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* + 1. Detailed pharmacokinetic (PK) methodology

NUC-1031 was administered intravenously *via* central line (CVAD), on day 1 and day 8 of a 21‑day cycle.

NUC-1031 prepared in Flushing Solution (80:20 mix of Dimethylacetamide [DMA] and 0.9% w/v saline) was administered by slow intravenous injection over 15-30 minutes using a syringe driver. Prior to and after the administration of NUC-1031, the central line was flushed with the Flushing Solution which was followed by a final flush with normal saline for injection 0.9% to clear the line.

* + 1. Pharmacokinetic Sample Collection

Blood samples were collected for PK analysis in cycle 1 on day 1 only; Pre-dose, 0.05, 0.55, 2.05, and 24 hours following line flush at the end of NUC-1031 infusion.

* + 1. Pharmacokinetic Assay Methods

Plasma samples were assayed for NUC-1031, dFdC, and dFdU, with plasma concentrations determined using the process described in the sections below.

* + - 1. Blood collection

Blood (6 mL) was collected using heparinised blood collection tubes spiked with tetrahydrouridine (25 μg/mL) in order to inhibit cytidine deaminase (CDA) activity. After centrifugation, plasma was separated and stored at -80°C until time of analysis.

* + - 1. Sample extraction

Human plasma was processed in 100 µL samples. The plasma for calibration standards was spiked with tetrahydrouridine (25 µg/mL) in order to inhibit CDA activity. Plasma proteins were precipitated by addition of ice-cold methanol (75:25, v/v) and vortex mixed for 30 seconds. The mixture was incubated on ice for 30 minutes, after which samples were centrifuged at 10,000 G (4oC) for 10 minutes. The supernatant of each sample was transferred to a new Eppendorf and evaporated to dryness in a speed vac. Dried extracts were reconstituted in 100 µL of 10% acetonitrile (ACN). The reconstituted extracts were transferred to liquid chromatography-mass spectrometry (LC-MS) vials and 10 µL were injected onto the ultra-performance liquid chromatography tandem mass spectrometry (UPLC‑MS/MS) system.

* + - 1. Sample analysis

Stock solutions (10 mg/mL) of all analytes were prepared and aliquots frozen at -80°C until use. Fresh calibration standards were prepared by diluting the stock solution in blank human plasma spiked with tetrahydrouridine (25 µg/mL) in order to inhibit CDA activity.

* + - 1. Chromatography method

Analytes were resolved using a UPLC-MS/MS system (Accela UPLC, Thermo Scientific, UK) equipped with ACE Ultracore 2.5 µm, Super C18, 100 × 2.1 mm column and a mobile phase consisting of a mixture of Water containing 10 mM NH4Ac (A), and acetonitrile (B). The mobile phase gradient was employed, comprising: buffer A =80% at 0 - 1 min, from 80 to 20% over 2 minutes, held at 20% for 2 minutes, from 20 to 80% over 0.1 minutes, ending with 80% for 2.9 minutes, all at a flow rate of 250 µL/min.

* + - 1. Mass spectrometry method

Eluting compounds of interest were detected using a triple stage quadrupole Vantage mass spectrometry system (Thermo Scientific, UK) equipped with an electrospray ion source. Samples were analyzed in the Multiple Reaction Monitoring (MRM), positive (+ve) and negative (-ve) ion modes at a spray voltage of 3500 and 3000 V, respectively. Nitrogen was used as sheath and auxiliary gases at a flow rate of 50 and 20 arbitrary units, respectively. Argon was used as collision gas with pressure of 1.5 mTorr. The optimum transitional daughter ions mass and collision energy (CE) of each analyte were as follows: NUC-1031 was: +ve m/z 581.2 → 246.2 (CE 13 V), D5-NUC-1031: +ve m/z 586.2 → 246.2 (CE 13 V), dFdU -ve m/z 263.1 → 221.2 (CE 20 V), dFdC +ve m/z 264.1 → 112.2 (CE 15 V) and DC +ve m/z 228.1 → 112.2 (CE 15 V).

