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### Use of cannabinoids in the treatment of epilepsy

#### Abstract

The present invention relates to the use of cannabidiol (CBD) in the treatment of patients with childhood-onset epilepsy who are concurrently taking immunosuppressant drugs. In particular the immunosuppressant drug is a calcineurin inhibitor. More particularly the immunosuppressant drug is tacrolimus. Where the CBD is used in combination with an immunosuppressant drug, caution should be taken. For example, the dose of either the CBD and/or the immunosuppressant drug may be required to be reduced. Moreover, the patient may need to be monitored for side effects of said drug-drug interaction. Preferably the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w) and the propyl analogue of CBD, cannabidivarin, (CBDV) is present in amounts of up to 1%. Alternatively, the CBD may be a synthetically produced CBD.

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#### References Cited

##### U.S. PATENT DOCUMENTS

| Patent No. | Issued Date | Patentee Name  | U.S. Cl. | CPC |
|------------|-------------|----------------|----------|-----|
| 2304669    | 12/1941     | Adams          | N/A      | N/A |
| 6383513    | 12/2001     | Watts et al.   | N/A      | N/A |
| 6403126    | 12/2001     | Webster        | N/A      | N/A |
| 6949582    | 12/2004     | Wallace        | N/A      | N/A |
| 7025992    | 12/2005     | Whittle et al. | N/A      | N/A |

|          |         |                     |     |     |
|----------|---------|---------------------|-----|-----|
| 8222292  | 12/2011 | Goskonda et al.     | N/A | N/A |
| 8293786  | 12/2011 | Stinchcomb          | N/A | N/A |
| 8603515  | 12/2012 | Whittle             | N/A | N/A |
| 8632825  | 12/2013 | Velasco Diez et al. | N/A | N/A |
| 8673368  | 12/2013 | Guy et al.          | N/A | N/A |
| 8790719  | 12/2013 | Parolaro et al.     | N/A | N/A |
| 9017737  | 12/2014 | Kikuchi et al.      | N/A | N/A |
| 9023322  | 12/2014 | Van Damme et al.    | N/A | N/A |
| 9066920  | 12/2014 | Whalley et al.      | N/A | N/A |
| 9095554  | 12/2014 | Lewis et al.        | N/A | N/A |
| 9095555  | 12/2014 | Winnicki            | N/A | N/A |
| 9125859  | 12/2014 | Whalley et al.      | N/A | N/A |
| 9168278  | 12/2014 | Guy et al.          | N/A | N/A |
| 9259449  | 12/2015 | Raderman            | N/A | N/A |
| 9474726  | 12/2015 | Guy et al.          | N/A | N/A |
| 9477019  | 12/2015 | Li et al.           | N/A | N/A |
| 9492438  | 12/2015 | Pollard             | N/A | N/A |
| 9522123  | 12/2015 | Whalley et al.      | N/A | N/A |
| 9630941  | 12/2016 | Elsohly et al.      | N/A | N/A |
| 9675654  | 12/2016 | Parolaro et al.     | N/A | N/A |
| 9680796  | 12/2016 | Miller et al.       | N/A | N/A |
| 9730911  | 12/2016 | Verzura et al.      | N/A | N/A |
| 9949936  | 12/2017 | Guy et al.          | N/A | N/A |
| 9949937  | 12/2017 | Guy et al.          | N/A | N/A |
| 9956183  | 12/2017 | Guy et al.          | N/A | N/A |
| 9956184  | 12/2017 | Guy et al.          | N/A | N/A |
| 9956185  | 12/2017 | Guy et al.          | N/A | N/A |
| 9956186  | 12/2017 | Guy et al.          | N/A | N/A |
| 9962341  | 12/2017 | Stott et al.        | N/A | N/A |
| 10039724 | 12/2017 | Stott et al.        | N/A | N/A |
| 10092525 | 12/2017 | Guy et al.          | N/A | N/A |
| 10098867 | 12/2017 | Javid et al.        | N/A | N/A |
| 10111840 | 12/2017 | Guy et al.          | N/A | N/A |
| 10137095 | 12/2017 | Guy et al.          | N/A | N/A |
| 10220005 | 12/2018 | Martinez-Orgado     | N/A | N/A |
| 10226433 | 12/2018 | DiMarzo et al.      | N/A | N/A |
| 10583096 | 12/2019 | Guy et al.          | N/A | N/A |
| 10603288 | 12/2019 | Guy et al.          | N/A | N/A |
| 10653641 | 12/2019 | Robson et al.       | N/A | N/A |
| 10709671 | 12/2019 | Guy et al.          | N/A | N/A |
| 10709673 | 12/2019 | Guy et al.          | N/A | N/A |
| 10709674 | 12/2019 | Guy et al.          | N/A | N/A |
| 10729665 | 12/2019 | Whalley et al.      | N/A | N/A |
| 10758514 | 12/2019 | Liu et al.          | N/A | N/A |
| 10765643 | 12/2019 | Guy et al.          | N/A | N/A |
| 10799467 | 12/2019 | Whalley et al.      | N/A | N/A |
| 10807777 | 12/2019 | Whittle             | N/A | N/A |
| 10849860 | 12/2019 | Guy et al.          | N/A | N/A |
| 10918608 | 12/2020 | Guy et al.          | N/A | N/A |
| 10925525 | 12/2020 | Nakaji              | N/A | N/A |
| 10966939 | 12/2020 | Guy et al.          | N/A | N/A |
| 11000486 | 12/2020 | Liu et al.          | N/A | N/A |
| 11065209 | 12/2020 | Guy et al.          | N/A | N/A |
| 11065227 | 12/2020 | Stott et al.        | N/A | N/A |
| 11096905 | 12/2020 | Guy et al.          | N/A | N/A |
| 11147776 | 12/2020 | Stott et al.        | N/A | N/A |
| 11147783 | 12/2020 | Stott et al.        | N/A | N/A |
| 11154516 | 12/2020 | Guy et al.          | N/A | N/A |
| 11154517 | 12/2020 | Guy et al.          | N/A | N/A |
| 11160757 | 12/2020 | Wilkhu et al.       | N/A | N/A |
| 11160795 | 12/2020 | Guy et al.          | N/A | N/A |
| 11207292 | 12/2020 | Guy et al.          | N/A | N/A |
| 11224600 | 12/2021 | Vangara et al.      | N/A | N/A |
| 11229612 | 12/2021 | Wright et al.       | N/A | N/A |
| 11291631 | 12/2021 | Shah                | N/A | N/A |
| 11311498 | 12/2021 | Guy et al.          | N/A | N/A |
| 11318109 | 12/2021 | Whalley et al.      | N/A | N/A |
| 11331279 | 12/2021 | Vangara et al.      | N/A | N/A |
| 11357741 | 12/2021 | Guy et al.          | N/A | N/A |
| 11400055 | 12/2021 | Guy et al.          | N/A | N/A |
| 11406623 | 12/2021 | Guy et al.          | N/A | N/A |
| 11413266 | 12/2021 | Biro et al.         | N/A | N/A |
| 11419829 | 12/2021 | Whalley et al.      | N/A | N/A |
| 11426362 | 12/2021 | Wright et al.       | N/A | N/A |
| 11446258 | 12/2021 | Guy et al.          | N/A | N/A |

|              |         |                   |        |            |
|--------------|---------|-------------------|--------|------------|
| 11590087     | 12/2022 | Guy et al.        | N/A    | N/A        |
| 11633369     | 12/2022 | Guy et al.        | N/A    | N/A        |
| 11679087     | 12/2022 | Guy et al.        | N/A    | N/A        |
| 11684598     | 12/2022 | Stott et al.      | N/A    | N/A        |
| 11701330     | 12/2022 | Guy et al.        | N/A    | N/A        |
| 11709671     | 12/2022 | Joubert et al.    | N/A    | N/A        |
| 11766411     | 12/2022 | Guy et al.        | N/A    | N/A        |
| 11793770     | 12/2022 | Stott et al.      | N/A    | N/A        |
| 11806319     | 12/2022 | Wilkhut et al.    | N/A    | N/A        |
| 11865102     | 12/2023 | Guy et al.        | N/A    | N/A        |
| 11963937     | 12/2023 | Guy et al.        | N/A    | N/A        |
| 12023305     | 12/2023 | Whalley et al.    | N/A    | N/A        |
| 12064399     | 12/2023 | Guy et al.        | N/A    | N/A        |
| 2004/0034108 | 12/2003 | Whittle           | N/A    | N/A        |
| 2004/0049059 | 12/2003 | Mueller           | N/A    | N/A        |
| 2004/0110828 | 12/2003 | Chowdhury et al.  | N/A    | N/A        |
| 2004/0147767 | 12/2003 | Whittle et al.    | N/A    | N/A        |
| 2005/0042172 | 12/2004 | Whittle           | N/A    | N/A        |
| 2005/0266108 | 12/2004 | Flockhart et al.  | N/A    | N/A        |
| 2006/0039959 | 12/2005 | Wessling          | N/A    | N/A        |
| 2006/0167283 | 12/2005 | Flockhart et al.  | N/A    | N/A        |
| 2007/0060638 | 12/2006 | Olmstead          | N/A    | N/A        |
| 2007/0099987 | 12/2006 | Weiss et al.      | N/A    | N/A        |
| 2007/0238786 | 12/2006 | Hobden et al.     | N/A    | N/A        |
| 2008/0112895 | 12/2007 | Kottayil et al.   | N/A    | N/A        |
| 2008/0119544 | 12/2007 | Guy et al.        | N/A    | N/A        |
| 2008/0188461 | 12/2007 | Guan              | N/A    | N/A        |
| 2009/0036523 | 12/2008 | Stinchcomb et al. | N/A    | N/A        |
| 2009/0264063 | 12/2008 | Tinsley et al.    | N/A    | N/A        |
| 2009/0306221 | 12/2008 | Guy et al.        | N/A    | N/A        |
| 2010/0239693 | 12/2009 | Guy et al.        | N/A    | N/A        |
| 2010/0273895 | 12/2009 | Stinchcomb et al. | N/A    | N/A        |
| 2010/0317729 | 12/2009 | Guy et al.        | N/A    | N/A        |
| 2011/0028431 | 12/2010 | Zerbe et al.      | N/A    | N/A        |
| 2011/0033529 | 12/2010 | Samantaray et al. | N/A    | N/A        |
| 2011/0038958 | 12/2010 | Kikuchi et al.    | N/A    | N/A        |
| 2011/0082195 | 12/2010 | Guy et al.        | N/A    | N/A        |
| 2011/0150825 | 12/2010 | Buggy et al.      | N/A    | N/A        |
| 2012/0004251 | 12/2011 | Whalley et al.    | N/A    | N/A        |
| 2012/0165402 | 12/2011 | Whalley et al.    | N/A    | N/A        |
| 2012/0183606 | 12/2011 | Bender et al.     | N/A    | N/A        |
| 2012/0202891 | 12/2011 | Stinchcomb et al. | N/A    | N/A        |
| 2012/0270845 | 12/2011 | Bannister         | N/A    | N/A        |
| 2013/0143894 | 12/2012 | Bergstrom et al.  | N/A    | N/A        |
| 2013/0209483 | 12/2012 | McAllister        | N/A    | N/A        |
| 2013/0245110 | 12/2012 | Guy et al.        | N/A    | N/A        |
| 2013/0296398 | 12/2012 | Whalley et al.    | N/A    | N/A        |
| 2014/0100269 | 12/2013 | Goskonda et al.   | N/A    | N/A        |
| 2014/0155456 | 12/2013 | Whalley et al.    | N/A    | N/A        |
| 2014/0243405 | 12/2013 | Whalley et al.    | N/A    | N/A        |
| 2014/0335208 | 12/2013 | Cawthorne et al.  | N/A    | N/A        |
| 2014/0343044 | 12/2013 | Ceulemans         | N/A    | N/A        |
| 2015/0111939 | 12/2014 | Gruening et al.   | N/A    | N/A        |
| 2015/0181924 | 12/2014 | Llamas            | N/A    | N/A        |
| 2015/0320698 | 12/2014 | Whalley et al.    | N/A    | N/A        |
| 2015/0335590 | 12/2014 | Whalley et al.    | N/A    | N/A        |
| 2015/0342902 | 12/2014 | Vangara et al.    | N/A    | N/A        |
| 2015/0343071 | 12/2014 | Vangara           | N/A    | N/A        |
| 2015/0359755 | 12/2014 | Guy               | 514/94 | A61K 31/35 |
| 2015/0359756 | 12/2014 | Guy et al.        | N/A    | N/A        |
| 2016/0010126 | 12/2015 | Poulos et al.     | N/A    | N/A        |
| 2016/0166498 | 12/2015 | Anastassov        | N/A    | N/A        |
| 2016/0166514 | 12/2015 | Guy et al.        | N/A    | N/A        |
| 2016/0166515 | 12/2015 | Guy et al.        | N/A    | N/A        |
| 2016/0220529 | 12/2015 | Guy et al.        | N/A    | N/A        |
| 2016/0256411 | 12/2015 | Aung-Din          | N/A    | N/A        |
| 2016/0317468 | 12/2015 | Sankar et al.     | N/A    | N/A        |
| 2016/0338974 | 12/2015 | Aung-Din          | N/A    | N/A        |
| 2017/0007551 | 12/2016 | Guy et al.        | N/A    | N/A        |
| 2017/0008868 | 12/2016 | Dialer et al.     | N/A    | N/A        |
| 2017/0172939 | 12/2016 | Guy et al.        | N/A    | N/A        |
| 2017/0172940 | 12/2016 | Guy et al.        | N/A    | N/A        |
| 2017/0172941 | 12/2016 | Guy et al.        | N/A    | N/A        |
| 2017/0173043 | 12/2016 | Guy et al.        | N/A    | N/A        |
| 2017/0173044 | 12/2016 | Guy et al.        | N/A    | N/A        |

|              |         |                     |     |     |
|--------------|---------|---------------------|-----|-----|
| 2017/0181982 | 12/2016 | Guy et al.          | N/A | N/A |
| 2017/0224634 | 12/2016 | Vangara et al.      | N/A | N/A |
| 2017/0231923 | 12/2016 | Guy et al.          | N/A | N/A |
| 2017/0239193 | 12/2016 | Guy et al.          | N/A | N/A |
| 2017/0246121 | 12/2016 | Guy et al.          | N/A | N/A |
| 2017/0266126 | 12/2016 | Guy et al.          | N/A | N/A |
| 2017/0273913 | 12/2016 | Guy et al.          | N/A | N/A |
| 2018/0028489 | 12/2017 | Vangara et al.      | N/A | N/A |
| 2018/0071210 | 12/2017 | Wilkhu et al.       | N/A | N/A |
| 2018/0228751 | 12/2017 | Stott et al.        | N/A | N/A |
| 2018/0338931 | 12/2017 | Guy et al.          | N/A | N/A |
| 2019/0031601 | 12/2018 | ElSohly et al.      | N/A | N/A |
| 2019/0083418 | 12/2018 | Guy et al.          | N/A | N/A |
| 2019/0091171 | 12/2018 | Guy et al.          | N/A | N/A |
| 2019/0160393 | 12/2018 | Marshall et al.     | N/A | N/A |
| 2019/0167583 | 12/2018 | Shah                | N/A | N/A |
| 2019/0175547 | 12/2018 | Stott et al.        | N/A | N/A |
| 2019/0247324 | 12/2018 | Whalley et al.      | N/A | N/A |
| 2019/0314296 | 12/2018 | Wright et al.       | N/A | N/A |
| 2019/0321307 | 12/2018 | Guy et al.          | N/A | N/A |
| 2019/0365667 | 12/2018 | Wright et al.       | N/A | N/A |
| 2020/0000741 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0069608 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0138738 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0179303 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0206152 | 12/2019 | Stott et al.        | N/A | N/A |
| 2020/0206153 | 12/2019 | Whalley et al.      | N/A | N/A |
| 2020/0237683 | 12/2019 | Whalley et al.      | N/A | N/A |
| 2020/0297656 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0323792 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0352878 | 12/2019 | Guy et al.          | N/A | N/A |
| 2020/0368179 | 12/2019 | Guy et al.          | N/A | N/A |
| 2021/0015789 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0052512 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0059949 | 12/2020 | Wilkhu et al.       | N/A | N/A |
| 2021/0059960 | 12/2020 | Wilkhu et al.       | N/A | N/A |
| 2021/0059976 | 12/2020 | Wilkhu et al.       | N/A | N/A |
| 2021/0069333 | 12/2020 | Velasco Diez et al. | N/A | N/A |
| 2021/0093581 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0100755 | 12/2020 | Whalley et al.      | N/A | N/A |
| 2021/0145765 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0167950 | 12/2020 | Arkko et al.        | N/A | N/A |
| 2021/0169824 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0196651 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0230145 | 12/2020 | Blankman et al.     | N/A | N/A |
| 2021/0244685 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0290565 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0308072 | 12/2020 | Wright et al.       | N/A | N/A |
| 2021/0330636 | 12/2020 | Guy et al.          | N/A | N/A |
| 2021/0401771 | 12/2020 | Guy et al.          | N/A | N/A |
| 2022/0000800 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0008355 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0016048 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0023232 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0040155 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0062197 | 12/2021 | Stott et al.        | N/A | N/A |
| 2022/0062211 | 12/2021 | Stott et al.        | N/A | N/A |
| 2022/0087951 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0096397 | 12/2021 | Wright et al.       | N/A | N/A |
| 2022/0168266 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0183997 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0184000 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0202738 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0211629 | 12/2021 | Wilkhu et al.       | N/A | N/A |
| 2022/0226257 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0233495 | 12/2021 | Silcock et al.      | N/A | N/A |
| 2022/0249396 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0257529 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0265573 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0288055 | 12/2021 | Silcock et al.      | N/A | N/A |
| 2022/0323375 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0362149 | 12/2021 | Shah                | N/A | N/A |
| 2022/0378714 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0378715 | 12/2021 | Guy et al.          | N/A | N/A |
| 2022/0378717 | 12/2021 | Guy et al.          | N/A | N/A |

|              |         |                  |     |     |
|--------------|---------|------------------|-----|-----|
| 2022/0378738 | 12/2021 | Guy et al.       | N/A | N/A |
| 2022/0387347 | 12/2021 | Whalley et al.   | N/A | N/A |
| 2022/0395470 | 12/2021 | Whalley et al.   | N/A | N/A |
| 2022/0395471 | 12/2021 | Guy et al.       | N/A | N/A |
| 2023/0000789 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0022487 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0024312 | 12/2022 | Whalley et al.   | N/A | N/A |
| 2023/0026079 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0032502 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0038423 | 12/2022 | Silcock et al.   | N/A | N/A |
| 2023/0068885 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0143812 | 12/2022 | Knappertz et al. | N/A | N/A |
| 2023/0235825 | 12/2022 | Thompson et al.  | N/A | N/A |
| 2023/0248664 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0263744 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0277560 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0277561 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0277562 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0277563 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285419 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285420 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285421 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285422 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285423 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285424 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285425 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285426 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285427 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0285428 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0301934 | 12/2022 | Whalley et al.   | N/A | N/A |
| 2023/0301936 | 12/2022 | Guy et al.       | N/A | N/A |
| 2023/0310464 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0346809 | 12/2022 | Craig et al.     | N/A | N/A |
| 2023/0372367 | 12/2022 | Checketts et al. | N/A | N/A |
| 2023/0372368 | 12/2022 | Checketts et al. | N/A | N/A |
| 2024/0016819 | 12/2023 | Craig et al.     | N/A | N/A |
| 2024/0025858 | 12/2023 | Silcock et al.   | N/A | N/A |
| 2024/0033229 | 12/2023 | Guy et al.       | N/A | N/A |
| 2024/0043388 | 12/2023 | Silcock et al.   | N/A | N/A |
| 2024/0050452 | 12/2023 | Craig et al.     | N/A | N/A |
| 2024/0091241 | 12/2023 | Guy et al.       | N/A | N/A |
| 2024/0130981 | 12/2023 | Wilkhu et al.    | N/A | N/A |
| 2024/0131041 | 12/2023 | Tse et al.       | N/A | N/A |
| 2024/0165048 | 12/2023 | Guy et al.       | N/A | N/A |
| 2024/0207220 | 12/2023 | Guy et al.       | N/A | N/A |
| 2024/0215910 | 12/2023 | Tse et al.       | N/A | N/A |
| 2024/0226032 | 12/2023 | Wilkhu et al.    | N/A | N/A |
| 2024/0226123 | 12/2023 | Tse et al.       | N/A | N/A |
| 2024/0238218 | 12/2023 | Silcock et al.   | N/A | N/A |
| 2024/0254066 | 12/2023 | Silcock et al.   | N/A | N/A |
| 2024/0254072 | 12/2023 | Silcock et al.   | N/A | N/A |
| 2024/0261234 | 12/2023 | Guy et al.       | N/A | N/A |
| 2024/0293762 | 12/2023 | Loft et al.      | N/A | N/A |

