**Supplemental Digital Content 1 : Methodology and results for the non-compartmental pharmacokinetic analyses of concentration-time data of plasma ABP-700 (both arterial and venous) and its primary metabolite**

**Methods :**

Non-compartmental pharmacokinetic analyses of concentration-time data of plasma ABP-700 and its primary metabolite (CPM-acid) were conducted using Phoenix®WinNonlin® version 6.3 (Pharsight Corporation, St. Louis, MO). Only plasma PK profiles which contained more than five consecutive data points with a quantifiable concentration value were considered evaluable. Actual elapsed times from dosing were used to estimate all individual plasma PK parameters for evaluable subjects. Observed pre-dose concentrations were set as missing in order to generate C0 values, which were calculated as the extrapolated concentration at time 0 (computed for parent only). Systematic exposure was calculated using the area under the drug concentration-time curve, AUC0-t, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (Ct). Extrapolation for exposure to infinity, AUC0-inf was calculated as the area under the drug concentration-time curve from time zero to infinity, *AUC0-inf=AUC0-t+Ct/kel*, where Ct is the last measurable concentration. The apparent terminal elimination rate constant (kel) was calculated by linear regression of the terminal linear portion of the log concentration versus time curve and the apparent elimination half-life (t1/2) was calculated as ln(2)/kel. The kel was determined by at least three data points in the terminal elimination phase for parent and metabolite compounds. Furthermore, the adjusted R2 value in the linear regression on the terminal linear phase of the semi-logarithmic plots of individual plasma concentration time data had to be greater than 70% and % AUCextrap (=Ct/kel)  had to be less than 20% for kel determinations. The following parameters were observed: Cmax being the maximum observed drug concentration, tlast being the time of the last measurable concentration. The total plasma clearance (CL) was calculated as Dose/AUC0-inf and was computed for parent drug only. VZ or the volume of distribution during the terminal elimination phase was defined as [Dose /(kel \* AUC0-inf)] and was computed for parent drug only. Total apparent volume of distribution or Vss following single IV dose administration was calculated as Vss= MRT0-inf x CL (computed for parent only), where MRT0-inf (mean residence time)*=* AUMC0-inf / AUC0-inf (for IV bolus) and where the area under the moment curve from time 0 to the last measurable concentration (Ct) or