**TABLE 1:** **Summary of Exposure to NUC-1031 and Carboplatin across all Cohorts**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cohort 1**  **NUC‑1031 750 mg/m2**  **+ carboplatin AUC4**  **n=6** | **Cohort 2**  NUC‑1031 750 mg/m2  + carboplatin AUC5  **n=1** | **Cohort 2B**  **NUC‑1031 500 mg/m2**  **+ carboplatin AUC5**  **n=12** | **Cohort 3**  NUC‑1031 625 mg/m2 + carboplatin AUC4  **n=6** | **All Patients**  **n=25** |
| Mean total dose of NUC-1031 received during study (mg)(mg) | 12,704 | 2,570 | 8,082 | 4,096 | 8,014 |
| [Dose range] (mg) | [8975 – 16,500] | [n/a] | [950 – 13,400] | [975 - 10,675] | [950-16,500] |
| Mean total dose per patient (mg) (% actual/planned) | 16,150 (79) | 10,400 (24.7) | 10,444 mg (77) | 10,170 (40) | 11,746 (68.2) |
| Mean duration on NUC-1031 (days) | 125 | 71 | 102 | 70 | 92 |
| Mean per patient total carboplatin received during study (mg) | 2,396 | 1,575 | 2,303 | 1,468 | 2,096 |
| [Dose range] (mg) | [2,100 – 2,550] | [n/a] | [450 – 3,360] | [400-2,700] | [400 – 3,360] |
| Mean total planned per patient (mg) (% received/planned) | 2,500 (96) | 1,800 (88) | 2,893 (80) | 2,135 (69) | 2,573 (81) |
| Duration on Carboplatin (days) | 120 | 71 | 88 | 67 | 87 |

**Table 2:** **Population pharmacokinetic parameters of NUC-1031, dFdC and dFdU**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Estimate** | **SEM (%)** | **CI (5th - 95th)** |
| CL (L) | 5.05 | 6.45 | 4.59 - 5.65 |
| Vc (L/h) | 0.353 | - | - |
| CLd1 (L) | 1.34 | 11.44 | 1.12 - 1.62 |
| Vp1 (L/h) | 0.51 | 8.94 | 0.44 - 0.59 |
| CLd2 (L) | 0.392 | - | - |
| Vp2 (L/h) | 3.58 | - | - |
| CL dFdC/Fm (L) | 839.84 | 15.45 | 641.84 - 1055.96 |
| Vc dFdC/Fm (L/h) | 1341.39 | 10.32 | 1140.9 - 1620.09 |
| CLd1 dFdC/Fm | 523.42 | 6.97 | 465.76 - 584.74 |
| Vp1 dFdC/Fm | 2197.01 | 7.34 | 1923.55 - 2456.7 |
| CLd2 dFdC/Fm | 17200 | - | - |
| Vp2 dFdC/Fm | 9.22 | - | - |
| CL dFdU/Fm | 10.21 | 18.99 | 7.43 – 14.21 |
| Vc dFdU/Fm | 431.87 | 18.18 | 349.43 – 593.65 |
| Fm dFdC/Fm | 0.9 | - | - |
| IIV CL | 0.12 | 34.78 | 0.06 – 0.21 |
| IIV CLd1 | 0.35 | 32.29 | 0.22 – 0.58 |
| IIV Vp1 | 0.28 | 32.17 | 0.17 – 0.45 |
| IIV CLd2 | 0.493 | - | - |
| IIV Vp2 | 1.77 | - | - |
| IOV OCC1 nuc | 0.157 | - | - |
| IOV OCC2 | 0.157 | - | - |
| IIV CL dFdC/Fm | 1.4 | 23.2 | 0.99 - 2 |
| IIV Vc dFdC/Fm | 1.04 | - | - |
| IIV CLd1 dFdC/Fm | 0.0666 | - | - |
| IIV OCC1 dFdC | 0.278 | - | - |
| IIV OCC2 dFdC | 0.278 | - | - |
| IIV CL dFdU/Fm | 2.11 | 21.1 | 1.54 – 2.91 |
| IIV Vc dFdU/Fm | 1.87 | 19.91 | 1.32 – 2.66 |
| EPS1 | 0.18 | 6.58 | 0.16 – 0.2 |
| EPS2 | 2.5e-07 | - | - |
| EPS3 | 0.19 | 6.77 | 0.17 – 0.22 |
| EPS4 | 5.44e-05 | 17.88 | - |
| EPS5 | 0.108 | 5.97 | 0.1 – 0.12 |
| EPS6 | 1.3e-04 | 32.08 | 6.3e-05 – 2.06e-04 |
| SEM: standard error of mean. CI: confidence interval. EPS1: proportional error of the combined NUC-1031 variability. EPS2: additive error of the combined NUC-1031 variability. EPS3: proportional error of the combined dFdC variability. EPS4: additive error of the combined dFdC variability. EPS5: proportional error of the combined dFdU variability. EPS6: additive error of the combined dFdU variability. | | | |