# FOREIGN PATENT DOCUMENTS

| Patent No.      | Application Date | Country | CPC |
|-----------------|------------------|---------|-----|
| 2 737 447       | 12/2011          | CA      | N/A |
| 2 859 934       | 12/2015          | CA      | N/A |
| 101040855       | 12/2006          | CN      | N/A |
| 103110582       | 12/2012          | CN      | N/A |
| 104490873       | 12/2014          | CN      | N/A |
| 108 236 608     | 12/2017          | CN      | N/A |
| 110 215 443     | 12/2018          | CN      | N/A |
| 110 279 617     | 12/2018          | CN      | N/A |
| 10 2012 105 063 | 12/2012          | DE      | N/A |
| 2 311 475       | 12/2010          | EP      | N/A |
| 2 448 637       | 12/2011          | EP      | N/A |
| 2 578 561       | 12/2012          | EP      | N/A |
| 3 157 512       | 12/2017          | EP      | N/A |
| 2002754         | 12/1978          | GB      | N/A |
| 2 377 633       | 12/2002          | GB      | N/A |
| 2 380 129       | 12/2002          | GB      | N/A |
| 2 381 194       | 12/2002          | GB      | N/A |
| 2384707         | 12/2002          | GB      | N/A |
| 2434097         | 12/2006          | GB      | N/A |

|                |         |    |     |
|----------------|---------|----|-----|
| 2434312        | 12/2006 | GB | N/A |
| 2450753        | 12/2008 | GB | N/A |
| 2456183        | 12/2008 | GB | N/A |
| 2471523        | 12/2010 | GB | N/A |
| 2478595        | 12/2010 | GB | N/A |
| 2479153        | 12/2010 | GB | N/A |
| 2485291        | 12/2011 | GB | N/A |
| 2471565        | 12/2011 | GB | N/A |
| 2478072        | 12/2011 | GB | N/A |
| 2478074        | 12/2011 | GB | N/A |
| 2492487        | 12/2012 | GB | N/A |
| 2487712        | 12/2014 | GB | N/A |
| 2 530 001      | 12/2015 | GB | N/A |
| 2531093        | 12/2015 | GB | N/A |
| 2531278        | 12/2015 | GB | N/A |
| 2531281        | 12/2015 | GB | N/A |
| 2531282        | 12/2015 | GB | N/A |
| 2539472        | 12/2015 | GB | N/A |
| 2 542 155      | 12/2016 | GB | N/A |
| 2438682        | 12/2016 | GB | N/A |
| 2551987        | 12/2017 | GB | N/A |
| 2584140        | 12/2019 | GB | N/A |
| WO 01/95899    | 12/2000 | WO | N/A |
| WO 2002/064109 | 12/2001 | WO | N/A |
| WO 02/089945   | 12/2001 | WO | N/A |
| WO 2003/099302 | 12/2002 | WO | N/A |
| WO 2004/016246 | 12/2003 | WO | N/A |
| WO 2004/016277 | 12/2003 | WO | N/A |
| WO 2004/026802 | 12/2003 | WO | N/A |
| WO 2005/120478 | 12/2004 | WO | N/A |
| WO 2006/054057 | 12/2005 | WO | N/A |
| WO 2006/017892 | 12/2005 | WO | N/A |
| WO 2006/133941 | 12/2005 | WO | N/A |
| WO 2007/032962 | 12/2006 | WO | N/A |
| WO 2007/052013 | 12/2006 | WO | N/A |
| WO 2007/083098 | 12/2006 | WO | N/A |
| WO 2007/138322 | 12/2006 | WO | N/A |
| WO 2008/019146 | 12/2007 | WO | N/A |
| WO 2008/021394 | 12/2007 | WO | N/A |
| WO 2008/094181 | 12/2007 | WO | N/A |
| WO 2008/129258 | 12/2007 | WO | N/A |
| WO 2008/144475 | 12/2007 | WO | N/A |
| WO 2008/146006 | 12/2007 | WO | N/A |
| WO 2009/007697 | 12/2008 | WO | N/A |
| WO 2009/007698 | 12/2008 | WO | N/A |
| WO 2009/020666 | 12/2008 | WO | N/A |
| WO 2009/093018 | 12/2008 | WO | N/A |
| WO 2011/001169 | 12/2010 | WO | N/A |
| WO 2011/121351 | 12/2010 | WO | N/A |
| WO 2012/033478 | 12/2011 | WO | N/A |
| WO 2012/093255 | 12/2011 | WO | N/A |
| WO 2012/160358 | 12/2011 | WO | N/A |
| WO 2013/032351 | 12/2012 | WO | N/A |
| WO 2013/045891 | 12/2012 | WO | N/A |
| WO 2014/168131 | 12/2012 | WO | N/A |
| WO 2014/108899 | 12/2013 | WO | N/A |
| WO 2014/146699 | 12/2013 | WO | N/A |
| WO 2015/065544 | 12/2014 | WO | N/A |
| WO 2015/142501 | 12/2014 | WO | N/A |
| WO 2015/184127 | 12/2014 | WO | N/A |
| WO 2015/193667 | 12/2014 | WO | N/A |
| WO 2015/193668 | 12/2014 | WO | N/A |
| WO 2016/059399 | 12/2015 | WO | N/A |
| WO 2016/059403 | 12/2015 | WO | N/A |
| WO 2016/059405 | 12/2015 | WO | N/A |
| WO 2016/084075 | 12/2015 | WO | N/A |
| WO 2015/187988 | 12/2015 | WO | N/A |
| WO 2016/118391 | 12/2015 | WO | N/A |
| WO 2016/147186 | 12/2015 | WO | N/A |
| WO 2016/022936 | 12/2015 | WO | N/A |
| WO 2016/176279 | 12/2015 | WO | N/A |
| WO 2016/191651 | 12/2015 | WO | N/A |
| WO 2016/199148 | 12/2015 | WO | N/A |
| WO 2016/203239 | 12/2015 | WO | N/A |
| WO 2017/042567 | 12/2016 | WO | N/A |

|                |         |    |     |
|----------------|---------|----|-----|
| WO 2017/139496 | 12/2016 | WO | N/A |
| WO 2017/168138 | 12/2016 | WO | N/A |
| WO 2017/203529 | 12/2016 | WO | N/A |
| WO 2017/204986 | 12/2016 | WO | N/A |
| WO 2018/002636 | 12/2017 | WO | N/A |
| WO 2018/002637 | 12/2017 | WO | N/A |
| WO 2018/002665 | 12/2017 | WO | N/A |
| WO 2018/011808 | 12/2017 | WO | N/A |
| WO 2018/037203 | 12/2017 | WO | N/A |
| WO 2018/115962 | 12/2017 | WO | N/A |
| WO 2018/200024 | 12/2017 | WO | N/A |
| WO 2018/234811 | 12/2017 | WO | N/A |
| WO 2019/020738 | 12/2018 | WO | N/A |
| WO 2019/097238 | 12/2018 | WO | N/A |
| WO 2019/145700 | 12/2018 | WO | N/A |
| WO 2019/207319 | 12/2018 | WO | N/A |
| WO 2019/210210 | 12/2018 | WO | N/A |
| WO 2019/211795 | 12/2018 | WO | N/A |
| WO 2020/225540 | 12/2019 | WO | N/A |
| WO 2020/234569 | 12/2019 | WO | N/A |
| WO 2021/019231 | 12/2020 | WO | N/A |

## OTHER PUBLICATIONS

Shih et al. Epilepsy & Behavior 2017, 69, 186-222 (Year: 2017). cited by examiner

Hauser et al. Case Reports in Transplantation, vol. 2016, Article ID 4028492, pp. 1-3 (Year: 2016). cited by examiner

Yamaori et al. Life Sciences 2011, 88, 730-736 (Year: 2011). cited by examiner

Iwasaki, K. Drug Metab. Pharmacokinet. 2007, 22, 328-335 (Year: 2007). cited by examiner

Christians et al. Expert Opin. Drug Metab. Toxicol. 2011, 7, 175-200 (Year: 2011). cited by examiner

Liu et al. World J. Gastroenterol 2009, 15, 3931-3936 (Year: 2009). cited by examiner

Racha et al. Drug Metab. Pharmacokin. 2003, 18, 128-138 (Year: 2003). cited by examiner

Galetin et al. Drug Metabolism and Disposition 2003, 31, 1108-111 (Year: 2003). cited by examiner

Tang et al. Scientific Reports, 2017, 7:42192 (Year: 2017). cited by examiner

Ciszek, M. Central European Journal of Urology 2013, 66, 350-351 (Year: 2013). cited by examiner

Gaber et al. Transplantation 2013, 96, 191-197 (Year: 2013). cited by examiner

Leino et al. Am. J. Transplant 2019, 19, 2944-2948 (Year: 2019). cited by examiner

U.S. Appl. No. 14/741,829, filed Jun. 17, 2015. cited by applicant

U.S. Appl. No. 15/519,244, filed Apr. 14, 2017. cited by applicant

U.S. Appl. No. 15/751,563, filed Feb. 9, 2018. cited by applicant

U.S. Appl. No. 16/314,569, filed Dec. 31, 2018. cited by applicant

U.S. Appl. No. 16/314,583, filed Dec. 31, 2018. cited by applicant

U.S. Appl. No. 16/328,209, filed Feb. 25, 2018. cited by applicant

U.S. Appl. No. 16/467,639, filed Jun. 7, 2019. cited by applicant

U.S. Appl. No. 16/486,750, filed Aug. 16, 2019. cited by applicant

U.S. Appl. No. 16/591,702, filed Oct. 3, 2019. cited by applicant

U.S. Appl. No. 16/624,106, filed Dec. 18, 2019. cited by applicant

U.S. Appl. No. 16/651,751, filed Mar. 27, 2020. cited by applicant

U.S. Appl. No. 16/737,707, filed Jan. 8, 2020. cited by applicant

U.S. Appl. No. 16/764,701, filed May 15, 2020. cited by applicant

U.S. Appl. No. 16/791,940, filed Feb. 14, 2020. cited by applicant

U.S. Appl. No. 16/893,018, filed Jun. 4, 2020. cited by applicant

U.S. Appl. No. 16/959,350, filed Jun. 30, 2020. cited by applicant

U.S. Appl. No. 16/959,357, filed Jun. 30, 2020. cited by applicant

U.S. Appl. No. 16/960,665, filed Jul. 8, 2020. cited by applicant

U.S. Appl. No. 16/989,605, filed Aug. 10, 2020. cited by applicant

U.S. Appl. No. 17/011,715, filed Sep. 3, 2020. cited by applicant

U.S. Appl. No. 17/025,130, filed Sep. 18, 2020. cited by applicant

U.S. Appl. No. 17/068,326, filed Oct. 12, 2020. cited by applicant

U.S. Appl. No. 17/119,873, filed Dec. 11, 2020. cited by applicant

U.S. Appl. No. 17/147,005, filed Jan. 12, 2021. cited by applicant

U.S. Appl. No. 17/188,766, filed Mar. 1, 2021. cited by applicant

U.S. Appl. No. 17/198,965, filed Mar. 11, 2021. cited by applicant

U.S. Appl. No. 17/242,075, filed Apr. 27, 2021. cited by applicant

[No Author Listed] Cannabidiol Therapy for Aicardi Syndrome, Aug. 2014, 4 pages. cited by applicant

[No Author Listed], Cannabinoid. Wikipedia. Retrieved on Jul. 9, 2015 from <https://en.wikipedia.org/wiki/Cannabinoid>, 15 pages. cited by applicant

No Author Listed], "Missouri House passes cannabis extract legislation," Kansas City Star, 2014, <https://kansascity.com/news/politics-government/article3467>

[No Author Listed], Cover and Table of Contents, J Pharmacology and Exp Therapeutics, Feb. 2010, 332(2), 4 pages. cited by applicant

AFINITOR® (everolimus) tablets, for oral use, and AFINITOR DISPERZ® (everolimus tablets for oral suspension) Prescribing Information, 2009, 49 pages.

Alger, "Not too excited? Thank your endocannabinoids," Neuron, 51(4):393-595 (2006). cited by applicant

Ames et al., "Anticonvulsant effect of cannabidiol," S Afr Med J., 69(1):14 (1986), 1 page. cited by applicant

American Epilepsy Society, "Three Studies Shed New Light on the Effectiveness of Cannabis in Epilepsy," Oct. 14, 2014, 2 pages. cited by applicant

Arain, "Pregabalin in the management of partial epilepsy," Neuropsychiatr Dis Treat., 5:407-413 (2009); Epub Aug. 20, 2009. cited by applicant

Arslan, A. & Tirnaksiz, F., "Self-emulsifying Drug Delivery Systems," F ABAD J Pharm Sci, 38(1):55-64 (2013). cited by applicant

Arimanoglou et al., "All children who experience epileptic falls do not necessarily have Lennox-Gastaut syndrome . . . but many do," Epileptic Discord, 13:S3

Avoli et al., "Cellular and molecular mechanisms of epilepsy in the human brain," Prog Neurobiol., 77(3):166-200 (2005). cited by applicant

Bakhsh, "Pregabalin in the management of partial epilepsy," Miftaah-al-Khazaain, 1930:607-608, with English translation, 4 pages. cited by applicant

Bancaud et al., "Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures," *Epilepsia*, 22(4):489-501 (1981). cited by applicant

Banerjee et al., "Case Report: Aicardi syndrome: A report of five Indian cases," *Neurology India*, 54(1):91-93 (2006). cited by applicant

Barker-Haliski et al., "How Clinical Development Can, and Should Inform Translational Science," *Neuron*, 84:582-593 (2014). cited by applicant

Benowitz et al., "Metabolic and Psychophysiologic studies of cannabidiol hexobarbital interaction," *Clin Pharmacol Ther.*, 28(1):115-120 (1980). cited by applicant

Bertram, "The Relevance of Kindling for Human Epilepsy," *Epilepsia*, 48(Suppl. 2):65-74 (2007). cited by applicant

Bhatt, V. P. & Vashishtha, D. P., "Indigenous plants in traditional healthcare system in Kedarnath valley of western Himalaya," *Indian J Tradit Knowl.*, 7(2):30 (2007). cited by applicant

Bhattacharyya et al., "Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis on Human Psychiatric Function," *Journal of Clinical Psychopharmacology*, 33(4):442-451 (2009); doi:10.1001/archgenpsychiatry.2009.17. cited by applicant

Bipolar Health Group (Charlotte's Web Hemp Remedy, available online at <http://bipolarhealthgroup.org/index.php/charlottes-web-hemp-remedy/>, accessed Sep. 11, 2014). cited by applicant

Booth, "Legalization's opening of medical pot research is dream and nightmare," *Denver Post*, Dec. 14, 2013, 6 pages. cited by applicant

Bostanci, M. O. & Bagirici, F., "The effects of octanol on penicillin induced epileptiform activity in rats: an in vivo study," *Epilepsy Research*, 71:188-194 (2003). cited by applicant

Braida, et al., "Post-ischemic treatment with cannabidiol prevents electroencephalographic flattening, hyperlocomotion and neuronal injury in gerbils," *Neuroscience Letters*, 420:101-104 (2007). cited by applicant

Brown et al., Child Neurology Foundation, "LGS" (Lennox-Gastaut Syndrome), available at <http://www.childneurologyfoundation.org/disorders/lgs-lennox-gastaut-syndrome/>, accessed Sep. 11, 2014. cited by applicant

Brust, J. C. M. et al., "Marijuana use and the risk of new onset seizures," *Trans Am Clin Climatol Assoc.*, 103:176-181 (1992). cited by applicant

Carlini et al., "Hypnotic and antiepileptic effects of cannabidiol," *J Clin Pharmacol.*, 21:417S-427S (1981). cited by applicant

Charlotte's Web [online], "When to expect Results from CW Hemp Oil," Mar. 13, 2017, retrieved on May 21, 2018, URL <https://www.cwhemp.com/blog/expecting-results-from-cw-hemp-oil/>, accessed Sep. 11, 2014. cited by applicant

Charlotte's Web [online], "Whole-Plant Phyto-Cannabinoids Outperform Single Molecular Compounds," Charlotte's Web Stanley Brothers, URL <https://www.stanleystanley.com/whole-plant-phyto-cannabinoids-outperform-single-molecular-compounds/>, accessed Sep. 11, 2014. cited by applicant

cannabinoids, Dec. 18, 2019, 3 pages. cited by applicant

Castel-Branco et al., "The Maximal Electroshock Seizure (MES) Model in the Preclinical 98. Assessment of Potential New Anti epileptic Drugs," *Methods Find Exp Clin Pharmacol*, 20(1):1-10 (1998). cited by applicant

ChildNeurologyFoundation.org [online], "Disorder Directory: Learn from the Experts—LGS (Lennox-Gastaut Syndrome)," Child Neurology Foundation, available at <http://www.childneurologyfoundation.org/disorders/lgs-Lennox-gastaut-syndrome/>, accessed Sep. 11, 2014. cited by applicant

URL <http://www.childneurologyfoundation.org/disorders/lgs-Lennox-gastaut-syndrome/>, 10 pages. cited by applicant

2 to 20 years: Girls Stature-for-age and Weight-for-age percentiles; [www.cdc.gov/growthcharts/](http://www.cdc.gov/growthcharts/), May 30, 2000 (accessed Apr. 11, 2019), 2019, 1 page. cited by applicant

Chiron, C. & Dulac, O., "The Pharmacologic Treatment of Dravet Syndrome," *Epilepsia*, 52 (Suppl. 2):72-75 (2011). cited by applicant

Chiu, P. et al., "The Influence of Cannabidiol and A-Tetrahydrocannabinol on Cobalt Epilepsy in Rats," *Epilepsia*, 20:365-375 (1979). cited by applicant

Chou, "Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies," *Pharmacol Rev.*, 58(3):245-295 (2006). cited by applicant

Clinical trials.gov [online], Identifier: NCT02544750, "An open-label Extension Trial of Cannabidiol (GWP42003-P, CBD) for Seizures in Tuberous Sclerosis Complex," U.S. National Library of Medicine, Oct. 1, 2018; Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02544750>, 6 pages. cited by applicant

Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, U.S. Department of Health and Human Services, Center for Drug Evaluation and Research (CDER), Jan. 2020, 27 pages. cited by applicant

Conry et al., "Clobazam in the treatment of Lennox-Gastaut syndrome," *Epilepsia*, 50:1158-1166 (2009). cited by applicant

Consroe et al., "Anticonvulsant nature of marihuana smoking," *JAMA*, 234(3):306-307 (1975). cited by applicant

Consroe et al., "Anticonvulsant drug antagonism of delta9tetrahydrocannabinol-induced seizures in rabbits," *Res Commun Chem Pathol Pharmacol.*, 16(1):1-10 (1977). cited by applicant

Consroe et al., "Anticonvulsant interaction of cannabidiol and ethosuximide in rats," *J Pharm Pharmacol.*, 29(8):500-501 (1977). doi:10.1111/j.2042-7158.1977.tb01111.x. cited by applicant

Consroe, P. & Wolkin, A., "Cannabidiol—antiepileptic drug comparisons and interactions in experimentally induced seizures in rats," *J Pharmacol Exp Ther.*, 237(2):455-461 (1986). cited by applicant

Consroe et al., "Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice," *Eur J Pharmacol.*, 83(3-4):293-298 (1982). cited by applicant

Consroe, P. & Snider, S. R., "Chapter 2. Therapeutic Potential of Cannabinoids in Neurological disorders," *Cannabinoids as Therapeutic Agents*, R. Mechoulam, ed., CRC Press, 1995, 1-10. cited by applicant

Consroe et al. Chapter 12, "Potential Role of Cannabinoids for Therapy of Neurological Disorders," in *Marijuana Cannabinoids: Neurobiology and Neuropharmacology*, R. Mechoulam, ed., CRC Press, 1995, 1-10. cited by applicant

Cortesi et al., "Potential therapeutic effects of cannabidiol in children with pharmacoresistant epilepsy," *Med Hypotheses*, 68(4):920-921 (2007). Epub Nov. 1, 2007. cited by applicant

Cortez & Snead, "Chapter 10: Pharmacologic Models of Generalized Absence Seizures in Rodents," *Models of Seizures and Epilepsy*, 111-126 (2006). cited by applicant

Crespel et al., "Lennox-Gastaut Syndrome," Chapter 14, in *Epileptic Syndromes in Infancy, Childhood, and Adolescence*, 5th Edition, ed. M. Bureau, et al., pp. 111-126 (2006). cited by applicant

Cunha et al., "Chronic administration of cannabidiol to healthy volunteers and epileptic patients." *Pharmacology*, 21(3):175-85 (1980). cited by applicant

Czapinski, et al., "Randomized 36-month comparative study of valproic acid (VPA), phenytoin (PHT), phenobarbital (PB) and carbamazepine (CBZ) efficacy in complex seizures." *J Neurolog Sci.*, 150:S162 (1997). cited by applicant

