

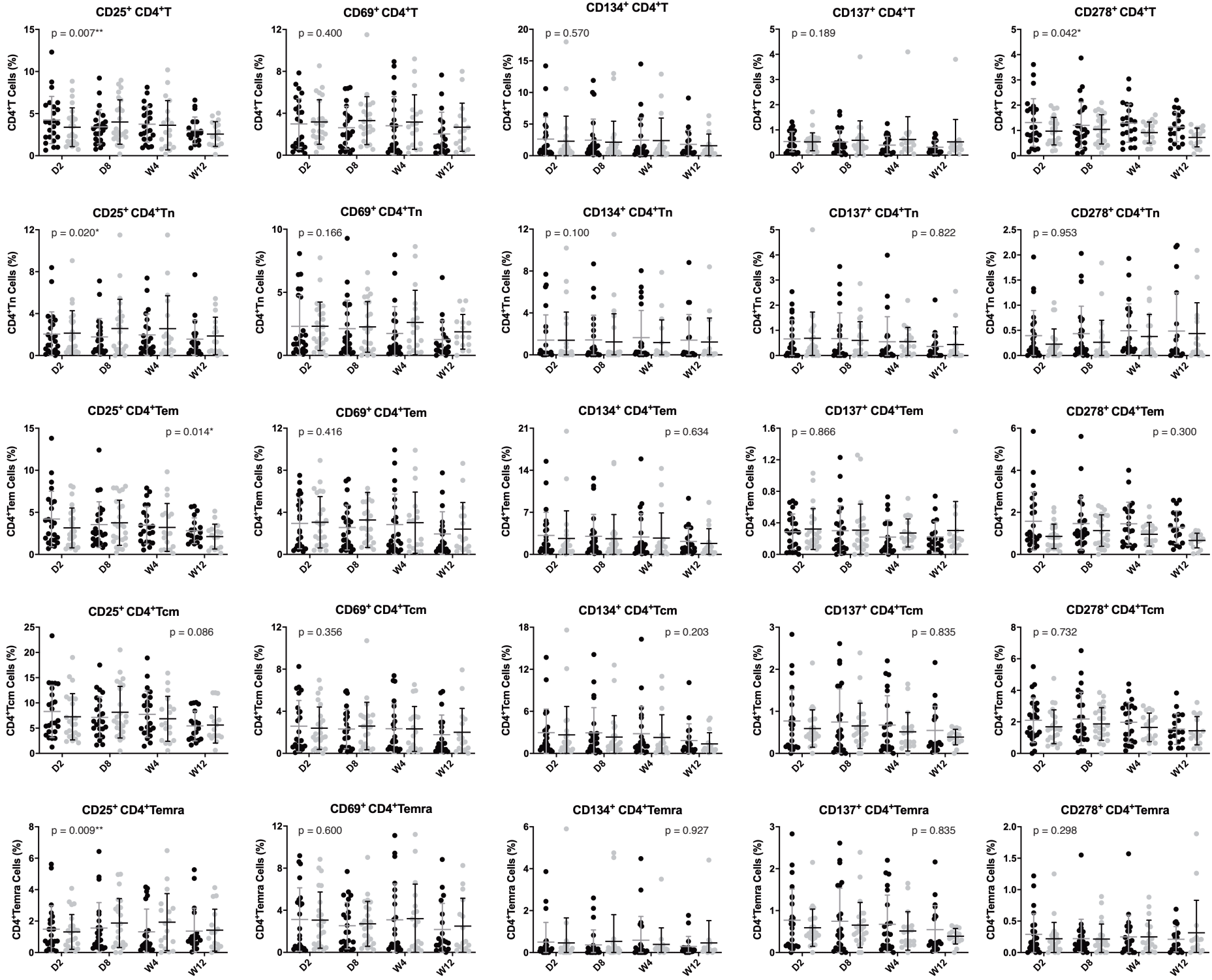
## Supplementary Figure Legend

Fig. S1: Subpopulations of CD4<sup>+</sup>T lymphocytes of the cannabidiol group compared with the placebo group at baseline (day 2), day 8, week 4 and week 12. Subpopulations of CD4<sup>+</sup>T lymphocytes are presented in column scatter plots. The mean and standard deviation (SD) are expressed with horizontal and vertical bars, respectively. \*Indicates p-value < 0.05. CD, cluster of differentiation; D, day; Tcm, T central memory; Tem, T effector memory; Temra, T effector memory RA; Tn, T naive; W, week.

