

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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Introduction

- A plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD; Epidyolex® [EU]/Epidiolex® [US]) is approved for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC)^{1–3}
- Causal inference modelling investigates cause–effect relationships between factors within populations; for example, between population characteristics, treatments, and outcomes in patients from randomised clinical trials (RCTs)⁴
- In this *post hoc* analysis of pooled data from the pivotal RCTs and their open-label extension (OLE) studies, causal inference modelling was employed to identify the determinants of seizure reduction and global improvements in the condition of patients with LGS, DS, or TSC receiving CBD

Objective

- To assess the causal relationship between seizure reduction and improvement in Caregiver Global Impression of Change (CGIC) as influenced by baseline characteristics, CBD administration, concurrent conditions, and adverse events (AEs) in the RCTs and OLE studies investigating CBD (Epidyolex®/Epidiolex®, 100 mg/mL oral solution) in patients with LGS, DS, or TSC

Methods

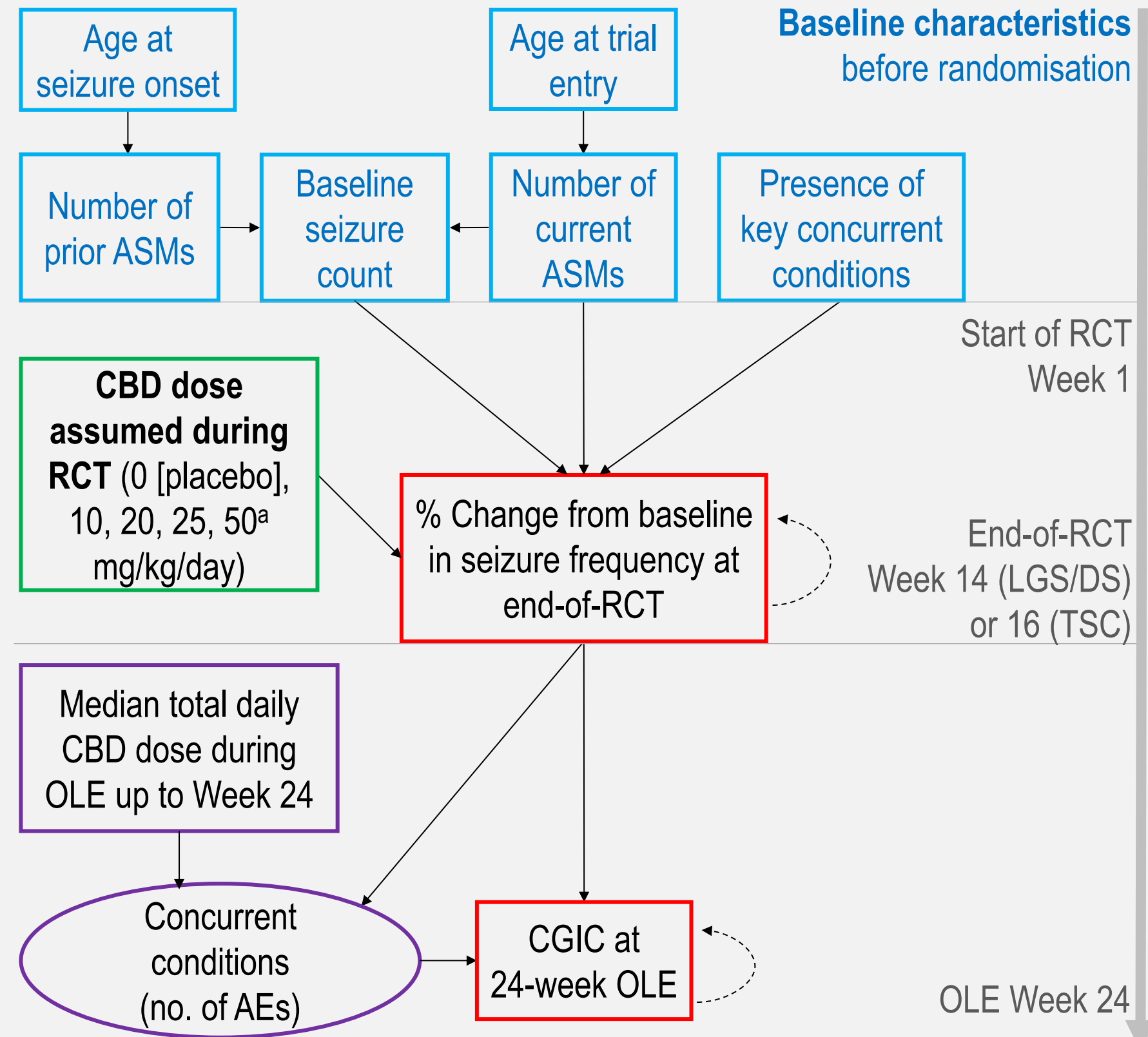
- Structural Causal Model (SCM) methodology was applied *post hoc* to pooled data from patients with LGS, DS, or TSC from RCTs and OLEs investigating highly purified CBD^{5–11} (**Table 1**)
- After consultation with experts, our initial model assumed a causal relationship between end-of-RCT seizure reduction and Week 24 CGIC (during the OLE) (**Figure 1**)
- The final SCM was selected using model fit statistics, model modification statistics, regression pathways ($P<0.05$), and clinical plausibility
- Direct/indirect effects that impact CGIC scores were estimated using mediation analysis
- The RCTs and OLE studies were conducted with Epidyolex®/Epidiolex®, and the results of this *post hoc* analysis do not apply to other CBD-containing products

