Supplementary Material

**Supplementary Table 1: Comparison of baseline characteristics in previously published Cannabidiol open-label and randomized controlled trials.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***Drug-resistant epilepsy*** | ***Dravet syndrome*** | ***Lennox-Gastaut syndrome*** |
|  | ***Devinsky******2016***(1) | ***Szaflarski******2018***(2) | ***Laux******2019***(3) | ***Our study*** | ***Devinsky******2017***(4) | ***Devinsky******2018***(5) | ***Devinsky******2019***(6) | ***Miller******2020***(7) | ***Our study*** | ***Devinsky******2018***(8) | ***Thiele******2018***(9) | ***Thiele******2019***(10) | ***Our study*** |
| Number of patients(Safety/efficacy) | 162 / 137 | 607/580 | 152/147 | 125 | 61 | ***34*** | 264 | 133 | 48 | 73, 76 | 86 | 366 | 62 |
| Age (years) | 10.5 (0.9-26.2) | 13.2 (0.4‐62.1) | 12 (1.7-51) | 9 [6-14] | 9.1 [2.5–18.0] | 7.6±1.8 | 9.3 (2.5-19.3) | 9.2 (2.3-17.7)9.3 (2.2-18.9) | 7 [5-10.3] | 15.4 ± 9.516 ± 10.8 | 14.2 (2.7–39.0) | 13.7 (3.0‐48.3) | 13 [8.25-15.8] |
| Gender (male) | 80 (49%) | 313 (52%) | 93 (61%) | 59 (47.2%) | 35 (57%) | *16 (47%)* | 133 (50%) | 27 (41%)36 (54%) | 18 (37.5%) | 40 (55%),45 (59%) | 45 (52%) | 198 (54%) | 35 (56.4%) |
| **Dravet** | 33 (20%) | 58 (10%) | 58 (39%) | 48 (38.4%) | 61 (100%) | 34 (100%) | 264 (100%) | 66 (100%)67 (100%) | 48 (100%) | - | - | - | - |
| **Lennox-Gastaut** | 31 (19%) | 94 (15%) | 94 (61%) | 62 (49.6%) | - | - | - | - | - | 149 (100%) | 86 (100%) | 366 (100%) | 62 (100%) |
| Number of AEDs | 3 (0-7) | 3 (0‐10) | 3 (0-10) | 3 [3-4] | 3.0±1.0 | 2.6 ± 0.9 | 3 (1-6) | 3 (1-5)3 (1-4) | 3 [3-4] | 3 [1–5],3 [0–5] | 3 [1–5] | 3 (0-9) | 3 [3-4] |
| CLB | 85 (52%) | 319 (53%) | 99 (65.1%) | 76 (60.8%) | 40 (66%) | 23 (68%) | 180 (68%) | 46 (68%)40 (60%) | 37 (77.1%) | 37 (51%),36 (47%) | 41 (48%) | 188 (51%) | 33 (53.2%) |
| VPA | 48 (30%) | 183 (30%) | 64 (42.1%) | 81 (64.8%) | 37 (61%) | 22 (65%) | 168 (64%) | 44 (67%)47 (70%) | 81 (64.8%) | 27 (37%),28 (37%) | 36 (42%) | 136 (37%) | 40 (64.5%) |
| STP | - | 16 (3%) | - | 38 (30.4%) | 30 (49%) | 7 (21%) | 101 (38%) | 25 (38%)22 (33%) | 38 (79.2%) | - | - | - | 0 (0%) |
| VNS | 17 (10%) | 18 (3%) | - | 16 (13%) | 6 (10%) | 2 (6%) | - | - | 0 (0%) | 15 (21%),17 (22%) | 26 (30%) | - | 14 (23%) |
| KD | 13 (8%) | 18 (3%) | - | 5 (4%) | 6 (10%) | 6 (18%) | - | - | 2 (4.1%) | 6 (8%),6 (8%) | 4 (5%) | - | 1 (2%) |
| Monthly frequency of TOTAL seizures | 60.5[19.6-151] | 72\*[22-196] | 63 [23-140] | 30.5[5-122] | 24.0 | - | 32.4 | 35 (10-104)26 (10-194) | 5.5[3.9-13.5] | 165.0 [81.3-359],174.3 [82.7-392.4] | 144.6[72.0-385.7] | 167.6 | 91.5[38.3-236.4] |

Data are n (%), mean ± standard deviation, median (range) or median [25th-75th percentile] and based on analysis group.

\*Based on efficacy group.