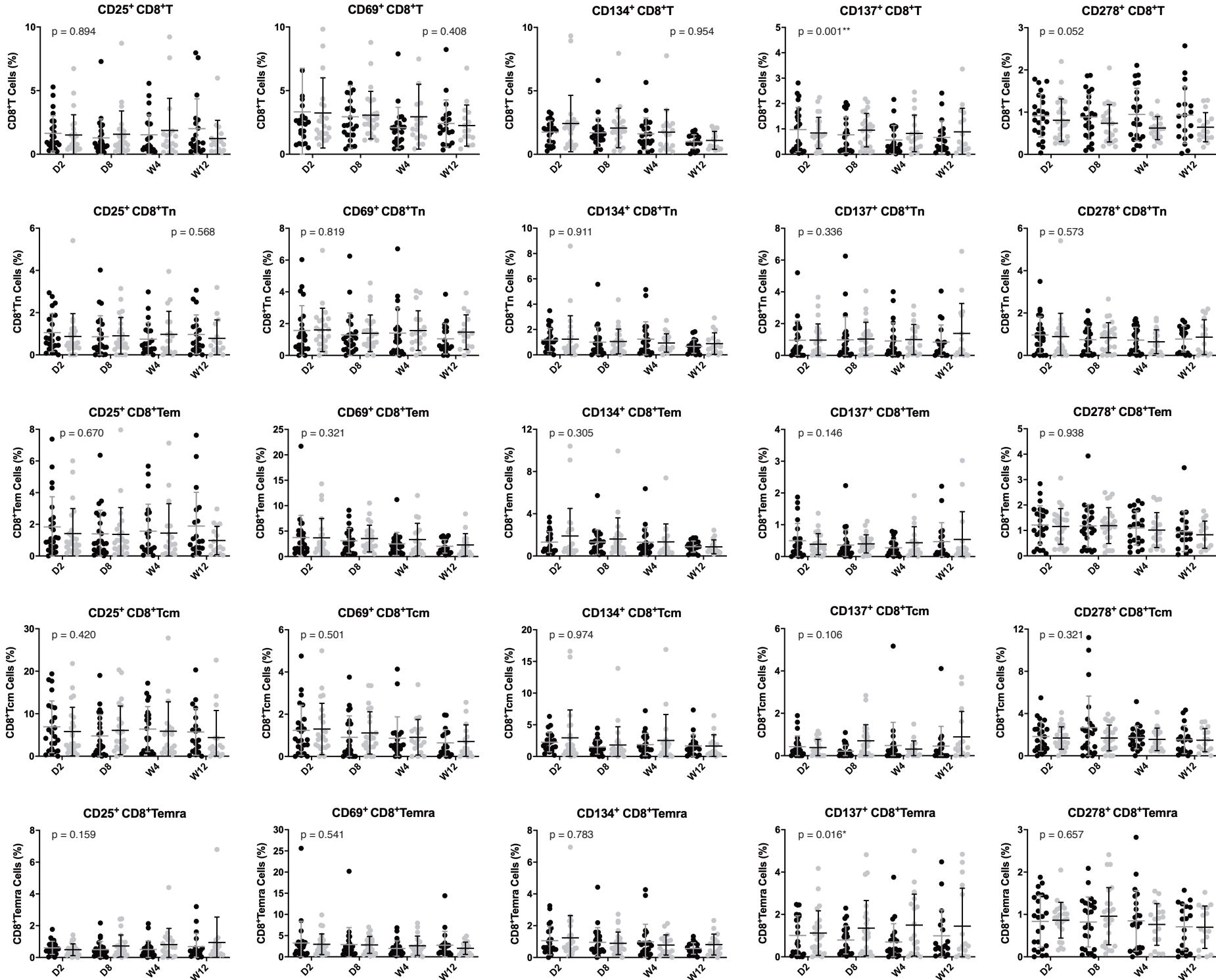
Fig. S2: Subpopulations of CD8<sup>+</sup>T lymphocytes of the cannabidiol group compared with the placebo group at baseline (day 2), day 8, week 4 and week 12. Subpopulations of CD8<sup>+</sup>T lymphocytes are presented in column scatter plots. The mean and standard deviation (SD) are expressed with horizontal and vertical bars, respectively. \*Indicates p-value < 0.05; \*\*Indicates p-value < 0.01. CD, cluster of differentiation; D, day; Tcm, T central memory; Tem, T effector memory; Temra, T effector memory RA; Tn, T naive; W, week.

