Experiment Number: K12013
Route: Gavage
Species/Strain: Rat/Harlan Sprague Dawley

Toxicokinetics Data Summary
Compound: Vinpocetine/ **Analyte:** Vinpocetine
CAS Number: 42971-09-5

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

Female

	Treatment Group (mg/kg)	
	5 Gavage Plasma[a]	**20 Gavage Plasma[a]**
Cmax_obs (ng/mL)	497	1420
Cmax_pred (ng/mL)	342 ± 36	948 ± 133
Tmax_obs (hour)	0.750	0.750
Tmax_pred (hour)	1.11 ± 0.28	1.37 ± 0.40
k01 ($hour^{-1}$)	2.44 ± 0.94	1.94 ± 0.88
k01 Half-life (hour)	0.284 ± 0.110	0.358 ± 0.162
k10 ($hour^{-1}$)	0.201 ± 0.015	0.173 ± 0.019
k10 Half-life (hour)	3.45 ± 0.25	4.02 ± 0.45
Cl1_F (mL/hr/kg)	2350 ± 240	2870 ± 390
V1_F (mL/kg)	11700 ± 1700	16700 ± 3300
AUC_0-T (ng/mL*hr)	1830	7020
AUCinf_pred (ng/mL*hr)	2120 ± 220	6960 ± 940

Female

Treatment Group (mg/kg)

	5 Gavage Amniotic Fluid[b]	**20 Gavage Amniotic Fluid[b]**
Cmax_obs (ng/mL)	21.4	45.0
Tmax_obs (hour)	1.00	0.750
Lambda_z ($hour^{-1}$)	0.178	0.184
Half-life (hour)	3.90	3.77
Cl1_F (mL/hr/kg)	50600	63300
V1_F (mL/kg)	285000	345000
AUC_0-T (ng/ mL*hr)	97.3	310
AUCinf_pred (ng/mL*hr)	98.7	316

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Female

	Treatment Group (mg/kg)	
	5 Gavage Fetus[c]	**20 Gavage Fetus[d]**
Cmax_obs (ng/g)	321	768
Tmax_obs (hour)	1.00	0.750
Lambda_z ($hour^{-1}$)	0.222	0.214
Half-life (hour)	3.12	3.23
Cl1_F (g/hr/kg)	4330	4650
V1_F (g/kg)	19500	21700
AUC_0-T (ng/mL*hr)	1150	4260
AUCinf_pred (ng/g*hr)	1160	4300

Experiment Number: K12013 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

Route: Gavage | **Compound:** Vinpocetine/ **Analyte:** Apovincaminic acid | **Request Time:** 10:03:16

Species/Strain: Rat/Harlan Sprague Dawley | **CAS Number:** 42971-09-5 | **Lab:** Battelle

Female

	Treatment Group (mg/kg)	
	5 Gavage Plasma[d]	**20 Gavage Plasma[d]**
Cmax_obs (ng/mL)	1070	2560
Tmax_obs (hour)	1.50	1.00
Lambda_z ($hour^{-1}$)	0.170	0.157
Half-life (hour)	4.07	4.41
Cl1_F (mL/hr/kg)	811	826
V1_F (mL/kg)	4760	5250
AUC_0-T (ng/mL*hr)	6060	23500
AUCinf_pred (ng/mL*hr)	6170	24200

Female

	Treatment Group (mg/kg)	
	5 Gavage Amniotic Fluid[e]	**20 Gavage Amniotic Fluid[f]**
Cmax_obs (ng/mL)	4.93	23.0
Tmax_obs (hour)	24.0	24.0
Lambda_z ($hour^{-1}$)	NA	NA
Half-life (hour)	NA	NA
Cl1_F (mL/hr/kg)	NA	NA
V1_F (mL/kg)	NA	NA
AUC_0-T (ng/mL*hr)	99.1	440
AUCinf_pred (ng/mL*hr)	NA	NA

Female

	Treatment Group (mg/kg)	
	5 Gavage Fetus[g]	**20 Gavage Fetus[h]**
Cmax_obs (ng/g)	25.0	83.7
Tmax_obs (hour)	8.00	4.00
Lambda_z ($hour^{-1}$)	0.136	0.108
Half-life (hour)	5.09	6.42
Cl1_F (g/hr/kg)	14100	15600
V1_F (g/kg)	104000	144000
AUC_0-T (ng/g*hr)	334	1160
AUCinf_pred (ng/g*hr)	353	1290

LEGEND

MODELING SOFTWARE

WinNonlin, Version 6.4

MODELING METHOD & BEST FIT MODEL

[a]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, one-compartment (Model 3. first order input, first order output and 1/Yhat2 weighting

[b]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting), All of the pre-dose and 24-hour samples for the 5 mg/kg/day group were estimated concentrations that were extrapolated below the lower limit of quantitation but were above the limit of detection

[c]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting), One 12-hour sample and all of the pre-dose and 24-hour samples for the 5 mg/kg/day group were estimated concentrations that were extrapolated below the lower limit of quantitation but were above the limit of detection.

