# Application of Causal Inference to Identify Determinants of Seizure Reduction and Quality of Life in Patients with Lennox-Gastaut Syndrome, Dravet Syndrome, and Tuberous Sclerosis Complex Treated with Cannabidiol

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# Disclosures

**Author disclosures:**

- All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship
- TG and MB are employees of Jazz Pharmaceuticals, Inc., Italy and Jazz Pharmaceuticals, Inc., USA, respectively, and hold stock and/or stock options in Jazz Pharmaceuticals, Inc.
- NS and SA have consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.

**Product disclosures:**

- Epidyolex® (cannabidiol) is approved in the UK and EU for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, in patients ≥2 years of age; it is additionally approved in the UK and EU for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age[1,2]
- Availability across Europe may vary; please refer to product information[1]
- Epidiolex® (cannabidiol) is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age[3]
- The product is also approved in some additional countries; please check local prescribing information
- This chart review was specific to patients receiving Epidyolex®, and results do not apply to other CBD-containing products

**Acknowledgements:**

- Medical writing and editorial support were provided by Lahoor Basha, PharmD, of Syneos Health, UK, funded by Jazz Pharmaceuticals, Inc.

**Contact information:** medinfo-de@jazzpharma.com

CBD, cannabidiol.

**1.** Electronic Medicines Compendium (eMC). Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2025. Available from: https://www.medicines.org.uk/emc/product/10781/smpc/print (Accessed 29 May 2024). **2.** European Medicines Agency. Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf (Accessed 20 September 2024). **3.** US Food and Drug Administration. Epidiolex® Prescribing Information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021lbl.pdf. (Accessed 29 May 2024).

# Aristotle on causality

A firm grasp of what a **cause** is,
and how many kinds of causes there are,
**is essential**
**for a successful investigation** of the
world around us.

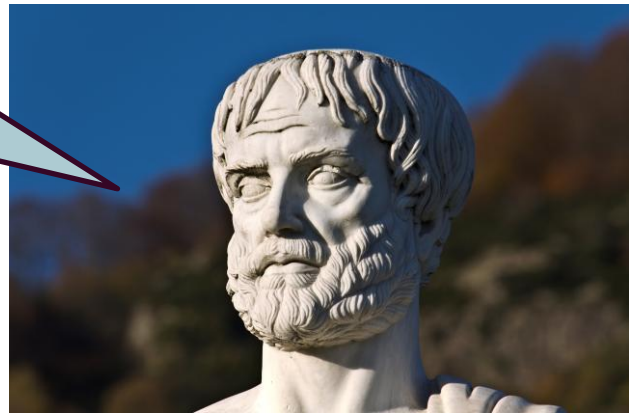

*Image © iStock.com*

The Stanford Encyclopedia of Philosophy. 2023. Available from: https://plato.stanford.edu/entries/aristotle-causality/. (Accessed 19 April 2025).

# Three-level causal hierarchy

**3. Counterfactuals (imagining, retrospection)**

*What if I had done…?*

Was it the treatment I took that stopped the symptom?
What if I had not taken it?

Infer probabilities under conditions that **change** (could be manipulated)

What would we observe if all patients had taken X=x?

**2. Intervention (doing, intervening)**

What if I do…?

If I take the treatment, will my symptom be cured?

**1. Association (observing, seeing)**

What if I see…?

What does the symptom tell me about the disease?

**1.** Forney A. Available from: https://forns.lmu.build/classes/spring-2019/cmsi-498/lecture-2T.html. (Accessed 20 March 2025). **2.** Pearl, J. *Biometrika.* 1995;82(4):669–710.
**3.** Pearl J. *Int J Biostat.* 2010;6(2):Article 7.

# Relationship between seizure reduction, CGIC, and CBD

**What would be** a reliable **causal-effect** relationship among key clinical factors in patients with LGS, DS, and TSC treated or not with CBD?

**What would be** the caregiver's perspective if a patient treated with CBD had a seizure reduction? **What if** they had not been treated?

How do we characterise the **direct/indirect effects** that determine CGIC?

*Image © iStock.com*

CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

# Manipulation

Neyman (1923), Rubin (1974), Holland (1988)

## No causation without manipulation[1–5]

**1.** Neyman J. *Statistical Science.* 1990;5(4):463–480. **2.** Holland PW. *J Am Stat Assoc.* 1986;81(396):945–960. **3.** Holland PW. *ETS Research Report Series*. 2003(1):i–21. **4.** Rubin DB. *Proc Soc Stat Sect Am Stat Assoc.* 1975:233–239. **5.** Bauer PC. 2020. Available from: https://bookdown.org/paul/applied-causal-analysis/causes-no-causation-without-manipulation.html. (Accessed 19 April 2025).

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A randomized controlled trial is the best scientific method to assess causal effects

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Estimate causal effect for interventions that we can imagine being randomised in a **hypothetical trial** (EMULATION)

| No direct intervention | Intervention |
|---|---|
| Race | Name on CV |
| Obesity | Bariatric surgery |
| Social economical status | Gift of money |

→ Manipulable, potentially actionable, well defined

→ Contrafactuals versus observed outcome

**1.** Neyman J. *Statistical Science.* 1990;5(4):463–480. **2.** Holland PW. *J Am Stat Assoc.* 1986;81(396):945–960. **3.** Holland PW. *ETS Research Report Series*. 2003(1):i–21. **4.** Rubin DB. *Proc Soc Stat Sect Am Stat Assoc.* 1975:233–239. **5.** Bauer PC. 2020. Available from: https://bookdown.org/paul/applied-causal-analysis/causes-no-causation-without-manipulation.html. (Accessed 19 April 2025).

