

## Supplementary Materials

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## eMethods

### Study Drugs

Standardised cannabis plant material is produced according to Good Manufacturing Practice (GMP) and meet the European Medicines Agency's contaminant levels for products used in the respiratory tract. The products are regulated by the Dutch government's Office of Medicinal Cannabis at the Dutch Ministry of Health, Welfare and Sport.

### Participants

#### Recruitment

Email advertisements were sent to staff and students at King's College London. After completing an initial phone screening, participants were invited to attend a baseline session at King's College Hospital.

#### Inclusion/Exclusion criteria

##### Inclusion criteria:

- i) Be aged between 21-50 years old
- ii) Have used cannabis at least once in the past
- iii) Willing and able to provide written informed consent
- iv) Willing to provide blood samples
- v) Be a fluent English speaker

##### Exclusion criteria:

- i) cannabis use more than one day per week on average over the last 12 months;
- ii) any past or present major mental illness
- iii) a past or present major physical illness
- iv) a score of 5 and above on the Michigan Alcoholism Screening Test <sup>1</sup>;
- v) a score of 5 and above on the Fagerstrom Test for Nicotine Dependence <sup>2</sup>;
- vi) a score of 5 and above on the Drug Abuse Screening Test (DAST-20) <sup>3</sup>;
- vii) past or present use of anti-psychotic or anti-depressant medication;
- viii) a first-degree relative with a psychotic disorder;
- ix) currently use of psychotropic medication;
- x) BMI classified as obese or underweight;
- xi) having taken part in any drug study within the last 30 days or taking part in another study over the course of the trial;
- xii) a known drug sensitivity/allergy towards cannabis or lorazepam; and
- xiii) pregnancy (current or planned) or lactation in women.

Urine pregnancy tests were performed in all female participants at the start of each study visit with drug administration only performed upon a negative result. In addition, participants were asked not to use recreational/illicit drugs at least 7 days and alcohol and tobacco for 24 hours before each visit, confirmed by a urine drug test, alcohol breath test (BAC=0) and carbon monoxide breath test (CO <10 ppm) at each study visit, respectively. Urine drug testing kits tested for amphetamines, benzodiazepines, buprenorphine, cocaine, cannabis, methadone, methamphetamines, morphine, and opiates. Failure to pass tests resulted in rescheduling of the study visit.

### Screening Visit

A study physician was present at screening visits to complete a general medical history and brief physical examination, to exclude subjects with medical conditions. Participants were given the opportunity to discuss the patient information sheet and ask questions before completing consent forms. Psychological scales were completed before the participant was discharged.

### Randomisation and masking

The study design was a 4 phase cross-over with each phase corresponding to one of the 4 CBD:THC dosing ratios: 0:1, 1:1, 2:1, 3:1. Each participant was required to complete all phases corresponding to all ratios of cannabis preparations. For 4 conditions there are 24 possible permutations of sequential order, e.g., Visit 1, 2:1 – Visit 2, 0:1 – Visit 3, 1:1 – Visit 4, 3:1. Randomised sequences were generated in blocks with the first 24 participants allocated each of the 24 possible orders of ratios, as were the next 24 and so on. Where there were fewer participants than possible order sequences, each participant received a random selection from the 24, sampled without replacement. The randomisation list was generated by a statistician not involved with the study, using a customised randomisation script generated in R software v 3.1 (available on request).

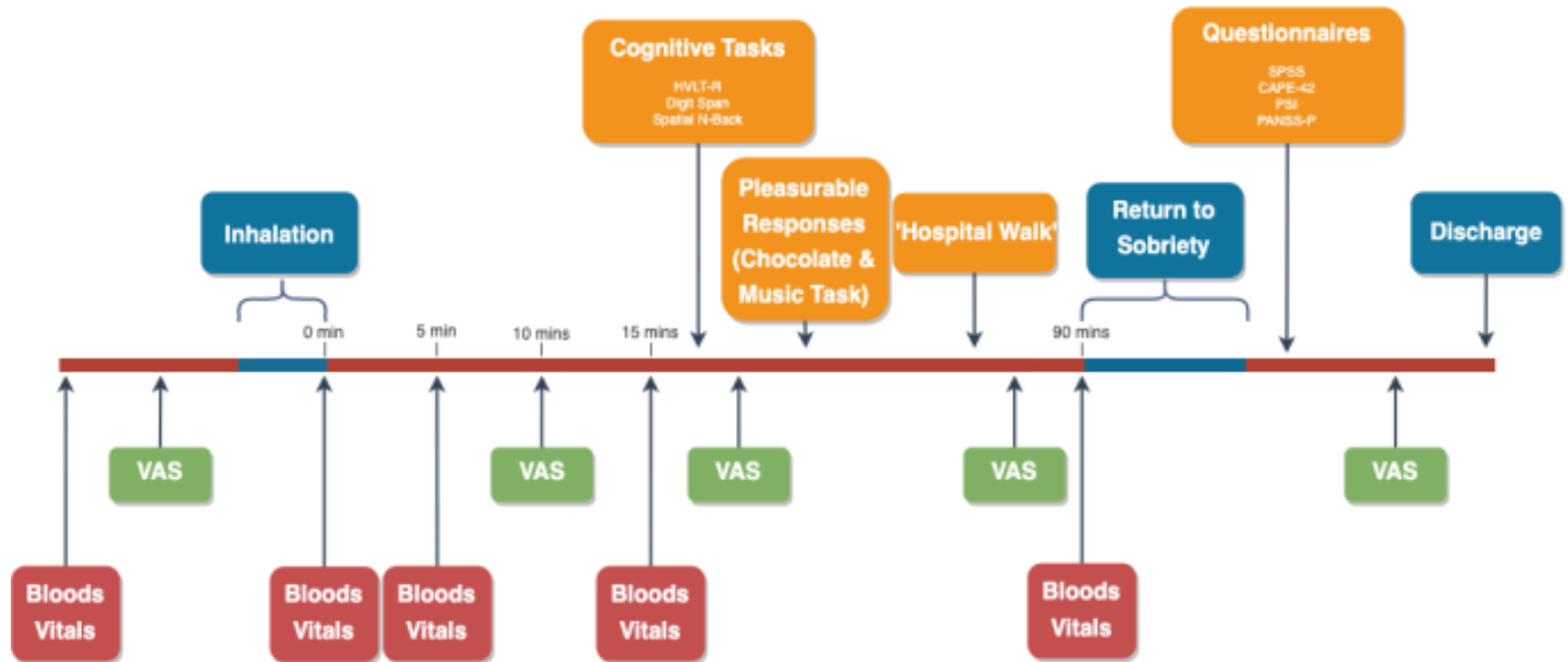
The randomisation was double blinded to both researchers and participants. The randomisation list was passed from the independent statistician to the Maudsley Pharmacy who prepared the cannabis preparations. The pharmacy dispensed the study drug to a blinded researcher. The cannabis preparation was then loaded into the filling chamber and vaporised by a research nurse at the Clinical Research Facility (CRF) who was not involved with any other study procedures. Once filled, this was encased with an opaque bag to ensure the blind was maintained (a higher CBD:THC ratio produces a denser vapour). Upon completion of data collection and entry the randomisation schedule was revealed to the research team prior to data analysis.

### Experimental visit

Experimental sessions were scheduled to begin at either 10AM or 12PM. Participants were asked to have a normal (by their own standards) amount of sleep and eat a normal breakfast before arriving. An intravenous cannula was inserted into the participants' arm before the administration of vaporised cannabis.

Rescue medication (oral Lorazepam, 1-2mg prn) was available on request of the participant should they become overly distressed by the effects of the drug but was never required. The participant remained in the CRF until the effects of the drug had worn off (roughly 3 hours after cannabis inhalation). Participants were discharged after completing a field sobriety test and vital signs, and told to avoid driving, operating heavy machinery, or cycling for the next 24 hours. The researchers ensured the participant had contact details to the study physician and knew to contact them with any concern relating to participation in the study or side-effects.

eFigure 1. Timeline of baseline and experimental sessions.



Bloods, blood sample; Vitals, vital signs (HR, BP, O<sub>2</sub> sat.); CAPE-42, Community assessment of Psychic Experiences – state<sup>4</sup>; Digit Span, Forward and reverse digit span; HVLt-R, Hopkins verbal learning task – Revised<sup>5</sup>; PANSS-P, Positive and negative syndrome scale – positive subscale<sup>6</sup>; PSI, Psychotomimetic states inventory<sup>7</sup>; Spatial N-Back task<sup>8</sup>; SPSS, State social paranoia scale<sup>9</sup>; VAS, Visual Analogue Scale.

The timings of the blood draws were based on the known pharmacokinetic profiles of inhaled THC and CBD.<sup>10,11</sup>

See study protocol for full description of timeline and tasks: <https://osf.io/kt3f7>

### Inhalation procedure

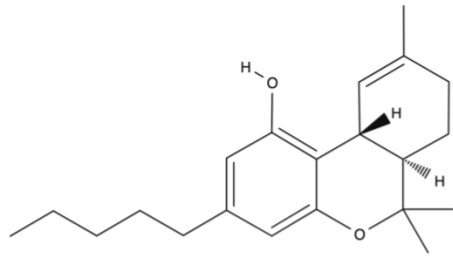
Participants were instructed to inhale and hold their breath for 8 seconds before exhaling fully and resting for 8 seconds. Participants inhaled the first balloon standing upright and the second lying on a clinical bed in preparation of blood sampling.

Vaporization of was chosen as the method of drug preparation replicates the bioavailability characteristics of with smoking, while avoiding toxic chemicals from burnt cannabis. A cup of hot lemon and honey water was provided to help with the abrasiveness of cannabis inhalation.

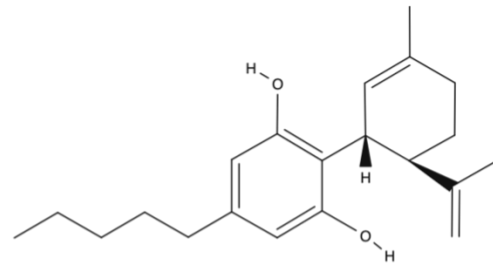
### Sample storage and transport

Plasma samples were stored at  $-80\text{ }^{\circ}\text{C}$  for 329 days (95%CI: 310 to 348) at King's College Hospital, before being transported via a temperature-controlled courier to Turku Metabolomics Centre (Turku Bioscience, Finland).

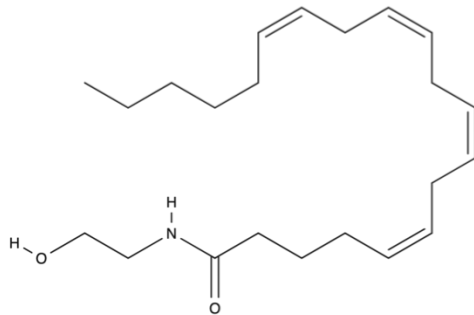
**eFigure 2.** Molecular structure of plant cannabinoids, endocannabinoids and biologically related compounds analysed from plasma samples



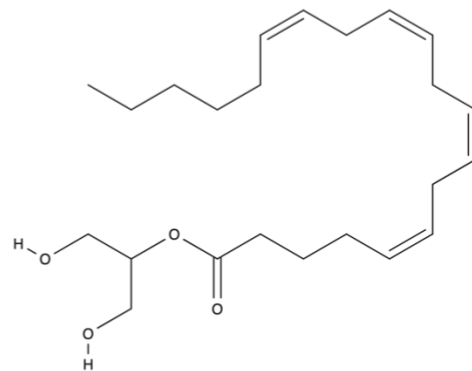
Delta-9-tetrahydrocannabinol - THC



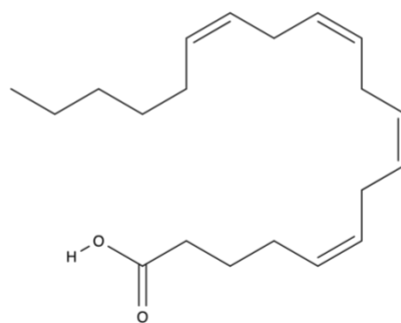
Cannabidiol - CBD



Anandamide - AEA

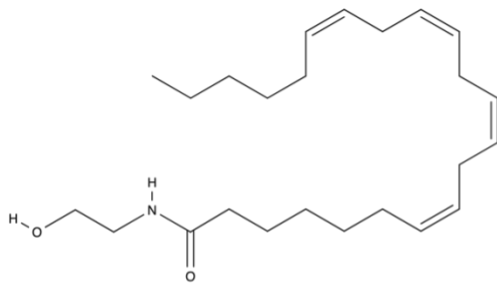


2-Arachidonoylglycerol - 2-AG

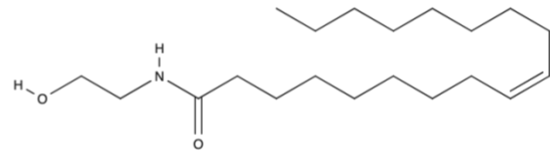


Arachidonic acid - AA

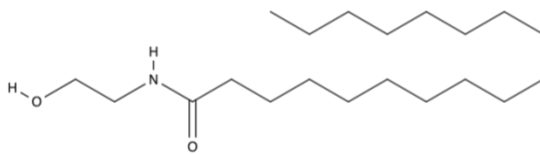
eFigure 2 continued.