[d]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting)

[e]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting), NA = not applicable, Animal 139 (5 mg/kg) at 24 hours was excluded from the TK analysis. Elimination half-life could not be determined for amniotic fluid as the concentrations were still increasing at the last measured time point of 24 hours.

[f]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting), NA = not applicable, Elimination half-life could not be determined for amniotic fluid as the concentrations were still increasing at the last measured time point of 24 hours.

[g]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting), one 0.75-hour, one 12-hour sample, and all of the pre-dose, 0.25, 0.5, and 24-hour samples for the 5 mg/kg/day group were estimated concentrations that were extrapolated below the LLOQ but were above the limit of detection. The 5 mg/kg profile for AVA in fetus was reanalyzed with the terminal linear phase manually set to include the 8-hour time point along with the 12- and 24-hour time points.

[h]WinNonlin, Version 6.4, Pharsight Corporation, Sunnyvale, CA, non-compartmental analysis (no weighting), one pre-dose sample for the 20 mg/kg/day group were estimated concentrations that were extrapolated below the LLOQ but were above the limit of detection.

ANALYTE

Vinpocetine

Apovincaminic acid

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax = Time at which Cmax predicted or observed occurs
Lambda_z = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim
Half-Life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
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
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
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

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Dam plasma, amniotic fluid, and fetus vinpocetine (VP) and Apovincaminic acid (AVA), a metabolite, concentrations were measured using liquid chromatography with tandem mass spectroscopy (LC-MS/MS). The target lower limit of quantitation (LLOQ) for VP and AVA in plasma was 0.5 ng/mL; in fetus was 5 ng/g, and in amniotic fluid was 0.5 ng/mL. The limit of detection (LOD) for VP and AVA in plasma were 0.0474 and 0.0567 ng/mL, in amniotic fluid were 0.0474 and 0.1398 ng/mL, and in fetus were 0.6690 and 0.7770 ng/g, respectively. Concentrations were reported to three significant figures.

TK_PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

5 mg/kg, 20 mg/kg Female

Timed-mated female Harlan Sprague Dawley rats received a daily gavage dose from GD 6 to GD 18, inclusive, of vinpocetine in 0.5 percent aqueous methylcellulose at 5 and 20 mg/kg. Dam plasma, amniotic fluid, and fetus samples were collected pre-dose and at 10 time points (0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, and 24 hours) after administration of the last dose on GD 18. Immediately following blood collection, each animal was humanely terminated via exsanguination by cutting the vena cava. The uterus was removed, opened, and amniotic fluid harvested from all fetuses in situ. Amniotic fluid was pooled by litter. Fetuses were collected and pooled by litter. At least three replicate concentrations were determined per time point.

TK_GAVAGE AMNIOTIC FLUID

5 mg/kg, 20 mg/kg Female

Timed-mated female Harlan Sprague Dawley rats received a daily gavage dose from GD 6 to GD 18, inclusive, of vinpocetine in 0.5 percent aqueous methylcellulose at 5 and 20 mg/kg. Dam plasma, amniotic fluid, and fetus samples were collected pre-dose and at 10 time points (0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, and 24 hours) after administration of the last dose on GD 18. Immediately following blood collection, each animal was humanely terminated via exsanguination by cutting the vena cava. The uterus was removed, opened, and amniotic fluid harvested from all fetuses in situ. Amniotic fluid was pooled by litter. Fetuses were collected and pooled by litter. At least three replicate concentrations were determined per time point.

TK_PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE FETUS

5 mg/kg, 20 mg/kg Female

Timed-mated female Harlan Sprague Dawley rats received a daily gavage dose from GD 6 to GD 18, inclusive, of vinpocetine in 0.5 percent aqueous methylcellulose at 5 and 20 mg/kg. Dam plasma, amniotic fluid, and fetus samples were collected pre-dose and at 10 time points (0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, and 24 hours) after administration of the last dose on GD 18. Immediately following blood collection, each animal was humanely terminated via exsanguination by cutting the vena cava. The uterus was removed, opened, and amniotic fluid harvested from all fetuses in situ. Amniotic fluid was pooled by litter. Fetuses were collected and pooled by litter. At least three replicate concentrations were determined per time point.