# Treatment-resistant epilepsies and cannabidiol (CBD)

Lennox-Gastaut syndrome (**LGS**)

Dravet syndrome (**DS**)

Tuberous sclerosis complex (**TSC**)

LGS, DS, and TSC-associated seizures are rare, severe **treatment-resistant epilepsies** with onset in infancy or early childhood[1–3]

Epidyolex® is a plant-derived, highly purified **CBD oral solution** (100 mg/mL) that is approved in the UK[4] and EU[5] in patients ≥2 years of age, as adjunctive **treatment for seizures associated with**:

- **LGS** or **DS**, in conjunction with clobazam
- **TSC**

CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

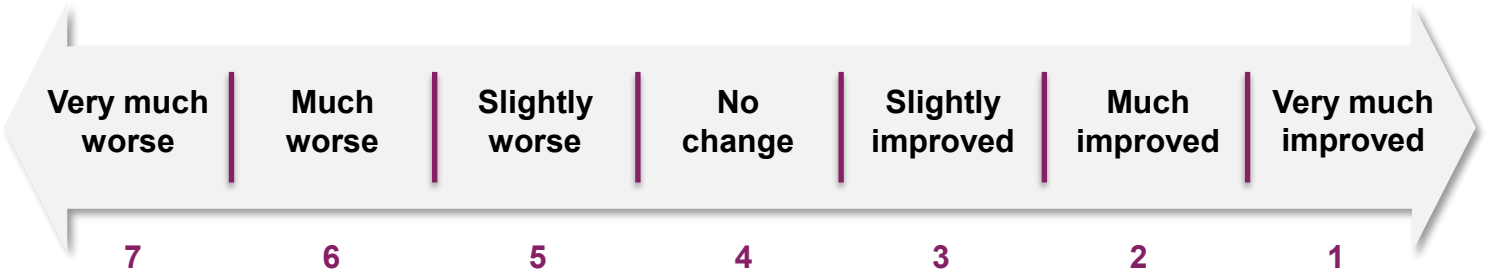
**1.** Specchio N, et al. *Epilepsia.* 2022;63(6):1398–1442. **2.** Zuberi SM, et al. *Epilepsia.* 2022;63(6):1349–1397. **3.** Specchio N, et al. *Eur J Paediatr Neurol.* 2023;47:25–34. **4.** Electronic Medicines Compendium (eMC). Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2025. Available from: https://www.medicines.org.uk/emc/product/10781/smpc/print. (Accessed 29 May 2024); **5.** European Medicines Agency. Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf (Accessed 29 May 2024).

# Caregiver Global Impression of Change (CGIC)

- **CGIC** is a scale used to assess overall change in a patient's condition from the perspective of their caregiver[1,2]

Three main domains for ratings

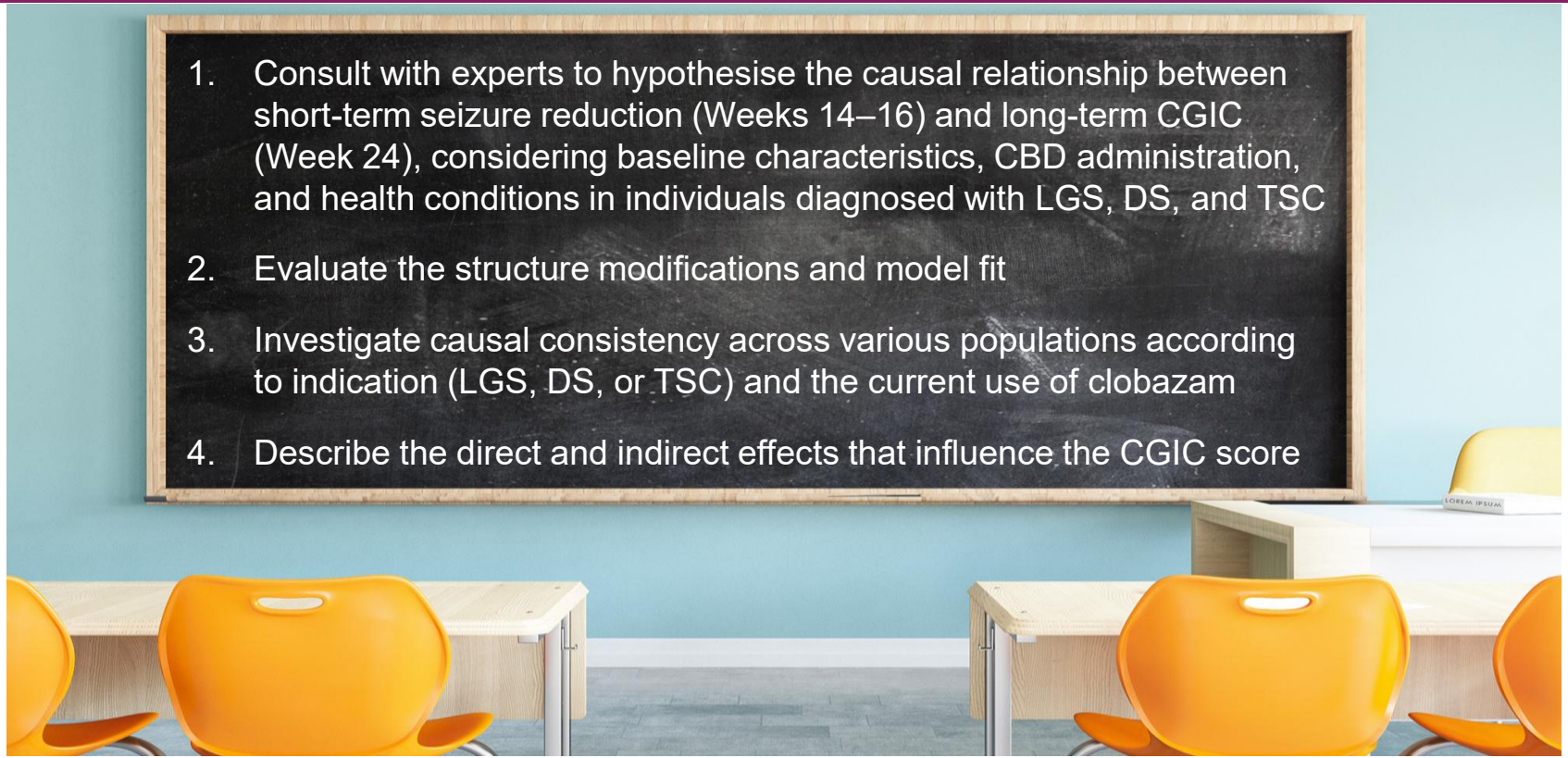
- **Overall improvement or deterioration** in condition
- **QoL**
- **Functional status**