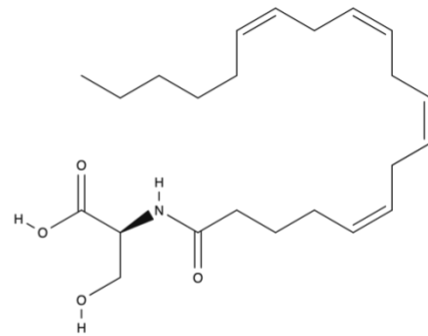
Docosatetraenylethanolamide - DEA



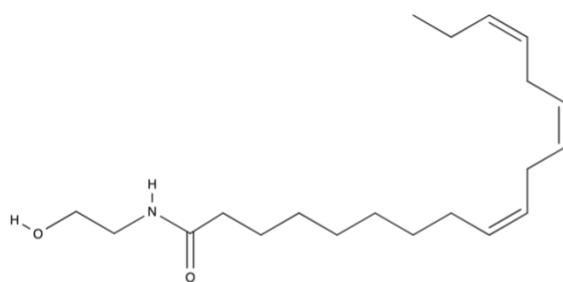
Oleoylethanolamide - OEA



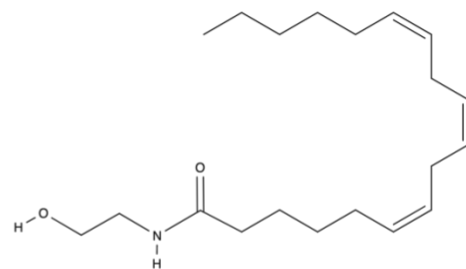
Stearoylethanolamide - SEA



N-arachidonyl-L-serine - ARA-S

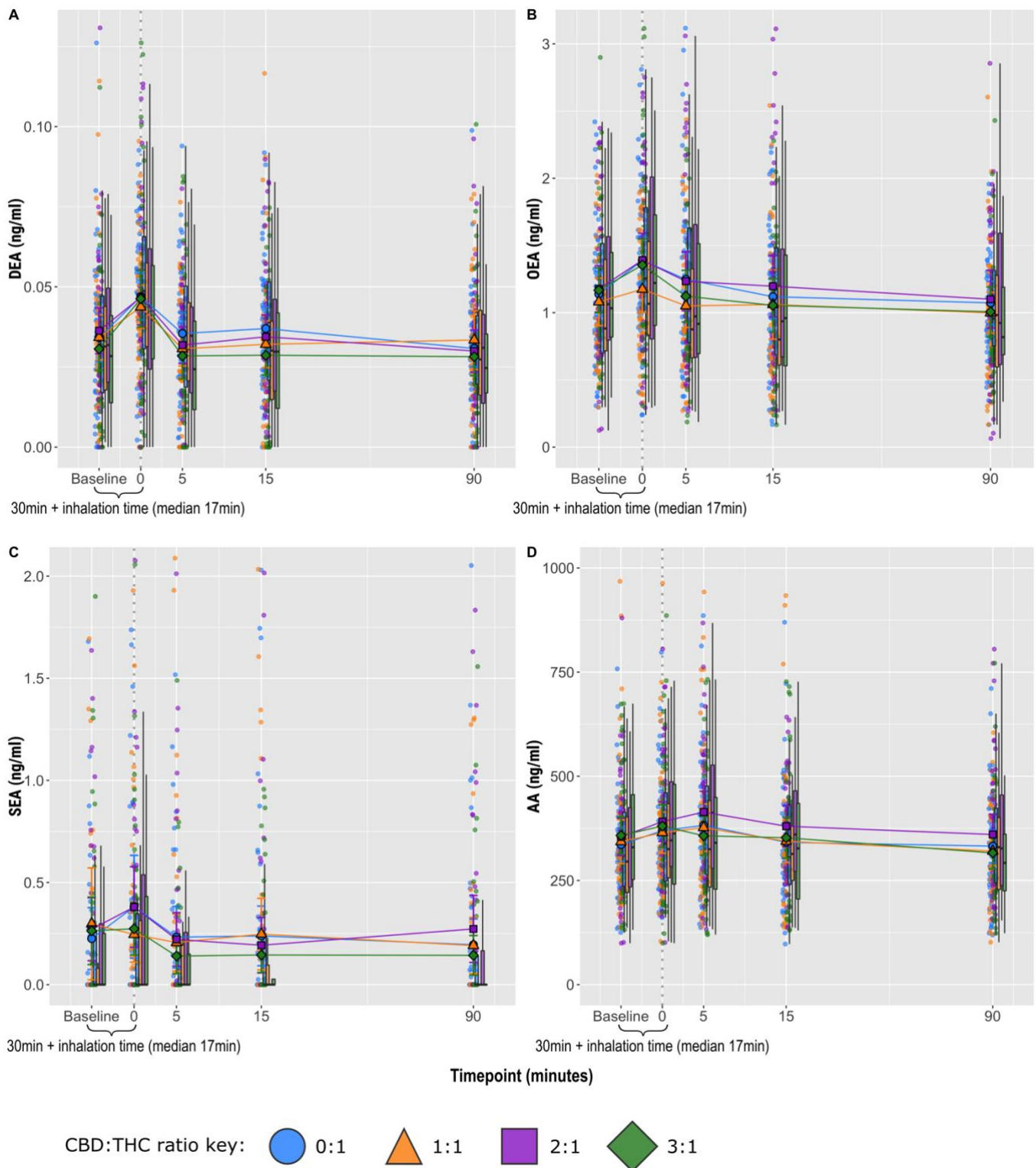


Alpha-linolenylethanolamide - aLEA



Gamma-linolenylethanolamide - gLEA

eFigure 3. Plasma concentration-time graphs, stratified by CBD:THC ratio

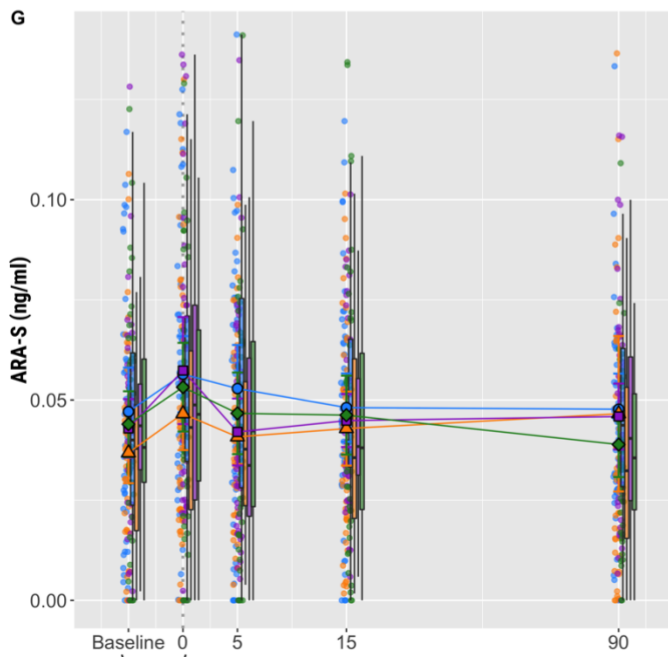
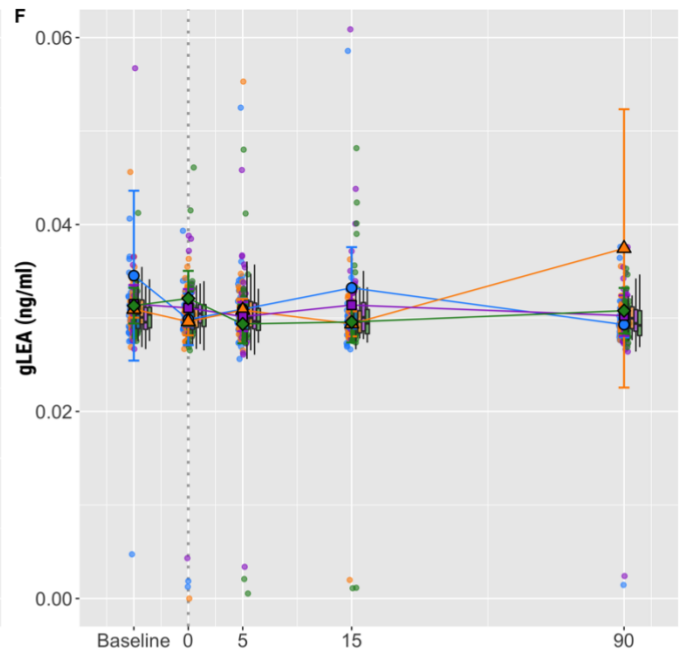
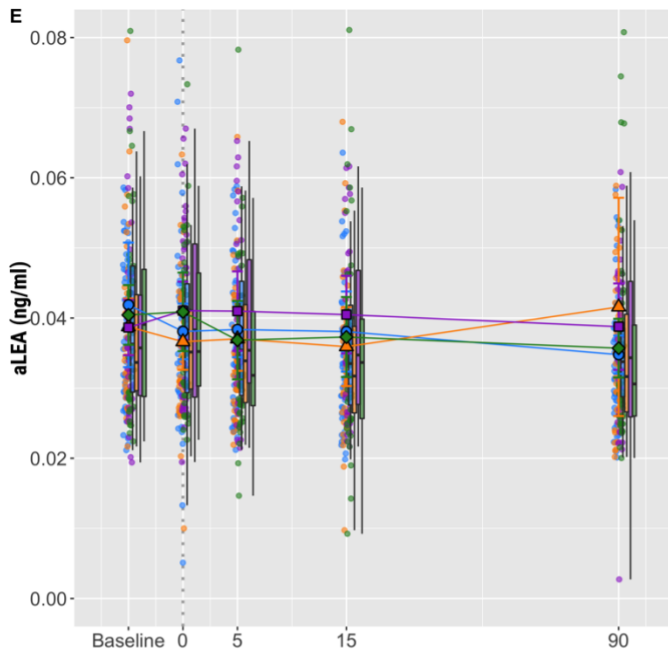


**A.** Docosatetraenylethanolamide (DEA), **B.** oleoylethanolamide (OEA), **C.** stearoylethanolamide (SEA), **D.** arachidonic acid (AA).

Circles show individual data points, larger shapes show mean values and boxplots show median and interquartile range.

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30min + inhalation time (median 17min)

Timepoint (minutes)

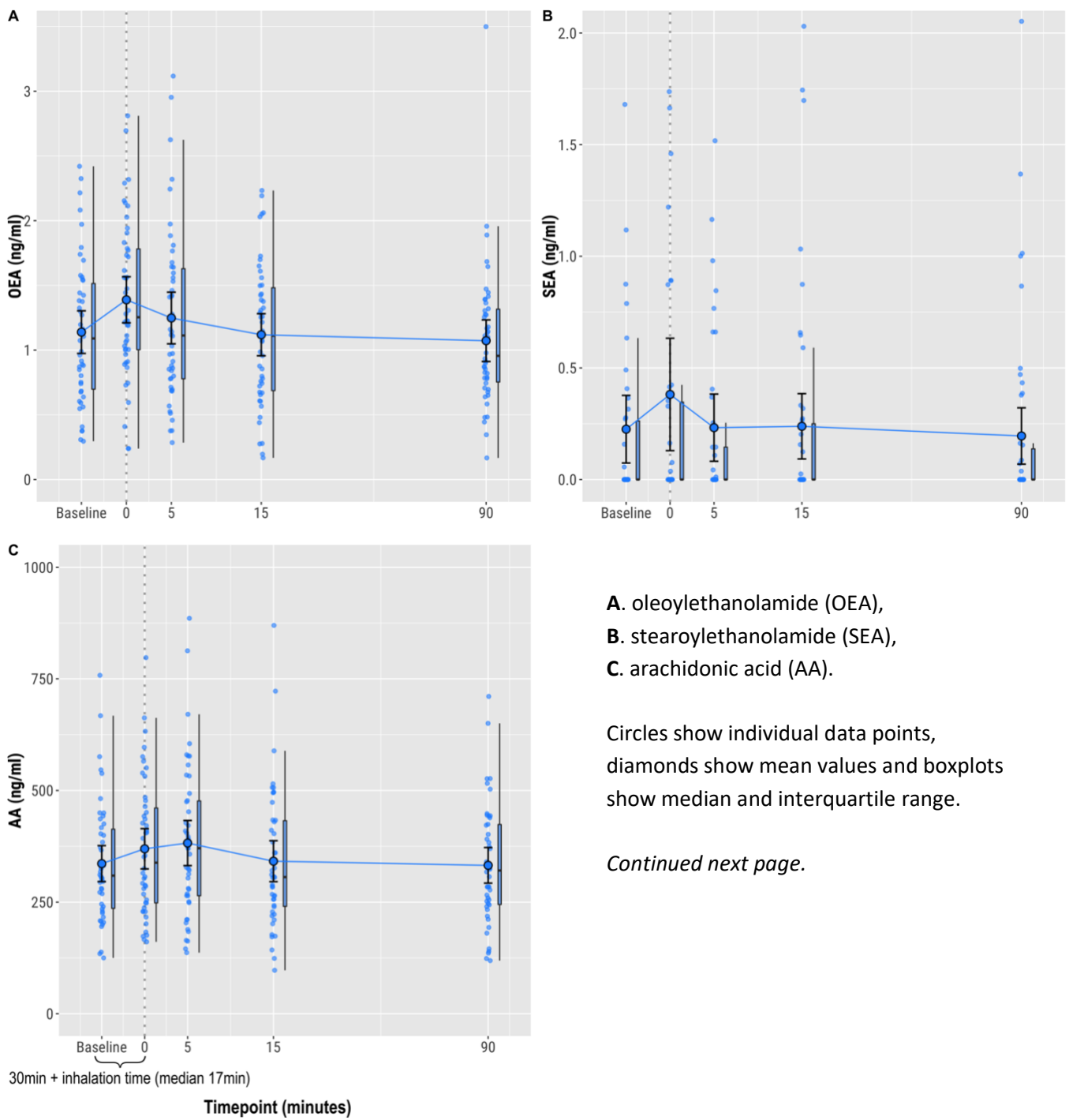
**eFigure 3 continued.**

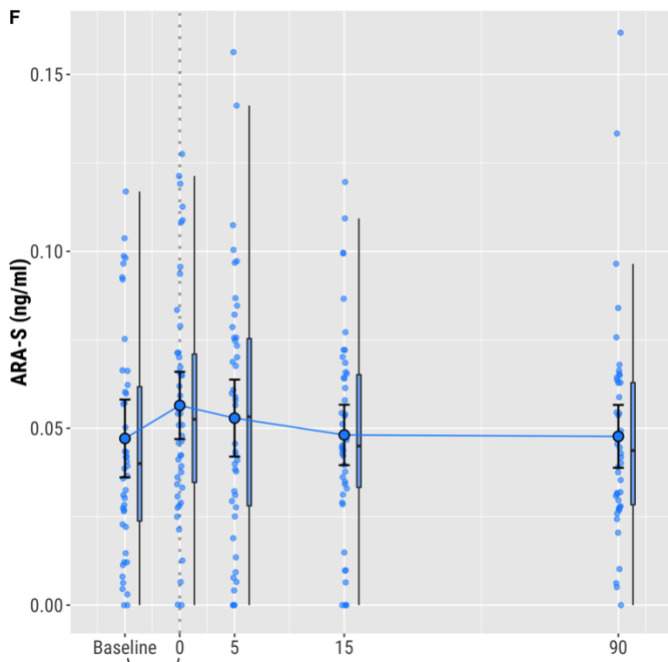
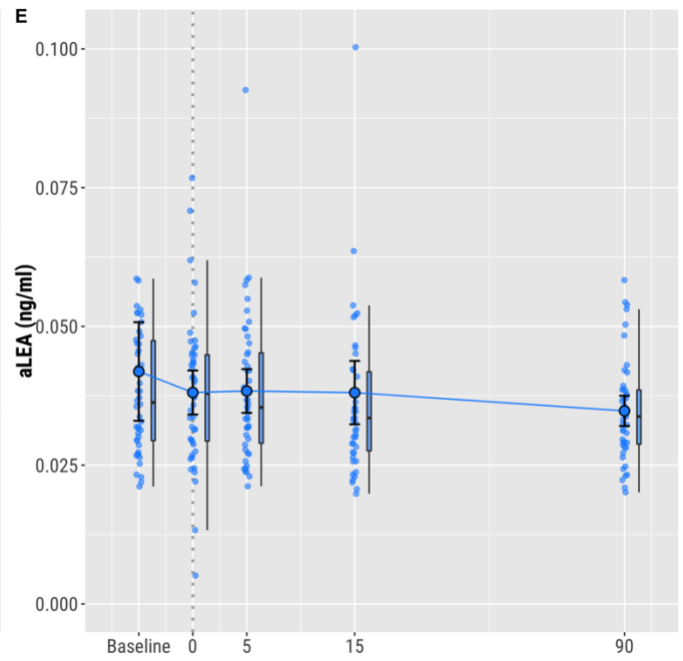
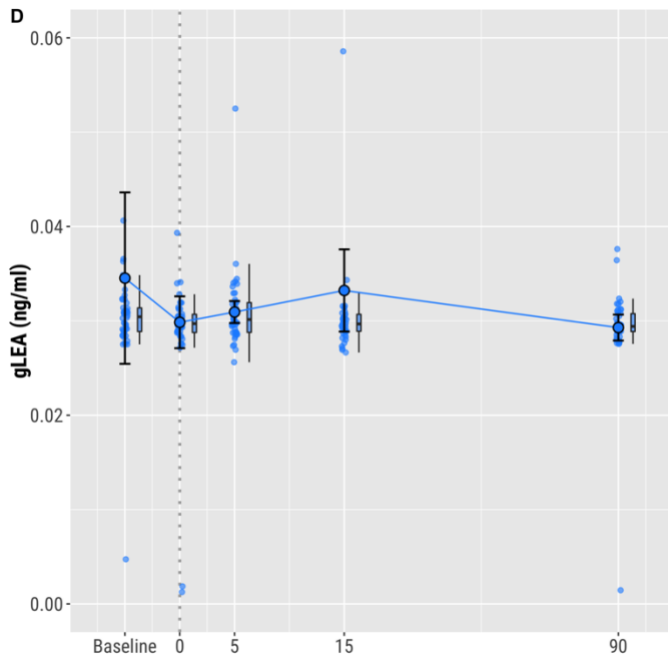
Plasma concentration-time graphs, stratified by CBD:THC ratio.

- E.** alpha-linolenylethanolamide (aLEA),
- F.** gamma-linolenylethanolamide (gLEA),
- G.** N-arachidonoyl-L-serine (ARA-S).

Circles show individual data points, larger shapes show mean values and boxplots show median and interquartile range.

eFigure 4. Plasma concentrations following 10mg THC, 0mg CBD (0:1 ratio).