AUMC0-inf = AUMC0-t + [(tlast x Ct)/ kel]+ Ct/(kel)2

**Results : (mean (standard deviation) or median [range])**

1. **Non-compartmental kinetics of ABP-700 (arterial samples)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Cmax (ng/mL)** | **tmax (min) a** | **AUC0-last (h.ng/mL)** | **AUC0-inf (h.ng/mL)** | **kel (1/min)** | **t1/2 (min)** | **tlast (min)** | **CL (L/h)** | **Vz (L)** | **C0 (ng/mL)** |
|  **0.03 mg/kg** | 856 (293) | 0.60 [0.56,0.65] | 37 (15) | 38 (15) | 0.137 (0.0569) | 5.6 (1.8) | 16.9 (4.4) | 71 (40.5) | 8.3 (1.4) | 3960 (1970) |
| **0.10 mg/kg** | 2430 (876) | 0.58 [0.54,0.60] | 116 (37) | 118 (37) | 0.065 (0.0206) | 12.1 (5.9) | 36.4 (14.3) | 72 (22.2) | 22.7 (18.5) | 13200 (6380) |
| **0.175 mg/kg** | 2040 (1660) | 0.56 [0.54,1.08] | 122 (74) | 123 (75) | 0.068 (0.0049) | 10.3 (0.7) | 45.1 (0.0) | 129 (51.0) | 31.4 (11.6) | 9850 (12800) |
| **0.25 mg/kg** | 5540 (3160) | 0.58 [0.54,0.68] | 381 (307) | 384 (307) | 0.054 (0.0105) | 13.1 (2.3) | 54.2 (8.4) | 78 (49.4) | 26.0 (18.9) | 52700 (61300) |
| **0.25b mg/kg** | 4300 (2850) | 0.60 [0.50,0.65] | 215 (126) | 217 (127) | 0.065 (0.0311) | 15.6 (13.9) | 60.3 (35.1) | 105 (52.2) | 29.5 (10.4) | 18900 (16800) |
| **0.35 mg/kg** | 6750 (4790) | 0.57 [0.56,0.67] | 414 (215) | 417 (215) | 0.051 (0.0231) | 16.2 (7.5) | 69.3 (20.3) | 80 (48.0) | 29.8 (22.0) | 44700 (41200) |
| **0.35c mg/kg** | 4310 (3020) | 0.65 [0.54,0.66] | 277 (143) | 279 (143) | 0.055 (0.0094) | 13.0 (2.1) | 61.9 (14.0) | 113 (65.1) | 35.0 (19.4) | 20400 (19100) |
| **0.50 mg/kg** | 11800 (5750) | 0.57 [0.56,0.58] | 643 (336) | 645 (337) | 0.061 (0.0124) | 11.6 (1.9) | 57.1 (6.7) | 84 (51.5) | 22.9 (14.7) | 76500 (50500) |
| **0.75 mg/kg** | 13600 (5180) | 0.56 [0.55,0.58] | 759 (194) | 761 (194) | 0.061 (0.0212) | 13.2 (7.1) | 72.1 (26.8) | 84 (22.5) | 28.4 (21.8) | 71200 (38900) |
| **1.00 mg/kg** | 15900 (10600) | 0.56 [0.56,0.58] | 969 (495) | 972 (495) | 0.046 (0.0216) | 18.2 (8.0) | 103 (27.8) | 98 (47.3) | 41.4 (24.1) | 80900 (90500) |

**B) Non-compartmental kinetics of ABP-700 : venous samples**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Cmax (ng/mL)** | **tmax (min) a** | **AUC0-last (h.ng/mL)** | **AUC0-inf (h.ng/mL)** | **kel (1/min)** | **t1/2 (min)** | **tlast (min)** | **CL (L/h)** | **Vz (L)** | **C0 (ng/mL)** |
|  **0.03 mg/kg** | NA (NA) | NA [NA,NA]] | NA (NA) | NA (NA) | NA (NA) | NA (NA) | NA (NA) | NA (NA) | NA (NA) | NA (NA) |
| **0.10 mg/kg** | 164 (48) | 1.67 [1.56.3.58] | 30 (5) | 32 (6) | 0.052 (0.0208) | 15.4 (8.0) | 48 (23) | 259 (52) | 92.1 (37.4) | 203 (105) |
| **0.175 mg/kg** | 244 (95) | 2.57 [1.56.7.17] | 67 (24) | 74 (27) | 0.066 (0.0021) | 10.5 (0.4) | 35 (< 0.1) | 196 (68) | 49.9 (18.7) | 227 (111) |
| **0.25 mg/kg** | 459 (180) | 1.63 [1.50.3.55] | 55 (14) | 88 (15) | 0.053 (0.0175) | 14.4 (5.1) | 60 (22) | 231 (41) | 79.9 (30.5) | 648 (402) |
| **0.25b mg/kg** | 491 (149) | 1.75 [1.54.1.93] | 83 (18) | 88 (22) | 0.067 (0.0254) | 12.9 (8.5) | 43 (18) | 213 (59) | 59.5 (23.2) | 820 (449) |
| **0.35 mg/kg** | 607 (293) | 1.79 [1.57.3.58] | 153 (55) | 158 (55) | 0.056 (0.0208) | 13.6 (4.4) | 67 (18) | 184 (87) | 56.1 (20.0) | 703 (394) |
| **0.35c mg/kg** | 920 (220) | 1.66 [1.61.3.59] | 157 (45) | 161 (47) | 0.052 (0.0181) | 14.4 (3.5) | 67 (18) | 163 (35) | 55.3 (16.7) | 1540 (930) |
| **0.50 mg/kg** | 817 (154) | 1.59 [1.55.1.84] | 184 (60) | 188 (61) | 0.058 (0.0236) | 13.1 (3.5) | 70 (20) | 246 (118) | 70.1 (10.1) | 1010 (311) |
| **0.75 mg/kg** | 925 (321) | 3.56 [1.76.7.21] | 269 (53) | 275 (51) | 0.042 (0.0091) | 17.1 (3.7) | 85 (21) | 227 (39) | 93.4 (26.0) | 850 (434) |
| **1.00 mg/kg** | 2530 (2360) | 1.61 [1.55.13.08] | 466 (161) | 469 (162) | 0.042 (0.0174) | 18.7 (6.7) | 118 (45) | 174 (42) | 75.8 (29.3) | 4100 (4690) |