| **Table 3:** **Summary Statistics (Geometric Mean [CV%]; Median [5th – 95th]) for Individual Plasma or Intracellular PK Parameters by Analyte and Dose (mg/m2) for Participants Enrolled in PRO-002** | | | | |
| --- | --- | --- | --- | --- |
| **Analyte** | **Parameter** | **500 mg/m2 (n = 9)** | **625 mg/m2 (n = 6)** | **750 mg/m2 (n = 7)** |
| NUC-1031 | Cmax (μg/mL) | 367 (46.5) | 588 (48.9) | 574 (30.0) |
| 412 [170-560] | 573 [352-1170] | 499 [396-793] |
| Cmax (μM) | 633 (46.5) | 1014 (48.9) | 950 (60.2) |
| 710 [293-965] | 988 [607-2017] | 860 [683-1367] |
| AUC0-24 (μg•h/mL) | 120 (16.0) | 174 (13.8) | 276 (36.7) |
| 118 [96.6-134] | 176 [148-201] | 259 [214-513] |
| AUC0-24 (μM•h) | 207 (16.0) | 300 (13.8) | 476 (36.7) |
| 204 [167-231] | 303 [255-347] | 378 [369-884] |
| AUC0-∞ (μg•h/mL) | 120 (16.0) | 174 (13.8) | 276 (36.7) |
| 118 [96.6-134] | 176 [148-201] | 259 [214-513] |
| AUC0-∞ (μM•h) | 207 (15.6) | 300 (13.8) | 476 (36.7) |
| 204 [167-231] | 303 [255-347] | 378 [369-884] |
| T1/2,α (h) | 0.0206 (14.6) | 0.0210 (23.7) | 0.0187 (51.5) |
| 0.0206 [0.0172-0.0245] | 0.0192 [0.0174-0.0298] | 0.0194 [0.0101-0.0381] |
| T1/2,β (h) | 0.162 (44.4) | 0.144 (39.1) | 0.143 (25.4) |
| 0.146 [0100-274] | 0.122 [0.107-0.262] | 0.134 [0.118-0.218] |
| T1/2,λ (h) | 2.08 (30.2) | 2.13 (30.9) | 1.57 (27.7) |
| 2.13 [1.28-2.79] | 2.35 [1.38-2.84] | 1.63 [1.12-2.21] |
| Vss (L) | 4.03 (25.8) | 4.21 (25.4) | 6.23 (57.8) |
| 4.07 [2.63-5.17] | 4.67 [2.92-5.13] | 5.17 [3.29-13.5] |
| CL (L/h) | 7.42 (10.9) | 6.66 (18.8) | 4.73 (42.1) |
| 7.47 [6.36-8.39] | 6.56 [5.36-8.46] | 5.51 [2.56-6.80] |
| dFdC | Cmax (μg/mL) | 1.24 (98.2) | 0.812 (27.2) | 0.506 (19.2) |
| 0.911 [0.0788-2.88] | 0.833 [0.574-1.10] | 0.521 [0.387-0.632] |
| Cmax (μM) | 4.71 (98.2) | 3.09 (27.2) | 1.92 (19.2) |
| 3.46 [0.300-10.95] | 3.17 [2.18-4.18] | 1.97 [1.47-2.40] |
| AUC0-24 (μg•h/mL) | 1.51 (102) | 0.522 (32.9) | 0.384 (65.5) |
| 0.986 [0.0504-3.48] | 0.536 [0.348-0.775] | 0.496 [0.148-0.722] |
| AUC0-24 (μM•h) | 5.74 (102) | 1.98 (32.9) | 1.46 (65.5) |
| 3.75 [0.191-13.2] | 2.04 [1.32-2.95] | 1.88 [0.563-2.74] |
| AUC0-∞ (μg•h/mL) | 1.54 (102) | 0.522 (32.9) | 0.384 (65.5) |
| 0.99 [0.0504-3.57] | 0.536 [0.348-0.776] | 0.496 [0.149-0.723] |
| AUC0-∞ (μM•h) | 5.84 (102) | 1.98 (32.9) | 1.46 (65.5) |