CGIC, Caregiver Global Impression of Change; QoL, quality of life.

**1.** Devinsky O, et al. *N Engl J Med.* 2017;376(21):2011–2020. **2.** Berg AT, et al. *Epilepsy Res.* 2024;200:107280.

# Objectives:
# Relationship between seizure reduction, CGIC, and CBD




CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

# Available data sources

Pooled from RCTs plus OLEs[1–7] of highly purified CBD (100 mg/mL oral solution)

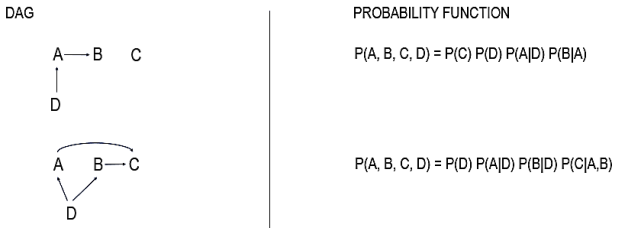
| Population | Number of patients in RCTs | Number of patients with CGIC assessment during OLE (%) |
|---|---|---|
| Overall | 960 | 371 (39%) |
| LGS | 396 | 138 (35%) |
| DS | 319 | 86 (27%) |
| TSC | 245 | 147 (60%) |
| CBD/Placebo + clobazam users | 459 | 173 (38%) |

CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial; TSC, tuberous sclerosis complex.
**1.** Devinsky O, et al. *N Engl J Med.* 2018;378(20):1888–1897 (NCT02224560). **2.** Thiele EA, et al. *Lancet.* 2018;391(10125):1085–1096 (NCT02224690). **3.** Devinsky O, et al. *N Engl J Med.* 2017;376(21):2011–2020 (NCT02091375). **4.** Miller I, et al. *JAMA Neurol.* 2020;77(5):613–621 (NCT02224703). **5.** Patel AD, et al. *Epilepsia.* 2021;62(9):2228–2239 (NCT02224573). **6.** Thiele EA, et al. *JAMA Neurol.* 2021;78(3):285–292 (NCT02544763). **7.** ClinicalTrials.gov. NCT02544750. Updated 14 July 2022. Available from: https://clinicaltrials.gov/study/NCT02544750. (Accessed April 2025).

# Structural causal model

Pearl (1995)

1. Structural Equation Model (SEM): system of structural functions assumed to be autonomous (each function is invariant to possible changes in the form of the other functions)
2. Potential-outcome framework (Neyman-Rubin causal model)
3. Graphical models
   - Assumptions/causal effects directly derivable from the causal graph (eg, variable role, causal relationship, covariance, d-separation, sufficient set)
   - Probabilistic approach to causation




**1.** Pearl, J. *Biometrika.* 1995;82(4):669–710. **2.** Pearl J. *Int J Biostat.* 2010;6(2):Article 7. **3.** Neuberg LG. *Econometric Theory.* 2003;19(4):675–685. **4.** Duncan OD. Studies in Population: Introduction to Structural Equation Models. Academic Press, 1975. **5.** Goldberger, AS. *Econometrica.* 1972;40(6):979–1001. **6.** Neyman, J. *Statistical Science.* 1990;5(4):465–480. **7.** Rubin, DB. *J Educ Psychol.* 1974;66(5):688–701.

# Structural causal model

Pearl (1995)

- ***do-notation:***

$$p(y|do(x_0))$$

Probability that event Y = y would occur if treatment condition X = $x_0$ were enforced uniformly over the population

[and let $x_0$ take different values on hypothetical copies of the population]

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- Extension of *effect* concept:

  Algebraic representation as a coefficient in an equation → general capacity to transmit changes among variables

**1.** Pearl, J. *Biometrika.* 1995;82(4):669–710. **2.** Pearl J. *Int J Biostat.* 2010;6(2):Article 7.

# Structural causal model

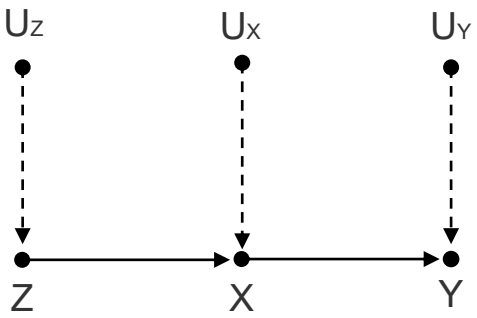
To **confirm** relationships between factors.