Table 1. Data pooled from RCTs plus OLEs of CBD^{5–11}

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.

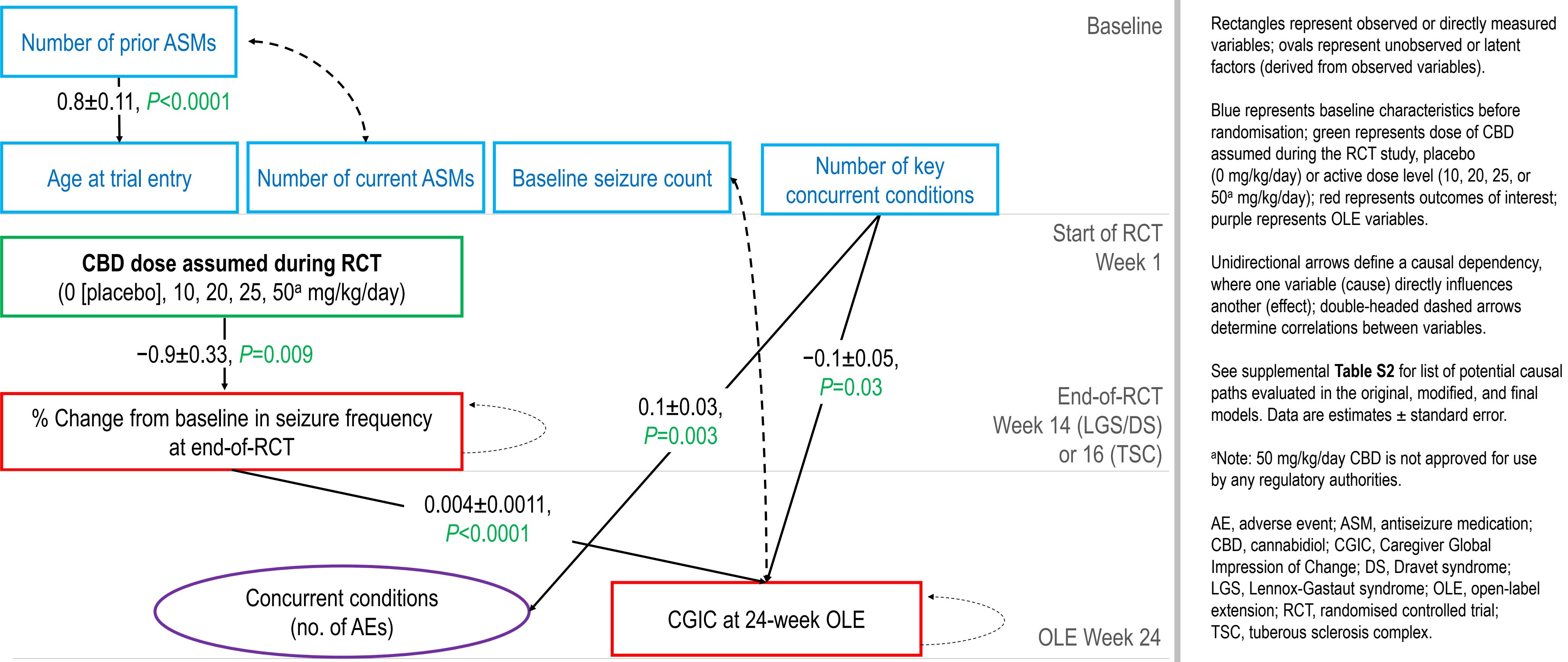
Figure 1. Assumed path diagram



Rectangles represent observed or directly measured variables; ovals represent unobserved or latent factors (derived from observed variables). Blue represents baseline characteristics before randomisation; green represents dose of CBD assumed during the RCT study, placebo (0 mg/kg/day) or active dose level (10, 20, 25, or 50^a mg/kg/day); red represents outcomes of interest; purple represents OLE variables. Unidirectional arrows define a causal dependency, where one variable (cause) directly influences another (effect); double-headed dashed arrows determine correlations between variables. ^aNote: 50 mg/kg/day CBD is not approved for use by any regulatory authorities. 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.