30min + inhalation time (median 17min)

Timepoint (minutes)

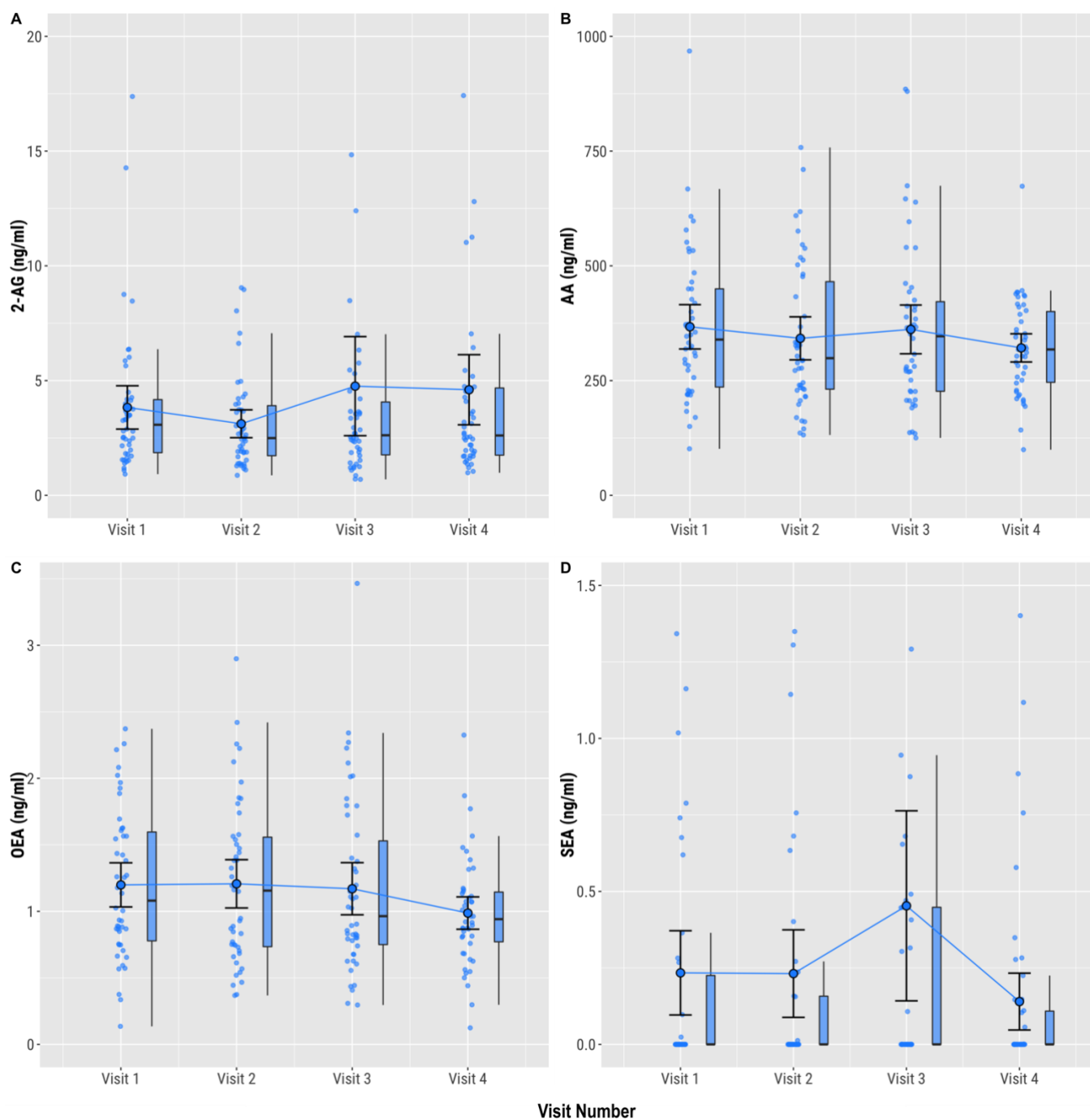
**eFigure 4 continued.**

Plasma concentrations following administration of 10mg THC, 0mg CBD (0:1 ratio).

**E.** gamma-linolenylethanolamide (gLEA),  
**F.** alpha-linolenylethanolamide (aLEA),  
**G.** N-arachidonoyl-L-serine (ARA-S).

Circles show individual data points, diamonds show mean values and boxplots show median and interquartile range.

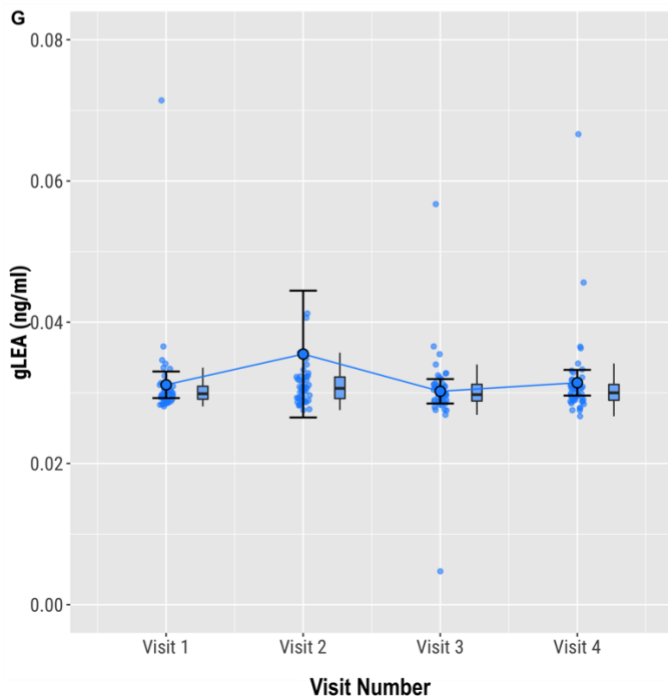
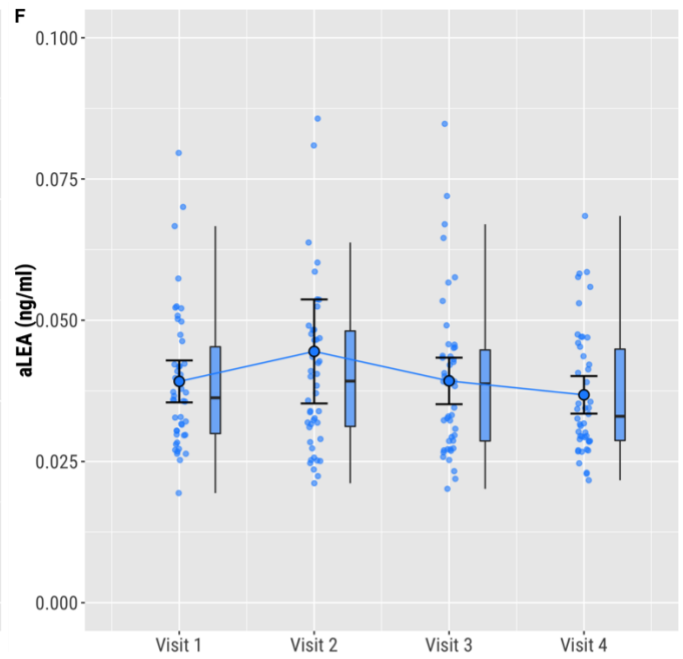
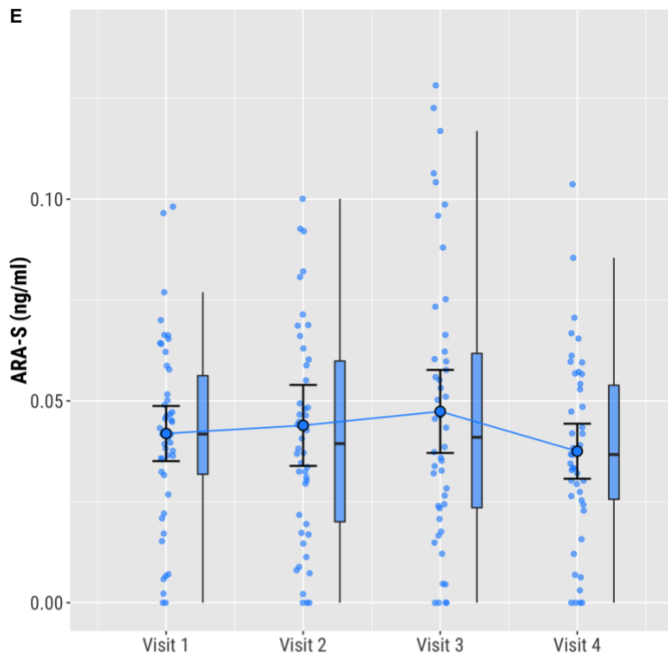
eFigure 5. Pre-inhalation plasma concentrations vs. visit number.



**A.** 2-arachidonoylglycerol (2-AG), **B.** arachidonic acid (AA), **C.** oleoylethanolamide (OEA),  
**D.** stearoylethanolamide (SEA).

Circles show individual data points, diamonds show mean values and boxplots show median and interquartile range.

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**eFigure 5 continued.**

Pre-inhalation plasma concentrations vs. visit number.

**E.** N-arachidonoyl-L-serine (ARA-S),  
**F.** alpha-linolenylethanolamide (aLEA),  
**G.** gamma-linolenylethanolamide (gLEA).

Circles show individual data points, diamonds show mean values and boxplots show median and interquartile range.

**eTable 1.** Pharmacokinetics for each contrast between CBD:THC ratios – Models 1 and 2

Statistically significant rows are presented in bold.

| <b>Contrast</b>                             | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>THC AUC</b>                              |   |                     |                     |                |
| 0:1 - 1:1                                   | -15.336                                   | -32.679             | 2.008               | 0.287          |
| 0:1 - 2:1                                   | -6.549                                    | -23.893             | 10.794              | 0.872          |
| 0:1 - 3:1                                   | -7.412                                    | -24.756             | 9.931               | 0.825          |
| 1:1 - 2:1                                   | 8.786                                     | -8.557              | 26.130              | 0.738          |
| 1:1 - 3:1                                   | 7.923                                     | -9.420              | 25.267              | 0.794          |
| 2:1 - 3:1                                   | -0.863                                    | -18.207             | 16.480              | 1.000          |
| <b>THC AUC (adjusted for visit number)</b>  |   |                     |                     |                |
| 0:1 - 1:1                                   | -16.038                                   | -33.514             | 1.437               | 0.256          |
| 0:1 - 2:1                                   | -7.112                                    | -24.571             | 10.347              | 0.845          |
| 0:1 - 3:1                                   | -6.943                                    | -24.495             | 10.609              | 0.856          |
| 1:1 - 2:1                                   | 8.927                                     | -8.524              | 26.377              | 0.732          |
| 1:1 - 3:1                                   | 9.095                                     | -8.499              | 26.689              | 0.726          |
| 2:1 - 3:1                                   | 0.169                                     | -17.475             | 17.813              | 1.000          |
| <b>THC Peak</b>                             |   |                     |                     |                |
| 0:1 - 1:1                                   | -9.255                                    | -21.379             | 2.869               | 0.418          |
| 0:1 - 2:1                                   | -0.085                                    | -12.209             | 12.039              | 1.000          |
| 0:1 - 3:1                                   | -1.013                                    | -13.137             | 11.111              | 0.998          |
| 1:1 - 2:1                                   | 9.170                                     | -2.954              | 21.294              | 0.426          |
| 1:1 - 3:1                                   | 8.242                                     | -3.882              | 20.366              | 0.521          |
| 2:1 - 3:1                                   | -0.928                                    | -13.052             | 11.196              | 0.999          |
| <b>THC Peak (adjusted for visit number)</b> |   |                     |                     |                |
| 0:1 - 1:1                                   | -9.255                                    | -21.843             | 2.631               | 0.418          |
| 0:1 - 2:1                                   | -0.085                                    | -12.508             | 11.944              | 1.000          |
| 0:1 - 3:1                                   | -1.013                                    | -13.449             | 11.132              | 0.998          |
| 1:1 - 2:1                                   | 9.170                                     | -2.896              | 21.544              | 0.426          |
| 1:1 - 3:1                                   | 8.242                                     | -3.872              | 20.768              | 0.521          |
| 2:1 - 3:1                                   | -0.876                                    | -13.232             | 11.479              | 0.999          |

eTable 1 continued.

| Contrast                                    | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value                 |
|---|------------------------------------|--------------|--------------|-------------------------|
| <b>CBD AUC</b>                              |                                    |              |              |                         |
| 0:1 - 1:1                                   | -123.709                           | -168.682     | -78.736      | 9.088x10 <sup>-7</sup>  |
| 0:1 - 2:1                                   | -244.322                           | -289.295     | -199.349     | 1.565x10 <sup>-14</sup> |
| 0:1 - 3:1                                   | -345.036                           | -390.009     | -300.063     | <2.22x10 <sup>-16</sup> |
| 1:1 - 2:1                                   | -120.613                           | -165.586     | -75.640      | 1.722x10 <sup>-6</sup>  |
| 1:1 - 3:1                                   | -221.327                           | -266.300     | -176.354     | 2.975x10 <sup>-14</sup> |
| 2:1 - 3:1                                   | -100.714                           | -145.687     | -55.741      | 8.148x10 <sup>-5</sup>  |
| <b>CBD AUC (adjusted for visit number)</b>  |                                    |              |              |                         |
| 0:1 - 1:1                                   | -124.426                           | -169.361     | -79.492      | 7.738x10 <sup>-7</sup>  |
| 0:1 - 2:1                                   | -245.398                           | -290.354     | -200.442     | 8.549x10 <sup>-15</sup> |
| 0:1 - 3:1                                   | -342.526                           | -387.656     | -297.397     | <2.22x10 <sup>-16</sup> |
| 1:1 - 2:1                                   | -120.972                           | -165.893     | -76.050      | 1.570x10 <sup>-6</sup>  |
| 1:1 - 3:1                                   | -218.100                           | -263.368     | -172.833     | 2.431x10 <sup>-14</sup> |
| 2:1 - 3:1                                   | -97.129                            | -142.478     | -51.779      | 1.798x10 <sup>-4</sup>  |
| <b>CBD Peak</b>                             |                                    |              |              |                         |
| 0:1 - 1:1                                   | -61.543                            | -87.712      | -35.374      | 3.197x10 <sup>-5</sup>  |
| 0:1 - 2:1                                   | -109.768                           | -135.936     | -83.599      | 2.828x10 <sup>-13</sup> |
| 0:1 - 3:1                                   | -153.819                           | -179.988     | -127.650     | 1.110x10 <sup>-16</sup> |
| 1:1 - 2:1                                   | -48.225                            | -74.394      | -22.056      | 0.002                   |
| 1:1 - 3:1                                   | -92.277                            | -118.445     | -66.108      | 3.820x10 <sup>-10</sup> |
| 2:1 - 3:1                                   | -44.052                            | -70.221      | -17.883      | 0.005                   |
| <b>CBD Peak (adjusted for visit number)</b> |                                    |              |              |                         |
| 0:1 - 1:1                                   | -61.743                            | -87.989      | -35.496      | 3.200x10 <sup>-5</sup>  |
| 0:1 - 2:1                                   | -110.067                           | -136.327     | -83.808      | 2.964x10 <sup>-13</sup> |
| 0:1 - 3:1                                   | -153.120                           | -179.480     | -126.759     | <2.22x10 <sup>-16</sup> |
| 1:1 - 2:1                                   | -48.325                            | -74.564      | -22.086      | 0.002                   |
| 1:1 - 3:1                                   | -91.377                            | -117.818     | -64.936      | 8.214x10 <sup>-10</sup> |
| 2:1 - 3:1                                   | -43.052                            | -69.541      | -16.563      | 0.007                   |

