Supplementary 1. Pharmacokinetic Parameters of M4, M5, M1 and M2 After a Single or Multiple Oral Doses of DA-8031

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| **Metabolites** | **Parameters** | **Treatment** |
| **20 mg** | **30 mg** | **40 mg** |
| **(N=8)** | **(N=8)** | **(N=8)** |
| **M4** | **Single dose (Day 1)** | **Tmax (h)a** | 2.0 (2.0-8.0) | 2.5 (1.0-5.0) | 2.5 (2.0-12.0) |
| **Cmax (μg/L)** | 8.3 ± 4.2 | 13.3 ± 7.2 | 11.4 ± 4.5 |
| **AUC0-24h (μg·h/L)** | 115.9 ± 41.6 | 159.9 ± 75.6 | 167.2 ± 58.4 |
| **AUCinf (μg·h/L)** | 188.4 ± 49.9 | 268.6 ± 44.1b | 291.6 ± 77.7c |
| **T1/2 (h)** | 18.1 ± 6.6 | 14.8 ± 3.6b | 16.3 ± 7.3c |
| **Metabolic ratio** | 0.63 ± 0.42 | 0.63 ± 0.43 | 0.32 ± 0.17 |
| **Multiple dose (Day 7)** | **Tmax,ss (h)a** | 2.0 (1.0-3.0) | 2.0 (1.0-4.0) | 4.0 (2.0-5.0) |
| **Cmax,ss (μg/L)** | 12.9 ± 4.4 | 15.7 ± 8.0 | 16.4 ± 4.1 |
| **AUC0-24h,ss (μg·h/L)** | 199.6 ± 56.3 | 233.7 ± 92.9 | 281.7 ± 62.0 |
| **T1/2 (h)** | 25.2 ± 9.4 | 27.4 ± 11.9 | 29.8 ± 9.3 |
| **Metabolic ratio** | 0.48 ± 0.30 | 0.40 ± 0.26 | 0.19 ± 0.08 |
| **Accumulation index** | 1.8 ± 0.4 | 5.1 ± 10.4 | 1.8 ± 0.4 |
| **M5** | **Single dose (Day 1)** | **Tmax (h)a** | 10.0 (6.0 – 24.0) | 8.0 (2.0 – 8.0) | 12.0 (8.0 – 24.0) |
| **Cmax (μg/L)** | 4.0 ± 1.7 | 6.7 ± 1.9 | 6.4 ± 2.4 |
| **AUC0-24 (μg·h/L)** | 75.1 ± 29.0 | 129.2 ± 36.9 | 121.6 ± 51.4 |
| **AUCinf (μg·h/L)** | 314.0 ± 141.4d | 603.0 ± 325.6e | 481.1 ± 365.7f |
| **T1/2 (h)** | 39.6 ± 21.5d | 66.4 ± 41.0e | 37.4 ± 32.8f |
| **Metabolic ratio** | 0.42 ± 0.28 | 0.51 ± 0.27 | 0.23 ± 0.14 |
| **Multiple dose (Day 7)** | **Tmax,ss (h)a** | 7.0 (2.0-8.0) | 7.0 (2.0-8.0) | 4.0 (1.0-8.0) |
| **Cmax,ss (μg/L)** | 10.0 ± 1.9 | 13.3 ± 5.8 | 16.2 ± 3.9 |
| **AUC0-24h,ss (μg·h/L)** | 195.8 ± 32.4 | 254.4 ± 107.5 | 330.1 ± 74.4 |
| **T1/2,ss (h)** | 36.2 ± 13.4 | 38.8 ± 19.9 | 39.2 ± 11.9 |
| **Metabolic ratio** | 0.46 ± 0.21 | 0.42 ± 0.26 | 0.22 ± 0.11 |
| **Accumulation index** | 3.0 ± 1.3 | 2.3 ± 0.6 | 3.1 ± 1.2 |
| **M1** | **Single dose (Day 1)** | **Tmax (h)a** | 3.0 (2.0-6.0) | 3.0 (1.0-24.0) | 2.0 (2.0-8.0) |
| **Cmax (μg/L)** | 1.2 ± 0.3 | 1.7 ± 0.6 | 2.6 ± 0.4 |
| **AUC0-24 (μg·h/L)** | 14.3 ± 7.9 | 20.2 ± 8.0 | 40.9 ± 9.9 |
| **AUCinf (μg·h/L)** | 55.5 ± 39.6g | 41.1 ± 16.7h | 120.2 ± 90.0i |
| **T1/2 (h)** | 37.0 ± 24.4g | 20.5 ± 8.9h | 35.1 ± 23.2i |
| **Metabolic ratio** | 0.06 ± 0.03 | 0.06 ± 0.03 | 0.07 ± 0.01 |
| **Multiple dose (Day 7)** | **Tmax,ss (h)a** | 2.0 (2.0-8.0) | 4.0 (1.0-6.0) | 3.0 (1.0-8.0) |
| **Cmax,ss (μg/L)** | 3.1 ± 1.1 | 5.9 ± 3.8 | 10.6 ± 4.6 |
| **AUC0-24h,ss (μg·h/L)** | 57.9 ± 26.9 | 107.1 ± 81.0 | 196.7 ± 74.6 |
| **T1/2,ss (h)** | 40.6 ± 24.2 | 39.8 ± 20.2 | 42.9 ± 10.3 |
| **Metabolic ratio** | 0.11 ± 0.03 | 0.12 ± 0.02 | 0.12 ± 0.02 |
| **Accumulation index** | 7.9 ± 10.7 | 5.4 ± 3.3 | 4.7 ± 1.2 |
| **M2j** | **Multiple dose (Day 7)k** | **Tmax,ss (h)a** | 8.0 (2.0-8.0) | 5.0 (2.0-8.0) | 7.0 (1.0-8.0) |
| **Cmax,ss (μg/L)** | 0.7 ± 0.0 | 0.9 ± 0.2 | 1.2 ± 0.3 |
| **AUC0-24h,ss (μg·h/L)** | 14.1 ± 0.8 | 18.3 ± 4.0 | 24.4 ± 7.5 |
| **T1/2,ss (h)** | 51.4 ± 23.9l | 61.9 ± 18.7m | 76.1 ± 26.1 |
| **Metabolic ratio** | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.02 ± 0.01 |
| **Accumulation index** | - | - | - |

