

## Supplementary Material (SI)

### Article Title:

Comparative Pharmacokinetics and Safety of Cannabidiol in a Powder Formulation, CBtru<sup>®</sup>, vs. an Oil-Based Formulation, Epidyolex<sup>®</sup>, Under Fasted and Fed Conditions in Healthy Participants: A Randomized Open-Label Cross-Over Phase I Study

### Journal:

CNS Drugs

### Authors:

Igor Bendik<sup>1†</sup>, Mareike Beck<sup>1†</sup>, Anu Manderna<sup>2</sup>, Franz F Roos<sup>1</sup>, Jun Wang<sup>2</sup>, Deanna McCarthy<sup>1</sup>, Christiane Schweiggert<sup>1</sup>, Ahmed Besheer<sup>1</sup>, Josh Baisley<sup>2</sup>, Zdravka Misic<sup>1</sup>, Bernd Mussler<sup>1</sup>, Adam Kuttenukeuler<sup>2</sup>, Daniele Piomelli<sup>3</sup>, Szabolcs Péter<sup>1\*</sup>

<sup>1</sup> dsm-firmenich AG, Kaiseraugst, Switzerland

<sup>2</sup> Nutrasource Pharmaceutical & Nutraceutical Services Inc., Guelph, Ontario, Canada

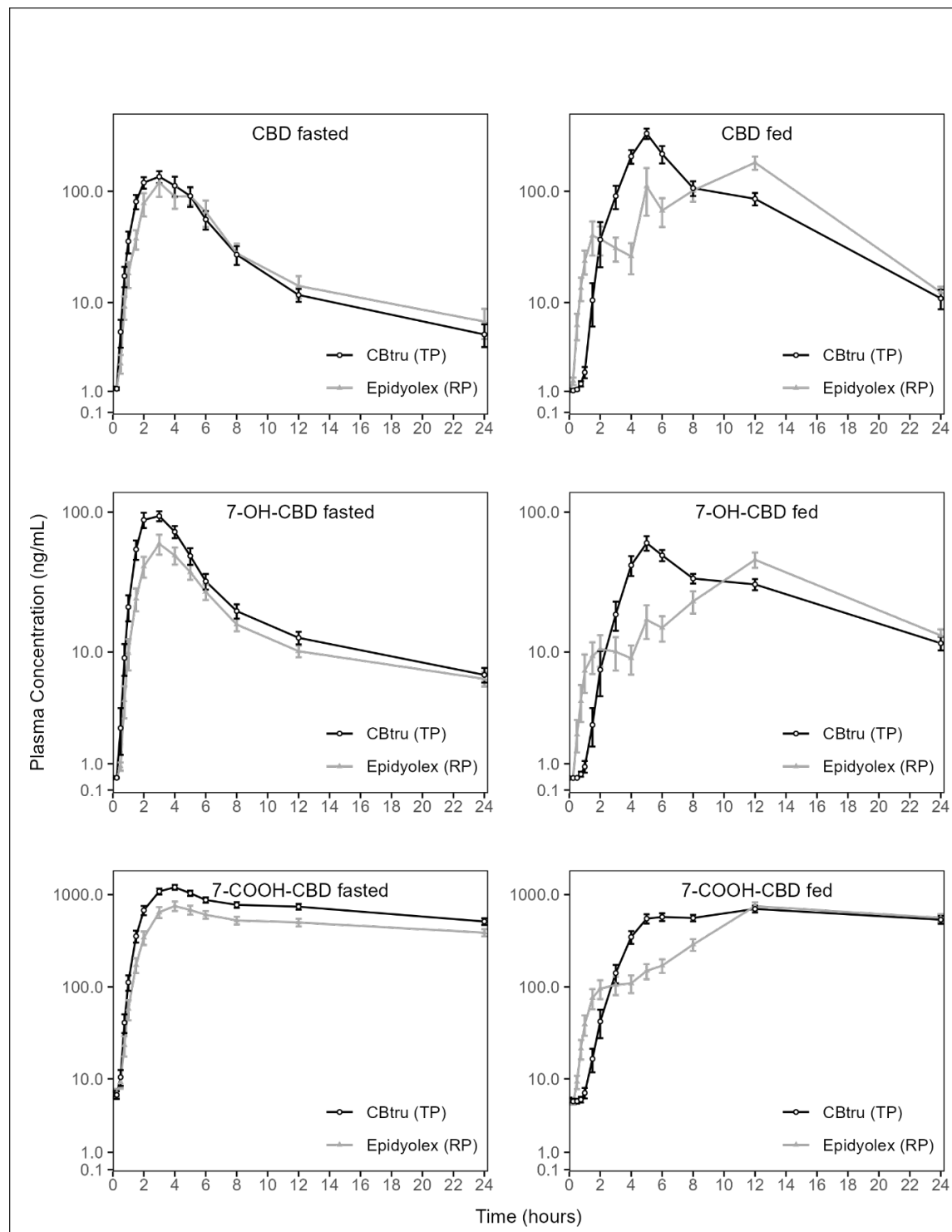
<sup>3</sup> Rhizotomos Consulting, Irvine, California, USA