It can be interpreted for cause and effect when the following conditions are met:

1. The hypothesised relationship (model structure) is a **valid representation** of reality
2. The factors' dependencies are **directed and acyclic**
3. Variables, conditioned on their parents, are **independent of their ancestors**
4. No possibility to come back from cause to effect (and no spurious correlations)

Madhanagopal B, Amrhein J. Paper 3765-2019 and 3240-2019 Analyzing Structural Causal Models Using the CALIS Procedure. McDougall Scientific Ltd, 2019.

# Structural causal model



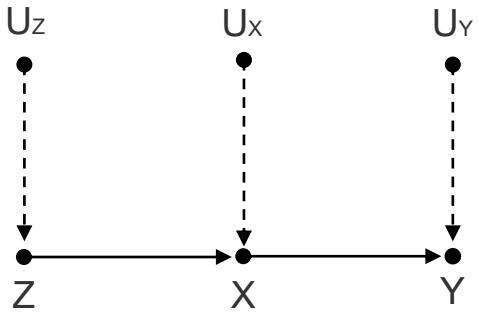

Exogenous variables: background (unexplained) factors

Endogenous variables: influenced by other factors

$$z = f_Z(u_z)$$
$$x = f_X(z, u_x)$$
$$y = f_Y(x, u_Y)$$

Pearl J. *Statistics Surveys*. 2009;3:96–146.

# Structural causal model



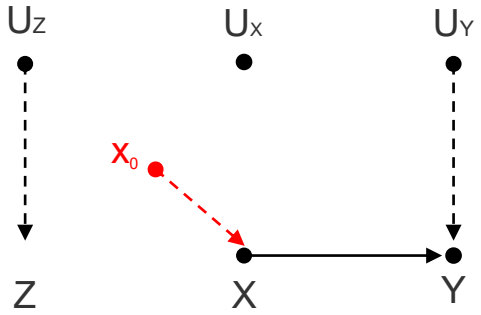

$z = f_Z(u_z)$

$x = f_X(z, u_x)$

$y = f_Y(x, u_Y)$

*pre-intervention join distribution*
*P(z, x, y)*

*do(X=x₀)*




$z = f_z(u_Z)$

$x = x_0$

$y = f_Y(x, u_Y)$

*post-intervention join distribution*
*P(z, y | do(x₀))*

Pearl J. *Statistics Surveys*. 2009;3:96–146.

# Structural causal model

## Identification question

*Can the controlled (post-intervention) distribution P(z, y | d(x))*

*be estimated from the data by the pre-intervention distribution P(z, x, y)?*

Pearl J. *Statistics Surveys*. 2009;3:96–146.

# Structural causal model

## Identification question

**Causal Markov Condition + Truncated Factorization**

For any Markovian model, the distribution generated by an intervention $do(X=x_0)$ on a set of endogenous variables ($V_i$), is given by

$$P(V_1, V_2, \ldots, V_n \mid do(X_0)) = \prod_{V_i \neq X} P(V_i \mid pa_i)|_{x=x_0}$$

$P(z, y \mid do(x_0)) = P(z)\, P(y \mid x_0)$ ~~$P(x \mid z)$~~ trunked because x=x0

Pa, parent variable.
Pearl J. *Statistics Surveys.* 2009;3:96–146.

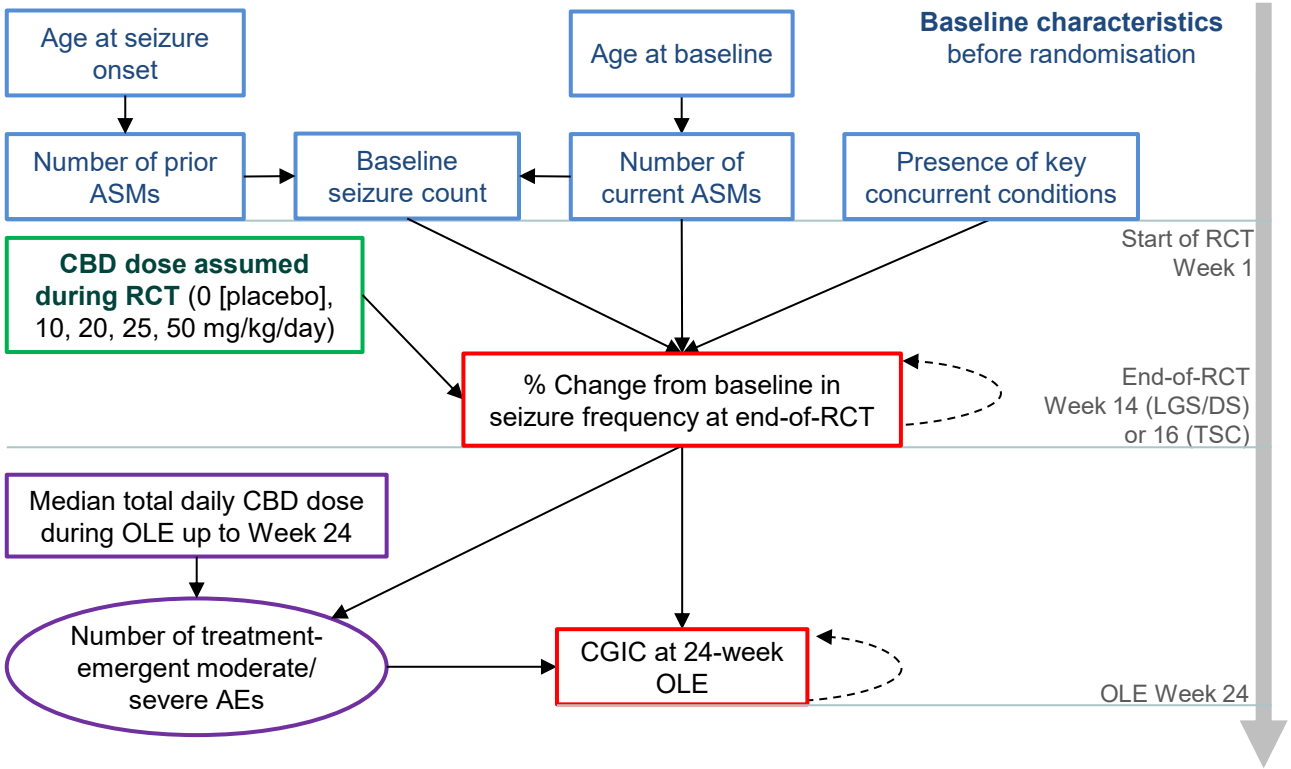
# Application of SCM methodology to CBD trial data