**Notes**: Values are presented as the mean ± standard deviation.

a Values are presented as the median (minimum-maximum)

b N=7; Terminal elimination constants of one subject of the 30 mg dose group were not estimated.

c N=7; Terminal elimination constants of one subject of the 40 mg dose group were not estimated.

d N=3; Terminal elimination constants of five subjects of the 20 mg dose group were not estimated.

e N=7; Plasma M5 concentration was not detected at any time points in one subject of the 30 mg dose group.

f N=3; Terminal elimination constants of five subjects of the 40 mg dose group were not estimated.

g N=7; Terminal elimination constants of one subject of the 20 mg dose group were not estimated.

h N=7; Terminal elimination constants of one subject of the 30 mg dose group were not estimated.

i N=7; Terminal elimination constants of one subject of the 40 mg dose group were not estimated.

j Plasma M2 concentration was not detected at any time points in all subjects after a single dose.

k N=7; Plasma M2 concentration was not detected at any time points in three subjects of the 20 mg dose group and one subject of the 30 mg dose group.

l N=3; Terminal elimination constants of two subjects of the 20 mg dose group were not estimated.

m N=6; Terminal elimination constants of one subject of the 30 mg dose group were not estimated.

**Abbreviations**: AUC0-24h, area under the curve from 0 hours to 24 hours; AUC0-24h,ss, area under the curve from o hours to 24 hours at steady state; AUCinf, area under the curve from 0 hours to infinity; AUCinf,ss, area under the curve from 0 hours to infinity at steady state, CL/F, total clearance; CLss/F, total clearance at steady state; Cmax, maximum concentration; Cmax,ss, maximum concentration at steady state; T1/2, half-life; T1/2,ss, half-life at steady state, Tmax, time of Cmax