Dasa et al., "Key Attributes of TKDL: Ganja," *Brhat Nighantu Ratnakara* (Saligramanighantubhusanam), RS/4336, vol. IV. 1997:170, with English translation. cited by applicant

Davis et al., "Antiepileptic action of marijuana-active substances," *Federation Proceedings*, 8:284-285 (1949). cited by applicant

Davis et al., "A predominant role for inhibition of the adenylate cyclase/protein kinase A pathway in ERK activation by cannabinoid receptor 1 in NIE-115 neuroblastoma cells," *J Neurosci.*, 23(10):4000-4008 (2003). Epub Sep. 29, 2003. cited by applicant

De Oliveira, et al., "Anticonvulsant activity of  $\beta$ -caryophyllene against pentylenetetrazol-induced seizures." *Epilepsy Behav.*, 56:26-31 (2016). doi: 10.1016/j.yebeh.2016.05.011. cited by applicant

Devinsky et al., "Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders," *Epilepsia*, 55(6):791-802 (2014). cited by applicant

Dravet, "The core Dravet syndrome phenotype," *Epilepsia*. 52 Suppl 2:3-9. doi: 10.1111/j. 1528-1167.2011.02994.x. (2011). cited by applicant

Dreifus et al., "Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures," *Epilepsie*, 22:489-501 (1981). cited by applicant

Dulac, "Use of Lamotrigine in Lennox-Gastaut and Related Epilepsy Syndromes," *J. Child Neurolog.*, 12(Supplement 1):S23-S29 (1997). cited by applicant

Dulac, "Vigabatrin in Childhood Epilepsy," *J. Child Neurolog.*, 6(Supplement 2), S30-S37 (1991). cited by applicant

Eadie, "Shortcomings in the current treatment of epilepsy," *Expert Rev Neurother.*, 12(12):1419-1427 (2012). cited by applicant

Ebrahimi-Fakhari, D. et al., "Cannabidiol Elevates mTOR Inhibitor Levels In Tuberous Sclerosis Complex Patients," (2020) *Pediatric Neurology*, 12 pages; https://doi.org/10.1016/j.pneuro.2020.05.001. cited by applicant

Elsobhy and Gul, "Constituents of Cannabis Sariva," Chapter 1, *Handbook of Cannabis*, ed. Roger G. Pertwee, pp. 3-22 (2014). cited by applicant

Ettienne De Meijer, "The Chemical Phenotypes (Chemotypes) of Cannabis," Chapter 5, *Handbook of Cannabis*, Handbook of Cannabis, Roger G. Pertwee (ed.), CRC Press, 2014, 1-10. cited by applicant

Engel, "Report of the ILAE classification core group," *Epilepsia*, 47(9):1558-1568 (2006). cited by applicant

Engel, "Chapter 1: What Should be Modeled?" In *Models Seizure Epilepsy*, 2006, 14 pages. cited by applicant

Eggers, "Temporal lobe epilepsy is a disease of faulty neuronal resonators rather than oscillators, and all seizures are provoked, usually by stress," *Med Hypotheses*, 68(4):920-921 (2007). cited by applicant

EPIDIOLEX® (cannabidiol) oral solution, CV, Prescribing Information, 2018, 30 pages. cited by applicant

Fariello, "Parenteral Penicillin in Rats: An Experimental Model of Multifocal Epilepsy," *Epilepsia*, 17:217-222 (1976). cited by applicant

Ferdinand, et al., "Cannabis—psychosis pathway independent of other types of psychopathology," *Schizophr Res.*, 79(2-3):289-295 (2005). cited by applicant

Fisher et al., "The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions," *Epilepsy Res.*, 41(1):39-51 (2000). cited by applicant

Gabor et al., "Lorazepam versus phenobarbital: Candidates for drug of choice for treatment of status epilepticus," *J Epilepsy*, 3(1):3-6 (1990). cited by applicant

Galilly et al., "Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol," *Pharmacology & Pharmacy Research*, 2019, 1-10. cited by applicant

Gardner [online], "Comes Now Epidiolex (FDA Approves IND Studies of CBD)," *BeyondTHC.com*, Oct. 22, 2013, retrieved on Jan. 31, 2018, URL <http://www.beyondthc.com/news/comes-now-epidiolex-fda-approves-ind-studies-of-cbd/>, 4 pages. cited by applicant

Gastaut, "Clinical and electroencephalographical classification of epileptic seizures," *Epilepsia*, 11(1): 102-113 (1970). cited by applicant

Gedde [online], "Clinical Experience with Cannabis in Treatment-Resistant Pediatric Epilepsy," *Marijuana for Medical Professionals Conference*, Sep. 9-11, 2014, [http://www.theroc.us/images/gedde\\_presentation.pdf](http://www.theroc.us/images/gedde_presentation.pdf), Sep. 9-11, 2014, 45 pages. cited by applicant

Geffrey et al., "Cannabidiol (CBD) Treatment for Refractory Epilepsy," *American Epilepsy Society, Annual Meeting Abstract 2.427*, 2014, retrieved on Feb. 1, 2018, URL [https://www.aesnet.org/meetings\\_events/annual\\_meeting\\_abstracts/view/1868979](https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868979), 2 pages. cited by applicant



Green, "CBD: An Unconventional Therapy," available online at <http://nugs.com/article/cbd-an-unconventional-therapy.html>, published Mar. 24, 2014, 5 pages.

Gresham et al., "Treating Lennox-Gastaut syndrome in epileptic pediatric patients with third generation rufinamide," *Neuropsychiatr Dis Treat.*, 6:639-645, Oct. 2009. cited by applicant

Gross et al., "Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center," *Neurology*, 62(11):2095-2097 (2004). cited by applicant

Guimaraes et al., "Antianxiety effect of cannabidiol in the elevated plus-maze," *Psychopharmacology (Berl.)*, 62(11):2095-2097 (2004). cited by applicant

Guerrini et al., "Lamotrigine and Seizure Aggravation in Severe Myoclonic Epilepsy," *Epilepsia*, 39(5):508-512 (1998). cited by applicant

GWPharm [online], "GW Pharmaceuticals Announces Epidiolex(R) Receives Fast Track Designation from FDA for the Treatment of Dravet Syndrome," GWPharm [online], Mar. 1, 2017, URL <https://www.gwpharm.com/about-US/news/gw-pharmaceuticals-announces-epidiolex%C2%AE-receives-fast-track-designation-fda-treatment-dravet-syndrome>, 8 pages. cited by applicant

GWPharm [online], "GW Pharmaceuticals Provides Update on Orphan Program in Childhood Epilepsy for Epidiolex®," GW Pharmaceuticals Press Release, Mar. 1, 2017, URL <https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-provides-update-orphan-program-childhood-epilepsy-epidiolex%C2%AE>, 5 pages. cited by applicant

GWPharm [online], "GW Pharmaceuticals Receives Orphan Drug Designation by FDA for Epidiolex® in the treatment of Lennox-Gastaut Syndrome," GWPharm [online], Feb. 10, 2017, URL <https://www.gwpharm.com/about-us/news/gw-pharmaceuticals-receives-orphan-drug-designation-fda-epidiolex%C2%AE-treatment-lennox-gastaut-syndrome>, 8 pages. cited by applicant

Heinemann et al., "An Overview of in Vitro Seizure Models in Acute and Organotypic Slices," Chapter 4, 35-44 (2006). cited by applicant

Hill et al., "Δ9-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats," *Epilepsia*, 51(8):1522-1532 (2010); doi: 10.1111/j.1528-3593.2010.02611.x. cited by applicant

Hill, "Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB 1 receptor-independent mechanism," *British Journal of Pharmacology*, 157(1):1-11 (2009). cited by applicant

Holmes et al., "Choosing the correct AED: From Animal Studies to the Clinic," *Pediatr Neurol.*, 38(3):151-162 (2008). cited by applicant

Iannotti et al., "Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) receptors of neuronal hyperexcitability," *ACS Chem Neurosci.*, 5(11):1131-1141 (2014); doi: 10.1021/cn5000524. cited by applicant

ICE Epilepsy Alliance, the Dravet Syndrome Spectrum, Nov. 2, 2008, 2 pages. cited by applicant

IUPHAR/BPS Guide to Pharmacology [online], "Entry for Δ 9-tetrahydrocannabidiol," available on or before Mar. 29, 2016, retrieved on Jun. 20, 2018, URL <http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=biology&ligandID=242>, 2 pages. cited by applicant

Iuvone et al., "Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells," *J Neurochem.*, 119(2):205-215 (2011). cited by applicant

Izzo et al., "Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb," *Trends in Pharmacological Sciences*, 30(10):515-527 (2009). cited by applicant

Jacobson, "Survey of Current Cannabidiol Use in Pediatric Treatment-Resistant Epilepsy," Poster, Apr. 22, 2013, 1 page. cited by applicant

Jaeger, W. et al., "Inhibition of cyclosporine and tetrahydrocannabinol metabolism by cannabidiol in mouse and human microsomes," *Xenobiotica*, 26(3):275-284 (1996). cited by applicant

Jeavons et al., "Sodium valproate in treatment of epilepsy," *Br Med J.*, 15; 2(5919):584-586 (1974). cited by applicant

Jones et al. [online], Info & Metrics / Article Information, "Cannabidiol Displays Antiepileptiform and Antiseizure Properties in Vitro and in Vivo," *J Pharmacol Exp Ther.*, 364(1):1-11 (2018), URL: <http://jpet.aspetjournals.org/content/332/2/569/tab-article-info>, 9 pages. cited by applicant

Joy, et al. "Marijuana and Medicine. Assessing the Science Base." National Academy Press. Washington D.C. 1999. 170 pages. cited by applicant

Kahan et al., "Risk of selection bias in randomized trials," *Trials*, 16:405 (2015); doi: 10.1186/s13063-015-0920-x. cited by applicant

Kaplan, "F.D.A. Panel Recommends Approval of Cannabis-Based Drug for Epilepsy," *NY Times*, Apr. 19, 2018, retrieved on Jun. 20, 2018, URL <https://www.nytimes.com/2018/04/19/health/fda-panel-recommends-approval-of-cannabis-based-drug-for-epilepsy.html>, 3 pages. cited by applicant

Karler et al., "The cannabinoids as potential antiepileptics," *J Clin Pharmacol*, 21(8-9 Suppl): 437S-447S (1981). cited by applicant

Kelley et al., "Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress," *Developmental Medicine & Child Neurology*, 52(988)-993 (2010). cited by applicant

Khan et al., "Key Attributes of TKDL: Laoq-e-Qinnab/Barai Zeequn-Nafs," Khazaain-al-Advia, 1911 (with English translation), 2 pages. cited by applicant

Khan et al., "Key Attributes of TKDL: Nushka-e-Qutoor, Muheet-e-Azam, 1887 (with English translation), 2 pages. cited by applicant

Khan et al., "Key Attributes of TKDL: Sufoof-e-Qinnab Barae Waja," Khazaain-al-Advia, 1911, (with English translation), 5 pages. cited by applicant

Khan et al., "Key Attributes of TKDL: Usaara-e-Qinnab Barai Qoolanj," Khazaain-al-Advia, 1911 (with English translation), 6 pages. cited by applicant

Khan et al., "Key Attributes of TKDL: Zimad-e-Qinnab," Khazaain-al-Advia, 1911 (with English translation), 5 pages. cited by applicant

Klitgaard et al., "Electrophysiological, neurochemical and regional effects of levetiracetam in the rat pilocarpine model of temporal lobe epilepsy," *Seizure*, 12(1):1-10 (2003). cited by applicant

Klitgaard et al., "Evidence for a unique profile of levetiracetam in rodent models of seizures and epilepsy," *European journal of Pharmacology*, 353(2):191-201 (2002). cited by applicant

Kramer et al., "Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children," *Epilepsia*, 52(11):1167-1167.2011.03250.x. Epub Aug. 29, 2011. cited by applicant

Kuhn et al., "Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma," *Leukemia*, 24(12):2151-2159 (2010). cited by applicant

Kwan et al., "Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies," *Epilepsia*, 50(2):1075-1093 (2009). cited by applicant

LeafScience.com [online], "What are the Highest CBD Strains?" Oct. 15, 2014, retrieved on Feb. 16, 2017, URL [www.leafscience.com/2014/10/15/highest-cbd-strains/](http://www.leafscience.com/2014/10/15/highest-cbd-strains/), 1 page. cited by applicant

Leino, A. et al., "Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus: A case report," *American Journal of Transplantation*, 16(12):3601-3605 (2016). cited by applicant

Leo et al., "Cannabidiol and epilepsy: Rationale and therapeutic potential," *Pharmacological Research*, 107:85-92 (2016). cited by applicant

Lewis, "Mystery Mechanisms," *The Scientist.com*, Jul. 29, 2016, retrieved on Nov. 8, 2017, URL <https://www.the-scientist.com/?articles.view/articleNo/466646>, 1 page. cited by applicant

Lieu et al., "Assessment of self-selection bias in a pediatric unilateral hearing loss study," *Otolaryngol Head Neck Surz.*, 142(3):427-433 (2010). cited by applicant

Lindamood and Colasanti, "Effects of delta 9-tetrahydrocannabinol and cannabidiol on sodium-dependent high affinity choline uptake in the rat hippocampus," *Neuropharmacology*, 19(2):219-221 (1980). cited by applicant

Long et al., "The pharmacological actions of cannabidiol," *Drugs of the Future*, 30(7):747-53 (2005). cited by applicant

Loscher and Schmidt, "Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma," *Epilepsia*, 52(4):657-678 (2011); doi: 10.1111/j.1528-3593.2011.02611.x. cited by applicant

Lowenstein, "Chapter 363: Seizures and Epilepsy," *Diseases of the Central Nervous System*, 2498-2512 (2008). cited by applicant

Lutz, "On-demand activation of the endocannabinoid system in the control of neuronal excitability and epileptiform seizures," *Biochem Pharmacol*, 68(9):1695-1705 (2005). cited by applicant

Luttjohann et al., "A revised Racine's scale for PTZ-induced seizures in rats," *Physiol Behav.*, 98(5):579-586 (2009); doi: 10.1016/j.physbeh.2009.09.005. cited by applicant

Maa et al., "The case for medical marijuana in epilepsy," *Epilepsia*, 55(6):783-786 (2014); doi: 10.1111/epi.12610. cited by applicant

Mackie, "Cannabinoid receptors as therapeutic targets," *Annu Rev Pharmacol Toxicol.*, 46:101-22 (2006). cited by applicant

Majoosi et al., "Key Attributes of TKDL: Saoot Barae Sara," Kaamil-al-Sena'ah, Central Council for Research in Unani Medicine, 2005 (with English translation). cited by applicant

Malfait et al., "The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis," *PNAS*, 97(17):9402-9407 (2000). cited by applicant

Manni et al., "Obstructive Sleep Apnea in a Clinical Series of Adult Epilepsy Patients: Frequency and Features of the Comorbidity," *Epilepsia*, 44(6):836-840 (2003). cited by applicant

Manno, "Status Epilepticus: Current Treatment Strategies," *The Neurohospitalist*, 1(1):23-31 (2011). cited by applicant

Mattson et al., "Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures," *N. Engl J Med.*, 334(10):702-710 (1996). cited by applicant

Mattson et al., "Prognosis for total control of complex partial and secondary generalized tonic clonic seizures," *Neurology*, 47:68-76 (1996). cited by applicant

Mares et al., "Electrical Stimulation-Induced Models of Seizures in Model of Seizures," Chapter 12, In: *Models of Seizures and Epilepsy*, Philip A. Schwartzkrobin, ed., 1998, 1-12. cited by applicant

Marinol® Label, Unimed Pharmaceuticals, Inc., Jul. 2006, <[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2006/018651.s025s0261bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018651.s025s0261bl.pdf)>, 11 pages. cited by applicant

Martin et al., "Structure-Anticonvulsant Activity Relationships of Cannabidiol Analogs," National Institute on Drug Abuse, Research Monograph Series, 79:41-50 (2000). cited by applicant

McCormick et al., "On the cellular and network bases of epileptic seizures," *Annu Rev Physiol*, 63:815-846 (2001). cited by applicant

McNamara, "Chapter 19: Pharmacotherapy of the Epilepsies," Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed., McGraw-Hill Companies, 2006, 1-12. cited by applicant

Mechoulam et al., "Toward drugs derived from cannabis," *Naturwissenschaften*, 65(4):174-179 (1978). cited by applicant

Medicos [online], "Convulsive Disorders and their Interference with Driving," Medicos, 2014, retrieved Feb. 10, 2017, URL <<https://www.medicosporlasegur.com/diseases/convulsive-disorders-and-their-interference-with-driving>>, 3 pages. cited by applicant

Merlis, "Proposal for an International Classification of the Epilepsies," *Epilepsia*, 11:114-119 (1970). cited by applicant

Miller et al., "Mapping genetic modifiers of survival in a mouse model of Dravet syndrome," *Genes, Brain and Behavior*, 13:163-172 (2014). cited by applicant

Moral et al., "Pipeline on the Move," *Drugs of the Future*, Jan. 2014, 39(1): 49-56. cited by applicant

Morard et al., "Conversion to Sirolimus-Based Immunosuppression in Maintenance Liver Transplantation Patients," *Liver Transplantation*, 13:658-664 (2007)

Morelli et al., "The effects of cannabidiol and its synergism with bortezomib in multiple myeloma cell lines. A role for transient receptor potential Vanilloid type 1," cited by applicant

MyVirtualMedicalCentre [online], "Aicardi syndrome," mvvmc.com, Feb. 2004, retrieved on Jan. 25, 2019, <https://www.myvmc.com/diseases/aicardi-syndrome>

Nabissi et al., "Cannabinoids synergize with cofilin, reducing multiple myeloma cells viability and migration," *Oncotarget*, 7:77553 (2016). cited by applicant

Neto et al., "The role of polar phytochemicals on anticonvulsant effects of leaf extracts of Lippia Alba (Mill.) N.E. Brown chemotypes," *J. Pharm Pharmacol.*

Ng et al., "Illicit drug use and the risk of new-onset seizures," *Am J Epidemiol.*, 132(1):47-57 (1990). cited by applicant

Oakley et al., "Dravet Syndrome Insights into pathophysiology and therapy from a mouse model of Dravet syndrome," *Epilepsia*, 52(Suppl. 2):59-61 (2011).