<sup>†</sup> These authors contributed equally and are considered co-first authors.

### \*Corresponding Authors:

- Igor Bendik, email: [igor.bendik@dsm-firmenich.com](mailto:igor.bendik@dsm-firmenich.com)
- Szabolcs Peter, email: [szabolcs.peter@dsm-firmenich.com](mailto:szabolcs.peter@dsm-firmenich.com)

**Figure S1**



**Fig. S1 Mean ( $\pm$ standard error) plasma concentration-time profiles for cannabidiol (CBD), 7-hydroxy-cannabidiol (7-OH-CBD), and 7-carboxy-cannabidiol (7-COOH-CBD) after a single oral 400 mg CBD dose under fasted and fed conditions using semi-logarithmic scale (TP, powder formulation, CBtru®, the test product; RP, oil-based formulation, Epidyolex®, the reference product)**

**Table S1 Summary of Treatment Emergent Adverse Events**

|                                       |             | <b>Statistics - S (%) E</b>  |                              |                                 |                                 |                         |
|---------------------------------------|-------------|------------------------------|------------------------------|---------------------------------|---------------------------------|-------------------------|
|                                       |             | <b>TP<br/>Fed<br/>(N=30)</b> | <b>RP<br/>Fed<br/>(N=32)</b> | <b>TP<br/>Fasted<br/>(N=30)</b> | <b>RP<br/>Fasted<br/>(N=30)</b> | <b>Total<br/>(N=32)</b> |
| <b>Overall</b>                        |             | 6 (20.0%) 10                 | 6 (18.8%) 6                  | 8 (26.7%) 11                    | 5 (16.7%) 5                     | 14 (43.8%) 32           |
| <b>Relation</b>                       | Related     | 0 (0%) 0                     | 0 (0%) 0                     | 0 (0%) 0                        | 0 (0%) 0                        | 0 (0%) 0                |
|                                       | Suspected   | 4 (13.3%) 5                  | 3 (9.4%) 3                   | 5 (16.7%) 6                     | 3 (10.0%) 3                     | 8 (25.0%) 17            |
|                                       | Not related | 4 (13.3%) 5                  | 3 (9.4%) 3                   | 5 (16.7%) 5                     | 2 (6.7%) 2                      | 11 (34.4%) 15           |
| <b>Severity</b>                       | Severe      | 0 (0%) 0                     | 0 (0%) 0                     | 0 (0%) 0                        | 0 (0%) 0                        | 0 (0%) 0                |
|                                       | Moderate    | 1 (3.3%) 1                   | 0 (0%)                       | 0 (0%)                          | 0 (0%)                          | 1 (3.1%) 1              |
|                                       | Mild        | 5 (16.7%) 9                  | 6 (18.8%) 6                  | 8 (26.7%) 11                    | 5 (16.7%) 5                     | 14 (43.8%) 31           |
| <b>Serious</b>                        |             | 0 (0%) 0                     | 0 (0%) 0                     | 0 (0%) 0                        | 0 (0%) 0                        | 0 (0%) 0                |
| <b>Leading to<br/>Discontinuation</b> |             | 0 (0%) 0                     | 0 (0%) 0                     | 0 (0%) 0                        | 0 (0%) 0                        | 0 (0%) 0                |

