE

AZT HPLC

AZT RIA

AZT HPLC & RIA Average

TK PARAMETERS

Alpha Half-life = Half-life for the alpha phase

Beta Half-Life = Half-life for the beta phase

Cl = Clearance, includes total clearance

AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

The HPLC standard concentration range was 1 ug/mL to 300 ug/mL for AZT. The AZT limit of detection was less than 1 ug/mL for the RIA results. Results from the two methods (HPLC and RIA) were compared statistically (linear regression) using the analytical data from the plasma samples of the rats in this study as well as plasma samples from untreated control rats, spiked with known concentrations of AZT. A correlation coefficient of 0.9732 was obtained in a comparison of 100 samples where measurable levels of AZT were detected by HPLC and RIA. Plasma values from HPLC, RIA, and the average of the HPLC and RIA results were determined and used to calculate toxicokinetic parameters using NONLIN. These values are amended based on revised bleed time. The RIA analysis method was more sensitive.

TK_GAVAGE PLASMA

125 mg/kg,250 mg/kg, 500 mg/kg, 1000 mg/kg, 2000 mg/kg Male

This study is the first in a series of studies intended to provide toxicity data for prolonged exposure to daily oral doses of AZT and was used to design subsequent toxicity studies with combinations of therapy with a lessened chance for 3'-Azido-3'-deoxythimidine (AZT) toxicity. Male F344 rats averaging 99 days old and with a body weight range of 286.5 and 380.6 grams were administered a single oral gavage dose of 125-2000 mg AZT/kg. The doses from 125-1000 mg/kg were used in the rat 13-week subchronic AZT toxicity study C88072 test article number M88195. There were no vehicle controls in this toxicokinetic study. Male F344 rats were weighed before dosing. Blood samples were taken from the orbital sinus of each rat at two of the following time points: 0.25, 1, 2, 4, 8 and 24 hours after dosing giving an n=4 rats per dose group per time point. Plasma samples were analyzed for 3'-Azido-3'-deoxythimidine (AZT) and AZT-glucuronide (GAZT), a metabolite of AZT by HPLC; AZT concentration from each sample was also determined by radioimmunoassay (RIA). The RIA kit used was ZDV-Trac RIA, (Incstar Corporation, Stillwater, Minnesota). Aliquots of the same plasma samples were used to determine AZT concentrations by HPLC and by radioimmunoassay (RIA) from each animal at each time point.