| 3.77 [0.207-13.6] | 2.04 [1.32-2.95] | 1.88 [0.566-2.75] |
| T1/2,α (h) | 0.0271 (92.0) | 0.0261 (58.6) | 0.0306 (47.0) |
| 0.0179 [0.0097-0.0823] | 0.0289 [0.0131-0.0552] | 0.0376 [0.0160-0.0493] |
| T1/2,β (h) | 1.56 (80.1) | 0.649 (23.7) | 0.511 (39.8) |
| 1.36 [0.223-3.00] | 0.662 [0.487-0.877] | 0.572 [0.293-0.792] |
| T1/2,λ (h) | 1386 (8.9) | 1310 (0.309) | 1300 (0.382) |
| 1330 [1300-1570] | 1310 [1300-1310] | 1300 [1300-1310] |
| Vss (L) | 2419 (8.4) | 2400 (5.20) | 2460 (5.69) |
| 2340 [2270-2970] | 2380 [2290-2590] | 2470 [2310-2640] |
| CL (L/h) | 2293 (160) | 960 (32.1) | 1530 (71.6) |
| 678 [51.2-8260] | 998 [657-1450] | 1230 [791-4490] |
| dFdU | Cmax (μg/mL) | 1.62 (144) | 2.81 (85.3) | 0.859 (71.3) |
| 0.814 [0.341-6.65] | 3.65 [0.978-6.74] | 1.22 [0.377-1.96] |
| Cmax (μM) | 6.14 (144) | 10.6 (85.3) | 3.27 (71.3) |
| 3.08 [1.29-25.2] | 13.8 [3.70-25.5] | 4.64 [1.43-7.45] |
| AUC0-24 (μg•h/mL) | 14.7 (67.3) | 11.7 (47.0) | 18.2 (65.4) |
| 12.0 [4.85-30.4] | 9.70 [7.76-21.3] | 28.0 [8.19-33.8] |
| AUC0-24 (μM•h) | 55.8 (67.3) | 44.3 (47) | 69.2 (65.4) |
| 45.4 [20.2-115] | 36.7 [32.3-80.7] | 106 [31.1-128] |
| AUC0-∞ (μg•h/mL) | 31.6 (52.6) | 15.5 (88.7) | 92.0 (61.7) |
| 33.9 [4.92-50.1] | 9.72 [7.77-49.3] | 68.8 [51.1-222] |
| AUC0-∞ (μM•h) | 119.7 (52.6) | 58.7 (88.7) | 350 61.7) |
| 128 [18.6-190] | 36.8 [29.4-187] | 262 [194-844] |
| T1/2,β (h)a | 26.4 (120) | 1.63 (213) | 63.4 (77.3) |
| 15.4 [0.237-52.2] | 0.539 [0.302-24.9] | 78.5 [25.8-111] |
| Vss (L) | 318 (127) | 67.5 (131) | 520 (76.3) |
| 156 [18.6-705] | 42.8 [18.9-339] | 435 [219-1350] |
| CL (L/h) | 15.0 (123) | 28.7 (88.5) | 5.68 (62.2) |
| 7.46 [4.71-71.3] | 44.9 [9.31-58.2] | 8.28 [2.53-10.1] |
| dFdCTPb | Cmax (μg/mL) | 2.87 (38.0) | 4.53 (36.3 %) | 2.61 (95.4 %) |
| 2.66 (1.69-4.4) | 4.16 (3.12-7.26) | 3.22 (0.872-6.44) |
| Tmax (h) | — | — | — |
| 0.55 (0.55-2.05) | 0.55 (0.55-1.67) | 2.05 (1-17.4) |
| Tlast (h) | — | — | — |
| 2.05 (2.05-15.2) | 2.05 (2.05-2.05) | 24 (2.05-24) |
| AUC0-last (μg•h/mL) | 6.79 (108) | 6.39 (24.7 %) | 13.6 (244 %) |
| 4.64 (2.13-17.3) | 6.40 (4.8-8.77) | 15.9 (2.11-64.0) |
| 1. Note that the half-life estimate for dFdU is listed under T1/2,β as there is only one applicable half-life for that analyte 2. Intracellular PK parameters for dFdCTP derived using non-compartmental methods | | | | |