eTable 1 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|--|------------------------------------|--------------|--------------|---------|
| <b>Anandamide AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 0.007                              | -0.136       | 0.150        | 1.000   |
| 0:1 - 2:1  | -0.062                             | -0.206       | 0.081        | 0.825   |
| 0:1 - 3:1  | -0.015                             | -0.158       | 0.128        | 0.997   |
| 1:1 - 2:1  | -0.069                             | -0.213       | 0.074        | 0.774   |
| 1:1 - 3:1  | -0.022                             | -0.165       | 0.121        | 0.991   |
| 2:1 - 3:1  | 0.048                              | -0.096       | 0.191        | 0.913   |
| <b>Anandamide AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 0.018                              | -0.098       | 0.134        | 0.990   |
| 0:1 - 2:1  | -0.066                             | -0.182       | 0.050        | 0.673   |
| 0:1 - 3:1  | 0.007                              | -0.110       | 0.125        | 0.999   |
| 1:1 - 2:1  | -0.084                             | -0.200       | 0.033        | 0.487   |
| 1:1 - 3:1  | -0.011                             | -0.128       | 0.107        | 0.998   |
| 2:1 - 3:1  | 0.073                              | -0.046       | 0.192        | 0.617   |
| <b>Anandamide Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1  | 0.014                              | -0.028       | 0.057        | 0.912   |
| 0:1 - 2:1  | -0.009                             | -0.052       | 0.033        | 0.971   |
| 0:1 - 3:1  | -0.012                             | -0.055       | 0.030        | 0.942   |
| 1:1 - 2:1  | -0.024                             | -0.066       | 0.019        | 0.690   |
| 1:1 - 3:1  | -0.026                             | -0.069       | 0.016        | 0.612   |
| 2:1 - 3:1  | -0.003                             | -0.045       | 0.040        | 0.999   |
| <b>Anandamide Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1  | 0.013                              | -0.029       | 0.055        | 0.927   |
| 0:1 - 2:1  | -0.010                             | -0.052       | 0.031        | 0.962   |
| 0:1 - 3:1  | -0.005                             | -0.047       | 0.037        | 0.995   |
| 1:1 - 2:1  | -0.023                             | -0.065       | 0.019        | 0.692   |
| 1:1 - 3:1  | -0.018                             | -0.060       | 0.024        | 0.828   |
| 2:1 - 3:1  | 0.005                              | -0.038       | 0.048        | 0.996   |



eTable 1 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|--|------------------------------------|--------------|--------------|---------|
| <b>2-AG AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1  | -3.214                             | -11.042      | 4.613        | 0.849   |
| 0:1 - 2:1  | -4.005                             | -11.833      | 3.822        | 0.743   |
| 0:1 - 3:1  | -1.337                             | -9.164       | 6.491        | 0.987   |
| 1:1 - 2:1  | -0.791                             | -8.619       | 7.037        | 0.997   |
| 1:1 - 3:1  | 1.878                              | -5.950       | 9.705        | 0.965   |
| 2:1 - 3:1  | 2.669                              | -5.159       | 10.496       | 0.907   |
| <b>2-AG AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 1.068                              | -2.526       | 4.662        | 0.936   |
| 0:1 - 2:1  | 0.189                              | -3.391       | 3.770        | 1.000   |
| 0:1 - 3:1  | 3.068                              | -0.567       | 6.702        | 0.344   |
| 1:1 - 2:1  | -0.879                             | -4.467       | 2.709        | 0.962   |
| 1:1 - 3:1  | 1.999                              | -1.611       | 5.610        | 0.693   |
| 2:1 - 3:1  | 2.879                              | -0.784       | 6.541        | 0.408   |
| <b>2-AG Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1  | -1.656                             | -4.555       | 1.243        | 0.672   |
| 0:1 - 2:1  | 1.120                              | -1.778       | 4.018        | 0.870   |
| 0:1 - 3:1  | 0.463                              | -2.435       | 3.361        | 0.989   |
| 1:1 - 2:1  | 2.776                              | -0.108       | 5.661        | 0.231   |
| 1:1 - 3:1  | 2.119                              | -0.765       | 5.004        | 0.469   |
| 2:1 - 3:1  | -0.657                             | -3.541       | 2.227        | 0.969   |
| <b>2-AG Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1  | -1.711                             | -4.620       | 1.199        | 0.651   |
| 0:1 - 2:1  | 1.141                              | -1.758       | 4.041        | 0.864   |
| 0:1 - 3:1  | 0.180                              | -2.762       | 3.123        | 0.999   |
| 1:1 - 2:1  | 2.852                              | -0.053       | 5.757        | 0.216   |
| 1:1 - 3:1  | 1.891                              | -1.033       | 4.815        | 0.578   |
| 2:1 - 3:1  | -0.961                             | -3.923       | 2.000        | 0.918   |

eTable 1 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|--|------------------------------------|--------------|--------------|---------|
| <b>Arachidonic acid AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 36.986                             | -148.669     | 222.642      | 0.979   |
| 0:1 - 2:1  | -42.727                            | -228.383     | 142.929      | 0.969   |
| 0:1 - 3:1  | 83.001                             | -102.655     | 268.657      | 0.813   |
| 1:1 - 2:1  | -79.713                            | -265.369     | 105.942      | 0.831   |
| 1:1 - 3:1  | 46.015                             | -139.641     | 231.670      | 0.961   |
| 2:1 - 3:1  | 125.728                            | -59.928      | 311.384      | 0.540   |
| <b>Arachidonic acid AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 17.069                             | -132.965     | 167.104      | 0.996   |
| 0:1 - 2:1  | -68.190                            | -217.688     | 81.309       | 0.804   |
| 0:1 - 3:1  | 29.306                             | -123.244     | 181.856      | 0.981   |
| 1:1 - 2:1  | -85.259                            | -235.767     | 65.250       | 0.677   |
| 1:1 - 3:1  | 12.237                             | -139.517     | 163.990      | 0.999   |
| 2:1 - 3:1  | 97.495                             | -56.136      | 251.127      | 0.593   |
| <b>Arachidonic acid Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1  | 9.139                              | -48.117      | 66.395       | 0.989   |
| 0:1 - 2:1  | -21.807                            | -79.118      | 35.503       | 0.875   |
| 0:1 - 3:1  | 36.819                             | -20.516      | 94.154       | 0.584   |
| 1:1 - 2:1  | -30.946                            | -88.219      | 26.327       | 0.709   |
| 1:1 - 3:1  | 27.680                             | -29.609      | 84.970       | 0.775   |
| 2:1 - 3:1  | 58.626                             | 1.377        | 115.876      | 0.184   |
| <b>Arachidonic acid Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1  | 8.911                              | -48.980      | 66.802       | 0.990   |
| 0:1 - 2:1  | -19.579                            | -77.275      | 38.118       | 0.908   |
| 0:1 - 3:1  | 33.525                             | -25.289      | 92.339       | 0.673   |
| 1:1 - 2:1  | -28.489                            | -86.536      | 29.557       | 0.766   |
| 1:1 - 3:1  | 24.614                             | -33.931      | 83.160       | 0.839   |
| 2:1 - 3:1  | 53.103                             | -6.114       | 112.321      | 0.291   |

eTable 1 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|---|------------------------------------|--------------|--------------|---------|
| <b>DEA AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.013                              | -0.020       | 0.045        | 0.864   |
| 0:1 - 2:1   | 0.014                              | -0.018       | 0.047        | 0.814   |
| 0:1 - 3:1   | 0.005                              | -0.027       | 0.037        | 0.990   |
| 1:1 - 2:1   | 0.002                              | -0.031       | 0.034        | 1.000   |
| 1:1 - 3:1   | -0.008                             | -0.040       | 0.025        | 0.965   |
| 2:1 - 3:1   | -0.009                             | -0.042       | 0.023        | 0.938   |
| <b>DEA AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.013                              | -0.006       | 0.031        | 0.535   |
| 0:1 - 2:1   | 0.009                              | -0.010       | 0.027        | 0.785   |
| 0:1 - 3:1   | 0.015                              | -0.004       | 0.034        | 0.393   |
| 1:1 - 2:1   | -0.004                             | -0.023       | 0.015        | 0.976   |
| 1:1 - 3:1   | 0.002                              | -0.016       | 0.021        | 0.994   |
| 2:1 - 3:1   | 0.006                              | -0.013       | 0.025        | 0.915   |
| <b>DEA Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1   | 0.003                              | -0.006       | 0.012        | 0.894   |
| 0:1 - 2:1   | 0.001                              | -0.008       | 0.010        | 0.998   |
| 0:1 - 3:1   | 0.000                              | -0.009       | 0.009        | 1.000   |
| 1:1 - 2:1   | -0.002                             | -0.011       | 0.007        | 0.952   |
| 1:1 - 3:1   | -0.004                             | -0.013       | 0.006        | 0.867   |
| 2:1 - 3:1   | -0.001                             | -0.010       | 0.008        | 0.995   |
| <b>DEA Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1   | 0.004                              | -0.005       | 0.013        | 0.848   |
| 0:1 - 2:1   | 0.001                              | -0.008       | 0.010        | 0.998   |
| 0:1 - 3:1   | 0.002                              | -0.008       | 0.011        | 0.987   |
| 1:1 - 2:1   | -0.003                             | -0.012       | 0.006        | 0.926   |
| 1:1 - 3:1   | -0.002                             | -0.011       | 0.007        | 0.966   |
| 2:1 - 3:1   | 0.001                              | -0.009       | 0.010        | 0.999   |

eTable 1 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|---|------------------------------------|--------------|--------------|---------|
| <b>OEA AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.312                              | -0.469       | 1.093        | 0.859   |
| 0:1 - 2:1   | 0.048                              | -0.733       | 0.829        | 0.999   |
| 0:1 - 3:1   | 0.357                              | -0.424       | 1.138        | 0.802   |
| 1:1 - 2:1   | -0.264                             | -1.045       | 0.517        | 0.908   |
| 1:1 - 3:1   | 0.045                              | -0.736       | 0.826        | 0.999   |
| 2:1 - 3:1   | 0.310                              | -0.471       | 1.091        | 0.861   |
| <b>OEA AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.412                              | -0.242       | 1.066        | 0.599   |
| 0:1 - 2:1   | -0.008                             | -0.659       | 0.643        | 1.000   |
| 0:1 - 3:1   | 0.264                              | -0.398       | 0.927        | 0.859   |
| 1:1 - 2:1   | -0.420                             | -1.078       | 0.237        | 0.587   |
| 1:1 - 3:1   | -0.148                             | -0.809       | 0.514        | 0.971   |
| 2:1 - 3:1   | 0.273                              | -0.396       | 0.941        | 0.851   |
| <b>OEA Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1   | 0.188                              | -0.028       | 0.405        | 0.315   |
| 0:1 - 2:1   | 0.015                              | -0.201       | 0.231        | 0.999   |
| 0:1 - 3:1   | 0.047                              | -0.169       | 0.263        | 0.974   |
| 1:1 - 2:1   | -0.174                             | -0.390       | 0.043        | 0.390   |
| 1:1 - 3:1   | -0.142                             | -0.358       | 0.075        | 0.568   |
| 2:1 - 3:1   | 0.032                              | -0.184       | 0.248        | 0.991   |
| <b>OEA Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1   | 0.192                              | -0.028       | 0.412        | 0.312   |
| 0:1 - 2:1   | 0.019                              | -0.200       | 0.237        | 0.998   |
| 0:1 - 3:1   | 0.059                              | -0.163       | 0.281        | 0.954   |
| 1:1 - 2:1   | -0.173                             | -0.394       | 0.048        | 0.410   |
| 1:1 - 3:1   | -0.133                             | -0.355       | 0.089        | 0.635   |
| 2:1 - 3:1   | 0.040                              | -0.184       | 0.264        | 0.985   |

eTable 1 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|---|------------------------------------|--------------|--------------|---------|
| <b>SEA AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.431                              | -0.583       | 1.445        | 0.835   |
| 0:1 - 2:1   | 0.198                              | -0.815       | 1.212        | 0.980   |
| 0:1 - 3:1   | 0.472                              | -0.541       | 1.486        | 0.793   |
| 1:1 - 2:1   | -0.233                             | -1.246       | 0.781        | 0.969   |
| 1:1 - 3:1   | 0.041                              | -0.972       | 1.055        | 1.000   |
| 2:1 - 3:1   | 0.274                              | -0.740       | 1.288        | 0.951   |
| <b>SEA AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.164                              | -0.252       | 0.581        | 0.863   |
| 0:1 - 2:1   | 0.056                              | -0.358       | 0.471        | 0.993   |
| 0:1 - 3:1   | 0.295                              | -0.125       | 0.716        | 0.509   |
| 1:1 - 2:1   | -0.108                             | -0.525       | 0.309        | 0.956   |
| 1:1 - 3:1   | 0.131                              | -0.289       | 0.551        | 0.927   |
| 2:1 - 3:1   | 0.239                              | -0.186       | 0.664        | 0.682   |
| <b>SEA Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1   | 0.139                              | -0.114       | 0.392        | 0.700   |
| 0:1 - 2:1   | 0.003                              | -0.250       | 0.256        | 1.000   |
| 0:1 - 3:1   | 0.109                              | -0.144       | 0.363        | 0.828   |
| 1:1 - 2:1   | -0.136                             | -0.389       | 0.118        | 0.715   |
| 1:1 - 3:1   | -0.029                             | -0.282       | 0.224        | 0.996   |
| 2:1 - 3:1   | 0.106                              | -0.147       | 0.359        | 0.840   |
| <b>SEA Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1   | 0.142                              | -0.115       | 0.398        | 0.694   |
| 0:1 - 2:1   | 0.013                              | -0.242       | 0.268        | 1.000   |
| 0:1 - 3:1   | 0.103                              | -0.156       | 0.362        | 0.861   |
| 1:1 - 2:1   | -0.129                             | -0.386       | 0.128        | 0.754   |
| 1:1 - 3:1   | -0.039                             | -0.298       | 0.220        | 0.991   |
| 2:1 - 3:1   | 0.090                              | -0.172       | 0.351        | 0.905   |

eTable 1 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|---|------------------------------------|--------------|--------------|---------|
| <b>ARA-S AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1   | -0.008                             | -0.053       | 0.036        | 0.983   |
| 0:1 - 2:1   | -0.002                             | -0.046       | 0.043        | 1.000   |
| 0:1 - 3:1   | 0.004                              | -0.041       | 0.048        | 0.998   |
| 1:1 - 2:1   | 0.007                              | -0.038       | 0.051        | 0.991   |
| 1:1 - 3:1   | 0.012                              | -0.032       | 0.056        | 0.951   |
| 2:1 - 3:1   | 0.005                              | -0.039       | 0.050        | 0.995   |
| <b>ARA-S AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1   | 0.023                              | -0.004       | 0.050        | 0.352   |
| 0:1 - 2:1   | 0.011                              | -0.016       | 0.038        | 0.838   |
| 0:1 - 3:1   | 0.014                              | -0.013       | 0.042        | 0.723   |
| 1:1 - 2:1   | -0.011                             | -0.039       | 0.016        | 0.839   |
| 1:1 - 3:1   | -0.008                             | -0.036       | 0.019        | 0.932   |
| 2:1 - 3:1   | 0.003                              | -0.025       | 0.031        | 0.996   |
| <b>ARA-S Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1   | 0.007                              | -0.007       | 0.021        | 0.758   |
| 0:1 - 2:1   | -0.002                             | -0.016       | 0.012        | 0.991   |
| 0:1 - 3:1   | 0.002                              | -0.012       | 0.016        | 0.987   |
| 1:1 - 2:1   | -0.009                             | -0.023       | 0.005        | 0.575   |
| 1:1 - 3:1   | -0.005                             | -0.019       | 0.009        | 0.913   |
| 2:1 - 3:1   | 0.004                              | -0.010       | 0.018        | 0.923   |
| <b>ARA-S Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1   | 0.007                              | -0.007       | 0.021        | 0.764   |
| 0:1 - 2:1   | -0.002                             | -0.017       | 0.012        | 0.986   |
| 0:1 - 3:1   | 0.004                              | -0.011       | 0.018        | 0.957   |
| 1:1 - 2:1   | -0.009                             | -0.024       | 0.005        | 0.554   |
| 1:1 - 3:1   | -0.003                             | -0.018       | 0.011        | 0.968   |
| 2:1 - 3:1   | 0.006                              | -0.008       | 0.021        | 0.836   |

