Experiment Number: S0917
Route: IV, Gavage
Species/Strain: Rats/Sprague Dawley

Toxicokinetics Data Summary
Compound: Tamoxifen citrate/ **Analyte:** Tamoxifen, free base
CAS Number: 54965-24-1

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

Male

	Treatment Group (ug/kg) (Group O)				
	300 IV Plasma[a,b]	**300 IV Plasma[a,c]**	**300 IV Plasma[a,d]**	**300 IV Plasma[a,e]**	**300 IV Plasma[a,f]**
Cmax_obs (ug/L)	8.42	36.3	22.9	31.3	5.60
Tmax_obs (hour)	0.5	0	0	0	2
Beta ($hour^{-1}$)	0.05	0.47	0.67	0.44	0.02
Beta Half-life (hour)	15.4	1.49	1.03	1.57	38.1
AUC_0-T (hr*ug/L)	43.5	45.3	40.8	38.7	40.9
AUCinf_pred (hr*ug/L)	122	97.8	112	78.6	148

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Female

	Treatment Group (ug/kg) (Group S)					
	300 IV Plasma[a,g]	**300 IV Plasma[a,h]**	**300 IV Plasma[a,i]**	**300 IV Plasma[a,j]**	**300 IV Plasma[a,k]**	**300 IV Plasma[a,l]**
Cmax_obs (ug/L)	7.71	22.1	11.7	21.8	12.4	20.1
Tmax_obs (hour)	0	0	0.5	0	0	0.5
Beta ($hour^{-1}$)	0.53	0.35	0.25	0.39	0.14	0.37
Beta Half-life (hour)	1.32	2.00	2.80	1.79	4.99	1.86
AUC_0-T (hr*ug/L)	7.03	35.0	29.1	40.8	27.1	33.7
AUCinf_pred (hr*ug/L)	78.6	123	82.9	103	128	89.2

LEGEND

MODELING SOFTWARE

WinNonlin, Version 1.5A

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin, Version 1.5A, noncompartmental model for bolus iv dosing with uniform weighting- - WinNonlin Model 201
Group P, Group T (10ug), Group Q, Group U (100 ug), Group R, Group V (300 ug) were not modeled because no plasma concentrations from this treatment had TAM concentrations greater than or equal to the limit of quantitation

EXCEPTIONS

[b] The time T at which the concentration became less than the LOQ was 8 hours. 15 samples were collected with 10 above the LOD and 6 samples having a plasma concentration above the LOQ. For this animal in Study O, 64.5 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 1-8 hours.
[c] The time T at which the concentration became less than the LOQ was 4 hours. 15 samples were collected with 10 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study O, 53.7 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-4 hours.
[d] The time T at which the concentration became less than the LOQ was 4 hours. 10 samples were collected with 10 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study O, 63.5 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-2 hours.
[e] The time T at which the concentration became less than the LOQ was 4 hours. 15 samples were collected with 9 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study O, 50.7 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-4 hours.

EXCEPTIONS (cont'd)

[f] The time T at which the concentration became less than the LOQ was 8 hours. 12 samples were collected with 12 above the LOD and 4 samples having a plasma concentration above the LOQ. For this animal in Study O, 72.4 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 4-8 hours.

[g] The time T at which the concentration became less than the LOQ was 1 hour. 15 samples were collected with 12 above the LOD and 3 samples having a plasma concentration above the LOQ. For this animal, 91.1 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-1 hours.

[h] The time T at which the concentration became less than the LOQ was 4 hours. 14 samples were collected with 12 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal, 71.6 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-4 hours.

[l] The time T at which the concentration became less than the LOQ was 4 hours. 10 samples were collected with 9 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study S, 64.9 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 1-4 hours.

[j] The time T at which the concentration became less than the LOQ was 4 hours. 10 samples were collected with 10 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study S, 60.5 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-4 hours.

[k] The time T at which the concentration became less than the LOQ was 4 hours. 15 samples were collected with 13 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study S, 78.8 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 0.25-4 hours.

[l] The time T at which the concentration became less than the LOQ was 4 hours. 15 samples were collected with 11 above the LOD and 5 samples having a plasma concentration above the LOQ. For this animal in Study S, 62.2 percent of the AUC extrapolated to infinite time was determined from data outside the TAM calibration curve. Time period over which TAM concentrations were above or equal to LOQ is 1-4 hours.

ANALYTE

Tamoxifen

TK PARAMETERS

Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Beta = Hybrid rate constant of the beta phase
Beta Half-Life = Hybrid rate constant of the beta phase
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
AUCinf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Since cannulated animals were used in these studies, plasma concentration-time courses were obtained for each animal. Hence, the plasma concentration-time profiles were analyzed for each animal. All data were included in the pharmacokinetic analyses, and concentrations below the LOD or not detected were set equal to zero. The concentration of TAM in plasma at t equals 0 hr (C0) was not measured but back extrapolated. For O1 and O6, the TAM concentration in plasma did not decrease from the first sample time point to the second, hence C0 could not be estimated. Instead, C0 was set equal to the first observed. Due to the limited number of time points used to determine the terminal elimination rate constant, the estimate of beta_t1/2 may be unreliable.

TK_INTRAVENOUS PLASMA

<u>300 ug/kg Group O, Group S</u>

Animals were given a single bolus injection of tamoxifen citrate salt through the lateral tail vein but blood samples were collected from indwelling jugular cannula, whenever possible. Target post-dosing time points were 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, 64, and 72 hours but the time T at which the concentration became less than the LOQ varied among the animals (after 4 or 8 hr). Consequently, the pharmacokinetic parameters also varied among the animals. The limit of detection, LOD, and limit of quantitation, LOQ, were 0.03 and 1.00 ng/mL, respectively, for 0.4 mL of plasma extracted. Most plasma samples volumes were less than 400 uL resulting in LOD and LOQ values as high as .240 and 8.00 ng/mL respectively.

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

N/A

TK_GAVAGE PLASMA

10 ug/kg Group T, 100 ug/kg Group U, 300 ug/kg Group V

Data from Studies P, Q, R, T, U, and V were not analyzed because none of the plasma samples from any of the animal's contained TAM at concentrations greater than or equal to the limit of quantitation, LOQ. The limit of detection, LOD, and limit of quantitation, LOQ, were 0.03 and 1.00 ng/mL, respectively, for 0.4 mL of plasma extracted. Most plasma samples volumes were less than 400 uL resulting in LOD and LOQ values as high as .240 and 8.00 ng/mL respectively.