Obay et al., "Antiepileptic effects of ghrelin on pentylenetetrazole-induced seizures in rats," *Peptides*, 28(6):1214-1219. Epub Apr. 19, 2007. cited by applicant

Olyaei, A. J. et al., "Interaction Between Tacrolimus and Nefazodone in a Stable Renal Transplant Recipient," *Pharmacotherapy*, 18(6):1356-1359 (1998). cited by applicant

Pelliccia et al., [Online], "Treatment with CBD in oily solution of drug-resistant pediatric epilepsies," 2005 Congress on Cannabis and the Cannabinoids, Leiden, The Netherlands, as Medicine, 2005, 14, retrieved on Jun. 30, 2015, URL <[http://www.cannabis-med.org/studies/www\\_en\\_db\\_study\\_show.php?s\\_id=173&&search\\_pattern=EPILEPSIA](http://www.cannabis-med.org/studies/www_en_db_study_show.php?s_id=173&&search_pattern=EPILEPSIA)>

Pereira et al., "Study pharmacologic of the GABAergic and glutamatergic drugs on seizures and status epilepticus induced by pilocarpine in adult Wistar rats," *Epilepsia*, 48(1):100-105 (2007). cited by applicant

Pertwee, "Cannabinoid receptor ligands: clinical and neuropharmacological considerations, relevant to future drug discovery and development," *Expert Opin Ther Targets*, 10(1):1-12 (2006). cited by applicant

Pertwee, "The diverse CB1 and CB2 receptors pharmacology of three plant cannabinoids: Delta9 Tetrahydrocannabinol, cannabidiol and alpha9-tetrahydrocannabinol," cited by applicant

Pertwee, "Chapter 3: The Pharmacology and Therapeutic Potential of Cannabidiol," *Cannabinoids*, Ed Vincenzo Di Marzo ed., 2004, pp. 32-83. cited by applicant

Petrocellis et al., "Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes," *British Journal of Pharmacology*, 157(1):1-12 (2008). cited by applicant

Pohl et al., "Effects of flunarizine on Metrazol-induced seizures in developing rats," *Epilepsy*, 1(5):302-305 (1987). cited by applicant

Porter et al., "Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy," *Epilepsy Behav.*, 29(3):574-577 (2013)

Porter et al., "Randomized, multicenter, dose-ranging trial of retigabine for partial-onset seizures," *Neurology*, 68(15):1197-1204 (2007). cited by applicant

Poortman-Van Der Meer, "A contribution to the improvement of accuracy in the quantitation of THC," *Forensic Science International*, 101(1):1-8 (1999). cited by applicant

Potter, "Cannabis Horticulture," Chapter 4, *Handbook of Cannabis*, Roger G. Pertwee (ed.), pp. 65-88 (2014). cited by applicant

Pouton, "Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems," *Eur. J. Pharm Biopharm*, 64(1):1-14 (2007). cited by applicant

Press et al., "Parenteral reporting of response to oral cannabis extracts for treatment of refractory epilepsy," *Epilepsy Behav.*, 45:49-52 (2015). cited by applicant

Pruitt et al., "Ethanol in Liquid Preparations Intended for Children," *Pediatrics*, 73(3):405-407 (1984). cited by applicant

Raab et al., "Multiple myeloma," *Lancet*, 374(9686):314-339 (2009). cited by applicant

Rabinski [online], "CBD-A: Cannabidiol Acid Cannabinoid Profile," MassRoots, Jul. 2, 2015, retrieved on Jan. 31, 2018, URL <<https://www.massroots.com/lippia-alba/cbd-a-cannabidiol-acid-cannabinoid-profile>>

Ramantani et al., "Epilepsy in Aicardi—Goutières Syndrome," *Official J Eur Paediatric Neurology Society*, 18:30-37 (2014). cited by applicant

Rauca et al., "The role of superoxide dismutase and alpha-tocopherol in the development of seizures and kindling induced by pentylenetetrazol—influence of antioxidant treatment," *Brain Research*, 1009(1-2):203-212 (2004). cited by applicant

Resstel et al., "5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats," *Neuropharmacology*, 59(2):116-129 (2010). cited by applicant

Rosenberg et al., "Cannabinoids and Epilepsy," *Neurotherapeutics*, 12(4):747-768 (2015). cited by applicant

Rosenkrantz et al., "Oral and Parenteral Formulations of Marijuana Constituents," *J Pharm Sci*, 61(7):1106-1112 (1972). cited by applicant

Rubio et al., "In vivo Experimental Models of Epilepsy," *Central Nervous System Agents in Medicinal Chemistry*, 10:298-309 (2010). cited by applicant

Russo, "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," *British J. of Pharm.*, 163:1333-1364 (2011). cited by applicant

Sadanandasarma et al., "Key Attributes of TKDL: Suddha Bhanga Visista Gunah Aur Matra," *Rasatarangini 11th Ed.*, 720-723 (with English translation), 8 pages. cited by applicant

Sander, "The epidemiology of epilepsy revisited," *Curr Opin Neural*, 16(2):165-170 (2003). cited by applicant

Sastri et al., "Key Attributes of TKDL: Vijaya Kalpah (Apasmaranasaka)," *Anandakandam 1st ed.*, 1952:241 (with English translation), 5 pages. cited by applicant

Scuderi et al., "Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders," *Phytother Res.*, 23(5):597-602 (2009). cited by applicant

Silva et al., "Clobazam as Add-on Therapy in Children with Epileptic Encephalopathy," *Can. J. Neurol. Sci.*, 33:209-213 (2006). cited by applicant

Shukla [online], "New Automated Purification Strategies for Scale-Up," PCISynthesis.com, posted Dec. 25, 2017, <https://www.pcisynthesis.com/new-automated-purification-strategies-for-scale-up/>

Sperling et al., "Carisbamate as adjunctive treatment of partial onset seizures in adults in two randomized, placebo-controlled trials," *Epilepsia*, 51(3):333-343 (2010). cited by applicant

Stafstrom et al., "Models of Pediatric Epilepsies: Strategies and Opportunities," *Epilepsia*, 47(8): 1407-1414 (2006). cited by applicant

Stephenson, "In Memoriam: Professor Jean Aicardi (1926-2015)," *Pediatric Neurology*, 54:3-4 (2016). cited by applicant

Stott et al., "Cannabinoids for the pharmaceutical industry," *Euphytica*, 140:83-93 (2004). cited by applicant

Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," Table VIII, *Pharmaceutical Research*, 21(2):201-230 (2004). cited by applicant

Swann et al., "The effects of seizures on the connectivity and circuitry of the developing brain," *Ment Retard Dev Disabil Res Rev.*, 10(2):96-100 (2004). cited by applicant

Thomas et al., "Evidence that the plant cannabinoid Delta9-tetrahydrocannabinol is a cannabinoid CB1 and CB2 receptor antagonist," *Br J Pharmacol.*, 146(1):1-12 (2005). cited by applicant

Thumma et al., "Influence of plasticizers on the stability and release of a prodrug of Delta9-tetrahydrocannabinol incorporated in poly (ethylene oxide) matrices," *J Pharm Sci*, 97(1):1-12 (2008). cited by applicant

Thurman et al., "Standards for epidemiologic studies and surveillance of epilepsy," *Epilepsia*, 52 (Suppl 7):2-26 (2011). cited by applicant

Thurston, "Avoid Charlotte's Web for Epilepsy," Jun. 26, 2014, URL <<http://drthurstone.com/charlottes-web-not-safest-option-epilepsy-treatment/>>, 4 pages.

Tremblay & Sherman, "Double-blind clinical study of cannabidiol as a secondary anticonvulsant," *Marijuana '90 Int. Conf. on Cannabis and Cannabinoids*, Kluwer Academic Publishers, 1990, pp. 1-12. cited by applicant

Turkanis et al., "An Electrophysiological Analysis of the Anticonvulsant Action of Cannabidiol on Limbic Seizures in Conscious Rats," *Epilepsia*, 20:351-363 (1979). cited by applicant

U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), "Guidance for Industry: Efficacy and Safety Studies for the Treatment of Epilepsy in Adult Healthy Volunteers," Jul. 2005, 30 pages. cited by applicant

Usami et al., "Synthesis and pharmacological evaluation in mice of halogenated cannabidiol derivatives," *Chem Pharm Bull (Tokyo)*, 47(11):1641-1645 (1999)

Utah.gov [online], "2nd Agenda Controlled Substances Advisory Committee Meeting," Nov. 12, 2013, URL <<https://www.utah.gov/pmn/files/81459.pdf>>, 63 pages.

Van Rijkceversel, "Treatment of Lennox-Gastaut Syndrome: overview and recent findings," *Neuropsychiatr Dis Treat*, 4(6):1001-1019 (2008). cited by applicant

Velasco et al., "Anticancer mechanisms of cannabinoids," *Curr Oncol*, 23(2):S23-S32 (2016). cited by applicant

Velisek, "Chapter 11: Models of Chemically-Induced Acute Seizures," *Models of Seizures and Epilepsy*, pp. 127-152 (2006). cited by applicant

Veliskova, "Chapter 48: Behavioral Characterization of Seizures in Rats," *Models of Seizures and Epilepsy*, pp. 601-611 (2006). cited by applicant

Vollner et al., "Haschisch XX+[Schaschisch XX+]: Cannabidivarin, a new hashish substance," *Tetrahedron Letters*, 10(3):145-147 (1969). cited by applicant

Wahle et al., "Development of Tolerance to the Anticonvulsant Effect of Valproate but not to Ethosuximide in a Rat Model of Absence Epilepsy," *Eur J Pharmacol*, 169:155-160 (1989). cited by applicant

Wallace et al., "Pharmacotherapy for Dravet Syndrome," *Pediatr. Drugs*, 18:197-208 (2016). cited by applicant

Wallace et al., "Assessment of the role of CB 1 receptors in cannabinoid anticonvulsant effects," *Eur J Pharmacol.*, 428(1):51-57 (2001). cited by applicant

Weimer-Kruel, A. et al., "Cannabidiol Interacts Significantly with Everolimus—Report of a Patient with Tuberous Sclerosis Complex," *Neuropediatrics*, 50(6):665-668 (2019). cited by applicant

Weston et al., "Tetrahydrocannabivarin exhibits anticonvulsant effects in a piriform cortical brain slice model of epileptiform activity," *Proceedings of the British Association for the Study of Epilepsy*, 19(1):10-11 (2018). cited by applicant

URL <<http://www.pA2online.org/abstrat/abstract.jsp?abid=28533>>, 1 page, Abstract only. cited by applicant

Wingerchuk, "Cannabis for medical purposes: cultivating science, weeding out the fiction," *Lancet*, 364:315-316 (2004). cited by applicant

Yamaori, S. et al., "Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: Role of phenolic hydroxyl groups in the resorcinol moiety," *Life Sciences*, 72(1):1-10 (2003). cited by applicant

Yu et al., "Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy," *Nature Neuroscience*, 9(9):1142-1148 (2006). cited by applicant

Yuriev, "Endogenous cannabinoid system is a new perspective object of pharmacotherapeutic effect to disease of nervous system," *Ukrainsky Mnemotechny Ch*, 1(1):1-10 (2018). cited by applicant

Zhao et al., "Chapter 27: Repetitive Seizures in the Immature Brain," *Models of Seizures and Epilepsy*, 341-350 (2006). cited by applicant

Zhornitsky & Potvin, "Cannabidiol in Humans—The Quest for Therapeutic Targets," *Pharmaceuticals*, 5:529-552 (2012). cited by applicant

Zuardi et al., "Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug," *Braz J Med Biol Res.*, 39(4):421-429 (2006). cited by applicant

Zuardi et al., "Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action," *Rev Bras Psiquiatr*, 30(3):271-280 (2008). cited by applicant

U.S. Appl. No. 15/640,033, filed Jun. 30, 2017; Inventor(s): Jitinder Wilkhu et al. cited by applicant

U.S. Appl. No. 16/959,354, filed Jun. 30, 2020; Inventor(s): Jitinder Wilkhu et al. cited by applicant

U.S. Appl. No. 16/935,005, filed Jul. 21, 2020; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/012,448, filed Sep. 4, 2020; Inventor(s): Benjamin Whalley et al. cited by applicant

U.S. Appl. No. 17/050,956, filed Oct. 27, 2020; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/102,109, filed Nov. 23, 2020; Inventor(s): Guillermo Velasco Diez et al. cited by applicant

U.S. Appl. No. 17/231,625, filed Apr. 15, 2021; Inventor(s): Stephen Wright et al. cited by applicant

U.S. Appl. No. 17/296,066, filed May 21, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/296,076, filed May 21, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/424,682, filed Jul. 21, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/426,442, filed Jul. 28, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/406,401, filed Aug. 19, 2021; Inventor(s): Jitinder Wilkhu et al. cited by applicant

U.S. Appl. No. 17/435,892, filed Sep. 2, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/606,370, filed Oct. 25, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/611,824, filed Nov. 16, 2021; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/548,232, filed Dec. 10, 2021; Inventor(s): Stephen Wright et al. cited by applicant

U.S. Appl. No. 17/576,868, filed Jan. 14, 2022; Inventor(s): Benjamin Whalley et al. cited by applicant

U.S. Appl. No. 17/627,946, filed Jan. 18, 2022; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 17/585,415, filed Jan. 26, 2022; Inventor(s): Benjamin Whalley et al. cited by applicant

U.S. Appl. No. 17/631,069, filed Jan. 28, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/638,629, filed Feb. 25, 2022; Inventor(s): Benjamin Whalley et al. cited by applicant

U.S. Appl. No. 17/689,607, filed Mar. 8, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/689,245, filed Mar. 8, 2022; Inventor(s): Harshit Shah et al. cited by applicant

U.S. Appl. No. 17/768,048, filed Apr. 11, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/770,435, filed Apr. 20, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/770,436, filed Apr. 20, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/771,184, filed Apr. 22, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/771,190, filed Apr. 22, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/771,195, filed Apr. 22, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/771,183, filed Apr. 22, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/744,224, filed May 13, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/777,734, filed May 18, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/777,677, filed May 18, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/777,681, filed May 18, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/841,167, filed Jun. 15, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/786,949, filed Jun. 17, 2022; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 17/853,367, filed Jun. 29, 2022; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 17/817,753, filed Aug. 5, 2022; Inventor(s): Volker Knappertz et al. cited by applicant

U.S. Appl. No. 18/002,437, filed Dec. 19, 2022; Inventor(s): Jie Li et al. cited by applicant

U.S. Appl. No. 18/005,838, filed Jan. 17, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,841, filed Jan. 17, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,843, filed Jan. 17, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,845, filed Jan. 17, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,847, filed Jan. 17, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,848, filed Jan. 17, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,851, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,852, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,853, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,868, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,959, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,960, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/005,961, filed Jan. 18, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/006,121, filed Jan. 19, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/006,125, filed Jan. 19, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/006,127, filed Jan. 19, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/006,129, filed Jan. 19, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Application No. 18,006,131, filed Jan. 19, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Application No. 18,006,133, filed Jan. 19, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/161,603 cited by applicant

U.S. Appl. No. 18/170,235, filed Feb. 16, 2023; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 18/043,810, filed Mar. 2, 2023; Inventor(s): Michael Simon Loft et al. cited by applicant

U.S. Appl. No. 18/044,941, filed Mar. 10, 2023; Inventor(s): Kevin James Craig et al. cited by applicant

U.S. Appl. No. 18/245,856, filed Mar. 17, 2023; Inventor(s): Kevin James Craig et al. cited by applicant

U.S. Appl. No. 18/186,792, filed Mar. 20, 2023; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 18/311,221, filed May 2, 2023; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 18/256,307, filed Jun. 7, 2023; Inventor(s): Daniel Adam Checketts et al. cited by applicant

U.S. Appl. No. 18/257,373, filed Jun. 14, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/257,537, filed Jun. 14, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/257,479, filed Jun. 14, 2023; Inventor(s): Karen Ka-Yen Tse et al. cited by applicant

U.S. Appl. No. 18/258,485, filed Jun. 20, 2023; Inventor(s): Kevin James Craig et al. cited by applicant

U.S. Appl. No. 18/446,405, filed Aug. 8, 2023; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 18/546,254, filed Aug. 11, 2023; Inventor(s): Karen Ka-Yen Tse et al. cited by applicant

U.S. Appl. No. 18/548,003, filed Aug. 25, 2023; Inventor(s): Volker Knappertz et al. cited by applicant

U.S. Appl. No. 18/477,467, filed Sep. 28, 2023; Inventor(s): Jitinder Wilkhu et al. cited by applicant

U.S. Appl. No. 18/479,671, filed Oct. 2, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/560,316, filed Nov. 10, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/560,337, filed Nov. 10, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/560,341, filed Nov. 10, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/560,346, filed Nov. 10, 2023; Inventor(s): Alan James Silcock et al. cited by applicant

U.S. Appl. No. 18/526,795, filed Dec. 1, 2023; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 18/545,754, filed Dec. 19, 2023; Inventor(s): Geoffrey Guy et al. cited by applicant

U.S. Appl. No. 18/292,844, filed Jan. 26, 2024; Inventor(s): Volker Knappertz et al. cited by applicant

U.S. Appl. No. 18/597,717, filed Mar. 6, 2024; Inventor(s): Jonathan Oliver Whitehouse et al. cited by applicant

U.S. Appl. No. 61/969,070, filed Mar. 21, 2014, Kane et al. cited by applicant

U.S. Appl. No. 62/004,495, filed May 29, 2014, Vangara et al. cited by applicant

U.S. Appl. No. 62/154,660, filed Apr. 29, 2015, Vangara et al. cited by applicant

U.S. Appl. No. 14/724,351, filed May 28, 2015, Vangara et al. cited by applicant

Abati, E. et al., "Cannabidiol treatment of refractory epileptic spasms: an open label study," American Epilepsy Society, Annual Meeting, Abstract 3.404, 2015

treatment-of-refractory-epileptic-spasms--an-open-label-study. cited by applicant

Aagaard, L. et al., "Adverse Drug Reactions in the Paediatric Population in Denmark: A Retrospective Analysis of Reports Made to the Danish Medicines Agency," *Journal of Clinical Pharmacy and Therapeutics*, 40(1):1-10 (2015). cited by applicant

Adams, R. et al., "Isolation of Cannabinol, Cannabidiol and Quebrachitol from Red Oil of Minnesota Wild Hemp," *J. Am. Chem. Soc.* 1940, 62, 8, 2194-2196

[Aker, R. G. et al., "Chemically Induced Experimental Models of Absence Epilepsy," *Chemical-Induced Seizures: Mechanisms, Consequences and Treatment*, 1-10 (2012). cited by applicant

Akiyama, M. et al., "Dravet Syndrome: A Genetic Epileptic Disorder," *Acta Med. Okayama*, 66(5):369-376 (2012). cited by applicant

Allen, J. W., "Clobazam as an adjunctive treatment in refractory epilepsy," *British Medical Journal*, 286:1246-1247 (1983). cited by applicant

Anderson, C. L., "An Evaluation of Effectiveness of Cannabidiol as an Antiepileptic Drug for Children with Intractable Generalized Epilepsy," Dissertation, University of Florida, 2015. <https://ufdc.ufl.edu/UFE0050852/00001/pdf>. cited by applicant

Arik, A. E. et al., "Effect of levetiracetam on penicillin induced epileptic activity in rats," *Acta Neurobiol Exp*, 74:266-275 (2014). cited by applicant

[Allen G., "Florida Bill Would Allow Medical Marijuana For Child Seizures," Jan. 16, 2014, retrieved from <https://www.npr.org/sections/health-shots/2014/01/16/261111111/florida-bill-would-allow-medical-marijuana-for-child-seizures>, 16 pages. cited by applicant

[Anonymous], "GW Pharma—GW Pharmaceuticals Announces New Physician Reports of Epidiolex® Treatment Effect in Children and Young Adults With Treatment-Resistant Epilepsy," *GW Pharmaceuticals*, 2014. <https://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-announces-new-physician-reports-epidiolexr-0>, 4 pages. cited by applicant

[Anonymous], "Gw Pharmaceuticals Announces Epidiolex Receives Fast Track Designation from FDA for the Treatment of Dravet Syndrome," *GW Pharmaceuticals*, 2014. <http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20Epidiolex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20for%20the%20Treatment%20of%20Dravet%20Syndrome>, 5 pages. cited by applicant

[Anonymous], "Salutaris Drops Buy Salutaris Drops—Salutaris Drops," Oct. 12, 2014; <http://web.archive.org/web/20141012130255/http://salutarisdrops.com>

[Anonymous], "Salutaris Drops Cannabidiol for Aicardi Syndrome—Salutaris Drops," Oct. 12, 2014; <http://web.archive.org/web/20141012220050/http://salutarisdrops.com>

by applicant

[Anonymous], "GW Pharma Initiates Second Phase 3 Pivotal Study of Epidiolex® (CBD) in Lennox-Gastaut Syndrome," Jun. 11, 2015; <https://www.benzinga.com/news/press-releases/15/06/gw-pharma-initiates-second-phase-3-pivotal-trial-for-epidiolex-cbd-in-lennox-gastaut-syndrome>, 5 pages. cited by applicant

Approval Letter for NDA 210365 Epidiolex, Jun. 25, 2018, 12 pages. cited by applicant

Arzimanoglou et al., "All children who experience epileptic falls do not necessarily have Lennox-Gastaut syndrome . . . but many do," *Epileptic Disord.* 2011, 13(2):115-118. cited by applicant

[No Author Listed], "ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies," 2010, 2 pages. cited by applicant

[No Author Listed] "Orphan Drug Designation Granted for Epidiolex in Dravet syndrome by the FDA—Seven Expanded Access INDs granted by FDA to US patients with intractable epilepsy syndromes," *GW Pharmaceuticals Press Release* dated Nov. 14, 2013, 3 pages. cited by applicant

[No Author Listed] GW Pharmaceuticals Provides Update on Orphan Program in Childhood Epilepsy for Epidiolex, *GW Pharm.* Available online Nov. 14, 2013. cited by applicant

[No Author Listed] "What are the Highest CBD Strains?" accessed Feb. 16, 2017, published Oct. 15, 2014, 2 pages. cited by applicant

[No Author Listed] "Convulsive Disorders and Their Interference with Driving," *Medicos.*, Retrieved Feb. 10, 2017, Retrieved from internet: URL <https://www.medicos.com/convulsive-disorders-and-their-interference-with-driving/>, 2014, 3 pages. cited by applicant

[No Author Listed] "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers," *FDA Guidance for Industry*, 2011. cited by applicant

[No Author Listed] "Gw Pharmaceuticals Announces Physician Reports of Epidiolex Treatment Effect in Children and Young Adults with Treatment-resistant Epilepsy," *GW Pharmaceuticals Press Release* dated Jun. 17, 2014, 2 pages. cited by applicant

[No Author Listed], "High Rollers Bet On Cannabidiol (CBD)—Medical Marijuana Patients Come Up Short," Mar. 3, 2013, 9 pages; <https://www.420magazine.com/news/high-rollers-bet-on-cannabidiol-cbd-medical-marijuana-patients-come-up-short.185325/>. cited by applicant

[No Author Listed], "Selected Media Examples Of Pediatric Applications Of Cannabidiol (CBD)," Jun. 30, 2013, 4 pages; <https://www.420magazine.com/news/selected-media-examples-of-pediatric-applications-of-cannabidiol-cbd.192155/>. cited by applicant

[No Author Listed], "Medical Marijuana For N.J. Children? It's All In Gov. Christie's Hands," *CBS News New York*, Jun. 27, 2013, 3 pages; <https://www.cbsnews.com/news/medical-marijuana-for-n-j-children-its-all-in-gov-christies-hands/>. cited by applicant