eTable 1 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|--|------------------------------------|--------------|--------------|---------|
| <b>aLEA AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1  | -0.009                             | -0.038       | 0.021        | 0.939   |
| 0:1 - 2:1  | -0.022                             | -0.051       | 0.007        | 0.457   |
| 0:1 - 3:1  | -0.006                             | -0.036       | 0.023        | 0.972   |
| 1:1 - 2:1  | -0.013                             | -0.043       | 0.016        | 0.808   |
| 1:1 - 3:1  | 0.002                              | -0.027       | 0.031        | 0.999   |
| 2:1 - 3:1  | 0.015                              | -0.014       | 0.045        | 0.728   |
| <b>aLEA AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 0.001                              | -0.017       | 0.019        | 1.000   |
| 0:1 - 2:1  | -0.012                             | -0.029       | 0.006        | 0.554   |
| 0:1 - 3:1  | -0.003                             | -0.021       | 0.015        | 0.985   |
| 1:1 - 2:1  | -0.013                             | -0.030       | 0.005        | 0.492   |
| 1:1 - 3:1  | -0.004                             | -0.022       | 0.014        | 0.968   |
| 2:1 - 3:1  | 0.009                              | -0.010       | 0.027        | 0.787   |
| <b>aLEA Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1  | 0.001                              | -0.005       | 0.007        | 0.990   |
| 0:1 - 2:1  | -0.004                             | -0.009       | 0.002        | 0.626   |
| 0:1 - 3:1  | -0.003                             | -0.009       | 0.003        | 0.726   |
| 1:1 - 2:1  | -0.004                             | -0.010       | 0.001        | 0.432   |
| 1:1 - 3:1  | -0.004                             | -0.010       | 0.002        | 0.535   |
| 2:1 - 3:1  | 0.000                              | -0.005       | 0.006        | 0.998   |
| <b>aLEA Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1  | 0.001                              | -0.005       | 0.007        | 0.982   |
| 0:1 - 2:1  | -0.003                             | -0.009       | 0.002        | 0.652   |
| 0:1 - 3:1  | -0.003                             | -0.009       | 0.003        | 0.765   |
| 1:1 - 2:1  | -0.005                             | -0.011       | 0.001        | 0.424   |
| 1:1 - 3:1  | -0.004                             | -0.010       | 0.002        | 0.537   |
| 2:1 - 3:1  | 0.001                              | -0.006       | 0.007        | 0.998   |

eTable 1 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|--|------------------------------------|--------------|--------------|---------|
| <b>gLEA AUC</b>  |                                    |              |              |         |
| 0:1 - 1:1  | -0.011                             | -0.037       | 0.014        | 0.810   |
| 0:1 - 2:1  | -0.010                             | -0.035       | 0.015        | 0.866   |
| 0:1 - 3:1  | -0.009                             | -0.034       | 0.016        | 0.892   |
| 1:1 - 2:1  | 0.001                              | -0.024       | 0.027        | 0.999   |
| 1:1 - 3:1  | 0.002                              | -0.023       | 0.028        | 0.998   |
| 2:1 - 3:1  | 0.001                              | -0.024       | 0.026        | 1.000   |
| <b>gLEA AUC (adjusted for baseline concentration, visit number and time between visits)</b>  |                                    |              |              |         |
| 0:1 - 1:1  | 0.002                              | -0.006       | 0.009        | 0.963   |
| 0:1 - 2:1  | 0.001                              | -0.006       | 0.009        | 0.979   |
| 0:1 - 3:1  | 0.002                              | -0.006       | 0.009        | 0.974   |
| 1:1 - 2:1  | 0.000                              | -0.008       | 0.007        | 1.000   |
| 1:1 - 3:1  | 0.000                              | -0.008       | 0.007        | 1.000   |
| 2:1 - 3:1  | 0.000                              | -0.008       | 0.008        | 1.000   |
| <b>gLEA Peak</b>   |                                    |              |              |         |
| 0:1 - 1:1  | 0.000                              | -0.002       | 0.002        | 1.000   |
| 0:1 - 2:1  | 0.001                              | -0.001       | 0.003        | 0.886   |
| 0:1 - 3:1  | 0.002                              | -0.001       | 0.004        | 0.452   |
| 1:1 - 2:1  | 0.001                              | -0.001       | 0.003        | 0.907   |
| 1:1 - 3:1  | 0.001                              | -0.001       | 0.004        | 0.483   |
| 2:1 - 3:1  | 0.001                              | -0.001       | 0.003        | 0.874   |
| <b>gLEA Peak (adjusted for baseline concentration, visit number and time between visits)</b> |                                    |              |              |         |
| 0:1 - 1:1  | 0.000                              | -0.002       | 0.002        | 0.998   |
| 0:1 - 2:1  | 0.001                              | -0.001       | 0.003        | 0.900   |
| 0:1 - 3:1  | 0.002                              | 0.000        | 0.004        | 0.246   |
| 1:1 - 2:1  | 0.001                              | -0.002       | 0.003        | 0.957   |
| 1:1 - 3:1  | 0.002                              | 0.000        | 0.004        | 0.327   |
| 2:1 - 3:1  | 0.001                              | -0.001       | 0.003        | 0.640   |



**eTable 2.** Plasma concentrations vs. time following 10mg THC, 0mg CBD (0:1 ratio) – Model 3a

Statistically significant rows are presented in bold.  
Pre = pre-inhalation plasma sample.

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value      |
|---|------------------------------------|--------------|--------------|--------------|
| <b>Anandamide (ng/ml)</b>   |                                    |              |              |              |
| Pre – 0min  | -0.040                             | -0.070       | -0.010       | 0.069        |
| Pre – 5min  | 0.003                              | -0.027       | 0.033        | 1.000        |
| Pre – 15min   | 0.011                              | -0.019       | 0.041        | 0.949        |
| Pre – 90min   | 0.019                              | -0.011       | 0.049        | 0.735        |
| <b>0min – 5min</b>  | <b>0.043</b>                       | <b>0.013</b> | <b>0.073</b> | <b>0.040</b> |
| <b>0min – 15min</b>   | <b>0.051</b>                       | <b>0.021</b> | <b>0.081</b> | <b>0.008</b> |
| <b>0min – 90min</b>   | <b>0.059</b>                       | <b>0.029</b> | <b>0.089</b> | <b>0.001</b> |
| 5min – 15min  | 0.008                              | -0.022       | 0.038        | 0.985        |
| 5min – 90min  | 0.016                              | -0.014       | 0.046        | 0.845        |
| 15min – 90min   | 0.008                              | -0.022       | 0.038        | 0.988        |
| <b>Anandamide (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |                                    |              |              |              |
| Pre – 0min  | -0.040                             | -0.070       | -0.010       | 0.069        |
| Pre – 5min  | 0.003                              | -0.027       | 0.033        | 1.000        |
| Pre – 15min   | 0.011                              | -0.019       | 0.041        | 0.949        |
| Pre – 90min   | 0.019                              | -0.011       | 0.049        | 0.735        |
| <b>0min – 5min</b>  | <b>0.043</b>                       | <b>0.013</b> | <b>0.073</b> | <b>0.040</b> |
| <b>0min – 15min</b>   | <b>0.051</b>                       | <b>0.021</b> | <b>0.081</b> | <b>0.008</b> |
| <b>0min – 90min</b>   | <b>0.059</b>                       | <b>0.029</b> | <b>0.089</b> | <b>0.001</b> |
| 5min – 15min  | 0.008                              | -0.022       | 0.038        | 0.985        |
| 5min – 90min  | 0.016                              | -0.014       | 0.046        | 0.845        |
| 15min – 90min   | 0.008                              | -0.022       | 0.038        | 0.988        |

**eTable 2 continued.**

| <b>Contrast</b>   | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>2-AG (ng/ml)</b>   |   |                     |                     |                |
| Pre – 0min  | 0.513                                     | -1.451              | 2.478               | 0.986          |
| Pre – 5min  | 0.621                                     | -1.343              | 2.586               | 0.971          |
| Pre – 15min   | 0.891                                     | -1.073              | 2.855               | 0.898          |
| Pre – 90min   | 0.291                                     | -1.673              | 2.255               | 0.998          |
| 0min – 5min   | 0.108                                     | -1.856              | 2.072               | 1.000          |
| 0min – 15min  | 0.378                                     | -1.587              | 2.342               | 0.996          |
| 0min – 90min  | -0.222                                    | -2.187              | 1.742               | 0.999          |
| 5min – 15min  | 0.270                                     | -1.695              | 2.234               | 0.999          |
| 5min – 90min  | -0.330                                    | -2.295              | 1.634               | 0.997          |
| 15min – 90min   | -0.600                                    | -2.564              | 1.364               | 0.975          |
| <b>2-AG (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min  | 0.513                                     | -1.451              | 2.478               | 0.986          |
| Pre – 5min  | 0.621                                     | -1.343              | 2.586               | 0.971          |
| Pre – 15min   | 0.891                                     | -1.073              | 2.855               | 0.898          |
| Pre – 90min   | 0.291                                     | -1.673              | 2.255               | 0.998          |
| 0min – 5min   | 0.108                                     | -1.856              | 2.072               | 1.000          |
| 0min – 15min  | 0.378                                     | -1.587              | 2.342               | 0.996          |
| 0min – 90min  | -0.222                                    | -2.187              | 1.742               | 0.999          |
| 5min – 15min  | 0.270                                     | -1.695              | 2.234               | 0.999          |
| 5min – 90min  | -0.330                                    | -2.295              | 1.634               | 0.997          |
| 15min – 90min   | -0.600                                    | -2.564              | 1.364               | 0.975          |

**eTable 2 continued.**

| <b>Contrast</b>   | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>Arachidonic acid (ng/ml)</b>   |   |                     |                     |                |
| Pre – 0min  | -33.180                                   | -74.904             | 8.543               | 0.519          |
| Pre – 5min  | -46.043                                   | -87.767             | -4.320              | 0.193          |
| Pre – 15min   | -5.436                                    | -47.159             | 36.287              | 0.999          |
| Pre – 90min   | 3.859                                     | -37.865             | 45.582              | 1.000          |
| 0min – 5min   | -12.863                                   | -54.586             | 28.860              | 0.974          |
| 0min – 15min  | 27.744                                    | -13.979             | 69.468              | 0.684          |
| 0min – 90min  | 37.039                                    | -4.684              | 78.762              | 0.405          |
| 5min – 15min  | 40.607                                    | -1.116              | 82.331              | 0.310          |
| 5min – 90min  | 49.902                                    | 8.179               | 91.626              | 0.131          |
| 15min – 90min   | 9.295                                     | -32.429             | 51.018              | 0.992          |
| <b>Arachidonic acid (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min  | -33.180                                   | -74.904             | 8.543               | 0.519          |
| Pre – 5min  | -46.043                                   | -87.767             | -4.320              | 0.193          |
| Pre – 15min   | -5.436                                    | -47.159             | 36.287              | 0.999          |
| Pre – 90min   | 3.859                                     | -37.865             | 45.582              | 1.000          |
| 0min – 5min   | -12.863                                   | -54.586             | 28.860              | 0.974          |
| 0min – 15min  | 27.744                                    | -13.979             | 69.468              | 0.684          |
| 0min – 90min  | 37.039                                    | -4.684              | 78.762              | 0.405          |
| 5min – 15min  | 40.607                                    | -1.116              | 82.331              | 0.310          |
| 5min – 90min  | 49.902                                    | 8.179               | 91.626              | 0.131          |
| 15min – 90min   | 9.295                                     | -32.429             | 51.018              | 0.992          |

eTable 2 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI  | Upper 95% CI  | p-value      |
|--|------------------------------------|---------------|---------------|--------------|
| <b>DEA (ng/ml)</b>   |                                    |               |               |              |
| <b>Pre – 0min</b>  | <b>-0.013</b>                      | <b>-0.020</b> | <b>-0.005</b> | <b>0.011</b> |
| Pre – 5min   | -0.001                             | -0.009        | 0.006         | 0.998        |
| Pre – 15min  | -0.003                             | -0.011        | 0.005         | 0.952        |
| Pre – 90min  | 0.003                              | -0.004        | 0.011         | 0.907        |
| <b>0min – 5min</b>   | <b>0.012</b>                       | <b>0.004</b>  | <b>0.019</b>  | <b>0.029</b> |
| 0min – 15min   | 0.010                              | 0.002         | 0.018         | 0.084        |
| <b>0min – 90min</b>  | <b>0.016</b>                       | <b>0.008</b>  | <b>0.024</b>  | <b>0.000</b> |
| 5min – 15min   | -0.002                             | -0.009        | 0.006         | 0.995        |
| 5min – 90min   | 0.005                              | -0.003        | 0.012         | 0.756        |
| 15min – 90min  | 0.006                              | -0.001        | 0.014         | 0.504        |
| <b>DEA (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |                                    |               |               |              |
| <b>Pre – 0min</b>  | <b>-0.013</b>                      | <b>-0.020</b> | <b>-0.005</b> | <b>0.011</b> |
| Pre – 5min   | -0.001                             | -0.009        | 0.006         | 0.998        |
| Pre – 15min  | -0.003                             | -0.011        | 0.005         | 0.952        |
| Pre – 90min  | 0.003                              | -0.004        | 0.011         | 0.907        |
| <b>0min – 5min</b>   | <b>0.012</b>                       | <b>0.004</b>  | <b>0.019</b>  | <b>0.029</b> |
| 0min – 15min   | 0.010                              | 0.002         | 0.018         | 0.084        |
| <b>0min – 90min</b>  | <b>0.016</b>                       | <b>0.008</b>  | <b>0.024</b>  | <b>0.000</b> |
| 5min – 15min   | -0.002                             | -0.009        | 0.006         | 0.995        |
| 5min – 90min   | 0.005                              | -0.003        | 0.012         | 0.756        |
| 15min – 90min  | 0.006                              | -0.001        | 0.014         | 0.504        |

eTable 2 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value      |
|--|------------------------------------|--------------|--------------|--------------|
| <b>OEA (ng/ml)</b>   |                                    |              |              |              |
| Pre – 0min   | -0.250                             | -0.432       | -0.068       | 0.057        |
| Pre – 5min   | -0.109                             | -0.291       | 0.073        | 0.760        |
| Pre – 15min  | 0.020                              | -0.162       | 0.202        | 0.999        |
| Pre – 90min  | 0.066                              | -0.116       | 0.248        | 0.952        |
| 0min – 5min  | 0.141                              | -0.041       | 0.322        | 0.548        |
| <b>0min – 15min</b>  | <b>0.270</b>                       | <b>0.088</b> | <b>0.452</b> | <b>0.031</b> |
| <b>0min – 90min</b>  | <b>0.316</b>                       | <b>0.134</b> | <b>0.498</b> | <b>0.007</b> |
| 5min – 15min   | 0.129                              | -0.053       | 0.311        | 0.627        |
| 5min – 90min   | 0.175                              | -0.007       | 0.357        | 0.320        |
| 15min – 90min  | 0.046                              | -0.136       | 0.228        | 0.987        |
| <b>OEA (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |                                    |              |              |              |
| Pre – 0min   | -0.250                             | -0.432       | -0.068       | 0.057        |
| Pre – 5min   | -0.109                             | -0.291       | 0.073        | 0.760        |
| Pre – 15min  | 0.020                              | -0.162       | 0.202        | 0.999        |
| Pre – 90min  | 0.066                              | -0.116       | 0.248        | 0.952        |
| 0min – 5min  | 0.141                              | -0.041       | 0.322        | 0.548        |
| <b>0min – 15min</b>  | <b>0.270</b>                       | <b>0.088</b> | <b>0.452</b> | <b>0.031</b> |
| <b>0min – 90min</b>  | <b>0.316</b>                       | <b>0.134</b> | <b>0.498</b> | <b>0.007</b> |
| 5min – 15min   | 0.129                              | -0.053       | 0.311        | 0.627        |
| 5min – 90min   | 0.175                              | -0.007       | 0.357        | 0.320        |
| 15min – 90min  | 0.046                              | -0.136       | 0.228        | 0.987        |

**eTable 2 continued.**

| <b>Contrast</b>  | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|--|---|---------------------|---------------------|----------------|
| <b>SEA (ng/ml)</b>   |   |                     |                     |                |
| Pre – 0min   | -0.156                                    | -0.387              | 0.075               | 0.673          |
| Pre – 5min   | -0.007                                    | -0.238              | 0.224               | 1.000          |
| Pre – 15min  | -0.013                                    | -0.244              | 0.218               | 1.000          |
| Pre – 90min  | 0.030                                     | -0.201              | 0.261               | 0.999          |
| 0min – 5min  | 0.149                                     | -0.082              | 0.380               | 0.709          |
| 0min – 15min   | 0.143                                     | -0.088              | 0.374               | 0.741          |
| 0min – 90min   | 0.186                                     | -0.045              | 0.417               | 0.507          |
| 5min – 15min   | -0.006                                    | -0.237              | 0.225               | 1.000          |
| 5min – 90min   | 0.037                                     | -0.194              | 0.268               | 0.998          |
| 15min – 90min  | 0.043                                     | -0.188              | 0.274               | 0.996          |
| <b>SEA (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min   | -0.156                                    | -0.387              | 0.075               | 0.673          |
| Pre – 5min   | -0.007                                    | -0.238              | 0.224               | 1.000          |
| Pre – 15min  | -0.013                                    | -0.244              | 0.218               | 1.000          |
| Pre – 90min  | 0.030                                     | -0.201              | 0.261               | 0.999          |
| 0min – 5min  | 0.149                                     | -0.082              | 0.380               | 0.709          |
| 0min – 15min   | 0.143                                     | -0.088              | 0.374               | 0.741          |
| 0min – 90min   | 0.186                                     | -0.045              | 0.417               | 0.507          |
| 5min – 15min   | -0.006                                    | -0.237              | 0.225               | 1.000          |
| 5min – 90min   | 0.037                                     | -0.194              | 0.268               | 0.998          |
| 15min – 90min  | 0.043                                     | -0.188              | 0.274               | 0.996          |

