**Experiment Number:** K89007
**Route:** Gavage
**Species/Strain:** Mice/B6C3F1

**Toxicokinetics Data Summary**
**Compound:** 3'-Azido-3'-deoxythymidine|2',3'-Didoxycytidine
**Analyte:** 2',3'-Didoxycytidine
**CAS Number:** AZTDDCCOMB

**Request Date:** 8/12/2021
**Request Time:** 2:30:16
**Lab:** SO

**Male**

| | Treatment Group (mg/kg) | | |
|---|---|---|---|
| | **0\|500 Gavage Plasma** | **500\|500 Gavage Plasma** | **1000\|500 Gavage Plasma** |
| Alpha_Half-life (hour) | 0.52 | 1.28 | 1.34 |
| Beta_Half-life (hour) | 732 | | |
| Cl (mL/hr*kg) | 14.4 | 4950 | 4350 |
| AUC_0-T (ug*hr/mL) | 3470 | 101 | 115 |

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**Male**

| | Treatment Group (mg/kg) | | | |
|---|---|---|---|---|
| | **500\|0 Gavage Plasma** | **500\|10 Gavage Plasma** | **500\|500 Gavage Plasma** | **1000\|500 Gavage Plasma** |
| Alpha_Half-life (hour) | 0.57 | 0.48 | 0.44 | 0.79 |
| Cl (mL/hr*kg) | 1890 | 1330 | 1930 | 1590 |
| AUC_0-T (ug*hr/mL) | 265 | 377 | 259 | 630 |

LEGEND

MODELING METHOD & BEST FIT MODEL

Nonlin , No specific model information or variation (SD,SE) was given

ANALYTE

2',3'-Didoxycytidine, 3’-Azido-3’-deoxythymidine

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

Toxicokinetics – Plasma

0|500 mg/kg Mice Male

The intent of this study was to determine whether either drug 2',3'-didoxycytidine (ddC, CASRN 7481-89-2 ) or 3'-Azido-3'-deoxythymidine (AZT, CASRN 30516-87-1) had an effect on the absorption and/or clearance of the other drug in B6C3F1 mice and help select dose levels for the 28 day sub-chronic evaluation of ddC/AZT in combination. Single oral doses of ddC, AZT, or the combination (ddC/AZT) were administered as suspensions in 0.5% methylcellulose. There were no vehicle control groups in this study. Blood samples were taken from five mice per dose group at one of the following six time points (0.25, 1, 2, 4, 8 and 10 hours after dosing). One blood sample was taken from one mouse. Plasma was analyzed for ddC and AZT by HPLC. Limit of sensitivity is 2.4 ug/mL for ddC and 2.0 ug/mL for AZT. GAZT (AZT-beta-D-Glucuronide; also known as 3'azido-3'deoxy-5'-O-beta-D-glucopyranuronosylthymidine) concentrations were also measured; however, no detectable levels were found and no results for GAZT are reported. GAZT is a metabolite of AZT. Considerable variability was noted due to the small numbers of mice used and the large intra-animal variability. No ddC pharmacokinetic parameters were determined for group 1 (0 ddC + 500 AZT) or group 3 (500 ddC + 10 AZT) mg/kg concentrations. No AZT pharmacokinetic parameters were determined for group 2 (500 ddC + 0 AZT) mg/kg concentrations. NTP Test article is M890013. There was an anomaly for five animals (BM31-BM35 which is group 2, 15 minute) where AZT was detected in the plasma of mice given 500 mg of ddC/kg and 0 mg of AZT/kg. Plasma AZT values in these mice ranged from 1.5 to 49.2 ug/mL. It is possible that the peak resulted from an endogenous compound rather than AZT and that the interfering material leeched from the column over several injections. The apparent AZT peak progressively decreased between the first animal (BM31) and the last (BM35) [the 15 minute samples for this concentration]. NONLIN was used to determine the area under the plasma concentration vs. time curve (AUC), the half life (t1/2) of each phase of elimination, and the whole body clearance for both ddC and AZT. For reference from an earlier study single oral dose ddC at 375 mg/kg (without AZT) had AUC of 67.2 ug*hr/mL, t1.2 alpha of 0.50 hr, t1/2 beta 9.75 hr, and clearance of 5580 mL/hr*kg). Single oral dose of 750 mg/kg ddC (without AZT) had an AUC of 84.0 ug*hr/mL, t1/2 alpha of 0.60 hr, t1/2 beta of 7.90 hr, and clearance of 8930 mL/hr*kg). For the 500 mg/kg ddC/0 mg/kg AZT treatment, the AUC value (3470 ug*hr/mL) is unusually high and unrealistic due to the prolonged beta phase, as determined by the computer program, and the clearance value (14.4 mL/hr*kg) is unusually low and unrealistic due to the hgh value for AUC. For those treatments with the other 500 mg/kg ddC treatments and for all AZT pharmacokinetics in this study, t1/2 beta was not observed. Clearance is whole body clearance.