**APPENDIX 1:** Individual PK Parameter Estimates for Participants Enrolled in Study PRO-002

| **USUBJID** | **Dose (mg)** | **Dose (mg/m2)** | **Analyte** | **Cmax (μg/mL)** | **AUC0-24 (μg•h/mL)** | **AUC0-∞ (μg•h/mL)** | **T1/2,α (h)** | **T1/2,β (h)** | **T1/2,λ (h)** | **Vss (L)** | **CL (L/h)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 1325 | 750 | NUC1031 | 724 | 216 | 216 | 0.0105 | 0.138 | 2.25 | 13.1 | 6.26 |
| 1 | 1325 | 750 | dFdC | 0.432 | 0.171 | 0.171 | 0.0376 | 0.318 | 1300 | 2570 | 3510 |
| 1 | 1325 | 750 | dFdU | 2.17 | 35.1 | 49,1 | - | 12 | - | 186 | 10.7 |
| 2 | 1500 | 750 | NUC1031 | 703 | 213 | 213 | 0.0098 | 0.125 | 2.11 | 13.6 | 7.03 |
| 2 | 1500 | 750 | dFdC | 0.368 | 0.139 | 0.139 | 0.0394 | 0.282 | 1300 | 2670 | 4910 |
| 2 | 1500 | 750 | dFdU | 1.22 | 28 | 155 | - | 78.5 | - | 435 | 3.84 |
| 3 | 1475 | 750 | NUC1031 | 453 | 259 | 259 | 0.0194 | 0.118 | 1.63 | 5.17 | 5.65 |
| 3 | 1475 | 750 | dFdC | 0.554 | 0.496 | 0.496 | 0.0514 | 0.572 | 1300 | 2560 | 1330 |
| 3 | 1475 | 750 | dFdU | 0.379 | 8.45 | 68.8 | – | 113 | – | 1400 | 8.63 |
| 4 | 1300 | 750 | NUC1031 | 430 | 259 | 259 | 0.0246 | 0.159 | 1.46 | 4.15 | 5 |
| 4 | 1300 | 750 | dFdC | 0.654 | 0.756 | 0.757 | 0.0445 | 0.84 | 1310 | 2470 | 765 |
| 4 | 1300 | 750 | dFdU | 0.376 | 8.08 | 60.3 | – | 97.4 | – | 1210 | 8.61 |
| 5 | 1225 | 750 | NUC1031 | 381 | 219 | 219 | 0.0165 | 0.118 | 1.67 | 6.7 | 5.51 |
| 5 | 1225 | 750 | dFdC | 0.582 | 0.515 | 0.515 | 0.0276 | 0.606 | 1310 | 2380 | 1050 |
| 5 | 1225 | 750 | dFdU | 1.26 | 28.1 | 126 | – | 57.7 | – | 322 | 3.86 |
| 6 | 1225 | 750 | NUC1031 | 822 | 605 | 606 | 0.0439 | 0.243 | 1.12 | 2.92 | 2.02 |
| 6 | 1225 | 750 | dFdC | 0.521 | 0.642 | 0.642 | 0.0171 | 0.682 | 1310 | 2310 | 852 |
| 6 | 1225 | 750 | dFdU | 1.46 | 30.9 | 250 | – | 105 | – | 298 | 1.96 |