**eTable 2 continued.**

| <b>Contrast</b>  | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|--|---|---------------------|---------------------|----------------|
| <b>ARA-S (ng/ml)</b>   |   |                     |                     |                |
| Pre – 0min   | -0.009                                    | -0.021              | 0.003               | 0.552          |
| Pre – 5min   | -0.006                                    | -0.018              | 0.006               | 0.883          |
| Pre – 15min  | -0.001                                    | -0.013              | 0.011               | 1.000          |
| Pre – 90min  | -0.001                                    | -0.013              | 0.012               | 1.000          |
| 0min – 5min  | 0.004                                     | -0.009              | 0.016               | 0.978          |
| 0min – 15min   | 0.008                                     | -0.004              | 0.020               | 0.657          |
| 0min – 90min   | 0.009                                     | -0.003              | 0.021               | 0.614          |
| 5min – 15min   | 0.005                                     | -0.007              | 0.017               | 0.938          |
| 5min – 90min   | 0.005                                     | -0.007              | 0.017               | 0.918          |
| 15min – 90min  | 0.000                                     | -0.012              | 0.013               | 1.000          |
| <b>ARA-S (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min   | -0.009                                    | -0.021              | 0.003               | 0.552          |
| Pre – 5min   | -0.006                                    | -0.018              | 0.006               | 0.883          |
| Pre – 15min  | -0.001                                    | -0.013              | 0.011               | 1.000          |
| Pre – 90min  | -0.001                                    | -0.013              | 0.012               | 1.000          |
| 0min – 5min  | 0.004                                     | -0.009              | 0.016               | 0.978          |
| 0min – 15min   | 0.008                                     | -0.004              | 0.020               | 0.657          |
| 0min – 90min   | 0.009                                     | -0.003              | 0.021               | 0.614          |
| 5min – 15min   | 0.005                                     | -0.007              | 0.017               | 0.938          |
| 5min – 90min   | 0.005                                     | -0.007              | 0.017               | 0.918          |
| 15min – 90min  | 0.000                                     | -0.012              | 0.013               | 1.000          |

**eTable 2 continued.**

| <b>Contrast</b>   | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>aLEA (ng/ml)</b>   |   |                     |                     |                |
| Pre – 0min  | 0.004                                     | -0.003              | 0.011               | 0.820          |
| Pre – 5min  | 0.004                                     | -0.003              | 0.010               | 0.857          |
| Pre – 15min   | 0.004                                     | -0.003              | 0.011               | 0.817          |
| Pre – 90min   | 0.007                                     | 0.000               | 0.014               | 0.265          |
| 0min – 5min   | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 0min – 15min  | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 0min – 90min  | 0.003                                     | -0.004              | 0.010               | 0.882          |
| 5min – 15min  | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 5min – 90min  | 0.004                                     | -0.003              | 0.011               | 0.849          |
| 15min – 90min   | 0.003                                     | -0.004              | 0.010               | 0.884          |
| <b>aLEA (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min  | 0.004                                     | -0.003              | 0.011               | 0.820          |
| Pre – 5min  | 0.004                                     | -0.003              | 0.010               | 0.857          |
| Pre – 15min   | 0.004                                     | -0.003              | 0.011               | 0.817          |
| Pre – 90min   | 0.007                                     | 0.000               | 0.014               | 0.265          |
| 0min – 5min   | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 0min – 15min  | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 0min – 90min  | 0.003                                     | -0.004              | 0.010               | 0.882          |
| 5min – 15min  | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 5min – 90min  | 0.004                                     | -0.003              | 0.011               | 0.849          |
| 15min – 90min   | 0.003                                     | -0.004              | 0.010               | 0.884          |



**eTable 2 continued.**

| <b>Contrast</b>   | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>gLEA (ng/ml)</b>   |   |                     |                     |                |
| Pre – 0min  | 0.005                                     | -0.002              | 0.011               | 0.625          |
| Pre – 5min  | 0.004                                     | -0.003              | 0.010               | 0.817          |
| Pre – 15min   | 0.001                                     | -0.005              | 0.008               | 0.995          |
| Pre – 90min   | 0.005                                     | -0.001              | 0.012               | 0.516          |
| 0min – 5min   | -0.001                                    | -0.008              | 0.005               | 0.998          |
| 0min – 15min  | -0.003                                    | -0.010              | 0.003               | 0.849          |
| 0min – 90min  | 0.001                                     | -0.006              | 0.007               | 1.000          |
| 5min – 15min  | -0.002                                    | -0.009              | 0.004               | 0.959          |
| 5min – 90min  | 0.002                                     | -0.005              | 0.008               | 0.988          |
| 15min – 90min   | 0.004                                     | -0.003              | 0.010               | 0.762          |
| <b>gLEA (ng/ml)<br/>(adjusted for visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min  | 0.005                                     | -0.002              | 0.011               | 0.627          |
| Pre – 5min  | 0.004                                     | -0.003              | 0.010               | 0.818          |
| Pre – 15min   | 0.001                                     | -0.005              | 0.008               | 0.995          |
| Pre – 90min   | 0.005                                     | -0.001              | 0.012               | 0.518          |
| 0min – 5min   | -0.001                                    | -0.008              | 0.005               | 0.998          |
| 0min – 15min  | -0.003                                    | -0.010              | 0.003               | 0.850          |
| 0min – 90min  | 0.001                                     | -0.006              | 0.007               | 1.000          |
| 5min – 15min  | -0.002                                    | -0.009              | 0.004               | 0.959          |
| 5min – 90min  | 0.002                                     | -0.005              | 0.008               | 0.988          |
| 15min – 90min   | 0.004                                     | -0.003              | 0.011               | 0.764          |

**eTable 3.** Plasma concentrations vs. time following 10mg THC (all CBD:THC ratios) – Model 3b

Statistically significant rows are presented in bold.  
Pre = pre-inhalation plasma sample.

| Contrast   | Estimated marginal mean difference | Lower 95% CI  | Upper 95% CI  | p-value      |
|--|------------------------------------|---------------|---------------|--------------|
| <b>Anandamide (ng/ml)</b>  |                                    |               |               |              |
| <b>Pre – 0min</b>  | <b>-0.044</b>                      | <b>-0.064</b> | <b>-0.025</b> | <b>0.000</b> |
| Pre – 5min   | 0.003                              | -0.017        | 0.022         | 0.999        |
| Pre – 15min  | 0.001                              | -0.019        | 0.020         | 1.000        |
| Pre – 90min  | 0.017                              | -0.002        | 0.037         | 0.420        |
| <b>0min – 5min</b>   | <b>0.047</b>                       | <b>0.028</b>  | <b>0.067</b>  | <b>0.000</b> |
| <b>0min – 15min</b>  | <b>0.045</b>                       | <b>0.025</b>  | <b>0.065</b>  | <b>0.000</b> |
| <b>0min – 90min</b>  | <b>0.061</b>                       | <b>0.042</b>  | <b>0.081</b>  | <b>0.000</b> |
| 5min – 15min   | -0.002                             | -0.022        | 0.017         | 1.000        |
| 5min – 90min   | 0.014                              | -0.005        | 0.034         | 0.604        |
| 15min – 90min  | 0.016                              | -0.003        | 0.036         | 0.465        |
| <b>Anandamide (ng/ml) (adjusted for CBD:THC ratio, visit number and time between visits)</b> |                                    |               |               |              |
| <b>Pre – 0min</b>  | <b>-0.042</b>                      | <b>-0.062</b> | <b>-0.023</b> | <b>0.000</b> |
| Pre – 5min   | 0.003                              | -0.016        | 0.022         | 0.998        |
| Pre – 15min  | 0.002                              | -0.018        | 0.021         | 1.000        |
| Pre – 90min  | 0.018                              | -0.001        | 0.037         | 0.349        |
| <b>0min – 5min</b>   | <b>0.045</b>                       | <b>0.026</b>  | <b>0.065</b>  | <b>0.000</b> |
| <b>0min – 15min</b>  | <b>0.044</b>                       | <b>0.025</b>  | <b>0.063</b>  | <b>0.000</b> |
| <b>0min – 90min</b>  | <b>0.060</b>                       | <b>0.041</b>  | <b>0.080</b>  | <b>0.000</b> |
| 5min – 15min   | -0.001                             | -0.021        | 0.018         | 1.000        |
| 5min – 90min   | 0.015                              | -0.004        | 0.034         | 0.547        |
| 15min – 90min  | 0.016                              | -0.003        | 0.036         | 0.457        |

**eTable 3 continued.**

| <b>Contrast</b>  | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|--|---|---------------------|---------------------|----------------|
| <b>2-AG (ng/ml)</b>  |   |                     |                     |                |
| Pre – 0min   | 0.030                                     | -0.986              | 1.046               | 1.000          |
| Pre – 5min   | 0.251                                     | -0.765              | 1.267               | 0.989          |
| Pre – 15min  | 0.083                                     | -0.933              | 1.099               | 1.000          |
| Pre – 90min  | -0.521                                    | -1.537              | 0.496               | 0.853          |
| 0min – 5min  | 0.221                                     | -0.796              | 1.237               | 0.993          |
| 0min – 15min   | 0.053                                     | -0.963              | 1.069               | 1.000          |
| 0min – 90min   | -0.551                                    | -1.567              | 0.465               | 0.825          |
| 5min – 15min   | -0.168                                    | -1.184              | 0.848               | 0.998          |
| 5min – 90min   | -0.771                                    | -1.787              | 0.245               | 0.569          |
| 15min – 90min  | -0.603                                    | -1.619              | 0.413               | 0.771          |
| <b>2-AG (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min   | 0.030                                     | -0.985              | 1.045               | 1.000          |
| Pre – 5min   | 0.251                                     | -0.764              | 1.265               | 0.989          |
| Pre – 15min  | 0.083                                     | -0.932              | 1.098               | 1.000          |
| Pre – 90min  | -0.521                                    | -1.535              | 0.494               | 0.852          |
| 0min – 5min  | 0.221                                     | -0.794              | 1.235               | 0.993          |
| 0min – 15min   | 0.053                                     | -0.962              | 1.067               | 1.000          |
| 0min – 90min   | -0.551                                    | -1.565              | 0.464               | 0.824          |
| 5min – 15min   | -0.168                                    | -1.183              | 0.847               | 0.998          |
| 5min – 90min   | -0.771                                    | -1.786              | 0.244               | 0.568          |
| 15min – 90min  | -0.603                                    | -1.618              | 0.411               | 0.770          |

eTable 3 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI  | Upper 95% CI  | p-value      |
|--|------------------------------------|---------------|---------------|--------------|
| <b>Arachidonic acid (ng/ml)</b>  |                                    |               |               |              |
| Pre – 0min   | -28.446                            | -56.267       | -0.625        | 0.263        |
| Pre – 5min   | -34.638                            | -62.458       | -6.817        | 0.105        |
| Pre – 15min  | -6.587                             | -34.408       | 21.233        | 0.990        |
| Pre – 90min  | 15.642                             | -12.179       | 43.463        | 0.805        |
| 0min – 5min  | -6.192                             | -34.012       | 21.629        | 0.992        |
| 0min – 15min   | 21.859                             | -5.962        | 49.679        | 0.535        |
| <b>0min – 90min</b>  | <b>44.088</b>                      | <b>16.267</b> | <b>71.909</b> | <b>0.016</b> |
| 5min – 15min   | 28.050                             | 0.229         | 55.871        | 0.277        |
| <b>5min – 90min</b>  | <b>50.279</b>                      | <b>22.459</b> | <b>78.100</b> | <b>0.004</b> |
| 15min – 90min  | 22.229                             | -5.592        | 50.050        | 0.518        |
| <b>Arachidonic acid (ng/ml) (adjusted for CBD:THC ratio, visit number and time between visits)</b> |                                    |               |               |              |
| Pre – 0min   | -27.334                            | -54.956       | 0.287         | 0.296        |
| Pre – 5min   | -34.263                            | -61.885       | -6.641        | 0.107        |
| Pre – 15min  | -5.838                             | -33.460       | 21.784        | 0.994        |
| Pre – 90min  | 16.478                             | -11.144       | 44.100        | 0.768        |
| 0min – 5min  | -6.929                             | -34.550       | 20.693        | 0.988        |
| 0min – 15min   | 21.496                             | -6.126        | 49.118        | 0.545        |
| <b>0min – 90min</b>  | <b>43.812</b>                      | <b>16.191</b> | <b>71.434</b> | <b>0.016</b> |
| 5min – 15min   | 28.425                             | 0.803         | 56.047        | 0.257        |
| <b>5min – 90min</b>  | <b>50.741</b>                      | <b>23.119</b> | <b>78.363</b> | <b>0.003</b> |
| 15min – 90min  | 22.316                             | -5.306        | 49.938        | 0.507        |

eTable 3 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI  | Upper 95% CI  | p-value      |
|---|------------------------------------|---------------|---------------|--------------|
| <b>DEA (ng/ml)</b>  |                                    |               |               |              |
| <b>Pre – 0min</b>   | <b>-0.012</b>                      | <b>-0.016</b> | <b>-0.008</b> | <b>0.000</b> |
| Pre – 5min  | 0.002                              | -0.002        | 0.006         | 0.805        |
| Pre – 15min   | 0.001                              | -0.003        | 0.005         | 0.995        |
| Pre – 90min   | 0.003                              | -0.001        | 0.007         | 0.497        |
| <b>0min – 5min</b>  | <b>0.014</b>                       | <b>0.010</b>  | <b>0.018</b>  | <b>0.000</b> |
| <b>0min – 15min</b>   | <b>0.013</b>                       | <b>0.009</b>  | <b>0.017</b>  | <b>0.000</b> |
| <b>0min – 90min</b>   | <b>0.015</b>                       | <b>0.011</b>  | <b>0.019</b>  | <b>0.000</b> |
| 5min – 15min  | -0.001                             | -0.005        | 0.003         | 0.954        |
| 5min – 90min  | 0.001                              | -0.003        | 0.005         | 0.988        |
| 15min – 90min   | 0.002                              | -0.002        | 0.006         | 0.748        |
| <b>DEA (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |                                    |               |               |              |
| <b>Pre – 0min</b>   | <b>-0.012</b>                      | <b>-0.016</b> | <b>-0.008</b> | <b>0.000</b> |
| Pre – 5min  | 0.002                              | -0.002        | 0.006         | 0.795        |
| Pre – 15min   | 0.001                              | -0.003        | 0.005         | 0.995        |
| Pre – 90min   | 0.003                              | 0.000         | 0.007         | 0.412        |
| <b>0min – 5min</b>  | <b>0.014</b>                       | <b>0.010</b>  | <b>0.018</b>  | <b>0.000</b> |
| <b>0min – 15min</b>   | <b>0.012</b>                       | <b>0.008</b>  | <b>0.016</b>  | <b>0.000</b> |
| <b>0min – 90min</b>   | <b>0.015</b>                       | <b>0.011</b>  | <b>0.019</b>  | <b>0.000</b> |
| 5min – 15min  | -0.001                             | -0.005        | 0.002         | 0.952        |
| 5min – 90min  | 0.001                              | -0.003        | 0.005         | 0.973        |
| 15min – 90min   | 0.003                              | -0.001        | 0.007         | 0.669        |

eTable 3 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI  | Upper 95% CI  | p-value      |
|---|------------------------------------|---------------|---------------|--------------|
| <b>OEA (ng/ml)</b>  |                                    |               |               |              |
| <b>Pre – 0min</b>   | <b>-0.186</b>                      | <b>-0.296</b> | <b>-0.077</b> | <b>0.008</b> |
| Pre – 5min  | -0.023                             | -0.133        | 0.086         | 0.994        |
| Pre – 15min   | 0.033                              | -0.076        | 0.142         | 0.976        |
| Pre – 90min   | 0.096                              | -0.013        | 0.206         | 0.418        |
| <b>0min – 5min</b>  | <b>0.163</b>                       | <b>0.054</b>  | <b>0.272</b>  | <b>0.029</b> |
| <b>0min – 15min</b>   | <b>0.219</b>                       | <b>0.110</b>  | <b>0.329</b>  | <b>0.001</b> |
| <b>0min – 90min</b>   | <b>0.282</b>                       | <b>0.173</b>  | <b>0.392</b>  | <b>0.000</b> |
| 5min – 15min  | 0.056                              | -0.053        | 0.166         | 0.850        |
| 5min – 90min  | 0.119                              | 0.010         | 0.229         | 0.203        |
| 15min – 90min   | 0.063                              | -0.046        | 0.172         | 0.790        |
| <b>OEA (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |                                    |               |               |              |
| <b>Pre – 0min</b>   | <b>-0.184</b>                      | <b>-0.293</b> | <b>-0.076</b> | <b>0.008</b> |
| Pre – 5min  | -0.024                             | -0.133        | 0.084         | 0.992        |
| Pre – 15min   | 0.030                              | -0.079        | 0.138         | 0.984        |
| Pre – 90min   | 0.095                              | -0.013        | 0.204         | 0.420        |
| <b>0min – 5min</b>  | <b>0.160</b>                       | <b>0.051</b>  | <b>0.269</b>  | <b>0.032</b> |
| <b>0min – 15min</b>   | <b>0.214</b>                       | <b>0.105</b>  | <b>0.323</b>  | <b>0.001</b> |
| <b>0min – 90min</b>   | <b>0.280</b>                       | <b>0.171</b>  | <b>0.388</b>  | <b>0.000</b> |
| 5min – 15min  | 0.054                              | -0.055        | 0.163         | 0.866        |
| 5min – 90min  | 0.120                              | 0.011         | 0.228         | 0.194        |
| 15min – 90min   | 0.066                              | -0.043        | 0.174         | 0.757        |