**Supplementary Table 2. Comparison of Cannabidiol safety in previously published open-label and randomized controlled trials.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***Drug-resistant epilepsy*** | ***Dravet syndrome*** | ***Lennox-Gastaut syndrome*** |
|  | ***Devinsky******2016***(1) | ***Szaflarski******2018***(2) | ***Laux******2019***(3) | ***Our study*** | ***Devinsky******2017***(4) | ***Devinsky******2018***(5) | ***Devinsky******2019***(6) | ***Miller******2020***(7) | ***Our study*** | ***Devinsky******2018***(8) | ***Thiele******2018***(9) | ***Thiele******2019***(10) | ***Our study*** |
| Study | OL | EAP | EAP | OL | RCT | RCT | OLE | RCT | OL | RCT | RCT | OLE | OL |
| Period | *01/2014 - 01/2015* | *01/2014 - 12/2016* | *01/2014-12/2016* | *03/2019-09/2019* | *-* | *10/2014-03/2015* | *11/2016* | *04/2015-11/2017* | *03/2019-09/2019* | *06/2015 - 12/2015* | *04/2015 - 10/2015* | *11/2016* | *03/2019-09/2019* |
| Number of patients | 162 | 607 | 152 | 125 | 61 | 10, 8, 9 | 264 | 66, 67 | 48 | 67, 82 | 86 | 366 | 62 |
| Age of patients | 1-30 y | - | 1.7-51 | 2-20 y | 2-18 y | 4-10 y | 2-18 y | 2-18 y | 2-17 y | 2-55 y | 2-55 y | 2-55 y | 2-20 y |
| CBD titration | 2-5 mg/kg/w | 2-10 mg/kg/d | 2-10 mg/kg/d | 2.5 mg/kg/w | 10 mg/kg/w | - | 10 mg/kg/w | 1.1 mg/kg/d1.6 mg/kg/d | 2.5 mg/kg/w | 2.5-5 mg/kg/d | 10 mg/kg/w | 10 mg/kg/w | 2.5 mg/kg/w |
| CBD max dose (mg/kg/d) | 25-50 | 25-50 | 25-50 | 25 | 20 | 20 | 20-30 | 10, 20 | 20 | 10, 20 | 20 | 20-30 | 20 |
| CBD mean/median (mg/kg/d) | 22.9 ± 9.1 | 25 | 25 | 13.5 ± 4.2 | 20 | 5, 10, 20 | 21.2 ± 5.2 | 10, 20 | 14 ± 3.6 | 10, 20 | 20 | 22.8 ± 5 | 13.1 ± 4.5 |
| Study lenght | 12 w | 48 w [23-95] | 80.1 [20.7-107.7] | 27 w | 14 w | 3 w | 274 d (1-512) | 14 w | 27 w | 14 w | 14 w | 38 w (3-430 d) | 27 w |
| **Withdrawal** | 11 (6.8%) | 146 (24%) | 42 (27.6%) | 26 (20.8%) | 9 (14.7%) | 0, 1, 1 (7.4%) | 75 (28.4%) | 9 (6.7%) | 11 (23 %) | 2, 9 (7.4%) | 14 (16.3%) | 67 (18.3%) | 10 (16.1%) |
| AE | 5 (3%) | 31 (5.1%) | 5 (3.3%) | 2 (1.6%) | 8 (13.1%) | 2 (7.4%) | 19 (7.2%) | 5 (3.7%) | 1 ( 2%) | 1, 6 (4.7%) | 12 (14%) | 35 (9.6%) | 0 (0%) |
| Hepatoxicity | 1 (<1%) | - | ? | 0 (0%) | - | - | - |  | 0 (0%) | - | 2 (2.3%) | - | 0 (0%) |
| AST, AST | - | - | ? | 0 (0%) | 3 (4.9%) | 1 (3.7%) | 10 (3.8%) |  | 0 (0%) | 1, 4 (3.3%) | 6 (7%) | 5 (1.4%) | 0 (0%) |
| **AE, n (%)** | 128 (79%) | 536 (88.3%) | 138 (91.8%) | 61 (48.8%) | 57 (93.4%) | 8, 5, 7 (74%) | 246 (93.2%) |  | 30 (62.5 %) | 56, 77 (89.3%) | 74 (86%) | 337 (92.1%) | 26 (41.9%) |
| Somnolence | 41 (25%) | 136 (22.4%) | 45 (30%) | 26 (20.8%) | 22 (36%) | 2, 3, 0 (18.5%) | 65 (24.6%) | 16 (25%)16 (23%) | 11 (23%) | 14, 25 (26.2%) | 13 (15%) | 86 (23.5%) | 13 (21%) |
| Decr. appetit | 31 (19%) | 75 (12.4%) | 24 (16%) | 12 (9.6%) | 17 (28%) | 0, 1, 4 (18.5%) | 67 (25.4%) | 11 (17%)20 (29%) | 8 (16.7%) | 11, 21 (21.5%) | 11 (13%) | 65 (17.8%) | 3 (4.8%) |
| Diarrhea | 31 (19%) | 177 (29.2%) | 36 (24%) | 6 (4.8%) | 19 (31%) | - | 91 (34.5%) | 11 (17%)18 (26%) | 5 (10.4%) | 7, 12 (12.7%) | 16 (19%) | 98 (26.8%) | 1 (1.6%) |
| Fatigue | 21 (13%) | 65 (10.7%) | 24 (16%) | 20 (16%) | 12 (20%) | 0, 0, 1 (3.7%) | 27 (10.2%) | 5 (8%)15 (22%) | 9 (18.8%) | - | 9 (10.5%) | - | 8 (12.9%) |
| Behaviour disorder | 6 (3.7%) | - | - | 16 (12.8%) | - | 3, 0, 0 (11.1%) | - | 3 (3.8%)5 (11.9%) | 6 (12.5%) | - | 3 (3.5%) | - | 9 (14.5%) |
| Vomiting | 6 (3.7%) | 69 (11.4%) | 20 (13%) | 0 (0%) | 9 (15%) | 1, 1, 1 (11.1%) | 37 (14%) | 4 (6%)11 (16%) | 0 (0%) | 4, 10 (9.4%) | 9 (10.5%) | 65 (17.8%) | 0 (0%) |
| Convulsion | 18 (11%) | 102 (17%) | 36 (24%) | 1 (0.8%) | 7 (11%) | 0, 1 (3.7%), 0 | 40 (15.2%) | 5 (8%)7 (10%) | 1 (2%) | - | 5 (5.8%) | 78 (21.3%) | 0 (0%) |
| Liver function tests | 11 (7%) | 61 (10%) | 22 (15%) | 11 (9.6%) | 12 (19.7%) | 1, 1, 4 (22.2%) | 22/128 (17.2%) | 3 (5%)9 (13 %) | 7 (14.6%) | 3, 11 (9.4%) | 20 (23.2%) | 37 (10%) | 4 (6.5%) |