[No Author Listed], "Photo Release—Kannaway Back office Goes Live CBD-Rich Hemp Oil Products Offered for Sale," May 7, 2014, *Globe Newswire*, <http://www.globenewswire.com/Photo-Release-Kannaway-Back-Office-Goes-Live-CBD-Rich-Hemp-Oil-Products-Offered-for-Sale.html>, 6 pages. cited by applicant

[No Author Listed], GW and Otsuka Enter into Global Cannabinoid Research Collaboration, *News Release*, Jul. 9, 2007; <https://www.otsuka.co.jp/en/company/press-releases/2007/07/09/01.html>. cited by applicant

[No Author Listed], License Agreement between GW Pharma and GW Pharmaceuticals, PLC and Otsuka, Feb. 2007; [https://www.sec.gov/Archives/edgar/data/1401767/000140176707000001/gwpharm-20070201\\_license\\_agreement.htm](https://www.sec.gov/Archives/edgar/data/1401767/000140176707000001/gwpharm-20070201_license_agreement.htm). cited by applicant

63 pages. cited by applicant

Amada, N. et al., "Cannabidivarin (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression," 2013, PeerJ, 1: e214; applicant

AAN 67th Annual Meeting Abstract, Apr. 2015; <https://www.aan.com/PressRoom/Home/GetDigitalAsset/11570>, 1 page. cited by applicant

Andre, E. S. et al., "Spontaneous absence-like activity in Wistar rats: Behavioral and electrographic characteristics and the effects of antiepileptic drugs," *Acta* cited by applicant

Astruc-Diaz, F., "Cannabinoids delivery systems based on supramolecular inclusion complexes and polymeric nanocapsules for treatment of neuropathic pain" Jan. 23, 2014; <https://tel.archives-ouvertes.fr/tel-00935588> [accessed Nov. 1, 2019], 278 pages. cited by applicant

Babayeva et al., "Marijuana Compounds: A Non-Conventional Therapeutic Approach to Epilepsy in Children," *J. Addict. Neuropharmacol.*, 1:1 (2014); doi: 10.1007/s12081-014-0001-1

Bacca, A., "HempVap from HempMedsPX," Mar. 10, 2014; <https://cannabisnow.com/hempvap-from-hempmedspx/>, 3 pages. cited by applicant

Barton, M. E. et al., "Pharmacological characterization of the 6 Hz psychomotor seizure model of partial epilepsy," *Epilepsy Research*, 47:217-227 (2001). cited by applicant

Ben-Ari, Y., "Seizures Beget Seizures: The Quest for GABA as a Key Player," *Critical Reviews in Neurobiology*, 18(1-2):135-144 (2006). cited by applicant

Bhattacharyya, S. et al., "Opposite Effects of delta-9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology," *Neuropsychopharmacology*, 36:1039-1045 (2011). cited by applicant

Bell, J., "Treatment With CBD In Oily Solution Of Drug-Resistant Paediatric Epilepsies," Oct. 18, 2011, 3 pages; <https://www.420magazine.com/community/press-releases/resistant-paediatric-epilepsies.154896/>. cited by applicant

Benowitz & Jones "Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man," *J Clin Pharm*, 21:214S-223S, 1981. cited by applicant

Bergamaschi, M. M. et al., "Safety and Side Effects of Cannabidiol, a Cannabis sativa Constituent," *Current Drug Safety*, 6:237-249 (2011). cited by applicant

Bialer, M. & White, S., "Key factors in the discovery and development of new antiepileptic drugs," *Nat Rev Drug Discov*, 9(1):68-82 (2010); doi: 10.1038/nrd1000

Bienstock, D., "A Comprehensive History of Marijuana's Epilepsy-Treating Compound, CBD," Jun. 2014, Vice Article, retrieved from <https://www.vice.com/en/article/cbd-marijuana-epilepsy> cited by applicant

Bijnsdorp, I. V. et al., "Analysis of Drug Interactions," Chapter 34, *Cancer Cell Culture, Methods in Molecular Biology*, Second Edition, Ian A. Cree, Ed., 2011. cited by applicant

Bowman et al., "Epilepsy," *Encyclopedia of Life Sciences*, 1, 2001; [www.els.net](http://www.els.net), 8 pages. cited by applicant

Bromfield, E. B., Cavazos, J. I., Sirven (Ed.), *An Introduction to Epilepsy* [Internet], West Hartford, CT, American Epilepsy Society; 2006, PMID: 20821849.

Gardner, "Cannabidiols: Potential Use in Epilepsy & Other Neurological Disorders." Cannabidiol Conference at NYU School of Medicine, Oct. 2013. NYU School of Medicine. <URL: <http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 4 pages. cited by applicant

Camfield, "Definition and natural history of Lennox-Gastaut Syndrome," *Epilepsia*, 52:3-9 (2011). cited by applicant

Campos-Castello, "Rational approach to treatment options for Lennox-Gastaut syndrome," *Orphanet*, Mar. 2003; <https://www.orpha.net/data/patho/GB/uk-LennoxGastaut>

|Capal, J. K. & Franz, D. N., "Profile of everolimus in the treatment of tuberous sclerosis complex: an evidence-based review of its place in therapy," *Neuropsychopharmacology*, 34:1039-1045 (2011). cited by applicant

Carlini, E. A. et al., "Letter: Cannabidiol and Cannabis sativa extract protect mice and rats against convulsive agents," *J Pharm Pharmacol*. Aug. 1973;25(8):615-616. cited by applicant

Carlini, E. A. et al., "Anticonvulsant Activity of Four Oxygenated Cannabidiol Derivatives," *Research Communications in Chemical Pathology and Pharmacology*, 1:1-4 (1973). cited by applicant

Carvill, G. L. et al., "GABRA1 and STXBP1: Novel generic causes of Dravet Syndrome," *Neurology*, 82:1245-1253 (2014). cited by applicant

Chesney et al., "Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials," *Neuropsychopharmacology*, 45:1799-1806 (2010). cited by applicant

Chiron, S., "Stiripentol for the treatment of Dravet syndrome," *Orphan Drugs: Research and Reviews*, 4:29-38 (2014). cited by applicant

Cholongitas et al., "Systematic review: The model for end-stage liver disease—should it replace Child-Pugh's classification for assessing prognosis in cirrhosis?" *Alimentary Pharmacology and Therapeutics*, 20:1111-1121 (2006). doi: 10.1111/j.1365-2036.2005.02691.x. cited by applicant

Chou, T.-C., "Drug Combination Studies and Their Synergy Quantification Using the Chou-Talalay Method," *Cancer Res*, 70(2):440-446 (2010). cited by applicant

Chu-Shore, C. J. et al., "The natural history of epilepsy in tuberous sclerosis complex," *Epilepsia*, 51(7):1236-1241, 2010; doi: 10.1111/j.1528-1167.2009.02411.x

Ciccone, "Drop Seizure Frequency in Lennox-Gastaut Decrease With Cannabidiol," *Neurology Advisor*, Apr. 26, 2017; retrieved from the Internet: URL: <http://www.medscape.com/viewarticle/884931>, 6 pages. cited by applicant

|Cilio, Maria Roberta, M.D., Ph.D. of the Pediatric Epilepsy and Clinical Neurophysiology for the University of California, San Francisco presents her talk on "Cannabidiol in Epilepsy: A Systematic Review of the Literature," at NYU School of Medicine's Cannabidiol Conference (Oct. 4, 2013). Video published online. <<https://www.youtube.com/watch?v=V1=View#StudyPageTop>>, 44 pages. cited by applicant

Cilio, M. R. et al., "The case for assessing cannabidiol I epilepsy," *Epilepsia*, 55(6):787-790 (2014). cited by applicant

Citti et al., "Pharmaceutical and biomedical analysis of cannabinoids: A critical review," *Journal of Biopharmaceutical and Biomedical Analysis*, 147:565-579 (2014). cited by applicant

Clinical trials.gov [online], Identifier: NCT02224690, A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; Cbd) as Adjunctive Treatment of Dravet Syndrome in Children and Adults (GWPCARE4) Jazz Pharmaceuticals, U.S. National Library of Medicine, last update posted Sep. 8, 2022, 3 pages; Retrieved from <https://clinicaltrials.gov/ct2/show/study/NCT02224690> cited by applicant

Clinical trials.gov [online], Identifier: NCT02091206, A Dose Ranging Pharmacokinetics and Safety Study of GWP42003-P in Children With Dravet Syndrome (GWPCARE3) Jazz Pharmaceuticals, U.S. National Library of Medicine, last update posted Sep. 28, 2022, 9 pages; Retrieved from <https://clinicaltrials.gov/ct2/show/study/NCT02091206>. cited by applicant

Clinical trials.gov [online], Identifier: NCT02006628, A study to compare the change in symptom severity in participants with schizophrenia or related psychotic disorders in conjunction with existing anti-psychotic therapy over a period of six weeks, Jazz Pharmaceuticals, U.S. National Library of Medicine, last update posted Sep. 28, 2022, 3 pages; Retrieved from <https://clinicaltrials.gov/ct2/show/study/NCT02006628>. cited by applicant

Clinical trials.gov [online], Identifier: NCT02091375, Antiepileptic Efficacy Study of GWP42003-P in Children and Young Adults With Dravet Syndrome (GWPCARE4) Jazz Pharmaceuticals, U.S. National Library of Medicine, last update posted Sep. 28, 2022, 40 pages; Retrieved from <https://www.clinicaltrials.gov/ct2/show/study/NCT02091375>. cited by applicant

ClinicalTrials.gov archive, History of Changes for Study: NCT02324673, National Institute of Health U.S. National Library of Medicine (Dec. 19, 2014), <https://clinicaltrials.gov/ct2/show/study/NCT02324673>, V\_1=View#StudyPageTop, 13 pages. cited by applicant

Collins, T. R., "What Neurologists are Doing About Medical Marijuana?" *Neurology Today*, Apr. 17, 2014, vol. 4, issue 8, 8 pages. cited by applicant

Consroe, et al., "Controlled clinical trial of cannabidiol in Huntington's Disease," *Pharmacology Biochemistry & Behavior*, 40:701-708 (1991). cited by applicant

Consroe et al., "Therapeutic Potential of Cannabinoids in Neurological Disorders," *Cannabinoids as Therapeutic Agents*, R. Mechoulam, Ed., 1986, pp. 21-41. cited by applicant

Consroe et al., "Open label evaluation of cannabidiol in dystonic movement disorders," *International Journal of Neuroscience*, 30(4):277-282 (1986); doi: 10.3109/00207178608839000

Consroe et al., "Antiepileptic Potential of Cannabidiol Analogs," *J Clin Pharmacol.*, 21:428S-436S (1981). cited by applicant

Consroe et al., "Assay of Plasma Cannabidiol by Capillary Gas Chromatography/Ion Trap Mass Spectroscopy Following High-Dose Repeated Daily Oral Administration," *Pharmacology Biochemistry & Behavior*, 40:517-522 (1991). cited by applicant

Costa, B et al., "Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw," *Prostaglandins and Related Compounds*, 62:369-374 (2004). cited by applicant

Cotter, B., "Medicinal marijuana stops seizures, brings hope to little girl," *The Gazette*, Jun. 9, 2013, 8 pages; <https://gazette.com/health/medicinal-marijuana-stops-seizures-brings-hope-to-little-girl> 5c46-5d75-af95-bdd060f4a8b9.html. cited by applicant

Cotterell, A., "How One Young Girl Could Change Idaho's Strict Marijuana Laws," Jun. 17, 2014; <https://www.knkn.org/law/2014-06-19/how-one-young-girl-could-change-idaho-s-strict-marijuana-laws> cited by applicant

Crowther et al., "The Medication of Cannabis," The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, 2006. <http://qmul.ac.uk/xmlui/handle/123456789/2822>, 90 pages. cited by applicant

Crumrine, P. K., "Management of Seizures in Lennox-Gastaut Syndrome," *Pediatr Drugs*, 13(2):107-118 (2011). cited by applicant

Curato, P. et al., "Management of epilepsy associated with tuberous sclerosis complex (TSC)," *European Journal of Paediatric N*

Curia et al., "The pilocarpine model of temporal lobe epilepsy," *J Neuroscience Methods*, 172(2-4):143-157 (2008). cited by applicant

De Deyn et al., "Chemical models of epilepsy with some reference to their applicability in the development of anticonvulsants," *Epilepsy Research*, 12:87-110

Depakene (valproic acid) capsules and oral solution, CV, Prescribing Information, 1978, 54 pages; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013)

DeRosa et al., "Chapter XI: Epilepsy," *Significant Pharmaceuticals Reported in US Patents*, 1st Edition, May 2007, 10 pages. cited by applicant

Deshpande, et al., "Cannabinoid CB 1 receptor antagonists cause status epilepticus-like activity in the hippocampal neuronal culture model of acquired epilepsy," cited by applicant

De Meijer, "The Chemical Phenotypes (Chemotypes) of Cannabis," Chapter 5, *Handbook of Cannabis*, ed. Roger G. Pertwee, pp. 89-110 (2014). cited by applicant

Devinsky, Orrin, M.D. of the Department of Neurology for NYU Langone School of Medicine presents his talk on "Cannabidiols: A Brief History," at NYU School of Medicine. Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 16 pages. cited by applicant

[Devinsky et al., "Epidiolex (Cannabidiol) in Treatment Resistant Epilepsy," Apr. 2015; <https://epilepsyontario.org/wp-content/uploads/2015/Epidiolex-Cannabidiol-Poster-08Apr2015.pdf>, 1 page. cited by applicant

Devinsky et al., "Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistant epilepsy: Initial data from expanded access trial," *Lancet Neurology*, 15(3):270-278 (2015). cited by applicant

Devinsky et al., "Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial," *Lancet Neurology*, 15(3):270-278 (2015). cited by applicant

[Devinsky et al., "Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox-Gastaut syndrome (LGS): results of a dose-ranging, multi-center, randomized, controlled trial (GWPCARE3)," *Epilepsia*, 58:S13-S14 (2017), 2 pages. cited by applicant

[Devinsky et al., "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome," *N Engl J Med*, 376(21):2011-2020 (2017). cited by applicant

Devinsky et al., "Cannabidiol efficacy independent of clobazam: Meta-analysis of four randomized controlled trials," *Acta Neurol Scand.*, 142:531-540 (2020)

DIACOMIT™ Product Monograph, Submission Control 142417, Date of Preparation, Dec. 19, 2012, 37 pages. cited by applicant

Dilantin-125®, NDA 08762 Dilantin-125 (Phenytoin Oral Suspension, USP) FDA Approved Labeling Text dated Feb. 2013, 15 pages. cited by applicant

Di Marzo, Vincenzo, Ph.D. of the Endocannabinoid Research Group Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli, Napoli, Italy, presents his talk on "Mechanism of Action," at NYU School of Medicine's Cannabidiol Conference (Oct. 4, 2013). Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 16 pages. cited by applicant

DiMarzo, V., Declaration Under 37 C.F.R. 1.132, dated Aug. 24, 2017, 21 pages. cited by applicant

Dos Santos, R. G. et al., "Phytocannabinoids and epilepsy," *Journal of Clinical Pharmacy and Therapeutics*, 40:135-143 (2015). cited by applicant

Epilepsy Patients Flock to Colorado after Medical Pot Gives Them Hope, Nov. 18, 2013, CBS Colorado News, 4 pages. cited by applicant

Elsobhy, M. & Gul, W., "Chemical constituents of marijuana: The complex mixture of natural cannabinoids," *Life Sciences*, 78:539-548 (2005). cited by applicant

EPIDIOLEX 100 mg oral solution, Summary of Product Characteristics, European Medicines Compendium, Sep. 2019, 19 pages; <https://web.archive.org/web/20200920022105/https://www.medicines.org.uk/emc/product/10781/smpc>. cited by applicant

Evans, Randolph W., Neurology Case Studies, *Neurol Clin* 24, xi-xii, 2006, 2 pages. cited by applicant

Fabiano, V. et al., "Adverse drug reactions in newborns, infants and toddlers: pediatric pharmacovigilance between present and future," *Expert Opinion on Drug Safety*, 10:1517/14740338.2011.584531. cited by applicant

FDA, "Warning Letters and Test Results for Cannabidiol-Related Products," 2016 Warning Letters, 4 pages. cited by applicant

FDA, "Warning Letters and Test Results for Cannabidiol-Related Products," 2015 Warning Letters, 4 pages. cited by applicant

FDA, Guidance for Industry: Estimating the maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, U.S. Dept of Health and Human Services, Jul. 2005, 30 pages. cited by applicant

FDA's Guidance for Industry Q3A Impurities in New Drug Substances, Revision 2, Jun. 2008, 17 pages. cited by applicant

FDA Guidance for Industry: Botanical Drug Development, U.S. Dept. of Health and Human Services: Food and Drug Administration, Dec. 2016, 34 pages. cited by applicant

FDA Guidance for Industry: Q11 Development and Manufacture of Drug Substances, U.S. Dept. of Health and Human Services: Food and Drug Administration, Dec. 2016, 34 pages. cited by applicant

FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, published in 1987, 20 pages. cited by applicant

FDA Good Review Practice: Clinical Review of Investigational New Drug Applications, Office of New Drugs in the Center for Drug Evaluation and Research, U.S. Dept of Health and Human Services, 2013, 10 pages. cited by applicant

FDA Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Food and Drug Administration, Jul. 30, 2009, 4 pages. cited by applicant

Fernandez-Ruiz, J. et al., "Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?" *British Journal of Pharmacology*, 168:159-168 (2012). cited by applicant

Flatow, N., "How Medical Marijuana Is Giving a Six-Year-Old Boy New Life," Sep. 18, 2012, 2 pages; <https://archive.thinkprogress.org/how-medical-marijuana-is-giving-a-six-year-old-boy-new-life>. cited by applicant

Fryar, C. D. et al., Anthropometric reference data for children and adults: United States, 2011-2014, National Center for Health Statistics. *Vital Health Statistics*, 11:1-26 (2012). cited by applicant

French, Jacqueline A., M.D. Professor of Neurology at the NYU Epilepsy Center presents her talk on "Trials for Disease Modifying Therapies in Epilepsy," at NYU School of Medicine. Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 22 pages. cited by applicant

[French, J. A. et al., "Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, controlled trial," *Lancet*, 388:2153-2163 (2016). cited by applicant

Friedman, Daniel, M.D. Assistant Professor of Neurology at the NYU Comprehensive Epilepsy Center presents his talk on "Pharmacology of CBD in Human Epilepsy," at NYU School of Medicine. Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 14 pages. cited by applicant

Gaoni, Y. & Mechoulam, R., "The Isolation and Structure of  $\Delta^1$ -Tetrahydrocannabinol and Other Neutral Cannabinoids from Hashish," *J Am Chem Soc.* Jan. 1964, 86, 8, 1646-1647. cited by applicant

Gaoni, Y. & Mechoulam, R., "Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish," *J. Am. Chem. Soc.* 1964, 86, 8, 1646-1647. cited by applicant

Garde, D., "Gw Pharmaceuticals Announces Physician Reports of Epidiolex Treatment Effect in Children and Young Adults With Treatment-Resistant Epilepsy," Jun. 17, 2014, 4 pages; <https://www.fiercebitech.com/biotech/gw-pharmaceuticals-announces-physician-reports-of-epidiolex-r-treatment-effect-ch>

Gaston, T. E. et al., "Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy," *Epilepsy & Behavior*, 95:1-10 (2019). cited by applicant

Gaston, T. E. et al., "Cannabis for the Treatment of Epilepsy: an Update," *Curr Neurol Neurosci Rep.*, 18(11):73 (2018), 9 pages; doi: 10.1007/s11910-018-0811-1

Gauthier et al., "Clobazam: A Safe, Efficacious, and Newly Rediscovered Therapeutic for Epilepsy," *CNS Neurosci Ther.*, 21(7):543-548 (2015); doi: 10.1111/cns.12444

Gedde, Retrospective Case Review of High CBD, Low THC Cannabis Extract (Realm Oil) for Intractable Seizure Disorders, 2013 Realm of Caring Foundation, 2013, 10 pages. cited by applicant

Gedde et al., "Whole Cannabis Extract of High Concentration Cannabidiol May Calm Seizures in Highly Refractory Pediatric Epilepsies," *American Epilepsy Society Abstracts*, 2013, 10 pages. cited by applicant

Gedde & Maa "Whole Cannabis Extract of High Concentration Cannabidiol May Calm Seizures in Highly Refractory Pediatric Epilepsies," *American Epilepsy Society Abstracts*, 2013, 10 pages. cited by applicant

Geffrey, A. et al., "Cannabidiol (CBD) Treatment for Refractory Epilepsy in Tuberous Sclerosis Complex (TSC)," Dec. 4, 2014; [www.aesnet.org](http://www.aesnet.org), Abstract 2.4