**Abbreviations:** S, number of participants having experienced AE (adverse events); %, percentage of participants having experienced AE; E, number of adverse events; TP, test product (powder formulation CBtru®); RP, reference product (oil-based formulation Epidyolex®)

**Table S2 Summary of PK Parameters for CBD, 7-OH-CBD and 7-COOH-CBD by Treatment (PK Population)**

| PK Parameters                                |                  | TP Fasted<br>N=30 | RP Fasted<br>N=30 | TP Fed<br>N=30  | RP Fed<br>N=32   |
|----------------------------------------------|------------------|-------------------|-------------------|-----------------|------------------|
| <b>CBD</b>                                   |                  |                   |                   |                 |                  |
| <b>AUC<sub>0-24</sub> (h*ng/mL)</b>          | N                | 30                | 30                | 30              | 32               |
|                                              | Mean (SD)        | 771.2 (516.86)    | 717.4 (594.04)    | 2033.0 (856.91) | 2132.7 (955.11)  |
|                                              | Median           | 594.1             | 460.9             | 1894.9          | 1897.2           |
|                                              | Min, Max         | 228.5, 2054.4     | 225.4, 2247.0     | 980.4, 5005.6   | 358.8, 4138.9    |
|                                              | P25, P75         | 399.7, 1060.3     | 309.0, 912.9      | 1500.3, 2143.7  | 1423.5, 2625.2   |
|                                              | CV (%)           | 67.02             | 82.81             | 42.15           | 44.79            |
|                                              | Geometric Mean   | 633.2             | 549.3             | 1908.5          | 1910.8           |
|                                              | Geometric CV (%) | 70.02             | 80.79             | 35.08           | 54.36            |
| <b>AUC<sub>inf</sub> (h*ng/mL)</b>           | N                | 23                | 24                | 20              | 3                |
|                                              | Mean (SD)        | 755.3 (566.68)    | 809.2 (651.33)    | 2075.6 (839.45) | 2335.5 (1506.34) |
|                                              | Median           | 510.1             | 517.1             | 1901.3          | 1561.3           |
|                                              | Min, Max         | 251.5, 2088.3     | 241.9, 2295.2     | 999.9, 5041.3   | 1373.8, 4071.5   |
|                                              | P25, P75         | 347.8, 928.8      | 328.8, 1096.4     | 1638.9, 2167.6  | 1373.8, 4071.5   |
|                                              | CV (%)           | 75.02             | 80.49             | 40.44           | 64.50            |
|                                              | Geometric Mean   | 606.6             | 617.2             | 1959.3          | 2059.3           |
|                                              | Geometric CV (%) | 72.12             | 83.93             | 33.93           | 65.02            |
| <b>AUC<sub>0-24</sub> /AUC<sub>inf</sub></b> | N                | 23                | 24                | 20              | 3                |
|                                              | Mean (SD)        | 0.947 (0.031)     | 0.930 (0.042)     | 0.974 (0.011)   | 0.981 (0.009)    |
|                                              | Median           | 0.950             | 0.941             | 0.975           | 0.978            |
|                                              | Min, Max         | 0.836, 0.984      | 0.821, 0.979      | 0.947, 0.993    | 0.973, 0.992     |
|                                              | P25, P75         | 0.931, 0.966      | 0.912, 0.962      | 0.969, 0.981    | 0.973, 0.992     |
| <b>C<sub>max</sub> (ng/mL)</b>               | N                | 30                | 30                | 30              | 32               |
|                                              | Mean (SD)        | 189.8 (129.11)    | 177.8 (177.20)    | 376.5 (222.53)  | 316.2 (258.16)   |
|                                              | Median           | 157.1             | 81.7              | 326.7           | 297.8            |
|                                              | P25, P75         | 100.2, 264.6      | 56.8, 307.8       | 212.3, 514.7    | 163.1, 370.4     |
|                                              | CV (%)           | 68.04             | 99.68             | 59.10           | 81.66            |
|                                              | Geometric Mean   | 154.8             | 115.0             | 323.9           | 255.5            |
|                                              | Geometric CV (%) | 73.52             | 117.06            | 61.39           | 73.26            |
| <b>Elimination Rate</b>                      | N                | 23                | 24                | 20              | 3                |
|                                              | Mean (SD)        | 0.120 (0.041)     | 0.110 (0.038)     | 0.167 (0.031)   | 0.185 (0.033)    |
|                                              | Median           | 0.108             | 0.109             | 0.161           | 0.174            |
|                                              | Min, Max         | 0.064, 0.209      | 0.055, 0.194      | 0.123, 0.250    | 0.159, 0.221     |
|                                              | P25, P75         | 0.084, 0.156      | 0.076, 0.138      | 0.148, 0.183    | 0.159, 0.221     |

