Electronic supplement to manuscript AA-D-12-00529 R4

**Non-compartmental analysis of AZD3043 and THRX-108893**

**Statistics**: Pharmacokinetic parameters were calculated non-compartmentally using WinNonlin Professional (Pharsight Corporation, Mountain View, CA) and presented as geometric mean. Variability is expressed as coefficient of variation (CV%), being the ratio of the standard deviation to the mean, expressed as a percentage. The area under the curve from zero to infinity, AUC, was calculated by means of the linear-up/log-down method, with extrapolation from time of the last observed concentration to infinity if the extrapolated portion of the AUCextr was <25%. As the AUCextr was low (<10%) across all doses, the AUC is reported.

**Results pharmacokinetics**: Summary arterial pharmacokinetic parameters for AZD3043 are presented in Table ES1. For the carboxylate metabolite, THRX-108893, overall geometric mean (CV%) arterial pharmacokinetic parameters were: AUC/dose 1.39 min/L (26%), Cmax/dose 0.017 L−1 (17%) and terminal half-life (t½λz) 34 minutes (17%). Data for the different groups are presented in Table ES2. Exposure to AZD3043 and THRX-108893 increased approximately proportionally with dose (Table ES1 and ES2). An analysis of dose proportionality of AZD3043 is presented in the accompanying paper.13

**Discussion pharmacokinetics:** Overall, the non-compartmental pharmacokinetics of AZD3043 in humans reported here were as predicted from preclinical studies. The plasma clearance of AZD3043 exceeded the typical liver blood flow rate observed in non-sedated subjects by nearly 2-fold, and the renal contribution was negligible, which indicates that elimination via liver and kidneys contributes less than half of the total clearance.

**Table ES1.
Summary of AZD3043 pharmacokinetic parameters in arterial plasma**

|  |  |
| --- | --- |
| Geometric mean (CV%) | AZD3043 dose, mg/kg/h (30-minute infusion) |
| 1(n=5) | 3(n=6) | 6(n=6) | 12(n=6) | 18(n=6) | 27(n=6) | 36(n=6) | 54(n=6) | 81(n=6) |
|  AUC, µg•min/mL | 21.0 (11) | 57.2 (15) | 97.9 (15) | 205 (21) | 318 (15) | 485 (20) | 638 (12) | 939 (7) | 1450 (18) |
|  Cmax, µg/mL | 0.7 (14) | 1.9 (14) | 3.1 (22) | 6.6 (13) | 9.9 (10) | 14.2 (19) | 19.7 (12) | 24.3 (8) | 39.1 (12) |
|  CL, L/min | 1.75 (4) | 2.00 (11) | 2.28 (17) | 2.23 (19) | 2.29 (15) | 2.18 (7) | 2.12 (7) | 2.46 (5) | 2.19 (23) |
|  t½λz, min | 9.8 (25) | 9.9 (10) | 11.2 (13) | 13.1 (32) | 13.2 (30) | 15.5 (10) | 16.9 (11) | 16.4 (19) | 13.6 (26) |
|  Vz, L | 24.8 (24) | 28.4 (16) | 36.8 (24) | 42.2 (42) | 43.4 (28) | 48.8 (12) | 51.7 (13) | 58.3 (21) | 42.8 (23) |

AUC, area under the concentration–time curve; Cmax, maximum plasma drug concentration; CL, clearance; t½λz, terminal half-life; Vz, volume of distribution during terminal phase

**Table ES2.**

**Summary of THRX-108893 pharmacokinetic parameters in arterial plasma**

|  |  |
| --- | --- |
| Geometric mean (CV%) | AZD3043 dose, mg/kg/h (30-minute infusion) |
| 1(n=5) | 3(n=6) | 6(n=6) | 12(n=6) | 18(n=6) | 27(n=6) | 36(n=6) | 54(n=6) | 81(n=6) |
|  AUC, µg•min/mL | 51.8 (15) | 127 (17) | 214 (14) | 472 (13) | 781 (11) | 1249 (15) | 1862 (13) | 3120 (43) | 5820 (19) |
|  Cmax, µg/mL | 0.7 (6) | 1.8 (6) | 3.4 (4) | 7.3 (6) | 10.7 (15) | 17.2 (6) | 25.3 (11) | 34.3 (25) | 59.3 (16) |
|  t½λz, min | 38 (13) | 35 (16) | 32 (13) | 34 (12) | 34 (8) | 34 (18) | 33 (13) | 36 (20) | 33 (37) |
|  MRT, min | 71 (7) | 69 (12) | 66 (8) | 68 (9) | 72 (7) | 72 (14) | 72 (11) | 81 (15) | 83 (13) |

AUC, area under the concentration–time curve; Cmax, maximum plasma metabolite concentration; t½λz, terminal half-life; MRT, mean residence time