Geffrey et al., "Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy," *Epilepsia*, 56(8):1246-1251 (2015). cited by applicant

Gemmell, R. M. et al., "Synergistic growth inhibition by Iressa and Rapamycin is modulated by VHL mutations in renal cell carcinoma," *British Journal of Cancer*, 100:100-105 (2009). cited by applicant

Gillen, D., "How Does Caffeine Affect CBD?," Apr. 21, 2019, available at: <https://web.archive.org/web/20191220210719/https://greendoorcbd.com/blogs/news/how-does-caffeine-affect-cbd>

Gloss, D. & Vickrey, B., "Cannabinoids for epilepsy (Review)," *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD009270, 9 pages; DOI: 10.1002/14697528.CD009270

Goldenberg, M. M., "Overview of Drugs Used For Epilepsy and Seizures," *P & T*, 35(7):392-415 (2010). cited by applicant

Greaves et al., "First Dose of Potential New Medicines to Humans: How Animals Help," *Nature Reviews Drug Discovery*, 3:226-236 (2004). cited by applicant

Green Roads CBD Coffee and Tea, Product Page, 2023, 5 pages; <https://greenroads.com/collections/cbd-tea-cbd-coffee?nfsn=2488702.aa938d>. cited by applicant

Grotenhermen et al., "The Therapeutic Potential of Cannabis and Cannabinoids," *Dtsch Arztebl Int*, 109(29-30): 495-501 (2012); doi:10.3238/arztebl.2012.0401



Gunning et al., "Cannabidiol in conjunction with clobazam: analysis of four randomized controlled trials," *Acta Neurol Scand*, 143:154-163 (2021). cited by applicant

Goodman & Gilman, *The Pharmacological Basis of Therapeutics* (Brunton, Laurence L.; Lazo, John S.; Parker, Keith, eds. (2006); New York: McGraw-Hill. cited by applicant

Epilepsies, 28 pages. cited by applicant

Gupta Video 2013, Weed—CNN Special; [https://www.youtube.com/watch?v=Z3IMfIQ\\_K6U](https://www.youtube.com/watch?v=Z3IMfIQ_K6U). cited by applicant

Gupta, S., "Why I changed my mind on weed," Aug. 8, 2013; <https://www.cnn.com/2013/08/08/health/gupta-changed-mind-marijuana/index.html>, 8 pages. cited by applicant

GWPharm [online], "Orphan Drug Designation Granted for Epidiolex in Dravet syndrome by the FDA—Seven Expanded Access INDs granted by FDA to US from intractable epilepsy syndromes," GW Pharmaceuticals Press Release, Nov. 15, 2013, 5 pages. cited by applicant

GWPharm [online], "GW Pharmaceuticals Announces Preliminary Results of Phase 2a Study for its Pipeline Compound GWP42006," GW Pharmaceuticals Press Release, Nov. 15, 2013, 5 pages. cited by applicant

Ha et al., "Epilepsy: Treatment and Management," *US Pharm.*, 38(1):35-39 (2013). cited by applicant

Haller, S. & Carroll, I., "Medical marijuana for kids? Some praise results while others worry about risks," Jul. 9, 2013, 3 pages; <https://www.nbcnews.com/health/medical-marijuana-for-kids-some-praise-results-while-others-worry-about-6c10506407>. cited by applicant

Hancock, E. C. & Cross, J. H., "Treatment of Lennox-Gastaut syndrome (Review)," *Cochrane Database of Systematic Reviews*, 2013, Issue 2. Art. No.: CD009049. cited by applicant

Hanus et al., "Phyto-cannabinoids: a unified critical inventory," Review Article, *Natural Product Reports*; Royal Society of Chemistry, vol. 33, No. 12, Dec. 2016, 1-12. cited by applicant

Hazenkamp, A. et al., "Quantitative Analysis of Cannabinoids from *Cannabis sativa* Using H-NMR," *Chem. Pharm. Bull.*, 52(6):718-721 (2004). cited by applicant

Hazenkamp, A., "Cannabis: extracting the medicine," Doctoral Thesis, 1976, Proefschrift Universiteit Leiden; <https://extractionmagazine.com/wp-content/uploads/2016/06/Hazenkamp-Thesis.pdf>, 187 pages. cited by applicant

Hefler, J., "Parents of epileptic N.J. tot lament medical marijuana delays," *The Philadelphia Enquirer*, Jun. 22, 2013, 5 pages; [https://www.inquirer.com/philly/health/20130623\\_Parents\\_of\\_epileptic\\_N\\_J\\_tot\\_lament\\_medical\\_marijuana\\_delays.html](https://www.inquirer.com/philly/health/20130623_Parents_of_epileptic_N_J_tot_lament_medical_marijuana_delays.html). cited by applicant

Hegde, M. et al., "Seizure exacerbation in two patients with focal epilepsy following marijuana cessation," *Epilepsy & Behavior*, 25:563-566 (2012). cited by applicant

Herlopian, A. et al., "Cannabidiol in treatment of refractory epileptic spasms: An open label study," *Epilepsy & Behavior*, 106:106988 (2020), 7 pages; <https://doi.org/10.1016/j.yebeh.2020.106988>. cited by applicant

Hess et al., "Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex," *Epilepsia*, 57(10):1617-1624 (2016). cited by applicant

Hill et al., "Cannabidivarin is anticonvulsant in mouse and rat," *Br. J Pharmacol*, 167(8):1629-1642 (2012). cited by applicant

Hill, A. J. et al., "Phytocannabinoids as novel therapeutic agents in CNS disorders," *Pharmacology & Therapeutics*, 133:79-97 (2012). cited by applicant

Hillig, K. W. & Mahlberg, P. G., "A chemotaxonomic analysis of cannabinoid variation in *Cannabis* (Cannabaceae)," *American Journal of Botany*, 91(6):966-975 (2004). cited by applicant

Holmes, G. L. et al., "Tuberous Sclerosis Complex and Epilepsy: Recent Developments and Future Challenges," *Epilepsia*, 48(4):617-630, 2007. cited by applicant

Hussain et al., "Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome," *Epilepsia*, 56(1):100-107 (2015). cited by applicant

ILEGAL Trailer, YouTube video, Mar. 27, 2014; <https://www.youtube.com/watch?v=CtJJ1pzMKxs>, 5 pages. cited by applicant

INSYS Therapeutics Submits Drug Master File For Cannabidiol Active Pharmaceutical Ingredient (API), Marketwired, May 29, 2014; <https://www.biospace.com/article/releases/insys-therapeutics-submits-drug-master-file-for-cannabidiol-active-pharmaceutical-ingredient-api-/>, 5 pages. cited by applicant

INSYS Therapeutics Commences Dosing in Phase 1/2 Safety and Pharmacokinetic Study of Cannabidiol Oral Solution in Pediatric Epilepsy Patients, BioSpace, May 29, 2014; <https://www.biospace.com/article/releases/insys-therapeutics-commences-dosing-in-phase-1-2-safety-and-pharmacokinetic-study-of-cannabidiol-oral-solution-in-pediatric-epilepsy-patients/>. cited by applicant

INSYS Therapeutics, Inc., Quarterly Report Form Q-10, U.S. Securities and Exchange Commission, Mar. 31, 2014; [insy20140331\\_10q.htm](https://www.insystherapeutics.com/sec-filings/q-10), 42 pages. cited by applicant

INSYS Therapeutics, Inc., Corporate Integrity Agreement and Conditional Exclusion Release, 2014, 100 pages. cited by applicant

Jacobson, C., "Treating Epilepsy with Pharmaceutical-Grade CBD," *Cannabis Science Today*, Podcast, 2023, transcript timeline 4 pages; <https://agriculturalgenetics.com/cannabis-science-today/podcast/treating-epilepsy-with-pharmaceutical-grade-cbd/>. cited by applicant

Jiang, R. et al., "Cannabidiol Is a Potent Inhibitor of the Catalytic Activity of Cytochrome P450 2C19," *Drug Metab. Pharmacokinet.*, 28(4):332-338 (2013). cited by applicant

Jones et al., "Cannabidiol Displays Antiepileptiform and Antiseizure Properties in Vitro and in Vivo," *J Pharmacol Exp Ther.*, 332(2):559-577 (2010). cited by applicant

Jones, N. A. et al., "Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures," *Seizure*, 21:344-352 (2012). cited by applicant

Jones, P. G. et al., "Cannabidiol," *Acta Cryst.*, B33:3211-3214 (1977). cited by applicant

Jutras-Aswad, Didier, M.D., M.S. of the Department of Psychiatry for the University of Montreal presents his talk on "CBD in Animal Models and Human Trials," Cannabidiol Conference (Oct. 4, 2013), 25 pages; Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>. cited by applicant

Kalenderoglou et al., "Cannabidiol Reduces Leukemic Cell Size—But Is It Important?," *Front. Pharmacol.*, Mar. 24, 2017, Sec. Ethnopharmacology, vol. 8—2017:125. cited by applicant

Karler et al., "The anticonvulsant activity of cannabidiol and cannabinol," *Life Science*, 13:1527-1531 (1973). cited by applicant

Kalepu, S. et al., "Oral lipid-based drug delivery systems—an overview," *Acta Pharmaceutica Sinica B*, 3(6):361-372 (2013). cited by applicant

Kassai et al., "Severe Myoclonic epilepsy in Infancy: A Systematic Review and a Meta-Analysis of Individual Patient Data," *Epilepsia*, 49(2):343-348 (2008). cited by applicant

Katz, Russell ("Rusty"), M.D. former Director of the Division of Neurology Products at the FDA presents his talk on "Dravet and Lennox-Gastaut Syndromes and the Role of Cannabidiol," Cannabidiol Conference (Oct. 4, 2013). Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 25 pages. cited by applicant

Kerr, D. N. S. & Pillai, P. M., "Clobazam as adjunctive treatment in refractory epilepsy," *British Medical Journal*, 286:1246-1247 (1983). cited by applicant

Kobayashi T., et al., "Renal Carcinogenesis, Hepatic Hemangiomatosis and Embryonic Lethality Caused by a Germ-Line Tsc2 Mutation in Mice," *Cancer Res*, 60:115-121 (2000). cited by applicant

Koek et al., "Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 33:100-110 (2009). cited by applicant

Kopka, M., "Cannabinoids in the treatment of epilepsy—an updated review," *Journal of Epileptology*, 2019, 27:35-42; 10.21307/jepil-2019-004. cited by applicant

Krasowski, M. D., "Antiepileptic Drugs. Therapeutic Drug Monitoring of the Newer Generation Drugs," Jun. 2013, *Clinical Laboratory News*, <https://www.aacp.org/press-releases/2013/06/2013-06-13-antiepileptic-drugs-therapeutic-drug-monitoring-of-the-newer-generation-drugs>. cited by applicant

Kruk-Slomka et al., "A comparison of mecamylamine and bupropion effects on memory-related responses induced by nicotine and scopolamine in the novel object recognition task," *Neuropharmacology*, 66(4):638-646 (2014). cited by applicant

Kurz & Blass, "Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child," *Cannabinoids*, 5(4):4-6 (2013). cited by applicant

LaPrarie et al., "Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor," *British J Pharmacology*, 172(20):4790-4805 (2015). cited by applicant

Leahy, J. T. et al., "Clobazam as an adjunctive therapy in treating seizures associated with Lennox-Gastaut syndrome," *Neuropsychiatric Disease and Treatment*, 10:100-107 (2014). cited by applicant

Leite et al., "New insights from the use of pilocarpine and kainate models," *Epilepsy Research*, 50:93-103 (2002). cited by applicant

Leo et al., "Antiepileptogenic effects of Ethosuximide and Levetiracetam in WAG/Rij rats are only temporary," *Pharmacological Reports*, 71:833-838 (2019). cited by applicant

Leo et al., "Cognitive impairment in the WAG/Rij rat absence model is secondary to absence seizures and depressive-like behavior," *Progress in Neuro-psychopharmacology and Biological Psychiatry*, 93:377-387 (2020). cited by applicant

Leonard, B. E., "Therapeutic Uses of Cannabis," British Medical Association (BMA). Harwood Academic Publishers, UK. 1997, pp. 592. cited by applicant

Lewis et al., "Chemical Profiling of Medical Cannabis Extracts," *ACS Omega*, 2:6091-6103 (2017). cited by applicant

Lodzki et al., "Cannabidiol—transdermal delivery and anti-inflammatory effect in a murine model," *Journal of Controlled Release*, 93:377-387 (2003). cited by applicant

Loscher, W. & Rogawski, M. A., "How theories evolved concerning the mechanism of action of barbiturates," *Epilepsia*, 53(Suppl. 8):12-25, 2012; doi: 10.1111/j.1528-3593.2012.04700.x. cited by applicant

Marks, W. J. et al., "Management of Seizures and Epilepsy," *Am Fam Physician*. 1998;57(7):1589-1600. cited by applicant

Malamut, M., "I Drank CBD Coffee for a Week. Here's What I Did to My Anxiety," Nov. 18, 2019, available at <https://www.healthline.com/health/mental-health/cbd-coffee-for-anxiety>. cited by applicant

MARINOL® Product Description, NDA 18-651/S-025 and S-026, Jul. 2006, pp. 3-13. cited by applicant

Masangkay, E. G., "FDA Confirms GW Pharmaceuticals' IND For Epidiolex Trial In Dravet Syndrome," May 9, 2014; <https://www.bioprocessonline.com/doc/2014/05/09/fda-confirms-gw-pharmaceuticals-ind-for-epidiolex-trial-in-dravet-syndrome-0001>, 2 pages. cited by applicant

Mead et al., "The Untold Story of the Cannabidiol (CBD) Revolution," *US Neurology*, 2018; 14(Suppl. 3):2-8. Published Online: Oct. 16, 2018. cited by applicant

Mechoulam, et al., "Toward drugs derived from cannabis," *Naturwissenschaften*, 65(4):174-9 (1978). cited by applicant

Mechoulam, R. et al., "Cannabidiol—Recent Advances," *Chemistry & Biodiversity*, vol. 4, pp. 1678-1692 (2007). cited by applicant

Mechoulam, R., "Conversation with Ralph Mechoulam," *Addiction* Jun. 2007;102(6):887-93. doi: 10.1111/j.1360-0443.2007.01795.x.. cited by applicant

Mechoulam, R. & Parker, L. A., "The Endocannabinoid System and the Brain," *Annu. Rev. Psychol.* 2013. 64:21-47. cited by applicant

Mechoulam, R. & Parker, L. A., "Towards a better cannabis drug," *British Journal of Pharmacology* (2013) 170 1363-1364. cited by applicant

Mechoulam et al., "Cannabidiol: an overview of some chemical and pharmacological aspects. Part I: chemical aspects," *Chemistry and Physics of Lipids*, 121

Mechoulam et al., "Hashish-I: The Structure of Cannabidiol," *Tetrahedron*, 19:2073-2078 (1963). cited by applicant

Montenegro et al., "Efficacy of Clobazam as Add-on Therapy for Refractory Epilepsy: Experience at a US Epilepsy Center," *Clinical Neuropharmacology*, 31

Montouris, "Rational approach to treatment options for Lennox-Gastaut syndrome," *Epilepsia*, 52:10-20 (2011). cited by applicant

Moore, Y. et al., "Cannabidiol reduced frequency of convulsive seizures in drug resistant Dravet Syndrome," *Structured Abstracts of Sentinel Articles: Pickett*, Educ Pract Ed Oct. 2018, vol. 103, No. 5., 2 pages. Abstract. cited by applicant

Morrison et al., "A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Drug Development," 8(8):1009-1031 (2019). cited by applicant

Mudigoudar et al., "Emerging Antiepileptic Drugs for Severe Pediatric Epilepsies," *Semin Pediatr Neurol*, 23:167-179 (2016). cited by applicant

Nair et al., "A simple practice guide for dose conversion between animals and human," *Journal of Basic and Clinical Pharmacy*, 7:27-31 (2016). cited by applicant

New Drug Application No. 210365 for Epidiolex (cannabidiol) 100 mg/ml oral solution, Jun. 25, 2018, 12 pages. cited by applicant

[No Author Listed], The Reuters Staff, BRIEF-GW Pharma receives FDA fast-track designation for Dravet syndrome treatment, Jun. 6, 2014, 1 page; <https://www.reuters.com/article/health/gw-pharma-receives-fda-fast-track-designation-for-dravet-syndrome-treatment-idUSFWNOOL01D20140606>. cited by applicant

[No Author Listed], "Medical Cannabis Community Wants To Remain Apart," *Medical Marijuana News*, Apr. 3, 2013, 3 pages; Kitsap Peninsula Business Journal, <https://www.420magazine.com/community/threads/medical-cannabis-community-wants-to-remain-apart.186955/>. cited by applicant

ONFI™ (clobazam) tablets Prescribing Information, NDA 202067 Onfi (clobazam) Tablets for oral use FDA Approved Labeling Text, dated Oct. 21, 2011, 28

Oguni, H. et al., "Long-Term Prognosis of Lennox-Gastaut Syndrome," *Epilepsia*, 37(Suppl 3):44-47 (1996). cited by applicant

Oguni, H. et al., "Severe myoclonic epilepsy in infants—a review based on the Tokyo women's Medical University series of 84 cases," *Brain Dev.*, 23:736-74

Ostendorf, A. P. & Ng, Y-T., "Treatment-resistant Lennox-Gastaut syndrome: therapeutic trends, challenges and future directions," *Neuropsychiatric Disease a*

Palmer, A. C. et al., "Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy," *Cell*, 171:1678-

Panikasiwill, D. et al., "An endogenous cannabinoid (2-AG) is neuroprotective after brain injury," *Nature* 413:527-531 (2001). cited by applicant

Pellicia, et al., International Association for Cannabis as Medicine, IACM 3rd Conference on Cannabinoids in Medicine, Sep. 9-10, 2005, 2005 Conference on

Perucca, "Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last?" *Journal of Epilepsy Research*, 7(2):61-76 (2017). cited by applicant

Pertwee, "Cannabidiol as a potential medicine," In: Mechoulam, R. (eds) *Cannabinoids as Therapeutics. Milestones in Drug Therapy MDT* (2005), pp. 47-65, X\_3. cited by applicant

Physician's Desk Reference, 63rd Ed., 2009, 423-461, 2192-2194, 2639-2242, 3019-3022. cited by applicant

Potter, C., "Cannabis Extract Brings Hope for Children with Epilepsy," Dec. 3, 2013, 3 pages. cited by applicant

"Pot or not? Why parents of kids with epilepsy want access to marijuana treatment," CTVNews.ca Staff, Published Thursday, Jul. 18, 2013; Last Updated Thursday, Jul. 18, 2013; <http://www.ctvnews.ca/health/health-headlines/pot-or-not-why-parents-of-kids-with-epilepsy-want-access-to-marijuana-treatment-1.1372695?cache=.> cited by applicant

Purcarin, G. & Ng, Y-T., "Experience in the use of clobazam in the treatment of Lennox-Gastaut syndrome," *Ther Adv Neurol Disord* 2014, vol. 7(3):169-176

Ragona, F. et al., "Dravet syndrome: early clinical manifestations and cognitive outcome in 37 Italian patients," *Brain Dev.*, 32:71-77 (2010). cited by applicant

Rison, R. A., "How to write a neurology case report," *Journal of Medical Case Reports*, 10:91 (2016); doi:10.1186/s13256-016-0867-x, 5 pages. cited by applicant

Rohrback, Brian G., Ph.D, MBA President of Infometrix, Inc. presents his talk on "Assays of Cannabinoids," at NYU School of Medicine's Cannabidiol Conference, <http://faces.med.nyu.edu/research-education/cannabidiol-conference>, 29 pages. cited by applicant

Romano et al., "Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol," *Phytomedicine*, 21:631-639 (2014)

Rosenkrantz et al., "Inhalation, Parenteral and Oral LD50 Values of Δ<sup>9</sup>-Tetrahydrocannabinol in Fischer Rats," *Toxicology and Applied Pharmacology*, 16:1-19 (1979)

Rowe, R. C. et al., "Handbook of Pharmaceutical Excipients," Pharmaceutical Press and American Pharmacists Association 2009, pp. 17-19; [https://www.academia.edu/16731682/Handbook\\_of\\_Pharmaceutical\\_Excipients\\_6th\\_Edition](https://www.academia.edu/16731682/Handbook_of_Pharmaceutical_Excipients_6th_Edition). cited by applicant

Russo et al., "Pharmacology of Epileptogenesis and Related Comorbidities in the WAG/Rij Rat Model of Genetic Absence Epilepsy," *Journal of Neuroscience*, 24:1051-1060 (2004)

Russo et al., "Upholding WAG/Rij Rats as a Model of Absence Epileptogenesis: Hidden Mechanisms and a New Theory on Seizure Development," *Neuroscience Letters*, 380:1-4 (2005)

Saade, D. & Joshi, C., "Pure Cannabidiol in the Treatment of Malignant Migrating Partial Seizures in Infancy: A Case Report," *Pediatric Neurology*, 52:544-550 (2005)