| PK Parameters                                |                  | TP Fasted<br>N=30 | RP Fasted<br>N=30 | TP Fed<br>N=30 | RP Fed<br>N=32 |
|----------------------------------------------|------------------|-------------------|-------------------|----------------|----------------|
| <b>T<sub>1/2</sub> (h)</b>                   | N                | 23                | 24                | 20             | 3              |
|                                              | Mean (SD)        | 6.446 (2.067)     | 7.118 (2.597)     | 4.280 (0.741)  | 3.823 (0.629)  |
|                                              | Median           | 6.443             | 6.342             | 4.300          | 3.983          |
|                                              | Min, Max         | 3.314, 10.753     | 3.573, 12.567     | 2.775, 5.647   | 3.130, 4.357   |
|                                              | P25, P75         | 4.430, 8.295      | 5.023, 9.065      | 3.787, 4.680   | 3.130, 4.357   |
| <b>T<sub>max</sub> (h)</b>                   | N                | 30                | 30                | 30             | 32             |
|                                              | Mean (SD)        | 3.084 (1.175)     | 4.483 (3.795)     | 5.972 (2.628)  | 9.398 (4.134)  |
|                                              | Median           | 3.000             | 3.500             | 5.000          | 8.009          |
|                                              | Min, Max         | 1.500, 6.000      | 2.000, 23.483     | 3.000, 12.050  | 1.500, 23.583  |
|                                              | P25, P75         | 2.000, 4.000      | 3.000, 5.000      | 5.000, 6.000   | 8.000, 12.000  |
| <b>7-OH-CBD</b>                              |                  |                   |                   |                |                |
| <b>AUC<sub>0-24</sub> (h*ng/mL)</b>          | N                | 30                | 30                | 30             | 32             |
|                                              | Mean (SD)        | 561.1 (268.68)    | 397.2 (224.39)    | 606.5 (231.62) | 577.6 (258.67) |
|                                              | Median           | 519.2             | 347.5             | 563.5          | 513.6          |
|                                              | Min, Max         | 211.4, 1200.0     | 112.8, 834.5      | 175.5, 1076.7  | 256.1, 1167.0  |
|                                              | P25, P75         | 359.5, 723.7      | 187.9, 511.8      | 443.9, 815.0   | 387.1, 739.3   |
|                                              | CV (%)           | 47.88             | 56.49             | 38.19          | 44.78          |
|                                              | Geometric Mean   | 501.7             | 336.4             | 558.6          | 523.6          |
|                                              | Geometric CV (%) | 52.11             | 66.37             | 45.63          | 47.92          |
| <b>AUC<sub>inf</sub> (h*ng/mL)</b>           | N                | 19                | 15                | 13             | 3              |
|                                              | Mean (SD)        | 652.2 (325.43)    | 516.7 (283.79)    | 734.0 (263.75) | 509.8 (228.38) |
|                                              | Median           | 605.6             | 457.2             | 727.6          | 475.2          |
|                                              | Min, Max         | 245.3, 1430.4     | 141.9, 978.8      | 331.4, 1084.5  | 300.7, 753.5   |
|                                              | P25, P75         | 320.9, 845.9      | 306.8, 802.5      | 499.0, 962.2   | 300.7, 753.5   |
|                                              | CV (%)           | 49.89             | 54.92             | 35.94          | 44.80          |
|                                              | Geometric Mean   | 576.5             | 440.8             | 686.5          | 475.7          |
|                                              | Geometric CV (%) | 56.20             | 66.75             | 40.81          | 48.47          |
| <b>AUC<sub>0-24</sub> /AUC<sub>inf</sub></b> | N                | 19                | 15                | 13             | 3              |
|                                              | Mean (SD)        | 0.878 (0.037)     | 0.865 (0.028)     | 0.865 (0.028)  | 0.887 (0.022)  |
|                                              | Median           | 0.881             | 0.866             | 0.863          | 0.899          |
|                                              | Min, Max         | 0.810, 0.931      | 0.814, 0.920      | 0.804, 0.906   | 0.861, 0.900   |
|                                              | P25, P75         | 0.842, 0.913      | 0.852, 0.888      | 0.853, 0.890   | 0.861, 0.900   |

