

Experiment Number: S0643

Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: Gavage

Compound: 3'-Azido-3'-Deoxythymidine/ Analyte: 3'-Amino-3'-deoxythymidine

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 30516-87-1

Lab: RTI

Male

Treatment Group (mg/kg)

100 Gavage Plasma^{a,d}

AUCinf_pred (hr*mg/L)	1.71
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Experiment Number: S0643
Route: Gavage
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: 3'-Azido-3'-Deoxythymidine/ **Analyte:** 3'-Amino-3'-deoxythymidine
CAS Number: 30516-87-1

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

Female

Treatment Group (mg/kg)

100 Gavage Plasma^{a,d}

AUCinf_pred (hr*mg/L)	2.50
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Experiment Number: S0643

Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: Gavage

Compound: 3'-Azido-3'-Deoxythymidine/ Analyte: 3'-amino-3'-deoxythymidine glucuronide

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 30516-87-1

Lab: RTI

Male

Treatment Group (mg/kg)

100 Gavage Plasma^{a,e}

AUCinf_pred (hr*mg/L)	6.28
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Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: Gavage

Compound: 3'-Azido-3'-Deoxythymidine/ Analyte: 3'-Amino-3'-deoxythymidine

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 30516-87-1

Lab: RTI

Female

Treatment Group (mg/kg)

100 Gavage Plasma^{a,e}

AUCinf_pred (hr*mg/L)	4.54
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Experiment Number: S0643

Route: Gavage

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: 3'-Azido-3'-Deoxythymidine

Analyte: 3'-Azido-3'-deoxy-5'-beta-D-glucofuranosylthymidine

CAS Number: 30516-87-1

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Male

Treatment Group (mg/kg)

100 Gavage Plasma^{a,f}

AUCinf_pred (hr*mg/L)	0.61
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Experiment Number: S0643

Route: Gavage

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: 3'-Azido-3'-Deoxythymidine

Analyte: 3'-Azido-3'-deoxy-5'-beta-D-glucopyranosylthymidine

CAS Number: 30516-87-1

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Female

Treatment Group (mg/kg)

100 Gavage Plasma^{a,f}

AUCinf_pred (hr*mg/L)	0.76
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Experiment Number: S0643

Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: Gavage, IV

Compound: 3'-Azido-3'-Deoxythymidine/ Analyte: 3'-Azido-3'-Deoxythymidine

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 30516-87-1

Lab: RTI

Male

Treatment Group (mg/kg)

100 Gavage Plasma^{b,h}

100 Gavage Plasma^c

Cmax_pred (mg/L)	58.6	
Tmax_pred (hour)	0.167	
Beta (hour ⁻¹)	1.24	
Beta Half-life (hour)	0.56	
k01 (hour ⁻¹)		11.1 ± 1.4
k10 (hour ⁻¹)		2.53 ± 0.24
Cl _{1_F} (L/hr/kg)	2.52	
V _{1_F} (L/kg)	2.02	1.12 ± 0.07
MRT (hour)	1.12	
AUC _{inf_pred} (hr*mg/L)	39.4	
F	0.67	

Experiment Number: S0643

Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: Gavage, IV

Compound: 3'-Azido-3'-Deoxythymidine/ Analyte: 3'-Azido-3'-Deoxythymidine

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 30516-87-1

Lab: RTI

Female

Treatment Group (mg/kg)

100 Gavage Plasma^{b,g}

100 Gavage Plasma^b

Cmax_pred (mg/L)	68.8	
Tmax_pred (hour)	0.167	
Beta (hour ⁻¹)	1.44	
Beta Half-life (hour)	0.48	
k01 (hour ⁻¹)		11.7 ± 2.2
k10 (hour ⁻¹)	1.68 ± 0.23	
Cl1_F (L/hr/kg)	1.94	
V1_F (L/kg)	1.34	1.23 ± 0.10
MRT (hour)	1.17	
AUCinf_pred (hr*mg/L)	52.0	
F	0.73	

Experiment Number: S0643

Route: Gavage, IV

Toxicokinetics Data Summary

Compound: 3'-Azido-3'-Deoxythymidine

Analyte: 3'-Amino-3'-Deoxythymidine/ 3'-amino-3'-deoxythymidine glucuronide

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

CAS Number: 30516-87-1

Request Date: 7/11/2023

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

Lab: RTI

LEGEND

MODELING SOFTWARE

WinNonlin, Version 1.5A

MODELING METHOD & BEST FIT MODEL

^aWinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, non-compartmental analysis (NCA) Model 200 Uniform weighting, curve stripping disabled

^bWinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, non-compartmental analysis (NCA) Model 200 Uniform weighting

^cWinNonlin, Version 1.5A, Pharsight Corp, Mountain View, CA, one-compartmental PK Model 3 with uniform weighting

EXCEPTIONS

^dAMT

^eGAMT

^fGAZT

^gbeta range 0.667- 3 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.

^hbeta range 0.25-5 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.

Experiment Number: S0643

Route: Gavage, IV

Toxicokinetics Data Summary

Compound: 3'-Azido-3'-Deoxythymidine

Analyte: 3'-Amino-3'-Deoxythymidine/ 3'-amino-3'-deoxythymidine glucuronide

3'-Azido-3'-deoxy-5'-beta-D-glucopyranosylthymidine/ 3'-Azido-3'-deoxythymidine

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Lab: RTI

ANALYTE

3'-Azido-3'-Deoxythymidine

3'-Azido-3'-deoxythymidine beta-D-glucuronide, sodium salt

TK PARAMETERS

Cmax_pred = Observed or Predicted Maximum plasma (or tissue) concentration

Tmax_pred = Time at which Cmax predicted or observed occurs

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

Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model

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

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Species/Strain: Mouse/B6C3F1

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

CAS Number: 30516-87-1

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Request Time: 10:03:16

Lab: RTI

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'-deoxythymidine (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

100 mg/kg Male and Female All Analytes

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'-deoxythymidine (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.