Experiment Number: K88072B
Route: Gavage
Species/Strain: Mouse/B6C3F1

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

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

Female

	Treatment Group (mg/kg)		
	15 IV Plasma[a]	**30 IV Plasma[a]**	**60 IV Plasma[a]**
Cmax_pred (ug/mL)	15.9 ± 2.6	41.8 ± 6.0	76.0 ± 23.8
Tmax_pred (minute)	6.7 ± 2.9	8.3 ± 2.9	8.3 ± 5.8
k10 ($minute^{-1}$)	0.0355 ± 0.0065	0.0400 ± 0.0389	0.0349 ± 0.0105
k10 Half-life (minute)	19.5	17.3	19.9
Cl1 (mL/min/kg)	34.3 ± 8.2	31.1 ± 4.0	28.9 ± 7.8
V1 (L/kg)	1.009 ± 0.378	0.778 ± 0.074	0.924 ± 0.524
Vss (L/kg)	0.941 ± 0.303	0.720 ± 0.077	0.851 ± 0.426
MRT (minute)	28.7 ± 4.7	25.2 ± 2.6	30.5 ± 9.2
AUC_0-T (ug/mL*min)	454.8 ± 110.6	975.8 ± 116.2	2163.8 ± 504.7
AUCinf_pred (ug/mL*min)	477.8 ± 92.1	1045.6 ± 73.5	2282.9 ± 414.0
F	1.000	1.000	1.000

Female

	Treatment Group (mg/kg)		
	15 Gavage Plasma[b]	**30 Gavage Plasma[b]**	**60 Gavage Plasma[b]**
Cmax_pred (ug/mL)	9.1 ± 1.5	18.9 ± 0.5	40.3 ± 7.2
Tmax_pred (minute)	18.3 ± 2.9	21.7 ± 7.6	15.0 ± 5.0
k01 (minute^{-1})	0.0807 ± 0.0308	0.0897 ± 0.0239	0.0892 ± 0.0490
k01 Half-life (minute)	8.6	7.7	7.8
k10 (minute^{-1})	0.0375 ± 0.0092	0.0419 ± 0.0120	0.0317 ± 0.0104
k10 Half-life (minute)	18.5	16.5	21.9
Cl1_F (mL/min/kg)	34.3 ± 8.3	31.1 ± 3.9	28.9 ± 7.8
Vss (L/kg)	1.331 ± 0.314	1.120 ± 0.052	1.281 ± 0.240
V1_F (L/kg)	0.971 ± 0.368	0.762 ± 0.106	0.964 ± 0.289
MRT (minute)	41.3 ± 1.8	36.9 ± 2.5	47.9 ± 8.5
AUC_0-T (ug/mL*min)	386.1 ± 56.6	798.1 ± 68.2	1981.2 ± 313.1
AUCinf_pred (ug/mL*min)	409.1 ± 42.0	810.6 ± 62.0	2102.3 ± 347.6
F	0.849	0.818	0.916

LEGEND

MODELING SOFTWARE

SIPHAR/Base

MODELING METHOD & BEST FIT MODEL

[a]SIPHAR/Base (SIMED, Creteil, Cedex, France), one compartment open model with first-order elimination (1/y weighting). ALL VARIANCE IS STANDARD DEVIATION (Not SE).

[b]SIPHAR/Base (SIMED, Creteil, Cedex, France), one compartment open model with first-order absorption and elimination (1/y weighting); ALL VARIANCE IS STANDARD DEVIATION (Not SE).

ANALYTE

3'-Azido-3'-deoxythimidine

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_pred = Time at which Cmax predicted or observed occurs
k01 = Absorption rate constant, ka
k01 Half-life = Half-life of the absorption process to the central compartment
k10 = Elimination rate constant from the central compartment also ke or kelim
k10 Half-life = Half-life for the elimination process from the central compartment
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
Vss = Volume of distribution at steady state
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
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
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

There were three replicate plasma samples (from three different mice) for each of 11 time points per dose level with two routes. Plasma concentration versus time data for each of the three individual data sets (11 samples per set) were determined for each concentration per route using SIPHAR/Base (SIMED, Creteil, Cedex, France) software. The mean and standard deviation of the parameters (n=3) for each dose level and each route is reported here. For the purpose of determining the bioavailability of AZT in this strain of mice the mean plasma concentrations for both oral and IV administration at each dose level were evaluated simultaneously (parameters not shown here but the bioavailability (CV %) values for PO-IV simultaneous analysis weas 0.908 (6.4%), 0.827 (6.6%), and 0.927 (10.4%) for 15, 30, and 60 mg/kg n=33 per dose, respectively). Mean extent of absorption (F) calculated as follows: mean AUCt (PO)/mean AUCt (IV) for each dose.

TK_INTRAVENOUS PLASMA

15 mg/kg, 30 mg/kg, 60 mg/kg Female

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.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

15 mg/kg, 30 mg/kg, 60 mg/kg Female

There were three replicate plasma samples (from three different mice) for each of 11 time points per dose level with two routes. Plasma concentration versus time data for each of the three individual data sets (11 samples per set) were determined for each concentration per route using SIPHAR/Base (SIMED, Creteil, Cedex, France) software. The mean and standard deviation of the parameters (n=3) for each dose level and each route is reported here. For the purpose of determining the bioavailability of AZT in this strain of mice the mean plasma concentrations for both oral and IV administration at each dose level were evaluated simultaneously (parameters not shown here but the bioavailability (CV %) values for PO-IV simultaneous analysis weas 0.908 (6.4%), 0.827 (6.6%), and 0.927 (10.4%) for 15, 30, and 60 mg/kg n=33 per dose, respectively). Mean extent of absorption (F) calculated as follows: mean AUCt (PO)/mean AUCt (IV) for each dose.