| PK Parameters                       |                  | TP Fasted<br>N=30    | RP Fasted<br>N=30    | TP Fed<br>N=30       | RP Fed<br>N=32    |
|-------------------------------------|------------------|----------------------|----------------------|----------------------|-------------------|
| <b>C<sub>max</sub> (ng/mL)</b>      | N                | 30                   | 30                   | 30                   | 32                |
|                                     | Mean (SD)        | 116.7 (55.02)        | 71.8 (48.98)         | 71.0 (34.31)         | 59.6 (30.85)      |
|                                     | Median           | 104.4                | 53.4                 | 62.0                 | 53.8              |
|                                     | Min, Max         | 40.2, 234.2          | 15.9, 186.1          | 13.8, 147.2          | 21.1, 136.4       |
|                                     | P25, P75         | 66.7, 160.6          | 30.2, 104.6          | 50.5, 102.3          | 36.7, 72.8        |
|                                     | CV (%)           | 47.14                | 68.24                | 48.33                | 51.77             |
|                                     | Geometric Mean   | 104.3                | 56.5                 | 63.0                 | 52.4              |
|                                     | Geometric CV (%) | 52.43                | 82.69                | 55.57                | 56.09             |
| <b>Elimination Rate</b>             | N                | 23                   | 22                   | 18                   | 5                 |
|                                     | Mean (SD)        | 0.075 (0.024)        | 0.067 (0.021)        | 0.084 (0.017)        | 0.085 (0.030)     |
|                                     | Median           | 0.071                | 0.066                | 0.089                | 0.094             |
|                                     | Min, Max         | 0.045, 0.145         | 0.034, 0.111         | 0.055, 0.118         | 0.043, 0.118      |
|                                     | P25, P75         | 0.056, 0.096         | 0.051, 0.080         | 0.069, 0.095         | 0.068, 0.104      |
| <b>T<sub>1/2</sub> (h)</b>          | N                | 23                   | 22                   | 18                   | 5                 |
|                                     | Mean (SD)        | 10.018 (2.771)       | 11.399 (3.848)       | 8.611 (1.932)        | 9.250 (4.190)     |
|                                     | Median           | 9.762                | 10.528               | 7.787                | 7.406             |
|                                     | Min, Max         | 4.784, 15.457        | 6.266, 20.261        | 5.874, 12.523        | 5.871, 16.159     |
|                                     | P25, P75         | 7.255, 12.361        | 8.625, 13.502        | 7.300, 10.083        | 6.640, 10.173     |
| <b>T<sub>max</sub> (h)</b>          | N                | 30                   | 30                   | 30                   | 32                |
|                                     | Mean (SD)        | 2.951 (0.833)        | 4.149 (3.805)        | 6.641 (4.051)        | 9.366 (4.407)     |
|                                     | Median           | 3.000                | 3.000                | 5.000                | 12.000            |
|                                     | Min, Max         | 1.500, 5.000         | 2.000, 23.483        | 3.000, 23.133        | 2.000, 23.583     |
|                                     | P25, P75         | 2.000, 3.000         | 3.000, 4.000         | 5.000, 6.000         | 5.500, 12.000     |
| <b>7-COOH-CBD</b>                   |                  |                      |                      |                      |                   |
| <b>AUC<sub>0-24</sub> (h*ng/mL)</b> | N                | 30                   | 30                   | 30                   | 32                |
|                                     | Mean (SD)        | 16186.7<br>(6229.29) | 11064.6<br>(5749.35) | 12136.0<br>(5223.31) | 10682.9 (5038.32) |
|                                     | Median           | 15978.3              | 11509.8              | 10894.5              | 9194.9            |
|                                     | Min, Max         | 5675.7, 35693.4      | 2743.6, 22473.5      | 3646.6, 26227.3      | 3262.8, 26342.2   |
|                                     | P25, P75         | 11752.4,<br>19089.9  | 6606.9, 15061.1      | 8858.8, 15339.7      | 7517.3, 13197.7   |
|                                     | CV (%)           | 38.48                | 51.96                | 43.04                | 47.16             |
|                                     | Geometric Mean   | 15031.6              | 9492.6               | 11066.5              | 9722.2            |
|                                     | Geometric CV (%) | 42.04                | 65.33                | 47.34                | 45.79             |