| 7 | 1150 | 750 | NUC1031 | 499 | 297 | 298 | 0.0222 | 0.134 | 1.12 | 4.84 | 3.81 |
| 7 | 1150 | 750 | dFdC | 0.488 | 0.417 | 0.417 | 0.0156 | 0.511 | 1300 | 2310 | 1230 |
| 7 | 1150 | 750 | dFdU | 0.5 | 11.2 | 55.6 | – | 65.2 | – | 779 | 8.28 |
| 8 | 750 | 500 | NUC1031 | 165 | 92.1 | 92.1 | 0.0176 | 0.118 | 1.64 | 4.89 | 8.12 |
| 8 | 750 | 500 | dFdC | 0.235 | 0.268 | 0.268 | 0.0826 | 0.744 | 1300 | 2890 | 1260 |
| 8 | 750 | 500 | dFdU | 0.217 | 4.81 | 34.5 | - | 97.3 | - | 1230 | 8.79 |
| 9 | 800 | 500 | NUC1031 | 189 | 109 | 109 | 0.0202 | 0.156 | 1.27 | 4.38 | 7.3 |
| 9 | 800 | 500 | dFdC | 0.109 | 0.0692 | 0.0692 | 0.00977 | 0.246 | 1300 | 2340 | 5240 |
| 9 | 800 | 500 | dFdU | 0.915 | 12 | 14.3 | - | 8.37 | - | 277 | 22.9 |
| 10 | 850 | 500 | NUC1031 | 177 | 107 | 107 | 0.0211 | 0.209 | 1.3 | 3.7 | 7.86 |
| 10 | 850 | 500 | dFdC | 0.0586 | 0.0379 | 0.0379 | 0.0109 | 0.208 | 1300 | 2430 | 10300 |
| 10 | 850 | 500 | dFdU | 7.29 | 6 | 6. | - | 0.205 | - | 17.3 | 58.3 |
| 11 | 1075 | 625 | NUC1031 | 516 | 156 | 156 | 0.0182 | 0.11 | 1.87 | 5.06 | 7.06 |
| 11 | 1075 | 625 | dFdC | 0.679 | 0.316 | 0.316 | 0.0307 | 0.466 | 1300 | 2420 | 1560 |
| 11 | 1075 | 625 | dFdU | 1.02 | 21.1 | 41 | - | 20.8 | - | 318 | 10.6 |
| 12 | 1100 | 625 | NUC1031 | 609 | 190 | 190 | 0.0245 | 0.178 | 2.53 | 3.59 | 6.09 |
| 12 | 1100 | 625 | dFdC | 0.896 | 0.481 | 0.481 | 0.0259 | 0.542 | 1310 | 2370 | 1050 |
| 12 | 1100 | 625 | dFdU | 3.65 | 8.38 | 8.39 | - | 0.651 | - | 50 | 53.2 |
| 13 | 1175 | 625 | NUC1031 | 538 | 162 | 162 | 0.0177 | 0.106 | 2.25 | 5.11 | 7.38 |
| 13 | 1175 | 625 | dFdC | 1.13 | 0.831 | 0.832 | 0.0326 | 0.928 | 1310 | 2390 | 633 |
| 13 | 1175 | 625 | dFdU | 0.988 | 21.6 | 50.9 | - | 24.9 | - | 330 | 9.17 |
| 14 | 1250 | 625 | NUC1031 | 295 | 145 | 145 | 0.0174 | 0.119 | 1.23 | 4.64 | 8.82 |