**C) Non-compartmental kinetics of the metabolite CPM-acid (from arterial samples)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Cmax(ng/mL)** | **tmax (min) a** | **AUC0-last (h.ng/mL)** | **AUC0-inf (h.ng/mL)** | **kel (1/min)** | **t1/2 (min)** | **tlast (min)** |
| **0.03 mg/kg** | 46 (6) | 8.07 [8.07,12.08] | 15 (3) | NA (NA) | NA (NA) | NA (NA) | 27 (5.8) |
| **0.10 mg/kg** | 126 (27) | 8.10 [8.05,12.05] | 84 (24) | NA (NA) | NA (NA) | NA (NA) | 66.4 (13.2) |
| **0.175 mg/kg** | 235 (37) | 12.08 [4.06,12.14] | 167 (23) | 192 (27) | 0.022 (0.0022) | 31.9 (3.8) | 104 (15.4) |
| **0.25 mg/kg** | 305 (47) | 12.07 [12.04,12.27] | 248 (38) | 280 (41) | 0.019 (0.0018) | 35.9 (3.4) | 114 (13.3) |
| **0.25b mg/kg** | 366 (112) | 12.11 [12.08,12.15] | 314 (106) | 353 (124) | 0.024 (0.0029) | 29.1 (3.4) | 115 (12.9) |
| **0.35 mg/kg** | 521 (98) | 12.09 [12.07,12.14] | 439 (58) | 475 (57) | 0.020 (0.0030) | 35.0 (5.4) | 132 (26.7) |
| **0.35c mg/kg** | 416 (102) | 12.13 [12.04,20.08] | 343 (68) | 375 (68) | 0.019 (0.0048) | 38.9 (14.1) | 129 (23.6) |
| **0.50 mg/kg** | 709 (96) | 12.04 [8.06,12.06] | 618 (184) | 646 (186) | 0.023 (0.0037) | 31.2 (4.8) | 145 (32.0) |
| **0.75 mg/kg** | 1140 (209) | 12.09 [12.05,20.08] | 1030 (125) | 1060 (117) | 0.020 (0.0035) | 36.2 (6.2) | 180 (0.5) |
| **1.00 mg/kg** | 1170 (115) | 12.08 [12.05,20.07] | 1050 (62) | 1100 (73) | 0.019 (0.0023) | 37.0 (4.6) | 169 (27.2) |

**Table Legend A-C :** The most important non-compartmental arterial (A) and venous (B) PK parameters for ABP-700 and its metabolite CPM-acid (from arterial samples) (C). Cmax is the maximum observed drug concentration; tmax is the time of the maximum drug concentration (obtained without interpolation); AUC0-last is the area under the drug concentration-time curve from time zero to the time of the last measurable concentration; AUC0-inf is the area under the drug concentration-time curve from time zero to infinity; kel is the apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration versus the time curve; t1/2 is the apparent elimination half-life, calculated as ln(2)/kel ; tlast is the time of the last measurable concentration; CL is the total plasma clearance calculated as [Dose/AUC0-inf] (computed for parent only); VZ is the volume of distribution during the terminal elimination phase, calculated as [Dose /(kel \* AUC0-inf)] (computed for parent only); and C0 is the extrapolated concentration at time 0 (computed for parent only).
a: median (range); b: 0.25 mg/kg ABP-700 with 1 µg/kg fentanyl; c: 0.35 mg/kg ABP-700 with 1 µg/kg fentanyl; NA: Not Applicable