| PK Parameters                       |                  | TP Fasted<br>N=30    | RP Fasted<br>N=30    | TP Fed<br>N=30       | RP Fed<br>N=32    |
|-------------------------------------|------------------|----------------------|----------------------|----------------------|-------------------|
| <b>C<sub>max</sub> (ng/mL)</b>      | N                | 30                   | 30                   | 30                   | 32                |
|                                     | Mean (SD)        | 1268.1 (413.20)      | 830.5 (443.45)       | 800.4 (322.63)       | 821.5 (392.50)    |
|                                     | Median           | 1259.0               | 824.2                | 756.4                | 763.6             |
|                                     | Min, Max         | 461.4, 2362.9        | 222.6, 1730.8        | 225.4, 1630.5        | 238.5, 1863.1     |
|                                     | P25, P75         | 1050.0, 1559.0       | 454.7, 1137.6        | 608.4, 991.2         | 525.4, 990.3      |
|                                     | CV (%)           | 32.58                | 53.39                | 40.31                | 47.78             |
|                                     | Geometric Mean   | 1195.6               | 707.7                | 734.6                | 739.0             |
|                                     | Geometric CV (%) | 37.95                | 66.46                | 46.39                | 49.76             |
| <b>Elimination Rate</b>             | N                | 27                   | 23                   | 8                    | 1                 |
|                                     | Mean (SD)        | 0.030 (0.010)        | 0.028 (0.010)        | 0.034 (0.011)        | 0.032 (N/A)       |
|                                     | Median           | 0.032                | 0.028                | 0.032                | 0.032             |
|                                     | Min, Max         | 0.010, 0.050         | 0.008, 0.049         | 0.020, 0.049         | 0.032, 0.032      |
|                                     | P25, P75         | 0.027, 0.036         | 0.020, 0.032         | 0.025, 0.046         | 0.032, 0.032      |
| <b>T<sub>1/2</sub> (h)</b>          | N                | 27                   | 23                   | 8                    | 1                 |
|                                     | Mean (SD)        | 27.106 (13.585)      | 29.774 (17.145)      | 22.448 (7.563)       | 21.459 (N/A)      |
|                                     | Median           | 21.953               | 24.406               | 22.019               | 21.459            |
|                                     | Min, Max         | 13.956, 67.320       | 14.031, 92.378       | 14.147, 35.221       | 21.459, 21.459    |
|                                     | P25, P75         | 19.267, 25.636       | 21.689, 35.161       | 15.157, 27.933       | 21.459, 21.459    |
| <b>T<sub>max</sub> (h)</b>          | N                | 30                   | 30                   | 30                   | 32                |
|                                     | Mean (SD)        | 3.834 (0.875)        | 5.083 (3.830)        | 10.837 (6.595)       | 12.657 (4.731)    |
|                                     | Median           | 4.000                | 4.000                | 12.000               | 12.000            |
|                                     | Min, Max         | 2.000, 6.000         | 3.000, 23.483        | 4.000, 24.033        | 2.000, 23.800     |
|                                     | P25, P75         | 3.000, 4.000         | 4.000, 5.000         | 5.000, 12.000        | 12.000, 12.017    |
| <b>TDE</b>                          |                  |                      |                      |                      |                   |
| <b>AUC<sub>0-24</sub> (h*ng/mL)</b> | N                | 30                   | 30                   | 30                   | 32                |
|                                     | Mean (SD)        | 16083.7<br>(5922.40) | 11197.4<br>(5675.67) | 13690.4<br>(5049.73) | 12435.8 (5167.93) |
|                                     | Median           | 16271.3              | 11475.6              | 12506.8              | 11280.0           |
|                                     | Min, Max         | 6089.6, 34204.7      | 3095.8, 21963.9      | 4789.2, 27098.7      | 6055.8, 27173.7   |
|                                     | P25, P75         | 11527.2,<br>19216.1  | 6625.0, 14450.5      | 10648.8,<br>17244.1  | 8664.4, 14735.2   |
|                                     | CV (%)           | 36.82                | 50.69                | 36.89                | 41.56             |
|                                     | Geometric Mean   | 15017.4              | 9717.4               | 12806.0              | 11566.9           |
|                                     | Geometric CV (%) | 40.38                | 61.81                | 39.35                | 39.08             |