**Steps to investigate the reliability of the assumed clinical pathway are the following:**

1. **Draw** your hypothesised path diagram
2. **Fit** the structural equation models
3. **Assess** the fit
4. **Refine** (modify) the model
5. **Repeat** steps 2, 3, and 4
6. **Display** final model diagram
7. Assess **Causality**

CBD, cannabidiol; SCM, structural causal model.

# Assumed path diagram




- An initial causal-effect relationship between end-of-RCT seizure reduction and Week 24 CGIC (during the OLE) was defined in consultation with clinical experts
- The final SCM was selected using model fit statistics, model modification statistics, regression pathways ($P$<0.05), and clinical reliability

AE, adverse event; ASM, antiseizure medication; CBD, cannabidiol; CGIC; Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial; TSC, tuberous sclerosis complex.

# Model fit statistics

| Index | Cut-off for a good fit |
|---|---|
| **Absolute indices** to compare the fitted model to a saturated model without accounting for model complexity: | |
| ★ Chi-square test | *P*-value >0.05 |
| ★ Standardized Root Mean Square Residual (SRMR) | <0.08 |
| **Parsimony indices** quantify the data fitting by penalising model complexity given from an increased number of parameters: | |
| Root Mean Square Error of Approximation (RMSEA) | <0.05 = close fit<br><0.08 = mediocre fit<br>>0.1 = poor fit<br><br>Narrow 90% confidence interval |
| Probability of Close Fit (PROBCLFIT)<br>A chi-square test in which the null hypothesis is 'close fit' | *P*-value >0.05 |
| Bozdogan Criterian Akaike's Information Criterion (CAIC) | Smaller is better |
| Schwarz Bayesian Criterion (SBC) | Smaller is better |
| Adjusted Goodness of Fit Index (AGFI) | >0.90 |
| **Incremental indices** to compare the fitted model to the null model: | |
| ★ Bentler Comparative Fit Index (CFI) | >0.90 |
| Bentler-Bonett Non-Normed Index (NNFI) or Tucker Lewis Index (TLI) | >0.90 |

**1.** Kline, RB. Principles and practice of structural equation modeling (4th Edn) The Guildford Press, 2015. **2.** Madhanagopal B, Amrhein J. Paper 3765-2019 and 3240-2019 Analyzing Structural Causal Models Using the CALIS Procedure. McDougall Scientific Ltd, 2019. **3.** Statistika. Goodness of fit Index. 2023. Available from: https://www.statistika.co/index.php/research-methods/sem-amos/goodness-of-fit-index-gfi (Accessed 12 May 2025).

# Modification index

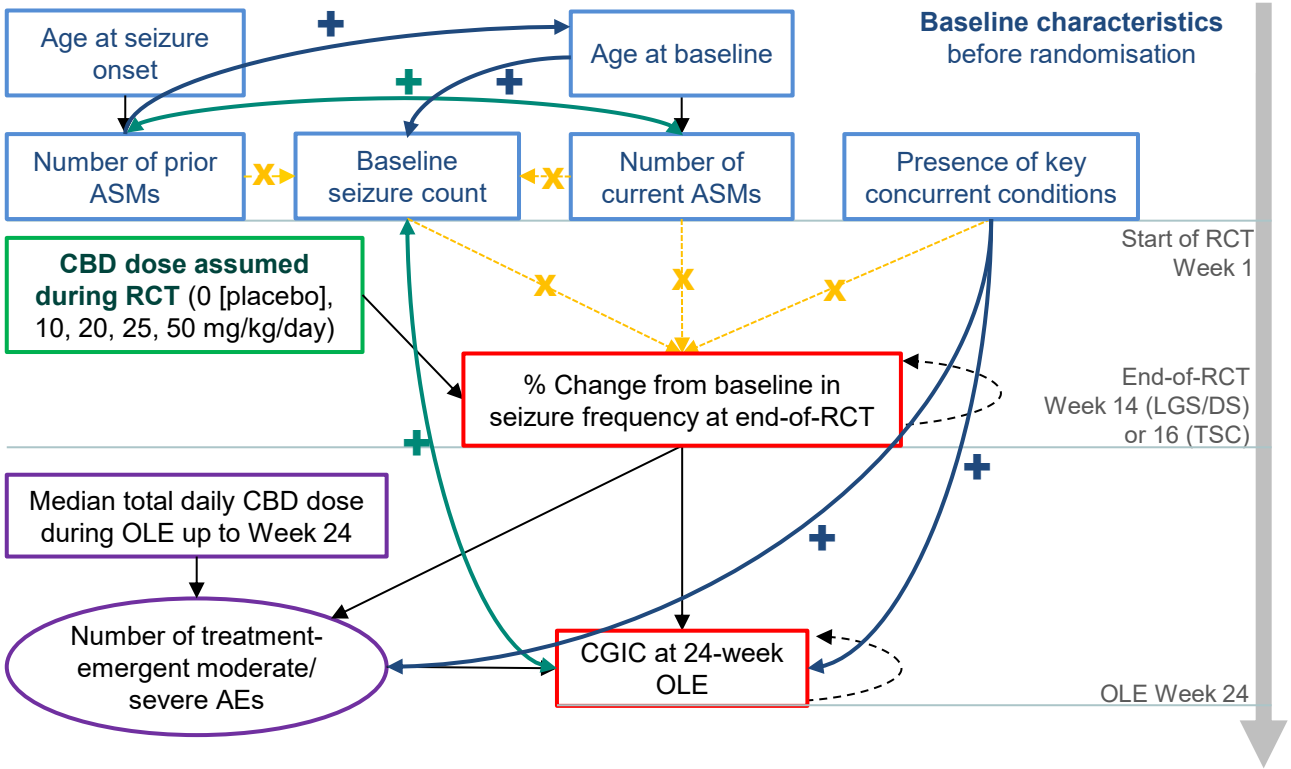
To advise on ways to improve the fit of the structural model.