<http://dx.doi.org/10.1016/j.pediatrneurol.2015.02.008>. cited by applicant

Samanta, D., "Cannabidiol: A Review of Clinical Efficacy and Safety in Epilepsy," *Pediatric Neurology*, 96:24-29 (2019). cited by applicant

Samanta et al., "Pharmacokinetics of Cannabidiol in Dogs," *Drug Metabolism and Disposition*, 16(3):469-472 (1988). cited by applicant

Sands, T. T. et al., "Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program," *Neurology*, 87(12):1203-1211 (2016)

<https://doi.org/10.1007/s40263-018-0589-2>. cited by applicant

Sarkisova et al., "The WAG/Rij Strain: A Genetic Animal Model of Absence Epilepsy with Comorbidity of Depression," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 57:1-10 (2015)

Sasidharan, S. et al., "Extraction, Isolation and Characterization of Bioactive Compounds from Plants' Extracts," *Afr J Tradit Complement Altern Med.*, 8(1):1-10 (2015)

Schafroth, M. A. et al., "Stereodivergent Total Synthesis of Δ<sup>9</sup>-Tetrahydrocannabinols," *Angew. Chem. Int. Ed.*, 53:13898-13901 (2014). cited by applicant

Schafroth et al., "Δ<sup>9</sup>-cis-Tetrahydrocannabinol: Natural Occurrence, Chirality, and Pharmacology," *Journal of Natural Products*, 84:2502-2510 (2021). cited by applicant

Scheffer, I. E., "Diagnosis and long-term course of Dravet syndrome," *Eur J of Paediatric Neurology* 16 (2012) S5-S8. cited by applicant

Schwieterman, M. L. et al., "Strawberry Flavor: Diverse Chemical Compositions, a Seasonal Influence, and Effects on Sensory Perception," *PLoS ONE*, 9(2):e6987 (2014)

Screenshot confirming date of Epidiolex (Cannabidiol) in Treatment Resistant Epilepsy, Apr. 2015; <https://epilepsyontario.org/wp-content/uploads/2015/Epidiolex-Poster08Apr2015.pdf>, 1 page. cited by applicant

Serra I., et al., "Cannabidiol modulates phosphorylated rpS6 signalling in a zebrafish model of Tuberous Sclerosis Complex," *Behavioural Brain Research*, 361:1-10 (2019)

Silva, R. et al., "Clobazam as Add-on Therapy in Children with Epileptic Encephalopathy," *Can. J. Neurol. Sci.*, 33:209-213 (2006). cited by applicant

Silvestro, S. et al., "Use of Cannabidiol in the Treatment of Epilepsy: Efficacy and Security in Clinical Trials," *Molecules* 2019, 24, 1459, 25 pages; doi:10.3390/molecules24141459

Sirven et al., Finding the Best Dosage of Medication, Epilepsy Foundation (Mar. 19, 2014); <https://www.epilepsy.com/treatment/medications/finding-best-dosage>

Sluss, R. J., "Comparison of Artificial Flavors in Commercial Products and Actual Natural Flavor via Gas Chromatography Mass Spectroscopy Data." (2009) <https://dc.etsu.edu/etd/1804>, 72 pages. cited by applicant

Smith, R. M., "Identification of Butyl Cannabinoids in Marijuana," *Journal of Forensic Sciences*, 42:610-618 (1997). cited by applicant

Smith et al., "Δ<sup>9</sup>-Tetrahydrocannabinol



Stewart, K., "University of Utah doctors: Say 'yes' to cannabis oil for kids," By Kirsten Stewart The Salt Lake Tribune, Nov. 13, 2013, 4 pages. cited by applicant

Stinchcomb, A. L. et al., "Human skin permeation of Δ.SUP.9-tetrahydrocannabinol, cannabidiol and cannabinol," JPP 2004, 56: 291-297. cited by applicant

Thiel, E. A., "Managing Epilepsy in Tuberous Sclerosis Complex," J Child Neurol 2004; 19:680-686. cited by applicant

Young, S., "Marijuana stops child's severe seizures," CNN Health online, Aug. 7, 2013, 4 pages; <https://www.cnn.com/2013/08/07/health/charlotte-child-med-marijuana/index.html#:~:text=The%20first%20time%20Paige%20Figi,seizures%20stopped%20for%20seven%20days.&text=The%20marijuana%20strain%20cited%20by%20applicant>

Study NCT02224690—A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) As Adjunctive Treatment for Seizures Associated with Tuberous Sclerosis Complex, Aug. 22, 2014; <https://clinicaltrials.gov/ct2/show/NCT02224690>, 1 page. cited by applicant

Tanya Lewis, Mystery Mechanisms, The Scientist Magazine, Jul. 29, 2016, 2 pages; <http://www.the-scientist.com/>. cited by applicant

Thomas et al., "Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro," British J Pharmacology, 150(5): 1002-1011 (2006). cited by applicant

Thomas et al., "Characterization of the Lipophilicity of Natural and Synthetic Analogs of Δ.SUP.9-Tetrahydrocannabinol and Its Relationship to Pharmacological Activity," Experimental Therapeutics, 255(2):624-630 (1990). cited by applicant

Thompson et al., "Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys," Toxicology and Applied Pharmacology, vol. 25, Issue 3, pp. 453-461 (1971). cited by applicant

Thompson et al., "Oral and Intravenous Toxicity of Δ.SUP.9-Tetrahydrocannabinol in Rhesus Monkeys," Toxicology and Applied Pharmacology, 27:648-665 (1973). cited by applicant

Tose, L. V. et al., "Isomeric separation of cannabinoids by UPLC combined with ionic mobility mass spectrometry (TWIM-MS)—Part I," International Journal of Mass Spectrometry and Ion Processes, 227:1-12 (2003). cited by applicant

Trost, B. M. & Dogra, K., "Synthesis of (-)-Δ9-trans-Tetrahydrocannabinol: Stereocontrol via Mo-Catalyzed Asymmetric Allylic Alkylation Reaction," Organic Letters, 12(12):2652-2655 (2011). cited by applicant

Turkkanis et al., "Excitatory and Depressant Effects of Delta-9-Tetrahydrocannabinol and Cannabidiol on Cortical Evoked Responses in the Conscious Rat," European Journal of Pharmacology, 172:155-162 (1989). cited by applicant

Uliss et al., "The conversion of 3,4-CIS- to 3,4-TRANS-cannabinoids," Tetrahedron, 34:1885-1888 (1978). cited by applicant

"Marinol®," label retrieved from: <[https://www.accessdata.fda.gov/dmgsatfda/docs/label/2006/018651\\_s025s026lbl.pdf](https://www.accessdata.fda.gov/dmgsatfda/docs/label/2006/018651_s025s026lbl.pdf)>, 11 pages. cited by applicant

Van Bakel et al., "The draft genome and transcriptome of *Cannabis sativa*," Genome Biology 2011, 12: R102, 18 pages; <http://genomebiology.com/2011/12/1/R102>

Van Straten et al., "Update on the Management of Lennox-Gastaut Syndrome," Pediatric Neurology, 47:153-161 (2012). cited by applicant

Velisek, L., "Models of Chemically-Induced Acute Seizures," In Models of Seizures and Epilepsy, 127-152, 2006. cited by applicant

Vrielynck, P., "Current and emerging treatments for absence seizures in young patients," Neuropsychiatric Disease and Treatment, 9:963-975 (2013). cited by applicant

Warzak et al., "Caffeine Consumption in Young Children," The Journal of Pediatrics, vol. 158, Issue 3, P508-509, Mar. 1, 2011. cited by applicant

Weed Wars, Video I, Dec. 10, 2011, Weed Wars: The Story of Jayden-Andrew DeAngelo; <https://www.youtube.com/watch?v=2WizdR5uHj0>. cited by applicant

Weed Wars, Video II, May 25, 2013, 3 pages; available at [https://www.youtube.com/watch?v=XBX\\_DB9sw5U](https://www.youtube.com/watch?v=XBX_DB9sw5U). cited by applicant

WeedWars, CNN Special, Decriminalise It, Dr. Sanjay Gupta, 2013; [https://www.youtube.com/watch?v=Z3lMfl1\\_K6U](https://www.youtube.com/watch?v=Z3lMfl1_K6U), 8 pages. cited by applicant

Weed Country, Episode 5, 2013; <https://www.youtube.com/watch?v=0isjCcMtxBk>; <https://www.youtube.com/watch?v=GitMYGvwC4E&t=212s>, 25 pages. cited by applicant

Weed Country, Episode 6, 2013; <https://www.youtube.com/watch?v=Uyzuy1fNqfQ>, 18 pages. cited by applicant

Nathaniel Morris (of Weed Country on Discovery Channel), Selected Media Examples of Pediatric Applications of Cannabidiol, 2013, 6 pages; available at <https://www.discovery.com/shows/weed-country>. cited by applicant

Whalley, Benjamin J. Ph.D. of the University of Reading presents his talk on "Cannabis and Epilepsy: Cannabidiol (CBD) and Cannabidavarin (CBDV) in Pediatric Epilepsy," at the University of Medicine's Cannabidiol Conference (Oct. 4, 2013). Video published online. <<http://faces.med.nyu.edu/research-education/cannabidiol-conference>>, 30 pages. cited by applicant

Wheless, J. W. et al., "Pharmacokinetics and Tolerability of Multiple Doses of Pharmaceutical-Grade Synthetic Cannabidiol in Pediatric Patients with Treatment-Resistant Epilepsy," Epilepsia, 55(1):100-107 (2014). doi: 10.1007/s40263-019-00624-4. cited by applicant

[Anonymous] "When to Expect Results from CW Hemp Oil", downloaded Sep. 5, 2017, <https://www.cwhemp.com/blog/expecting-results-from-hemp>, 9 pages. cited by applicant

Whittle et al., (2001). Prospects for New Cannabis-Based Prescription Medicines. Journal of Cannabis Therapeutics. 1(3-4); doi:10.1300/J175v01\_1(3-4), 23 pages. cited by applicant

Wilkey, R., "'Weed Wars': Five-Year-Old Takes Medical Marijuana On Reality Show (VIDEO)", Dec. 10, 2011, 7 pages; <https://www.huffpost.com/entry/weed-wars>. cited by applicant

Williams, "The Key to Healing Broken Bones May be Found in This Illegal Drug," Jul. 25, 2015; <https://www.fool.com/investing/high-growth/2015/07/25/the-key-to-healing-broken-bones-may-be-found-in-this-illegal-drug>. cited by applicant

Willis, L., "Final Report on the Safety Assessment of Sesame Oil," Journal of the American College of Toxicology, 12(3):261-277 (1993). cited by applicant

Wright et al., Cannabidiol (CBD) in Dravet Syndrome: A Randomised, Dose-Ranging Pharmacokinetics and Safety Trial (GWPCARE1), Epilepsia, 58(Suppl. 1):1-10 (2017). cited by applicant

Zamberletti et al., "Alterations of prefrontal cortex GABAergic transmission in the complex psychotic-like phenotype induced by adolescent delta-9-tetrahydrocannabinol," Neuropsychopharmacology, 39(1):63-75 (2014). cited by applicant

Zhang, T. et al., "Pre-seizure state identified by diffuse optical tomography," Scientific Reports, 4:3798 (2014); <https://doi.org/10.1038/srep03798>, 10 pages. cited by applicant

Zuardi et al., "Antipsychotic Effect of Cannabidiol," J Clin Psychiatry, 56(10):485-486 (1995). cited by applicant

Zuardi et al., "Cannabidiol for the treatment of psychosis in Parkinson's disease," Journal of Psychopharmacology, 23(8):979-983 (2009). cited by applicant

Zuardi A., et al., "Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol during Public Speaking in Real Life," Frontiers in Pharmacology, 10:1-10 (2019). cited by applicant

U.S. Appl. No. 15/640,033, filed Jun. 30, 2017. cited by applicant

U.S. Appl. No. 16/959,354, filed Jun. 30, 2020. cited by applicant

U.S. Appl. No. 16/935,005, filed Jul. 21, 2020. cited by applicant

U.S. Appl. No. 17/012,448, filed Sep. 4, 2020. cited by applicant

U.S. Appl. No. 17/050,956, filed Oct. 27, 2020. cited by applicant

U.S. Appl. No. 17/102,109, filed Nov. 23, 2020. cited by applicant

U.S. Appl. No. 17/231,625, filed Apr. 15, 2021. cited by applicant

U.S. Appl. No. 17/296,066, filed May 21, 2021. cited by applicant

U.S. Appl. No. 17/296,076, filed May 21, 2021. cited by applicant

U.S. Appl. No. 17/424,682, filed Jul. 21, 2021. cited by applicant

U.S. Appl. No. 17/426,442, filed Jul. 28, 2021. cited by applicant

U.S. Appl. No. 17/406,401, filed Aug. 19, 2021. cited by applicant

U.S. Appl. No. 17/435,892, filed Sep. 2, 2021. cited by applicant

U.S. Appl. No. 17/606,370, filed Oct. 25, 2021. cited by applicant

U.S. Appl. No. 17/611,824, filed Nov. 16, 2021. cited by applicant

U.S. Appl. No. 17/548,232, filed Dec. 10, 2021. cited by applicant

U.S. Appl. No. 17/576,868, filed Jan. 14, 2022. cited by applicant

U.S. Appl. No. 17/627,946, filed Jan. 18, 2022. cited by applicant

U.S. Appl. No. 17/585,485, filed Jan. 26, 2022. cited by applicant

U.S. Appl. No. 17/631,069, filed Jan. 28, 2022. cited by applicant

U.S. Appl. No. 17/638,629, filed Feb. 25, 2022. cited by applicant

U.S. Appl. No. 17/689,607, filed Mar. 8, 2022. cited by applicant

U.S. Appl. No. 17/689,245, filed Mar. 8, 2022. cited by applicant

U.S. Appl. No. 17/768,048, filed Apr. 11, 2022. cited by applicant

U.S. Appl. No. 17/770,435, filed Apr. 20, 2022. cited by applicant

U.S. Appl. No. 17/770,436, filed Apr. 20, 2022. cited by applicant  
U.S. Appl. No. 17/771,184, filed Apr. 22, 2022. cited by applicant  
U.S. Appl. No. 17/771,190, filed Apr. 22, 2022. cited by applicant  
U.S. Appl. No. 17/771,195, filed Apr. 22, 2022. cited by applicant  
U.S. Appl. No. 17/771,183, filed Apr. 22, 2022. cited by applicant  
U.S. Appl. No. 17/744,224, filed May 13, 2022. cited by applicant  
U.S. Appl. No. 17/777,734, filed May 18, 2022. cited by applicant  
U.S. Appl. No. 17/777,677, filed May 18, 2022. cited by applicant  
U.S. Appl. No. 17/777,681, filed May 18, 2022. cited by applicant  
U.S. Appl. No. 17/841,167, filed Jun. 15, 2022. cited by applicant  
U.S. Appl. No. 17/786,949, filed Jun. 17, 2022. cited by applicant  
U.S. Appl. No. 17/853,367, filed Jun. 29, 2022. cited by applicant  
U.S. Appl. No. 17/817,753, filed Aug. 5, 2022. cited by applicant  
U.S. Appl. No. 18/002,437, filed Dec. 19, 2022. cited by applicant  
U.S. Appl. No. 18/005,838, filed Jan. 17, 2023. cited by applicant  
U.S. Appl. No. 18/005,841, filed Jan. 17, 2023. cited by applicant  
U.S. Appl. No. 18/005,843, filed Jan. 17, 2023. cited by applicant  
U.S. Appl. No. 18/005,845, filed Jan. 17, 2023. cited by applicant  
U.S. Appl. No. 18/005,847, filed Jan. 17, 2023. cited by applicant  
U.S. Appl. No. 18/005,848, filed Jan. 17, 2023. cited by applicant  
U.S. Appl. No. 18/005,851, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/005,852, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/005,853, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/005,868, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/005,959, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/005,960, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/005,961, filed Jan. 18, 2023. cited by applicant  
U.S. Appl. No. 18/006,121, filed Jan. 19, 2023. cited by applicant  
U.S. Appl. No. 18/006,125, filed Jan. 19, 2023. cited by applicant  
U.S. Appl. No. 18/006,127, filed Jan. 19, 2023. cited by applicant  
U.S. Appl. No. 18/006,129, filed Jan. 19, 2023. cited by applicant  
U.S. Appl. No. 18/006,131, filed Jan. 19, 2023. cited by applicant  
U.S. Appl. No. 18/006,133, filed Jan. 19, 2023. cited by applicant  
U.S. Appl. No. 18/161,603, filed Jan. 30, 2023. cited by applicant  
U.S. Appl. No. 18/170,235, filed Feb. 16, 2023. cited by applicant  
U.S. Appl. No. 18/043,810, filed Mar. 2, 2023. cited by applicant  
U.S. Appl. No. 18/044,941, filed Mar. 10, 2023. cited by applicant  
U.S. Appl. No. 18/245,856, filed Mar. 17, 2023. cited by applicant  
U.S. Appl. No. 18/186,792, filed Mar. 20, 2023. cited by applicant  
U.S. Appl. No. 18/311,221, filed May 2, 2023. cited by applicant  
U.S. Appl. No. 18/256,307, filed Jun. 7, 2023. cited by applicant  
U.S. Appl. No. 18/257,373, filed Jun. 14, 2023. cited by applicant  
U.S. Appl. No. 18/257,537, filed Jun. 14, 2023. cited by applicant  
U.S. Appl. No. 18/257,479, filed Jun. 14, 2023. cited by applicant  
U.S. Appl. No. 18/258,485, filed Jun. 20, 2023. cited by applicant  
U.S. Appl. No. 18/446,405, filed Aug. 8, 2023. cited by applicant  
U.S. Appl. No. 18/546,254, filed Aug. 11, 2023. cited by applicant  
U.S. Appl. No. 18/548,003, filed Aug. 25, 2023. cited by applicant  
U.S. Appl. No. 18/477,467, filed Sep. 28, 2023. cited by applicant  
U.S. Appl. No. 18/479,671, filed Oct. 2, 2023. cited by applicant  
U.S. Appl. No. 18/560,316, filed Nov. 10, 2023. cited by applicant  
U.S. Appl. No. 18/560,337, filed Nov. 10, 2023. cited by applicant  
U.S. Appl. No. 18/560,341, filed Nov. 10, 2023. cited by applicant  
U.S. Appl. No. 18/560,346, filed Nov. 10, 2023. cited by applicant  
U.S. Appl. No. 18/526,795, filed Dec. 1, 2023. cited by applicant  
U.S. Appl. No. 18/545,754, filed Dec. 19, 2023. cited by applicant  
U.S. Appl. No. 18/292,844, filed Jan. 26, 2024. cited by applicant  
U.S. Appl. No. 18/597,717, filed Mar. 6, 2024. cited by applicant  
Notice of Opposition to European Patent Application No. EP18737374.1, Patent No. EP3641819, dated Jul. 12, 2024, 23 pages. cited by applicant  
Advagraf 0.5 mg prolonged-release hard capsules, Advagraf 1 mg prolonged-release hard capsules, Advagraf 3 mg prolonged-release hard capsules, Advagraf  
of Product Characteristics, retrieved on Aug. 13, 2024, 6 pages. cited by applicant  
Devarbhavi, "An update on drug-induced liver injury," J. Clinical and Experimental Hepatology, 2(3):247-259 (2012. cited by applicant  
Kelley, "Medical Cannabis Community Wants to Remain Apart," Kitsap Peninsula Business Journal, Apr. 3, 2013; available at <https://www.420magazine.com/remain-apart.186955/>, 4 pages. cited by applicant  
KLONOPIN® Tablets (clonazepam) KLONOPIN® Wafers (clonazepam orally disintegrating tablets) Product Label, revised Apr. 4, 2009, 18 pages. cited by  
Rosenkrantz et al., "Toxicity of Short-Term Administration of Cannabinoids to Rhesus Monkeys," Toxicology and Applied Pharmacology, 58:118-131 (1981).  
EPIDIOLEX® (cannabidiol) oral solution, CV, Prescribing Information, 2021, 38 pages; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/210365](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210365)  
EPIDIOLEX® (cannabidiol) oral solution, CV, Prescribing Information, 2024, 32 pages; <https://pp.jazzpharma.com/pi/epidiolex.en.USPI.pdf>. cited by applica  
Feerman, D. E. & Lasker, J. M., "Metabolism of fentanyl, a synthetic opioid analgesic, by human liver microsomes. Role of CYP3A4," Drug Metabolism and  
<https://dmd.aspetjournals.org/content/24/9/932>, 4 pages. cited by applicant  
Manini et al., "Safety and Safety and Pharmacokinetics of Oral Cannabidiol When Administered Concomitantly With Intravenous Fentanyl in Humans," J Ad  
doi:10.1097/ADM.000000000000118. cited by applicant  
Morrison et al., "A Phase 1 Investigation Into the Potential Effects of Cannabidiol on CYP3A4-Mediated Drug-Drug Interactions in Healthy Volunteers," Abs  
Dec. 1, 2018, Published Date: Nov. 5, 2018; <https://aesnet.org/abstractslisting/a-phase-1-investigation-into-the-potential-effects-of-cannabidiol-on-cyp3a4-me>  
cited by applicant