Results

Figure 2. Final structural causal model with path coefficient estimates



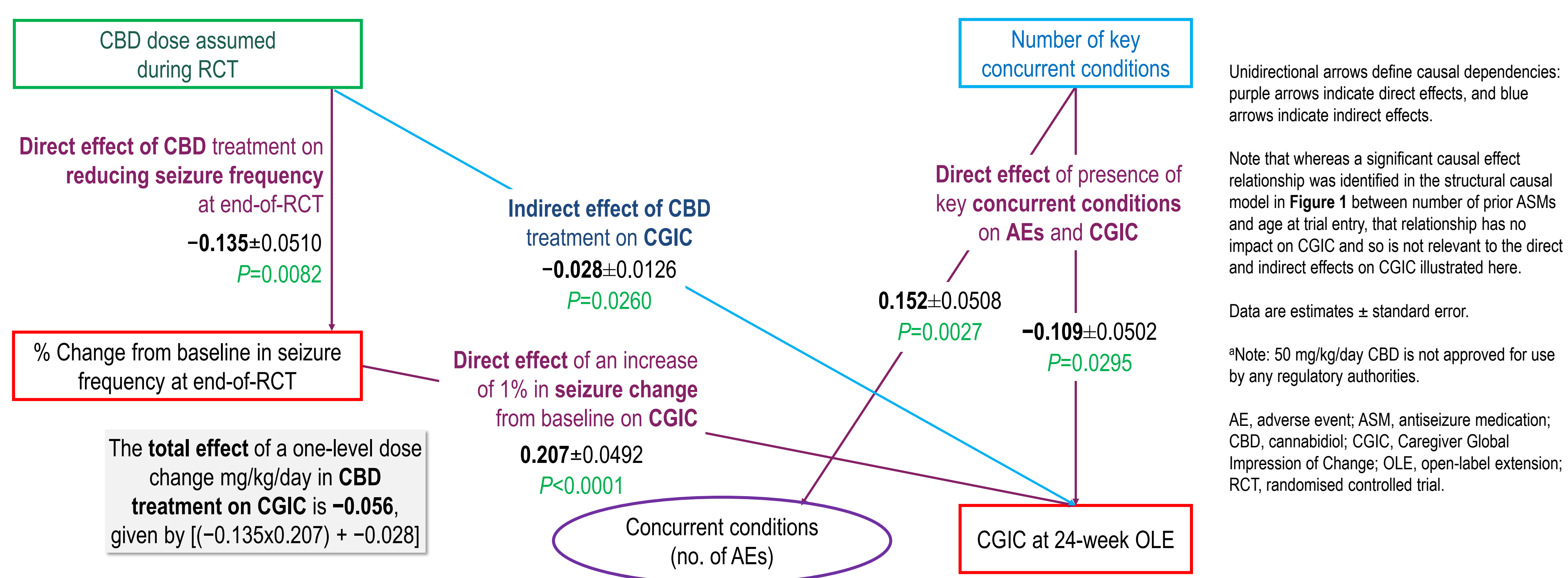
- Among the 371 patients overall in the final structural causal model (**Figure 2**), after modifications suggested by the data-learning process, a significant causal effect relationship between seizure reduction and improvement in CGIC was confirmed
- Significant causal effect relationships that were added (versus the assumed path) were an impact of baseline health status (measured as number of concurrent conditions) on CGIC, and the relationship between number of prior ASMs and age at trial entry
- Details of path coefficient estimates and model fit statistics can be viewed in the **Supplementary Material** via the QR code