- **Lagrange Multiplier (LM)** statistic suggests which parameters and error variances-covariances could be **included** in the model to improve the model fit in terms of chi-square value
- **Wald Test Indices** suggest paths to **remove** without affecting the chi-square statistic

Given that the modifications suggested by the LM and Wald statistics might not be substantively meaningful, **it is important to consult experts before applying any analytical modification to the hypothesised model**

1. Yung YF. Introduction to structural equation modeling using the CALIS procedure in SAS/STAT® software. Presented at Joint Statistical Meeting; August 4, 2010; Vancouver, Canada. **2.** UCLA: Statistical Consulting Group. Available from: https://stats.oarc.ucla.edu/other/mult-pkg/faq/general/faq-how-do-i-cite-web-pages-and-programs-from-the-ucla-statistical-consulting-group/ (Accessed 12 May 2025).

# Modified structural causal model




Metrics suggest to:

- **Remove the causal paths** as indicated; **X**
- **Include causal paths** as indicated; **+**
- **Include correlations** as indicated; **+**

AE, adverse event; ASM, antiseizure medication; CBD, cannabidiol; CGIC; Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial; TSC, tuberous sclerosis complex.

# Proc calis

```
proc calis data=webcov toteff mod;

 fitindex on(only) = [chisq df probchi srmsr rmsea agfi cfi];

 path
   prASM ---> ageBL = prASM_AgeBL,
   com ---> AE CGI = com_AE com_CGI,
   TRT ---> seizCHG1 = TRT_seizCHG,
   seizCHG1 ---> CGI = seizCHG_CGI;

 pcov
  prASM curASM = cov_prASM_curASM,
  seizBL1 CGI = cov_seizBL1_CGI
 ;
run;
```