Data are n (%), mean ± standard deviation or median (range), [25th-75th percentile].

Legend: CBD Cannabidiol, OL Open label, EAP Expanded Access Program, RCT Randomized controlled trial, OLE Open label extension, w week, d day, y years, CBD max maximum dose, AE adverse events, Decr. appetit decreased appetit.

**Supplementary Table 3. Comparison of Cannabidiol efficacy in previously published open-label and randomized controlled trials.**

One study was excluded because it lacks efficacy data4.

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***Drug-resistant epilepsy*** | ***Dravet syndrome*** | ***Lennox-Gastaut syndrome*** |
|  | ***Devinsky******2016***(1) | ***Szaflarski******2018***(2) | ***Laux******2019***(3) | ***Our study*** | ***Devinsky******2017***(4) | ***Devinsky******2019***(6) | ***Miller******2020***(7) | ***Our study*** | ***Devinsky******2018***(8) | ***Thiele******2018***(9) | ***Thiele******2019***(10) | ***Our study*** |
| Number of patients | 137 | 580 | 147 | 125 | 61 | 104 | 6767 | 48 | 7376 | 86 | 366 | 62 |
| CBD dosemean/median | 22.7 mg/kg/d(± 8.5) | 25 mg/kg/d | 25 mg/kg/d | 13.5 ± 4.2 mg/kg/d | 20 mg/kg/d | 21 mg/kg/d | 10 mg/kg/d,20 mg/kg/d | 14 ± 3.6 mg/kg/d | 10 mg/kg/d,20 mg/kg/d | 20 mg/kg/d | 22.8 mg/kg/d(± 8.5) | 13.1 ± 4.5 mg/kg/d |
| CONVULSIVEseizures | - | -51% (at 12 w) | - |  | -38.9 %[-69.5 to -4.8] | -44% (37-48w)[-83 to -5] | -48.7% (14w)-45.7% (14w) |  | - | - | - |  |
| DROPseizures | - | - | - |  | - | - | - |  | -37.2%,-41.9% | -43.9%[-69.6 to -1.9] | -60% (37-48 w)[-88 to -23] |  |
| TOTAL seizures(monthly frequency) | -34.6%[-66.7 to -9.8] | -48% (at 12 w) | -41 -46%(12w to 96 w) | -41± 37.5% at 27 w | -28.6%[-70 to -4] | -39.5% (37-48w)[-86 to +7] | - 56.4% (14 w)- 47.3% (14 w) | -43.9 ± 37.2%. at 27 w | -36.4%,-38.4% | -41.2%[-62.9 to -13] | -57% (37-48 w)[-82 to -22] | -42.1± 38.7% at 27 w |
| TOTAL seizures(≥50% reduction) | 51 (37%) | 211/431 (49%)(at 12 w) | Between 43 and 50% | 28 (37.8%) at 27 w | - | 42 (40%)(37-48w) | 29 (43.9%)33 (49.3%) | 8 (34.8%) at 27 w | - | - | 123/209 (59%)(37-48 w) | 18 (43.9%) at 27 w |

Data are n (%), mean ± standard deviation or median [25th to 75th percentile].

Legend: CBD Cannabidiol, CGI-I Clinical Global Impression-Improvement.

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