| 14 | 1250 | 625 | dFdC | 0.77 | 0.591 | 0.591 | 0.0125 | 0.64 | 1310 | 2290 | 948 |
| 14 | 1250 | 625 | dFdU | 5.23 | 8.59 | 8.6 | - | 0.411 | - | 35 | 58.9 |
| 15 | 1050 | 625 | NUC1031 | 1350 | 197 | 197 | 0.0204 | 0.126 | 2.45 | 4.7 | 6.12 |
| 15 | 1050 | 625 | dFdC | 0.54 | 0.446 | 0.446 | 0.0632 | 0.728 | 1310 | 2640 | 1090 |
| 15 | 1050 | 625 | dFdU | 3.66 | 7.53 | 7.54 | - | 0.424 | - | 34.4 | 56.2 |
| 16 | 975 | 625 | NUC1031 | 608 | 202 | 202 | 0.0315 | 0.291 | 2.94 | 2.7 | 5.12 |
| 16 | 975 | 625 | dFdC | 1.01 | 0.608 | 0.608 | 0.0149 | 0.683 | 1310 | 2300 | 729 |
| 16 | 975 | 625 | dFdU | 7.17 | 10.7 | 10.8 | - | 0.267 | - | 14.11 | 36.6 |
| 18 | 885 | 500 | NUC1031 | 351 | 138 | 138 | 0.0169 | 0.0981 | 2.65 | 5.63 | 6.6 |
| 18 | 885 | 500 | dFdC | 0.511 | 0.342 | 0.342 | 0.0417 | 0.56 | 1300 | 2480 | 1160 |
| 18 | 885 | 500 | dFdU | 0.535 | 12 | 44.1 | – | 46.4 | – | 539 | 8.05 |
| 19 | 825 | 500 | NUC1031 | 590 | 140 | 140 | 0.0226 | 0.135 | 2.83 | 3.94 | 6.14 |
| 19 | 825 | 500 | dFdC | 1.31 | 1.63 | 1.64 | 0.0266 | 1.98 | 1360 | 2340 | 191 |
| 19 | 825 | 500 | dFdU | 1.22 | 26.5 | 49.6 | - | 14.6 | - | 117 | 5.54 |
| 20 | 925 | 500 | NUC1031 | 484 | 141 | 141 | 0.023 | 0.163 | 2.04 | 3.33 | 7.08 |
| 20 | 925 | 500 | dFdC | 2.21 | 2.9 | 2.94 | 0.0141 | 2.85 | 1430 | 2280 | 88.4 |
| 20 | 925 | 500 | dFdU | 0.713 | 14 | 33.3 | - | 18.8 | - | 187 | 6.88 |
| 21 | 950 | 500 | NUC1031 | 473 | 128 | 128 | 0.018 | 0.104 | 2.22 | 4.2 | 8.59 |
| 21 | 950 | 500 | dFdC | 2.14 | 3.14 | 3.22 | 0.0217 | 3.09 | 1450 | 2320 | 78.1 |
| 21 | 950 | 500 | dFdU | 1.48 | 33 | 50.6 | - | 9.07 | - | 56.9 | 4.35 |
| 22 | 750 | 500 | NUC1031 | 510 | 103 | 103 | 0.0255 | 0.317 | 2.71 | 2.16 | 7.64 |
| 22 | 750 | 500 | dFdC | 3.33 | 3.7 | 3.8 | 0.0097 | 2.8 | 1650 | 2270 | 33.3 |
| 22 | 750 | 500 | dFdU | 0.59 | 9.64 | 20.3 | - | 16.1 | - | 124 | 5.34 |