| PK Parameters                 |                  | TP Fasted<br>N=30  | RP Fasted<br>N=30  | TP Fed<br>N=30     | RP Fed<br>N=32   |
|-------------------------------|------------------|--------------------|--------------------|--------------------|------------------|
| <b>ADE</b>                    |                  |                    |                    |                    |                  |
| AUC <sub>0-24</sub> (h*ng/mL) | N                | 30                 | 30                 | 30                 | 32               |
|                               | Mean (SD)        | 1305.2<br>(690.55) | 1095.4<br>(740.72) | 2610.2<br>(941.49) | 2682.3 (1138.82) |
|                               | Median           | 1100.2             | 736.0              | 2449.6             | 2265.6           |
|                               | Min, Max         | 440.4, 2672.3      | 364.7, 2881.5      | 1356.9, 5527.7     | 638.3, 5142.6    |
|                               | P25, P75         | 795.4, 1675.2      | 523.4, 1462.4      | 2089.4, 2865.0     | 1776.3, 3190.1   |
|                               | CV (%)           | 52.91              | 67.62              | 36.07              | 42.46            |
|                               | Geometric Mean   | 1142.6             | 898.8              | 2480.7             | 2448.4           |
|                               | Geometric CV (%) | 56.61              | 69.24              | 31.98              | 47.20            |

**Abbreviations:** TP, test product (powder formulation CBtru®); RP, reference product (oil-based formulation Epidyolex®); CBD, cannabidiol; 7-OH-CBD, 7-hydroxy-cannabidiol; 7-COOH-CBD, 7-carboxy-cannabidiol; AUC<sub>0-24</sub>, area under the plasma concentration-time curve over 24 h; AUC<sub>0-∞</sub>, area under the concentration-time curve from zero to infinity; C<sub>max</sub>, maximum concentration in plasma; T<sub>max</sub>, time to maximum (peak) plasma concentration; T<sub>1/2</sub>, elimination half-life; N, number of participants exposed; PK, pharmacokinetic