Patsalos et al., "Clinical implications of trials investigating drug-drug interactions between cannabidiol or inhibitors or common antiepileptic drugs and other antiepileptic drugs," *Epilepsia*, 50(1):1-10 (2009). cited by applicant

Notice of Opposition to European Patent Application No. EP19702670.1, Patent No. EP3743053, dated Aug. 27, 2024, 22 pages. cited by applicant

Actiq™ (Oral Transmucosal Fentanyl Citrate), Clinical Pharmacology and Biopharmaceutics Review, Reviewer Suresh Doddapaneni, Ph.D., Center for Drug Evaluation Research, FDA, dated Nov. 11, 1996, Review Date: Apr. 22, 1997, 25 pages. cited by applicant

Afternoon Session, Panel 1—Living with TSC and LAM, Official Transcript (Part 3 of 4) of the Video "Externally-Led Patient-Focused Drug Development Meeting," available on You Tube at <https://www.youtube.com/watch?v=qoxOKR3WpFs>, 24 pages. cited by applicant

Afternoon Session, Panel 2—Current and Future Approaches to Treating TSC and LAM, Official Transcript (Part 4 of 4) of the Video "Externally-Led Patient-Focused Drug Development Meeting," available on You Tube at <https://www.youtube.com/watch?v=qoxOKR3WpFs>, 17 pages. cited by applicant

[No Author Listed] The Voice of the Patient, A Report from the Tuberous Sclerosis Alliance's Externally-Led Patient-Focused Drug Development Meeting, Report No. 1, dated June 2017, 10 pages. cited by applicant

Conference Book of the 2017 International Research Conference on TSC and LAM: Innovating Through Partnerships, Washington, D.C., Jun. 22-24, 2017, 10 pages. cited by applicant

Devinsky et al., Trial Protocol, Supplementary Material to "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome," *N Engl J Med*, 376(21):2011-2020 (2017). cited by applicant

Franz, D. N. & Capal, J. K., "mTOR inhibitors in the pharmacologic management of tuberous sclerosis complex and their potential role in other rare neurodevelopmental disorders," *Neurotherapeutics*, 12:51 (2017), 9 pages; doi: 10.1186/s13023-017-0596-2. cited by applicant

Krueger et al., "Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Sclerosis Complex Consensus Conference," *Neurotherapeutics*, 9(1):1-10 (2016). cited by applicant

Labroo et al., "Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy and toxicity," *Drug Metabolism and Pharmacokinetics*, 16(1):1-10 (1997). cited by applicant

Morning Session, Panel 1—Living with TSC and LAM, Official Transcript (Part 1 of 4) of the Video "Externally-Led Patient-Focused Drug Development Meeting," available on You Tube at <https://www.youtube.com/watch?v=qoxOKR3WpFs>, 26 pages. cited by applicant

Morning Session, Panel 2—Current and Future Treatments for TSC, Official Transcript (Part 2 of 4) of the Video "Externally-Led Patient-Focused Drug Development Meeting," available on You Tube at <https://www.youtube.com/watch?v=qoxOKR3WpFs>, 19 pages. cited by applicant

Nazario et al., "Caffeine protects against memory loss induced by high and non-anxiolytic dose of cannabidiol in adult zebrafish (*Danio rerio*)," *Pharmacol Biochem Behav*, 10.1016/j.pbb.2015.06.008. Epub Jun. 20, 2015. cited by applicant

[No Author Listed], European Medicines Agency (EMA), "Public summary of opinion on orphan designation—Cannabidiol for the treatment of Dravet syndrome," <https://www.ema.europa.eu/en/documents/orphandesignation/eu3141339-public-summary-opinion-orphan-designation-cannabidiol-treatment-dravetsyndrome.pdf>, 10 pages. cited by applicant

Peron, A. et al., Agenda Program and Description of the "2nd Early Tuberous Sclerosis Complex Researcher Meeting," Washington, DC, Jun. 21, 2017, 6 pages. cited by applicant

Shrivastava et al., "Cannabidiol Induces Programmed Cell Death in Breast Cancer Cells by Coordinating the Cross-talk Between Apoptosis and Autophagy," *Cell Death and Disease*, 7:e2572 (2016). cited by applicant

Vezyroglou, K. & Cross, J. H., "Targeted Treatment in Childhood Epilepsy Syndromes," *Curr Treat Options Neurol*, 18:29 (2016), Published online May 7, 2016. cited by applicant

Wirrell, E. C., "Treatment of Dravet Syndrome," *Can J Neurol Sci.*, 43:S13-S18 (2016). cited by applicant

Cunetti, L. et al., "Chronic Pain Treatment with Cannabidiol in Kidney Transplant Patients in Uruguay," *Transplantation Proceedings*, vol. 30 (Suppl. 2): 390-391 (1998). cited by applicant

Timmings et al., "Lamotrigine as an Add-On Drug in the Management of Lennox-Gastaut Syndrome," *European Neurology*, 32(6):305-307 (1992). cited by applicant

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## Background/Summary

### CROSS-REFERENCE TO RELATED APPLICATIONS

(1) This application claims the benefit of International PCT Application No. PCT/GB2018/053483, filed Nov. 30, 2018; and Great Britain Application No. 1720020.5, filed Dec. 1, 2017; all of which are incorporated herein by reference to their entirety.

### FIELD OF THE INVENTION

(2) The present invention relates to the use of cannabidiol (CBD) in the treatment of patients with childhood-onset epilepsy who are concurrently taking immunosuppressant drugs.

(3) In particular the immunosuppressant drug is a calcineurin inhibitor. More particularly the immunosuppressant drug is tacrolimus.

(4) Where the CBD is used in combination with an immunosuppressant drug, caution should be taken. For example, the dose of either the CBD and/or the immunosuppressant drug may be required to be reduced. Moreover, the patient may need to be monitored for side effects of said drug-drug interaction.

(5) Preferably the CBD used is in the form of a highly purified extract of cannabis such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular the cannabinoid tetrahydrocannabinol (THC) has been substantially removed, to a level of not more than 0.15% (w/w) and the propyl analogue of CBD, cannabidivarin, (CBDV) is present in amounts of up to 1%. Alternatively, the CBD may be a synthetically produced CBD.

### BACKGROUND TO THE INVENTION

(6) Epilepsy occurs in approximately 1% of the population worldwide, (Thurman et al., 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AEDs). However, 30% of this patient group, (Eadie et al., 2012), are unable to obtain seizure freedom from the AED that are available and as such are termed as suffering from intractable or "treatment-resistant epilepsy" (TRE).

(7) Intractable or treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2009).

(8) Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment-resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

(9) Childhood-onset epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

(10) When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

(11) The main symptom of epilepsy is repeated seizures. In order to determine the type of epilepsy or the epileptic syndrome that a patient is suffering from, an investigation into the type of seizures that the patient is experiencing is undertaken. Clinical observations and electroencephalography (EEG) tests are conducted and the type(s) of seizures are classified according to the ILAE classification described below.

(12) The International classification of seizure types proposed by the ILAE was adopted in 1981 and a revised proposal was published by the ILAE

in 2010 and not yet superseded the 1981 classification. The 2010 proposal for revised terminology changes to replace the terminology of partial with focal. In addition, the term “simple partial seizure” has been replaced by the term “focal seizure where awareness/responsiveness is not impaired” and the term “complex partial seizure” has been replaced by the term “focal seizure where awareness/consciousness is impaired”.

(13) Generalised seizures, where the seizure arises within and rapidly engages bilaterally distributed networks, can be split into six subtypes: Tonic-Clonic (grand mal) seizures; Absence (petit mal) Seizures; Clonic Seizures; Tonic Seizures; Atonic Seizures and Myoclonic Seizures.

(14) Focal (partial) seizures where the seizure originates within networks limited to only one hemisphere, are also split into sub-categories. Here the seizure is characterized according to one or more features of the seizure, including aura, motor, autonomic and awareness/responsiveness. Where a seizure begins as a localized seizure and rapidly evolves to be distributed within bilateral networks this seizure is known as a Bilateral convulsive seizure, which is the proposed terminology to replace Secondary Generalised Seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).

(15) Epileptic syndromes often present with many different types of seizure and identifying the types of seizure that a patient is suffering from is important as many of the standard AEDs are targeted to treat or are only effective against a given seizure type/sub-type.

(16) One such childhood epilepsy syndrome is Lennox-Gastaut syndrome (LGS). LGS is a severe form of epilepsy, where seizures usually begin before the age of 4. Seizure types, which vary among patients, include tonic (stiffening of the body, upward deviation of the eyes, dilation of the pupils, and altered respiratory patterns), atonic (brief loss of muscle tone and consciousness, causing abrupt falls), atypical absence (staring spells), and myoclonic (sudden muscle jerks). There may be periods of frequent seizures mixed with brief, relatively seizure-free periods.

(17) Seizures in LGS are often described as “drop seizures”. Such drop seizures are defined as an attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.

(18) Most patients with LGS experience some degree of impaired intellectual functioning or information processing, along with developmental delays, and behavioural disturbances.

(19) LGS can be caused by brain malformations, perinatal asphyxia, severe head injury, central nervous system infection and inherited degenerative or metabolic conditions. In 30-35% of cases, no cause can be found.

(20) The first line treatment for drop seizures, including the treatment of drop seizures in patients with LGS, usually comprises a broad-spectrum AED, such as sodium valproate often in combination with rufinamide or lamotrigine. Other AEDs that may be considered include felbamate, clobazam and topiramate.

(21) AEDs such as carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine and vigabatrin are contra-indicated in drop seizures.

(22) Common AEDs defined by their mechanisms of action are described in the following tables:

(23) TABLE-US-00001 TABLE 1 Examples of narrow spectrum AEDs

| Narrow-spectrum AED   | Mechanism        | Indication                            |
|---|------------------|---------------------------------------|
| Phenytoin   | Sodium channel   | Complex partial                       |
| Tonic-clonic  | Phenobarbital    | GABA/Calcium                          |
| Partial seizures  | Tonic-clonic     | Carbamazepine                         |
| Sodium channel  | Partial seizures | Tonic-clonic                          |
| Mixed seizures  | Oxcarbazepine    | Sodium channel                        |
| Partial seizures  | Tonic-clonic     | Mixed seizures                        |
| Gabapentin  | Calcium channel  | Partial seizures                      |
| Mixed seizures  | Pregabalin       | Calcium channel                       |
| Adjunct therapy for partial seizures with or without secondary generalisation | Lacosamide       | Sodium channel                        |
| Adjunct therapy for partial seizures  | Vigabatrin       | GABA                                  |
| Secondarily generalized tonic-clonic seizures                                 | Partial seizures | Infantile spasms due to West syndrome |

(24) TABLE-US-00002 TABLE 2 Examples of broad spectrum AEDs

| Broad-spectrum AED   | Mechanism                             | Indication  |
|--|---------------------------------------|---|
| Valproic acid  | GABA                                  | First-line treatment for tonic-clonic seizures, absence seizures and myoclonic seizures |
| Second-line treatment for partial seizures and infantile spasms.                 | Intravenous use in status epilepticus | Lamotrigine   |
| Sodium channel   | Partial seizures                      | Tonic-clonic  |
| Seizures associated with Lennox-Gastaut syndrome                                 | Ethosuximide                          | Calcium channel   |
| Absence seizures   | Topiramate                            | GABA/Seizures associated with Sodium channel  |
| Lennox-Gastaut syndrome  | Zonisamide                            | GABA/Calcium/Adjunctive therapy in adults   |
| Sodium channel with partial-onset seizures                                       | Infantile spasm                       | Mixed seizure   |
| Lennox-Gastaut syndrome  | Myoclonic                             | Generalised tonic-clonic seizure  |
| Levetiracetam  | Calcium channel                       | Partial seizures  |
| Adjunctive therapy for partial, myoclonic and tonic-clonic seizures              | Clonazepam                            | GABA  |
| Typical and atypical absences  | Infantile myoclonic                   | Myoclonic seizures  |
| Akinetic seizures  | Rufinamide                            | Sodium channel  |
| Adjunctive treatment of partial seizures associated with Lennox-Gastaut syndrome |                                       |   |

(25) TABLE-US-00003 TABLE 3 Examples of AEDs used specifically in childhood epilepsy

| AED  | Mechanism       | Indication                                     |
|--|-----------------|--|
| Clobazam   | GABA            | Adjunctive therapy in complex partial seizures |
| Status epilepticus                                     | Myoclonic       | Myoclonic-absent                               |
| Simple partial   | Complex partial | Absence seizures                               |
| Lennox-Gastaut syndrome                                | Stiripentol     | GABA   |
| Severe myoclonic epilepsy in infancy (Dravet syndrome) |                 |  |

(26) The present invention describes surprising data from a patient that was taking an immunosuppressant drug, tacrolimus during the open label extension part of a clinical trial into childhood-onset epilepsy.

(27) It was noted that there was a significant increase in the subjects blood urea nitrogen (BUN) and serum creatine levels during the time the subject was taking CBD. Such an interaction is unexpected and as such the use of these drugs in combination should be done with close monitoring of the patient.

#### BRIEF SUMMARY OF THE DISCLOSURE

(28) In accordance with a first aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of childhood-onset epilepsy in patients who are concurrently taking an immunosuppressant drug characterised in that the blood levels of the immunosuppressant drug and associated markers are monitored to ensure the levels do not become toxic.

(29) Preferably the dose of CBD is lowered. Alternatively the dose of the immunosuppressant drug is lowered.

(30) Preferably the immunosuppressant drug is tacrolimus.

(31) Preferably the CBD is in the form of a highly purified extract of cannabis which comprises at least 98% (w/w) CBD which comprises less than 0.15% THC and up to 1% CBDV. Alternatively, the CBD is present as a synthetic compound.

(32) Preferably the dose of CBD is below 50 mg/kg/day. More preferably the dose of CBD is greater than 20 mg/kg/day.

(33) Preferably the childhood-onset epilepsy is: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) and brain abnormalities.

(34) In accordance with a second aspect of the present invention there is provided a method of treating childhood-onset epilepsy in an individual in need thereof, comprising administering to the patient a therapeutically effective amount of cannabidiol with caution, wherein the individual is taking an immunosuppressant drug concurrently.

(35) Preferably the said caution comprises lowering the dose of cannabidiol. Alternatively the said caution comprises lowering the dose of the immunosuppressant drug.

(36) Preferably the immunosuppressant drug is tacrolimus.

(37) Preferably the said caution comprises monitoring said individual for side effects.

(38) More preferably the said caution further comprises discontinuing cannabidiol if said side effects are observed.

(39) More preferably still the said caution comprises advising said individual of side effects from said concurrent therapy.

(40) Preferably the individual is a human.

#### Definitions

(41) Definitions of some of the terms used to describe the invention are detailed below:

(42) The cannabinoids described in the present application are listed below along with their standard abbreviations.

(43) TABLE-US-00004 TABLE 4 Cannabinoids and their abbreviations

| Cannabinoid | Abbreviation       |
|-------------|--------------------|
| CBD         | Cannabidiol        |
| CBDA        | Cannabidiolic acid |

- (44) The table above is not exhaustive and merely details the cannabinoids which are identified in the present application for reference. So far over 60 different cannabinoids have been identified and these cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).
- (45) “Phytocannabinoids” are cannabinoids that originate from nature and can be found in the cannabis plant. The phytocannabinoids can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.
- (46) “Highly purified cannabinoid extracts” are defined as cannabinoids that have been extracted from the cannabis plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been substantially removed, such that the highly purified cannabinoid is greater than or equal to 98% (w/w) pure.
- (47) “Synthetic cannabinoids” are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.
- (48) Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For example, it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.
- (49) “Treatment-resistant epilepsy” (TRE) or “intractable epilepsy” is defined as per the ILAE guidance of 2009 as epilepsy that is not adequately controlled by trials of one or more AED.
- (50) “Childhood epilepsy” refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of some of these are as follows: Dravet Syndrome; Myoclonic-Absence Epilepsy; Lennox-Gastaut syndrome; Generalized Epilepsy of unknown origin; CDKL5 mutation; Aicardi syndrome; tuberous sclerosis complex; bilateral polymicrogyria; Dup15q; SNAP25; and febrile infection related epilepsy syndrome (FIRES); benign rolandic epilepsy; juvenile myoclonic epilepsy; infantile spasm (West syndrome); and Landau-Kleffner syndrome. The list above is non-exhaustive as many different childhood epilepsies exist.

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## Description

### BRIEF DESCRIPTION OF THE DRAWINGS

- (1) Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which
- (2) FIG. 1 shows the Daily doses of Tacrolimus (Tac) and Cannabidiol (CBD) during study period; and
- (3) FIG. 2 shows the Tacrolimus dose normalised trough concentration.

### DETAILED DESCRIPTION

- (4) Preparation of Highly Purified CBD Extract
- (5) The following describes the production of the highly-purified (>98% w/w) cannabidiol extract which has a known and constant composition was used in the Examples below.
- (6) In summary the drug substance used is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 98% CBD. Although the CBD is highly purified because it is produced from a cannabis plant rather than synthetically there is a small number of other cannabinoids which are co-produced and co-extracted with the CBD. Details of these cannabinoids and the quantities in which they are present in the medication are as described in Table 5 below.
- (7) TABLE-US-00005 TABLE 5 Composition of highly purified CBD extract Cannabinoid Concentration CBD >98% w/w CBDA NMT 0.15% w/w CBDV NMT 1.0% w/w Δ<sup>9</sup>THC NMT 0.15% w/w CBD-04 NMT 0.5% w/w >—greater than NMT—not more than
- Example 1: Drug-Drug Interaction Between Cannabidiol (CBD) and Immunosuppressants
- (8) The patient was a 33 year old female with refractory epilepsy receiving the immunosuppressant drug tacrolimus for interstitial nephritis.
- (9) The patient had been stable on tacrolimus at a dose of 5 mg twice per day for a year prior to entry into a clinical trial on the use of CBD to treat childhood-onset epilepsy. At the time of entry into the study her blood level of tacrolimus was between 3.9 and 8.4 ng/mL. She also had a baseline Serum Creatine level of 1.16 mg/dL.
- (10) The patient was initially randomized to the sesame oil placebo arm of the trial, during this phase there was no change in the levels of tacrolimus or serum creatine.
- (11) However, when the patient entered into the open label phase of the study and began receiving CBD she showed signs of tacrolimus toxicity with a serum creatine level of 2.4 mg/dL.
- (12) The dose of tacrolimus was reduced repeatedly while receiving CBD as described in FIG. 1. A dose of 0.5 mg twice per day (a 10-fold reduction) was finally reached. At this dose the tacrolimus concentrations were normalised as shown in FIG. 2.
- (13) Such a finding delineates an important concern for the transplant community with the increasing legalization of marijuana. This drug-drug interaction may have implications in solid organ transplant recipients which are not correctly monitored over the course of their treatment.

### CONCLUSIONS

- (14) Patients that are taking immunosuppressant drugs such as tacrolimus should be carefully monitored over the course of their treatment with CBD to ensure toxicity does not occur.

## Claims

1. A method of treating childhood-onset epilepsy in a patient who is concurrently taking tacrolimus, comprising: administering to the patient a drug substance comprising at least 98% (w/w) cannabidiol (CBD) and less than 0.15% (w/w) THC; detecting toxic blood levels of tacrolimus or one or more associated markers; and reducing the dose of tacrolimus to no more than 5 mg per day.
2. The method according to claim 1, wherein the dose of CBD is lowered.
3. The method according to claim 1, wherein the drug substance is in the form of a highly purified extract of cannabis which comprises at least 98% (w/w) CBD.
4. The method according to claim 1, wherein the CBD is present as a synthetic compound.
5. The method according to claim 3, wherein the extract further comprises up to 1% (w/w) CBDV.
6. The method according to claim 1, wherein the dose of CBD is below 50 mg/kg/day.
7. The method according to claim 1, wherein the dose of CBD is greater than 20 mg/kg/day.
8. The method according to claim 1, wherein the childhood-onset epilepsy is: Lennox-Gastaut Syndrome; Myoclonic Absence Epilepsy; Tuberous Sclerosis Complex; Dravet Syndrome; Doose Syndrome; Jeavons Syndrome; CDKL5; Dup15q; Neuronal ceroid lipofuscinoses (NCL) or brain abnormalities.
9. The method of claim 1, wherein the associated markers comprise serum creatine.

10. The method of claim 9, wherein the serum creatine become toxic when the blood levels are 2.4 mg/dL or more.
  11. The method of claim 1, wherein the dose of tacrolimus is reduced by up to 10-fold.
  12. The method of claim 1, wherein the dose of tacrolimus is reduced to 0.5 mg twice per day.
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