Mediation analysis and modified index

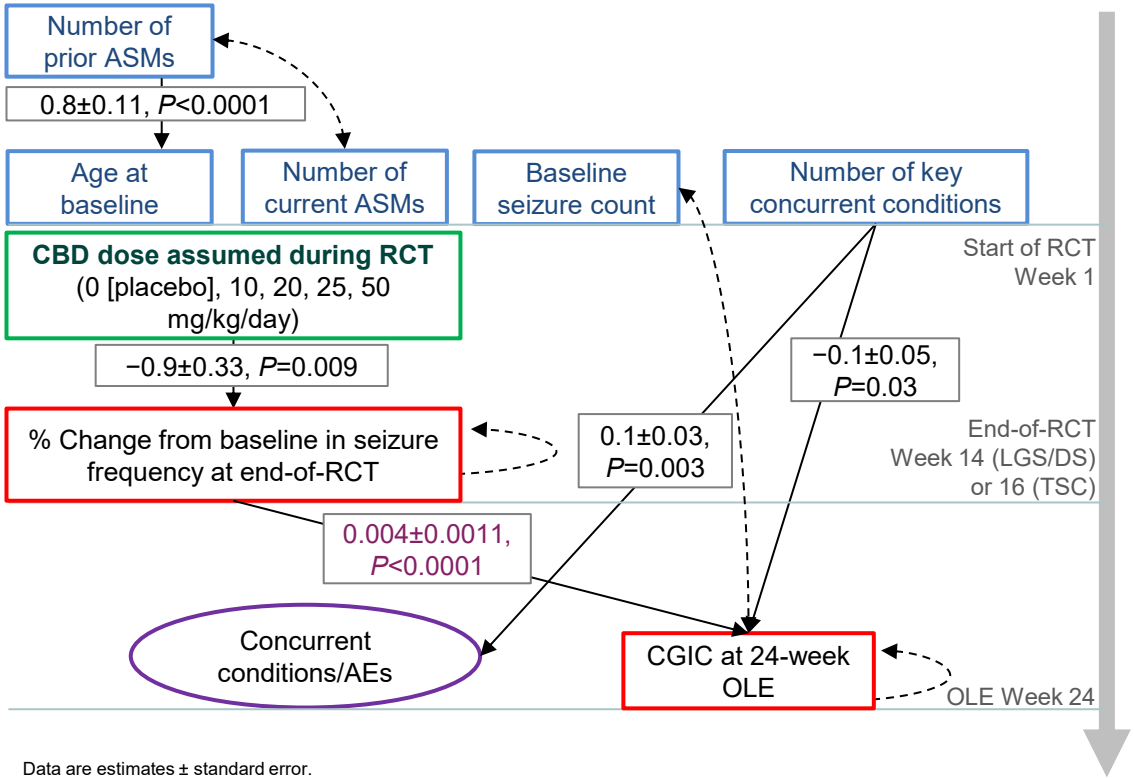
Fit statistics

Path coefficients

Error covariances


**1.** Madhanagopal B, Amrhein J. Paper 3765-2019 and 3240-2019 Analyzing Structural Causal Models Using the CALIS Procedure. McDougall Scientific Ltd, 2019.
**2.** Yung YF. Introduction to structural equation modeling using the CALIS procedure in SAS/STAT® software. Presented at Joint Statistical Meeting; August 4, 2010; Vancouver, Canada.

# Final structural causal model with path coefficient estimates




- Among the 371 patients overall, a significant causal-effect relationship between seizure reduction and CGIC was confirmed
- This relationship was also significant ($P$<0.05) in patients with LGS (n=138) or TSC (n=147), but not in those with DS (n=86)

Data are estimates ± standard error.
AE, adverse event; ASM, antiseizure medication; CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial; TSC, tuberous sclerosis complex.

# Model fit statistics in the overall population

| Fit summary N=371 | | Original model fit | Modified model fit | Final model fit |
|---|---|---|---|---|
| Absolute index | Chi-square | 103.9384 | 85.1180 | 34.4911 |
| | Chi-square DF | 33 | 34 | 20 |
| | Pr > Chi-square | <0.0001 | <0.0001 | <0.0230 |
| | SRMR | 0.0620 | 0.0578 | 0.0449 |
| Parsimony index | AGFI | 0.9078 | 0.9260 | 0.9554 |
| | RMSEA estimate | 0.0762 | 0.0637 | 0.0443 |
| Incremental index | Bentler comparative fit index | 0.6375 | 0.7388 | 0.8546 |

AGFI, adjusted goodness of fit index; DF, degrees of freedom; SRMR, standardised root mean square residual; RMSEA, root mean square error of approximation.

# Path coefficient estimates in the overall population

| Path (N=371) | | | Original model *P*-value | Modified model *P*-value | Final model *P*-value |
|---|---|---|---|---|---|
| Age at seizure onset | ==> | Number of prior ASMs | 0.7411 | 0.7411 | |
| Number of prior ASMs | ==> | Baseline seizure count | 0.1097 | | |
| Number of prior ASMs | ==> | Age at baseline | | <0.0001 | <0.0001 |
| Age at baseline | ==> | Number of current ASMs | 0.0056 | | |
| Age at baseline | ==> | Baseline seizure count | | 0.1113 | |
| Number of current ASMs | ==> | Baseline seizure count | 0.8314 | | |
| Number of current ASMs | ==> | % Change in seizure freq. at eoRCT | 0.8792 | | |
| Baseline seizure count | ==> | % Change in seiz. freq. at eoRCT | 0.8208 | | |
| Presence of key concurrent cond. | ==> | % Change in seiz. freq. at eoRCT | 0.4238 | 0.4254 | |
| Presence of key concurrent cond. | ==> | Moderate/severe adverse events | | 0.0021 | 0.0031 |
| Presence of key concurrent cond. | ==> | CGIC | | 0.0214 | 0.0305 |
| CBD dose assumed during RCT | ==> | % Change in seiz. freq. at eoRCT | 0.0089 | 0.0088 | 0.0088 |
| % Change in seiz. freq. at eoRCT | ==> | Moderate/severe adverse events | 0.3030 | 0.3582 | |
| % Change in seiz. freq. at eoRCT | ==> | CGIC | <0.0001 | <0.0001 | <0.0001 |
| Median daily CBD dose during OLE | ==> | Moderate/severe adverse events | 0.0827 | 0.0554 | |
| Moderate/severe adverse events | ==> | CGIC | 0.4053 | 0.2059 | |

ASM, antiseizure medication; CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; eoRCT, end-of-RCT; OLE, open-label extension; RCT, randomised controlled trial.

# Model fit and parameter estimation in subpopulations

## Seizure reduction-CGIC path coefficient estimate in subpopulations

| Path | | LGS (n=138) | DS (n=86) | TSC (n=147) | CBL users (n=173) |
|---|---|---|---|---|---|
| % Change in seiz. freq. at eoRCT | ==> CGIC | 0.0059 | 0.1748 | 0.0202 | 0.0257 |

## Model fit statistics in subpopulations

| Fit summary | | LGS (n=138) | DS (n=86) | TSC (n=147) | CBL users (n=173) |
|---|---|---|---|---|---|
| Absolute index | Chi-square | 20.8120 | 37.9957 | 30.0175 | 27.6497 |
| | Chi-square DF | 20 | 20 | 20 | 20 |
| | Pr > Chi-square | 0.4083 | 0.0089 | 0.0696 | 0.1180 |
| | SRMR | 0.0579 | 0.0808 | 0.0626 | 0.0602 |
| Parsimony index | AGFI | 0.9292 | 0.8269 | 0.9087 | 0.9158 |
| | RMSEA estimate | 0.0172 | 0.1029 | 0.0586 | 0.0512 |
| Incremental index | Bentler comparative fit index | 0.9673 | 0.6631 | 0.5947 | 0.6711 |

AGFI, adjusted goodness of fit index; CBL, clobazam; CGIC, Caregiver Global Impression of Change; DF, degrees of freedom; DS, Dravet syndrome; eoRCT, end-of-RCT; LGS, Lennox-Gastaut syndrome; RCT, randomised controlled trial; RMSEA, root mean square error of approximation; SRMR, standardised root mean square residual; TSC, tuberous sclerosis complex.