**eTable 3 continued.**

| <b>Contrast</b>   | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>SEA (ng/ml)</b>  |   |                     |                     |                |
| Pre – 0min  | -0.056                                    | -0.163              | 0.052               | 0.847          |
| Pre – 5min  | 0.065                                     | -0.043              | 0.172               | 0.762          |
| Pre – 15min   | 0.058                                     | -0.049              | 0.166               | 0.822          |
| Pre – 90min   | 0.064                                     | -0.043              | 0.171               | 0.770          |
| 0min – 5min   | 0.120                                     | 0.013               | 0.227               | 0.181          |
| 0min – 15min  | 0.114                                     | 0.007               | 0.221               | 0.226          |
| 0min – 90min  | 0.119                                     | 0.012               | 0.227               | 0.186          |
| 5min – 15min  | -0.006                                    | -0.113              | 0.101               | 1.000          |
| 5min – 90min  | -0.001                                    | -0.108              | 0.106               | 1.000          |
| 15min – 90min   | 0.005                                     | -0.102              | 0.113               | 1.000          |
| <b>SEA (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min  | -0.056                                    | -0.168              | 0.046               | 0.846          |
| Pre – 5min  | 0.065                                     | -0.052              | 0.162               | 0.761          |
| Pre – 15min   | 0.058                                     | -0.059              | 0.155               | 0.821          |
| Pre – 90min   | 0.064                                     | -0.053              | 0.161               | 0.769          |
| 0min – 5min   | 0.120                                     | 0.010               | 0.224               | 0.179          |
| 0min – 15min  | 0.114                                     | 0.003               | 0.217               | 0.224          |
| 0min – 90min  | 0.119                                     | 0.008               | 0.222               | 0.185          |
| 5min – 15min  | -0.006                                    | -0.114              | 0.100               | 1.000          |
| 5min – 90min  | -0.001                                    | -0.109              | 0.105               | 1.000          |
| 15min – 90min   | 0.005                                     | -0.102              | 0.112               | 1.000          |

eTable 3 continued.

| Contrast  | Estimated marginal mean difference<br>ARA-S (ng/ml) (adjusted for<br>CBD:THC ratio and visit number) | Lower 95% CI  | Upper 95% CI  | p-value      |
|---|--|---------------|---------------|--------------|
| <b>Pre – 0min</b>   | <b>-0.011</b>  | <b>-0.017</b> | <b>-0.004</b> | <b>0.007</b> |
| Pre – 5min  | -0.003   | -0.009        | 0.003         | 0.895        |
| Pre – 15min   | -0.003   | -0.009        | 0.003         | 0.903        |
| Pre – 90min   | -0.002   | -0.008        | 0.004         | 0.967        |
| 0min – 5min   | 0.008  | 0.002         | 0.014         | 0.104        |
| 0min – 15min  | 0.008  | 0.002         | 0.014         | 0.098        |
| 0min – 90min  | 0.009  | 0.002         | 0.015         | 0.054        |
| 5min – 15min  | 0.000  | -0.006        | 0.006         | 1.000        |
| 5min – 90min  | 0.001  | -0.005        | 0.007         | 0.999        |
| 15min – 90min   | 0.001  | -0.006        | 0.007         | 0.999        |
| <b>ARA-S (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |  |               |               |              |
| <b>Pre – 0min</b>   | <b>-0.011</b>  | <b>-0.017</b> | <b>-0.004</b> | <b>0.008</b> |
| Pre – 5min  | -0.003   | -0.009        | 0.003         | 0.890        |
| Pre – 15min   | -0.002   | -0.008        | 0.004         | 0.964        |
| Pre – 90min   | -0.002   | -0.008        | 0.004         | 0.977        |
| 0min – 5min   | 0.008  | 0.001         | 0.014         | 0.114        |
| 0min – 15min  | 0.008  | 0.002         | 0.015         | 0.060        |
| 0min – 90min  | 0.009  | 0.002         | 0.015         | 0.050        |
| 5min – 15min  | 0.001  | -0.005        | 0.007         | 0.999        |
| 5min – 90min  | 0.001  | -0.005        | 0.007         | 0.998        |
| 15min – 90min   | 0.000  | -0.006        | 0.006         | 1.000        |



**eTable 3 continued.**

| <b>Contrast</b>  | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|--|---|---------------------|---------------------|----------------|
| <b>aLEA (ng/ml)</b>  |   |                     |                     |                |
| Pre – 0min   | 0.001                                     | -0.003              | 0.005               | 0.995          |
| Pre – 5min   | 0.002                                     | -0.002              | 0.005               | 0.918          |
| Pre – 15min  | 0.002                                     | -0.002              | 0.006               | 0.843          |
| Pre – 90min  | 0.002                                     | -0.002              | 0.006               | 0.782          |
| 0min – 5min  | 0.001                                     | -0.003              | 0.005               | 0.992          |
| 0min – 15min   | 0.001                                     | -0.003              | 0.005               | 0.971          |
| 0min – 90min   | 0.001                                     | -0.002              | 0.005               | 0.945          |
| 5min – 15min   | 0.000                                     | -0.003              | 0.004               | 1.000          |
| 5min – 90min   | 0.001                                     | -0.003              | 0.004               | 0.998          |
| 15min – 90min  | 0.000                                     | -0.004              | 0.004               | 1.000          |
| <b>aLEA (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min   | 0.001                                     | -0.003              | 0.005               | 0.993          |
| Pre – 5min   | 0.002                                     | -0.002              | 0.005               | 0.921          |
| Pre – 15min  | 0.002                                     | -0.002              | 0.006               | 0.861          |
| Pre – 90min  | 0.002                                     | -0.002              | 0.006               | 0.779          |
| 0min – 5min  | 0.001                                     | -0.003              | 0.005               | 0.995          |
| 0min – 15min   | 0.001                                     | -0.003              | 0.005               | 0.981          |
| 0min – 90min   | 0.001                                     | -0.002              | 0.005               | 0.952          |
| 5min – 15min   | 0.000                                     | -0.004              | 0.004               | 1.000          |
| 5min – 90min   | 0.001                                     | -0.003              | 0.004               | 0.998          |
| 15min – 90min  | 0.000                                     | -0.004              | 0.004               | 1.000          |

**eTable 3 continued.**

| <b>Contrast</b>  | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|--|---|---------------------|---------------------|----------------|
| <b>gLEA (ng/ml)</b>  |   |                     |                     |                |
| Pre – 0min   | 0.001                                     | -0.002              | 0.004               | 0.891          |
| Pre – 5min   | 0.002                                     | -0.001              | 0.005               | 0.788          |
| Pre – 15min  | 0.001                                     | -0.002              | 0.004               | 0.940          |
| Pre – 90min  | 0.000                                     | -0.003              | 0.003               | 1.000          |
| 0min – 5min  | 0.000                                     | -0.003              | 0.003               | 0.999          |
| 0min – 15min   | 0.000                                     | -0.003              | 0.003               | 1.000          |
| 0min – 90min   | -0.001                                    | -0.004              | 0.002               | 0.920          |
| 5min – 15min   | -0.001                                    | -0.004              | 0.002               | 0.996          |
| 5min – 90min   | -0.002                                    | -0.005              | 0.001               | 0.831          |
| 15min – 90min  | -0.001                                    | -0.004              | 0.002               | 0.960          |
| <b>gLEA (ng/ml) (adjusted for<br/>CBD:THC ratio, visit number<br/>and time between visits)</b> |   |                     |                     |                |
| Pre – 0min   | 0.001                                     | -0.002              | 0.004               | 0.892          |
| Pre – 5min   | 0.002                                     | -0.001              | 0.005               | 0.784          |
| Pre – 15min  | 0.001                                     | -0.002              | 0.004               | 0.965          |
| Pre – 90min  | 0.000                                     | -0.003              | 0.003               | 1.000          |
| 0min – 5min  | 0.000                                     | -0.003              | 0.003               | 0.999          |
| 0min – 15min   | 0.000                                     | -0.003              | 0.003               | 0.999          |
| 0min – 90min   | -0.001                                    | -0.004              | 0.002               | 0.918          |
| 5min – 15min   | -0.001                                    | -0.004              | 0.002               | 0.989          |
| 5min – 90min   | -0.002                                    | -0.005              | 0.001               | 0.821          |
| 15min – 90min  | -0.001                                    | -0.004              | 0.002               | 0.977          |

**eTable 4.** Pre-inhalation plasma concentrations vs. visit number – Model 4a.

Statistically significant rows are presented in bold.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value      |
|--|------------------------------------|--------------|--------------|--------------|
| <b>Anandamide (ng/ml)</b>                                    |                                    |              |              |              |
| Visit 1 – Visit 2  | 0.006                              | -0.030       | 0.042        | 0.988        |
| 1 – 3  | 0.021                              | -0.015       | 0.057        | 0.651        |
| <b>1 – 4</b>   | <b>0.060</b>                       | <b>0.024</b> | <b>0.096</b> | <b>0.007</b> |
| 2 – 3  | 0.015                              | -0.021       | 0.051        | 0.838        |
| <b>2 – 4</b>   | <b>0.054</b>                       | <b>0.018</b> | <b>0.090</b> | <b>0.019</b> |
| 3 – 4  | 0.039                              | 0.003        | 0.075        | 0.154        |
| <b>Anandamide (ng/ml) (adjusted for time between visits)</b> |                                    |              |              |              |
| 1 – 2  | 0.006                              | -0.035       | 0.048        | 0.990        |
| 1 – 3  | 0.025                              | -0.015       | 0.065        | 0.606        |
| <b>1 – 4</b>   | <b>0.063</b>                       | <b>0.024</b> | <b>0.103</b> | <b>0.010</b> |
| 2 – 3  | 0.019                              | -0.018       | 0.055        | 0.745        |
| <b>2 – 4</b>   | <b>0.057</b>                       | <b>0.021</b> | <b>0.093</b> | <b>0.013</b> |
| 3 – 4  | 0.038                              | 0.002        | 0.074        | 0.156        |
| <b>2-AG (ng/ml)</b>  |                                    |              |              |              |
| 1 – 2  | 0.713                              | -1.171       | 2.596        | 0.877        |
| 1 – 3  | -0.927                             | -2.810       | 0.957        | 0.765        |
| 1 – 4  | -0.771                             | -2.654       | 1.113        | 0.850        |
| 2 – 3  | -1.639                             | -3.523       | 0.244        | 0.317        |
| 2 – 4  | -1.483                             | -3.367       | 0.400        | 0.407        |
| 3 – 4  | 0.156                              | -1.727       | 2.040        | 0.998        |
| <b>2-AG (ng/ml) (adjusted for time between visits)</b>       |                                    |              |              |              |
| 1 – 2  | 1.070                              | -0.990       | 3.130        | 0.734        |
| 1 – 3  | -0.452                             | -2.447       | 1.543        | 0.970        |
| 1 – 4  | -0.327                             | -2.301       | 1.646        | 0.988        |
| 2 – 3  | -1.522                             | -3.358       | 0.314        | 0.360        |
| 2 – 4  | -1.397                             | -3.237       | 0.443        | 0.439        |
| 3 – 4  | 0.125                              | -1.696       | 1.946        | 0.999        |

eTable 4 continued.

| Contrast   | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value      |
|--|------------------------------------|--------------|--------------|--------------|
| <b>Arachidonic acid (ng/ml)</b>  |                                    |              |              |              |
| Visit 1 – Visit 2  | 25.080                             | -30.462      | 80.623       | 0.808        |
| 1 – 3  | 5.628                              | -49.914      | 61.171       | 0.997        |
| 1 – 4  | 45.946                             | -9.596       | 101.489      | 0.362        |
| 2 – 3  | -19.452                            | -74.995      | 36.090       | 0.900        |
| 2 – 4  | 20.866                             | -34.677      | 76.408       | 0.880        |
| 3 – 4  | 40.318                             | -15.225      | 95.860       | 0.480        |
| <b>Arachidonic acid (ng/ml)<br/>(adjusted for time between visits)</b> |                                    |              |              |              |
| 1 – 2  | 24.413                             | -38.909      | 87.735       | 0.871        |
| 1 – 3  | 8.438                              | -52.837      | 69.712       | 0.993        |
| 1 – 4  | 48.571                             | -12.031      | 109.174      | 0.391        |
| 2 – 3  | -15.975                            | -72.233      | 40.283       | 0.943        |
| 2 – 4  | 24.158                             | -32.240      | 80.557       | 0.832        |
| 3 – 4  | 40.134                             | -15.653      | 95.920       | 0.487        |
| <b>DEA (ng/ml)</b>   |                                    |              |              |              |
| 1 – 2  | 0.003                              | -0.005       | 0.011        | 0.866        |
| 1 – 3  | 0.004                              | -0.004       | 0.012        | 0.694        |
| <b>1 – 4</b>   | <b>0.011</b>                       | <b>0.003</b> | <b>0.019</b> | <b>0.031</b> |
| 2 – 3  | 0.001                              | -0.007       | 0.009        | 0.989        |
| 2 – 4  | 0.008                              | 0.000        | 0.016        | 0.192        |
| 3 – 4  | 0.007                              | -0.001       | 0.015        | 0.335        |
| <b>DEA (ng/ml) (adjusted<br/>for time between visits)</b>              |                                    |              |              |              |
| 1 – 2  | 0.002                              | -0.008       | 0.011        | 0.988        |
| 1 – 3  | 0.004                              | -0.005       | 0.012        | 0.848        |
| 1 – 4  | 0.010                              | 0.002        | 0.019        | 0.086        |
| 2 – 3  | 0.002                              | -0.006       | 0.010        | 0.954        |
| 2 – 4  | 0.009                              | 0.001        | 0.017        | 0.130        |
| 3 – 4  | 0.007                              | -0.001       | 0.015        | 0.329        |

**eTable 4 continued.**

| <b>Contrast</b>                                       | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>OEA (ng/ml)</b>                                    |   |                     |                     |                |
| Visit 1 – Visit 2                                     | -0.008                                    | -0.205              | 0.189               | 1.000          |
| 1 – 3   | 0.029                                     | -0.168              | 0.226               | 0.991          |
| 1 – 4   | 0.212                                     | 0.014               | 0.409               | 0.151          |
| 2 – 3   | 0.037                                     | -0.160              | 0.234               | 0.982          |
| 2 – 4   | 0.220                                     | 0.022               | 0.417               | 0.128          |
| 3 – 4   | 0.183                                     | -0.015              | 0.380               | 0.263          |
| <b>OEA (ng/ml) (adjusted for time between visits)</b> |   |                     |                     |                |
| 1 – 2   | -0.083                                    | -0.310              | 0.143               | 0.886          |
| 1 – 3   | -0.036                                    | -0.254              | 0.183               | 0.988          |
| 1 – 4   | 0.151                                     | -0.065              | 0.368               | 0.512          |
| 2 – 3   | 0.048                                     | -0.153              | 0.248               | 0.965          |
| 2 – 4   | 0.235                                     | 0.034               | 0.435               | 0.100          |
| 3 – 4   | 0.187                                     | -0.012              | 0.385               | 0.249          |
| <b>SEA (ng/ml)</b>                                    |   |                     |                     |                |
| 1 – 2   | 0.002                                     | -0.256              | 0.260               | 1.000          |
| 1 – 3   | -0.219                                    | -0.477              | 0.039               | 0.339          |
| 1 – 4   | 0.094                                     | -0.164              | 0.352               | 0.889          |
| 2 – 3   | -0.222                                    | -0.480              | 0.037               | 0.329          |
| 2 – 4   | 0.091                                     | -0.167              | 0.349               | 0.897          |
| 3 – 4   | 0.313                                     | 0.055               | 0.571               | 0.082          |
| <b>SEA (ng/ml) (adjusted for time between visits)</b> |   |                     |                     |                |
| 1 – 2   | -0.007                                    | -0.290              | 0.276               | 1.000          |
| 1 – 3   | -0.260                                    | -0.534              | 0.015               | 0.246          |
| 1 – 4   | 0.056                                     | -0.216              | 0.328               | 0.977          |
| 2 – 3   | -0.253                                    | -0.508              | 0.002               | 0.209          |
| 2 – 4   | 0.063                                     | -0.193              | 0.319               | 0.962          |
| 3 – 4   | 0.316                                     | 0.062               | 0.569               | 0.070          |

eTable 4 continued.