Table 2. Seizure reduction–CGIC path coefficient estimates in subpopulations

Path	LGS (n=138)	DS (n=86)	TSC (n=147)	CLB users (n=173)
% Change in seizure frequency at eoRCT ==> CGIC	0.003±0.0011 $P=0.0059$	0.002±0.0018 $P=0.1748$	0.005±0.0024 $P=0.0202$	0.005±0.0023 $P=0.0257$

- The significant causal effect relationship between seizure reduction and improvement in CGIC from the overall population was also observed in subgroups of patients with LGS (n=138) or TSC (n=147), but not in those with DS (n=86) (**Table 2**)

Figure 3. Causal relationship: Direct and indirect effects



- Increasing dose level of CBD (0, 10, 20, 25, 50^a mg/kg/day) significantly contributes to CGIC improvement at the 24-week follow-up (**Figure 3**)

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 suitable to select patients who may benefit from treatment
- The **causal relationship appears to be driven by CBD administration, seizure reduction, and concurrent conditions at baseline**
 - The presence of moderate/severe AEs does not appear to be a determinant of CGIC
- These findings illustrate how the direct and indirect effects of trial interventions on multifaceted endpoints such as CGIC can be estimated
 - Modelling such as this may be useful to consider how more specific nonseizure outcomes may be affected by clinical trial interventions

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Supplementary Material

Table S1. Model fit statistics in the overall population

Fit summary (N=371)		Original model fit	Modified model fit	Final model fit
Absolute indices	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 indices	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

Green represents a good fit, amber represents a moderate fit, red represents a poor fit.
AGFI, adjusted goodness of fit index; DF, degrees of freedom; SRMR, standardised root mean square residual; RMSEA, root mean square error of approximation.

➤ The values in green indicate that the final model shown in **Figure 2** was a good fit with the observed data in the overall population

- **Absolute indices** are used to compare the model with a perfect model, without considering how complex the model is
- **Parsimony indices** are used to evaluate how well the model fits the data, while accounting for the complexity added by more parameters
- **Incremental indices** are used to compare the fitted model with the null model; that is, they are step-by-step measures that compare the model with a basic model with no causal effects

Table S2. *P*-values of path coefficient estimates in the overall population

Path (N=371)			Original model <i>P</i> -value	Modified model <i>P</i> -value	Final model <i>P</i> -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 frequency at eoRCT	0.8792		
Baseline seizure count	==>	% Change in seizure frequency at eoRCT	0.8208		
Number of key concurrent conditions	==>	% Change in seizure frequency at eoRCT	0.4238	0.4254	
Number of key concurrent conditions	==>	Moderate/severe adverse events		0.0021	0.0031
Number of key concurrent conditions	==>	CGIC		0.0214	0.0305
CBD dose assumed during RCT	==>	% Change in seizure frequency at eoRCT	0.0089	0.0088	0.0088
% Change in seizure frequency at eoRCT	==>	Moderate/severe adverse events	0.3030	0.3582	
% Change in seizure frequency 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	

Green denotes a significant *P*-value (<0.05), amber indicates a non-significant but borderline *P*-value, red indicates non-significance.
Data are estimates ± standard error.
ASM, antiseizure medication; CBD, cannabidiol; CGIC, Caregiver Global Impression of Change; eoRCT, end-of-RCT; OLE, open-label extension; RCT, randomised controlled trial.

- A significant *P*-value for a regression coefficient associated with a path in the structural equations represents a general capacity for change to be transmitted between the variables in that path
- The five causal paths with significant path coefficient estimates in the final model listed above are shown in **Figure 2**

Table S3. Model fit statistics in subpopulations

Fit summary		LGS (n=138)	DS (n=86)	TSC (n=147)	CLB 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

Green represents a good fit, amber represents a moderate fit, red represents a poor fit.
AGFI, adjusted goodness of fit index; CLB, clobazam; DF, degrees of freedom; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RMSEA, root mean square error of approximation; SRMR, standardised root mean square residual; TSC, tuberous sclerosis complex.

- When applied to subpopulations of patients by indication or clobazam use, the final model was a less good fit with the observed data than it was for the overall population above
- The significant causal–effect relationship between seizure reduction and improvement in CGIC held true in the LGS, TSC, and clobazam-use subgroups but not in the DS subpopulation (**Table 2**)