TK PARAMETERS PROTOCOL

Toxicokinetics – Plasma

500|0 mg/kg Mice Male, 500|500 mg/kg Mice Male,500|10 mg/kg Mice Male, 500|500 mg/kg Mice Male, 1000|500 mg/kg

The intent of this study was to determine whether either drug 2',3'-didoxycytidine (ddC, CASRN 7481-89-2 ) or 3'-Azido-3'-deoxythymidine (AZT, CASRN 30516-87-1) had an effect on the absorption and/or clearance of the other drug in B6C3F1 mice and help select dose levels for the 28 day sub-chronic evaluation of ddC/AZT in combination. Single oral doses of ddC, AZT, or the combination (ddC/AZT) were administered as suspensions in 0.5% methylcellulose. There were no vehicle control groups in this study. Blood samples were taken from five mice per dose group at one of the following six time points (0.25, 1, 2, 4, 8 and 10 hours after dosing). One blood sample was taken from one mouse. Plasma was analyzed for ddC and AZT by HPLC. Limit of sensitivity is 2.4 ug/mL for ddC and 2.0 ug/mL for AZT. GAZT (AZT-beta-D-Glucuronide; also known as 3'azido-3'deoxy-5'-O-beta-D-glucopyranuronosylthymidine) concentrations were also measured; however, no detectable levels were found and no results for GAZT are reported. GAZT is a metabolite of AZT. Considerable variability was noted due to the small numbers of mice used and the large intra-animal variability. No ddC pharmacokinetic parameters were determined for group 1 (0 ddC + 500 AZT) or group 3 (500 ddC + 10 AZT) mg/kg concentrations. No AZT pharmacokinetic parameters were determined for group 2 (500 ddC + 0 AZT) mg/kg concentrations. NTP Test article is M890013. NONLIN was used to determine the area under the plasma concentration vs. time curve (AUC), the half life (t1/2) of each phase of elimination, and the whole body clearance for both ddC and AZT. For reference from an earlier study single oral dose ddC at 375 mg/kg (without AZT) had AUC of 67.2 ug*hr/mL, t1.2 alpha of 0.50 hr, t1/2 beta 9.75 hr, and clearance of 5580 mL/hr*kg). Single oral dose of 750 mg/kg ddC (without AZT) had an AUC of 84.0 ug*hr/mL, t1/2 alpha of 0.60 hr, t1/2 beta of 7.90 hr, and clearance of 8930 mL/hr*kg). For the 500 mg/kg ddC/0 mg/kg AZT treatment, the AUC value (3470 ug*hr/mL) is unusually high and unrealistic due to the prolonged beta phase, as determined by the computer program, and the clearance value (14.4 mL/hr*kg) is unusually low and unrealistic due to the hgh value for AUC. For those treatments with the other 500 mg/kg ddC treatments and for all AZT pharmacokinetics in this study, t1/2 beta was not observed. Clearance is whole body clearance.