APPENDIX 2: Individual PK Parameter Estimates for Intracellular dFdCTP for Participants Enrolled in Study PRO-002

| **USUBJID** | **Dose (mg)** | **Dose (mg/m2)** | **Analyte** | **Tmax (h)** | **Cmax (μg/mL)** | **Cmax**  **(mM)** | **Tlast (h)** | **AUClast (μg•h/mL)** | **AUClast (mM•h)** | **AUC0-24 (μg•h/mL)** | **AUC0-24 (mM•h)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 1325 | 750 | dFdCTP | 24 | 5.19 | 4.45 | 24 | 74.5 | 63.9 | 74.5 | 74.5 |
| 2 | 1500 | 750 | dFdCTP | 2.05 | 0.962 | 0.825 | 24 | 15.9 | 13.6 | 15.9 | 15.9 |
| 3 | 1475 | 750 | dFdCTP | 2.05 | 6.97 | 5.98 | 2.05 | 12.2 | 10.5 |  |  |
| 4 | 1300 | 750 | dFdCTP | 2.05 | 3.22 | 2.76 | 2.05 | 3.97 | 3.40 |  |  |
| 5 | 1225 | 750 | dFdCTP | 2.05 | 3.58 | 3.07 | 24 | 39.5 | 33.9 | 39.5 | 39.5 |
| 6 | 1225 | 750 | dFdCTP | 2.05 | 2.48 | 2.13 | 24 | 29.1 | 25.0 | 29.1 | 29.1 |
| 7 | 1150 | 750 | dFdCTP | 0.55 | 0.834 | 0.72 | 2.05 | 1.31 | 1.12 |  |  |
| 8 | 750 | 500 | dFdCTP | 0.55 | 3.58 | 3.07 | 2.05 | 6.21 | 5.33 |  |  |
| 9 | 800 | 500 | dFdCTP | 0.55 | 2.19 | 1.88 | 24 | 24.4 | 20.9 | 24.4 | 20.9 |
| 10 | 850 | 500 | dFdCTP | 0.55 | 3.66 | 3.14 | 2.05 | 5.5 | 4.72 |  |  |
| 11 | 1075 | 625 | dFdCTP | 0.55 | 3.91 | 3.35 | 2.05 | 5.77 | 4.95 |  |  |
| 12 | 1100 | 625 | dFdCTP | 0.55 | 4.42 | 3.79 | 2.05 | 6.74 | 5.78 |  |  |
| 13 | 1175 | 625 | dFdCTP | 0.55 | 3.7 | 3.17 | 2.05 | 6.07 | 5.21 |  |  |
| 14 | 1250 | 625 | dFdCTP | 0.55 | 6.09 | 5.22 | 2.05 | 6.82 | 5.85 |  |  |
| 15 | 1050 | 625 | dFdCTP | 2.05 | 7.65 | 6.56 | 2.05 | 9.42 | 8.08 |  |  |
| 16 | 975 | 625 | dFdCTP | 0.55 | 2.92 | 2.50 | 2.05 | 4.48 | 3.84 |  |  |
| 18 | 885 | 500 | dFdCTP | 2.05 | 4.82 | 4.13 | 2.05 | 6.75 | 5.79 |  |  |
| 19 | 825 | 500 | dFdCTP | 0.55 | 1.73 | 1.48 | 2.05 | 2.48 | 2.13 |  |  |
| 20 | 925 | 500 | dFdCTP | 0.55 | 1.67 | 1.43 | 2.05 | 1.89 | 1.62 |  |  |
| 21 | 950 | 500 | dFdCTP | 2.05 | 2.92 | 2.50 | 2.05 | 3.78 | 3.24 |  |  |
| 22 | 750 | 500 | dFdCTP | 2.05 | 2.4 | 2.06 | 2.05 | 3.31 | 2.84 |  |  |