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|---|------------------------------------|--------------|--------------|---------|
| <b>ARA-S (ng/ml)</b>                                    |                                    |              |              |         |
| Visit 1 – Visit 2                                       | -0.002                             | -0.012       | 0.008        | 0.981   |
| 1 – 3   | -0.005                             | -0.016       | 0.005        | 0.726   |
| 1 – 4   | 0.004                              | -0.006       | 0.015        | 0.840   |
| 2 – 3   | -0.003                             | -0.014       | 0.007        | 0.913   |
| 2 – 4   | 0.006                              | -0.004       | 0.017        | 0.620   |
| 3 – 4   | 0.010                              | -0.001       | 0.020        | 0.246   |
| <b>ARA-S (ng/ml) (adjusted for time between visits)</b> |                                    |              |              |         |
| 1 – 2   | -0.001                             | -0.013       | 0.011        | 0.998   |
| 1 – 3   | -0.004                             | -0.015       | 0.007        | 0.902   |
| 1 – 4   | 0.006                              | -0.006       | 0.017        | 0.747   |
| 2 – 3   | -0.003                             | -0.013       | 0.008        | 0.949   |
| 2 – 4   | 0.007                              | -0.004       | 0.017        | 0.570   |
| 3 – 4   | 0.010                              | -0.001       | 0.020        | 0.255   |
| <b>aLEA (ng/ml)</b>                                     |                                    |              |              |         |
| 1 – 2   | -0.005                             | -0.013       | 0.002        | 0.480   |
| 1 – 3   | 0.000                              | -0.007       | 0.007        | 1.000   |
| 1 – 4   | 0.002                              | -0.005       | 0.010        | 0.918   |
| 2 – 3   | 0.005                              | -0.002       | 0.013        | 0.494   |
| 2 – 4   | 0.008                              | 0.000        | 0.015        | 0.165   |
| 3 – 4   | 0.002                              | -0.005       | 0.010        | 0.910   |
| <b>aLEA (ng/ml) (adjusted for time between visits)</b>  |                                    |              |              |         |
| 1 – 2   | -0.007                             | -0.015       | 0.001        | 0.314   |
| 1 – 3   | -0.001                             | -0.009       | 0.007        | 0.987   |
| 1 – 4   | 0.001                              | -0.007       | 0.009        | 0.991   |
| 2 – 3   | 0.006                              | -0.002       | 0.013        | 0.403   |
| 2 – 4   | 0.008                              | 0.001        | 0.016        | 0.118   |
| 3 – 4   | 0.003                              | -0.005       | 0.010        | 0.902   |

**eTable 4 continued.**

| <b>Contrast</b>  | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|--|---|---------------------|---------------------|----------------|
| <b>gLEA (ng/ml)</b>                                    |   |                     |                     |                |
| Visit 1 – Visit 2                                      | -0.004                                    | -0.011              | 0.002               | 0.563          |
| 1 – 3  | 0.001                                     | -0.006              | 0.008               | 0.993          |
| 1 – 4  | 0.000                                     | -0.007              | 0.006               | 1.000          |
| 2 – 3  | 0.005                                     | -0.001              | 0.012               | 0.395          |
| 2 – 4  | 0.004                                     | -0.003              | 0.011               | 0.618          |
| 3 – 4  | -0.001                                    | -0.008              | 0.005               | 0.984          |
| <b>gLEA (ng/ml) (adjusted for time between visits)</b> |   |                     |                     |                |
| 1 – 2  | -0.004                                    | -0.012              | 0.003               | 0.625          |
| 1 – 3  | 0.001                                     | -0.006              | 0.008               | 0.995          |
| 1 – 4  | 0.000                                     | -0.007              | 0.007               | 1.000          |
| 2 – 3  | 0.005                                     | -0.001              | 0.012               | 0.388          |
| 2 – 4  | 0.004                                     | -0.003              | 0.011               | 0.609          |
| 3 – 4  | -0.001                                    | -0.008              | 0.005               | 0.984          |

**eTable 5.** Pre-inhalation plasma concentrations of AEA and DEA vs. total CBD dose from previous visits – Models 4b, 4c and 4d.

Possible previous doses of CBD at beginning of:

Visit 2: 0, 10, 20 or 30mg

Visit 3: 10, 20, 30, 40 or 50mg

Visit 4: 30, 40, 50 or 60mg

| Contrast  | Estimated marginal mean difference | Lower 95% CI | Upper 95% CI | p-value |
|---|------------------------------------|--------------|--------------|---------|
| <b>Visit 2 - Anandamide (ng/ml)</b><br>(adjusted for time between visits) |                                    |              |              |         |
| 0mg – 10mg  | 0.007                              | -0.093       | 0.108        | 0.999   |
| 0mg – 20mg  | 0.028                              | -0.076       | 0.131        | 0.949   |
| 0mg – 30mg  | 0.044                              | -0.076       | 0.164        | 0.881   |
| 10mg – 20mg   | 0.020                              | -0.079       | 0.119        | 0.976   |
| 10mg – 30mg   | 0.036                              | -0.079       | 0.151        | 0.918   |
| 20mg – 30mg   | 0.016                              | -0.103       | 0.136        | 0.993   |
| <b>Visit 3 - Anandamide (ng/ml)</b><br>(adjusted for time between visits) |                                    |              |              |         |
| 30mg – 40mg   | -0.020                             | -0.146       | 0.105        | 0.998   |
| 30mg – 50mg   | 0.004                              | -0.105       | 0.113        | 1.000   |
| 30mg – 60mg   | 0.018                              | -0.115       | 0.151        | 0.999   |
| 30mg – 70mg   | 0.086                              | -0.049       | 0.221        | 0.700   |
| 40mg – 50mg   | 0.024                              | -0.081       | 0.129        | 0.990   |
| 40mg – 60mg   | 0.038                              | -0.087       | 0.164        | 0.972   |
| 40mg – 70mg   | 0.106                              | -0.031       | 0.243        | 0.530   |
| 50mg – 60mg   | 0.014                              | -0.100       | 0.128        | 0.999   |
| 50mg – 70mg   | 0.082                              | -0.040       | 0.203        | 0.656   |
| 60mg – 70mg   | 0.068                              | -0.076       | 0.211        | 0.875   |
| <b>Visit 4 - Anandamide (ng/ml)</b><br>(adjusted for time between visits) |                                    |              |              |         |
| 30mg – 40mg   | 0.038                              | -0.080       | 0.053        | 0.972   |
| 30mg – 50mg   | 0.024                              | -0.070       | 0.054        | 0.990   |
| 30mg – 60mg   | 0.086                              | -0.075       | 0.053        | 0.700   |
| 40mg – 50mg   | 0.018                              | -0.066       | 0.078        | 0.999   |
| 40mg – 60mg   | 0.004                              | -0.070       | 0.076        | 1.000   |
| 50mg – 60mg   | -0.020                             | -0.072       | 0.067        | 0.998   |



**eTable 5 continued.**

| <b>Contrast</b>                           | <b>Estimated marginal mean difference</b> | <b>Lower 95% CI</b> | <b>Upper 95% CI</b> | <b>p-value</b> |
|---|---|---------------------|---------------------|----------------|
| <b>Visit 2 - DEA (ng/ml)</b>              |   |                     |                     |                |
| <b>(adjusted for time between visits)</b> |   |                     |                     |                |
| 0mg – 10mg                                | 0.014                                     | -0.005              | 0.033               | 0.470          |
| 0mg – 20mg                                | 0.017                                     | -0.003              | 0.037               | 0.351          |
| 0mg – 30mg                                | -0.001                                    | -0.024              | 0.022               | 1.000          |
| 10mg – 20mg                               | 0.003                                     | -0.017              | 0.022               | 0.993          |
| 10mg – 30mg                               | -0.015                                    | -0.037              | 0.007               | 0.525          |
| 20mg – 30mg                               | -0.018                                    | -0.041              | 0.005               | 0.422          |
| <b>Visit 3 – DEA (ng/ml)</b>              |   |                     |                     |                |
| <b>(adjusted for time between visits)</b> |   |                     |                     |                |
| 30mg – 40mg                               | -0.003                                    | -0.034              | 0.028               | 1.000          |
| 30mg – 50mg                               | 0.000                                     | -0.027              | 0.026               | 1.000          |
| 30mg – 60mg                               | 0.013                                     | -0.019              | 0.044               | 0.931          |
| 30mg – 70mg                               | 0.022                                     | -0.010              | 0.055               | 0.634          |
| 40mg – 50mg                               | 0.003                                     | -0.024              | 0.029               | 1.000          |
| 40mg – 60mg                               | 0.016                                     | -0.015              | 0.047               | 0.844          |
| 40mg – 70mg                               | 0.025                                     | -0.008              | 0.059               | 0.549          |
| 50mg – 60mg                               | 0.013                                     | -0.014              | 0.040               | 0.871          |
| 50mg – 70mg                               | 0.023                                     | -0.006              | 0.052               | 0.517          |
| 60mg – 70mg                               | 0.010                                     | -0.025              | 0.044               | 0.978          |
| <b>Visit 4 – DEA (ng/ml)</b>              |   |                     |                     |                |
| <b>(adjusted for time between visits)</b> |   |                     |                     |                |
| 30mg – 40mg                               | -0.001                                    | -0.015              | 0.014               | 1.000          |
| 30mg – 50mg                               | -0.002                                    | -0.016              | 0.012               | 0.994          |
| 30mg – 60mg                               | 0.007                                     | -0.007              | 0.021               | 0.767          |
| 40mg – 50mg                               | -0.001                                    | -0.017              | 0.015               | 0.998          |
| 40mg – 60mg                               | 0.007                                     | -0.009              | 0.024               | 0.798          |
| 50mg – 60mg                               | 0.009                                     | -0.007              | 0.024               | 0.675          |

## eResults

### Sex differences

There were no significant sex differences between the endocannabinoids or related non-cannabinoid lipid responses to THC or CBD, with the exception of Model 3b (effect of drug administration: all CBD:THC ratios) and Model 4a (effect of visit number on plasma concentrations) for SEA:

#### Overall effect of THC

Mean SEA concentration in men rose by 127.2% (0.220ng/ml [95%CI: 0.075–0.364],  $t(854)=2.981$ ,  $p=0.025$ ) immediately post-inhalation, before falling to pre-inhalation levels by 5min. In women, there was no significant change in SEA concentration across the sampling timepoints ( $p>0.05$ ). However, an outlier was identified using Rosner's generalised extreme Studentised deviate test in a male participant (0 min, value= 4.527ng/ml, 55.8% higher than next highest value for that timepoint). When this outlier value was removed, there was no longer a significant change in mean SEA concentration in men ( $p=0.060$ ).

#### Effect of visit order on endocannabinoid levels

Over the four experimental visits, pre-inhalation plasma levels of SEA did not significantly change in men ( $p>0.05$ ) but did alter in women. Between visits 1 and 3, mean SEA concentrations rose by 315.6% (0.584ng/ml [95%CI: 0.192–0.975],  $t(140)=2.949$ ,  $p=0.019$ ), before falling again by visit 4 (-76.3%, 0.594ng/ml [95%CI: 0.221–0.967],  $t(131)=3.153$ ,  $p=0.011$ ). However, an outlier was identified using Rosner's generalised extreme Studentised deviate test in a female participant (visit 3, value= 5.830ng/ml, 115.6% higher than next highest value for that visit). When this outlier value was removed, there was no longer a significant change in pre-inhalation SEA between visits in women ( $p\geq 0.128$ ).

#### Effect of peak THC concentration

There was a negative correlation between peak THC plasma concentration and change in DEA plasma concentration immediately post-inhalation ( $R= -0.162$  [95%CI: -0.018 to -0.300],  $t(182)= -2.2181$ ,  $p=0.028$ ). This was no longer significant, however, when the model was fully adjusted for pre-inhalation concentration of DEA ( $p=0.279$ ).

There was no correlation between peak THC concentration and change in any of the other analytes ( $p>0.05$ ).

## References

1. Selzer ML. The Michigan Alcoholism Screening Test: The Quest for a New Diagnostic Instrument. *Am J Psychiatry* 1971;127(12):1653–1658; doi: 10.1176/ajp.127.12.1653.
2. Heatherton T, Kozlowski L, Frecker R, et al. The Fagerstrom Test for Nicotine Dependence: A Revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991;86(9):1119–1127.
3. Skinner HA. The Drug Abuse Screening Test. *Int J* 1983;1:363–371.
4. Stefanis NC, Hanssen M, Smirnis NK, et al. Evidence That Three Dimensions of Psychosis Have a Distribution in the General Population. *Psychol Med* 2002;32(2):347–58.
5. Brandt J. The Hopkins Verbal Learning Test: Development of a New Memory Test with Six Equivalent Forms. *Clin Neuropsychol* 1991;5(2):125–142; doi: 10.1080/13854049108403297.
6. Kay SR, Fiszbein A and Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr Bull* 1987;13(2):261–76.
7. Mason OJ, Morgan CJM, Stefanovic A, et al. The Psychotomimetic States Inventory (PSI): Measuring Psychotic-Type Experiences from Ketamine and Cannabis. *Schizophr Res* 2008;103(1–3):138–142; doi: 10.1016/j.schres.2008.02.020.
8. Freeman TP, Morgan CJA, Vaughn-Jones J, et al. Cognitive and Subjective Effects of Mephedrone and Factors Influencing Use of a ‘New Legal High.’ *Addiction* 2012;107(4):792–800; doi: 10.1111/j.1360-0443.2011.03719.x.
9. Freeman D, Pugh K, Green C, et al. A Measure of State Persecutory Ideation for Experimental Studies. *J Nerv Ment Dis* 2007;195(9):781–784; doi: 10.1097/NMD.0b013e318145a0a9.
10. Huestis MA. Pharmacokinetics and Metabolism of the Plant Cannabinoids,  $\Delta^9$ -Tetrahydrocannabinol, Cannabidiol and Cannabinol. In: *Handbook of Experimental Pharmacology*. (Pertwee RG. ed) Springer Nature: Berlin; 2005; pp. 657–690; doi: 10.1007/3-540-26573-2-23.
11. Hartman RL, Brown TL, Milavetz G, et al. Controlled Cannabis Vaporizer Administration: Blood and Plasma Cannabinoids with and without Alcohol. *Clin Chem* 2015;61(6):850–869; doi: 10.1373/clinchem.2015.238287.