# Mediation analysis

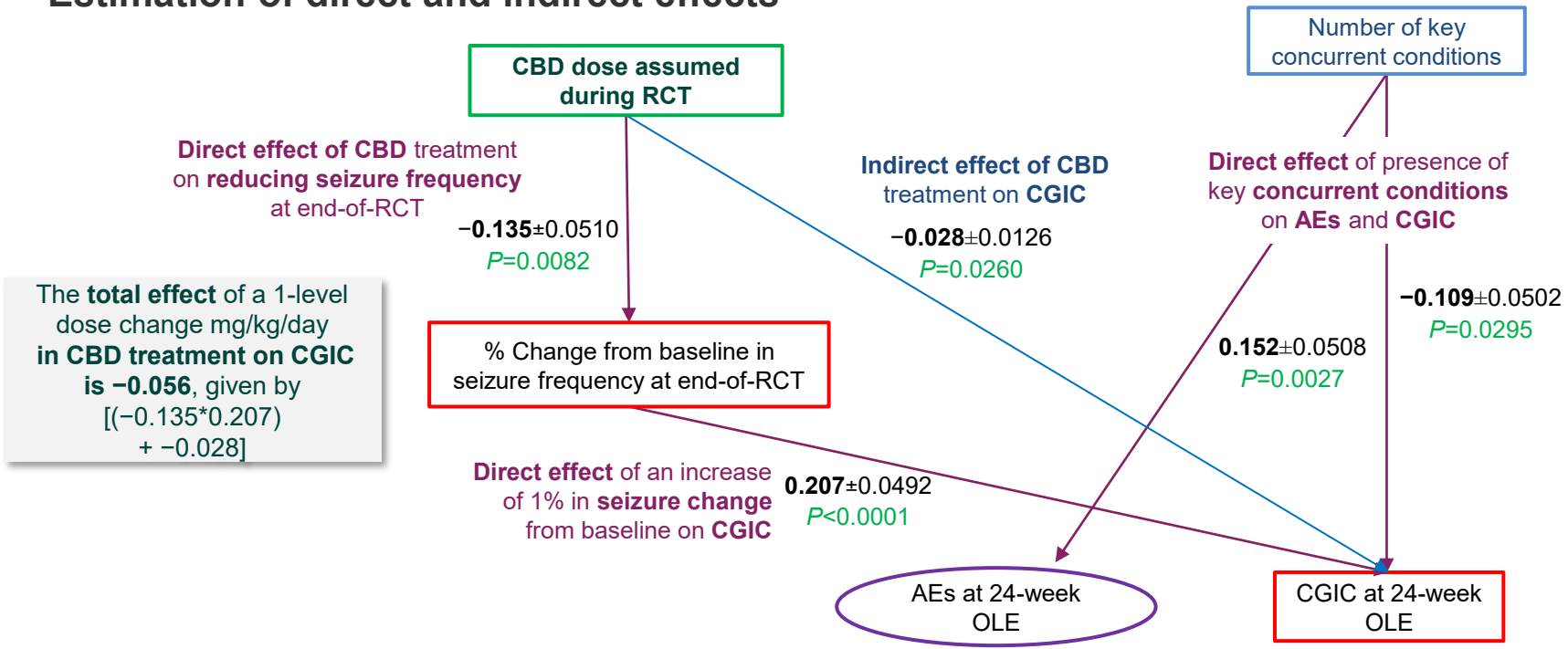
To evaluate the existence of direct connections (ie, no mediation variables between the parent and child nodes) or indirect connections (ie, existence of intermediate pathways between nodes)

- **Complete mediation:** The causal effect is only through the mediator: significant indirect path coefficient and not significant direct path coefficient
- **Partial mediation:** Part of the causal effect is mediated by a third variable: significant indirect and direct path coefficients
- **Inconsistent mediation:** Direct and indirect effects have different significative signs

Madhanagopal B, Amrhein J. Paper 3765-2019 and 3240-2019 Analyzing Structural Causal Models Using the CALIS Procedure. McDougall Scientific Ltd, 2019.

# Causal relationship: Effects on CGIC

## Estimation of direct and indirect effects




The **total effect** of a 1-level dose change mg/kg/day **in CBD treatment on CGIC is −0.056**, given by [(−0.135*0.207) + −0.028]

Data are estimates ± standard error.
AE, adverse event; CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; OLE, open-label extension; RCT, randomised controlled trial.

# Conclusions

- This analysis confirmed the expected **causal-effect relationship between seizure reduction and improvement in CGIC** (measuring overall condition, quality of life, and functional status)
  - The relationship was consistent in the LGS and TSC subpopulations
- No baseline characteristics were deemed useful to select patients who may benefit from treatment
- The **causal relationship is driven by CBD administration, seizure reduction, and concurrent conditions at baseline**
  - The presence of moderate/severe adverse events is not a determinant of CGIC

**The findings of this analysis may represent meaningful insights for considering nonseizure endpoints, such as CGIC, as key outcomes in future clinical trials of CBD as disease-modifying treatment**

CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

# Thank You