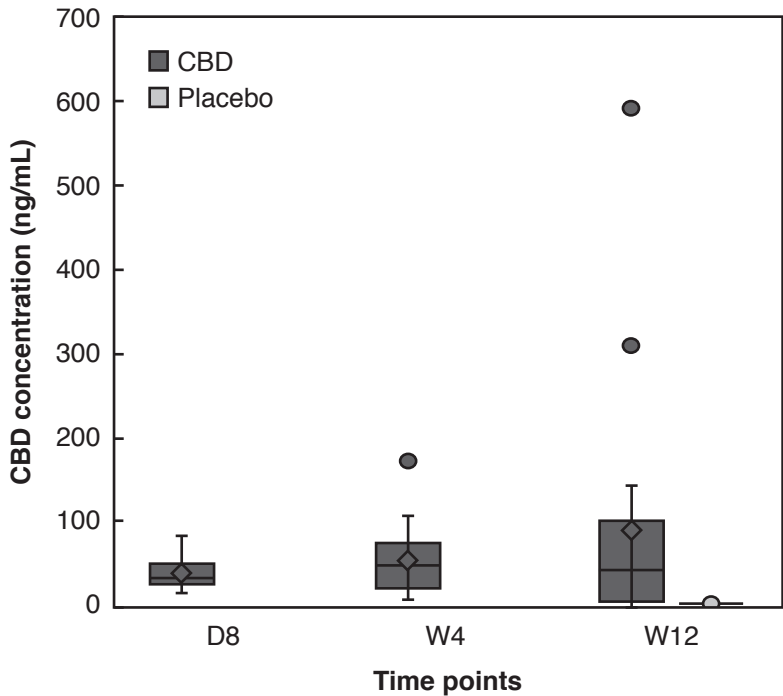
Fig. S3: Participants' CBD blood concentrations among treatment groups (adapted with permission from Mongeau-Pérusse et al., 2021(33)). Minimum, 1<sup>st</sup> quartile, median, 3<sup>rd</sup> quartile and maximum values are illustrated with box-whisker plots. Mean and outlier values are illustrated with diamonds and circles, respectively. CBD, cannabidiol; D, day; W, week.

- Placebo
- Cannabidiol



- Placebo
- Cannabidiol





**Table S1. List of monoclonal antibodies.**

Marker	Clone	Fluorochrome	Company
CD3	UCHT1	BUV395	BD Biosciences
CD3	UCHT1	APC-R700	BD Biosciences
CD3	UCHT1	FITC	BD Biosciences
CD4	RPA-T4	FITC	BD Biosciences
CD8	SK1	APC-H7	BD Biosciences
CD11b	ICRF44	APC-Cy7	BD Biosciences
CD11b	ICRF44	V450	BD Biosciences
CD11c	B-ly6	V450	BD Biosciences
CD14	M5E2	PerCPCy5.5	BD Biosciences
CD14	M5E2	FITC	BD Biosciences
CD16	3G8	PE-CF594	BD Biosciences
CD19	HIB21	PE	BD Biosciences
CD19	HIB21	PerCPCy5.5	BD Biosciences
CD20	2H7	APC-H7	BD Biosciences
CD24	ML5	PE-Cy7	BD Biosciences
CD25	NCAM16.2	APC-R700	BD Biosciences
CD27	M-T271	Alexa Fluor 700	BD Biosciences
CD33	WM53	APC	BD Biosciences
CD38	HIT2	PE	BD Biosciences
CD43	1G10	APC	BD Biosciences
CD45RA	HI100	PerCPCy5.5	BD Biosciences
CD56	NCAM16.2	FITC	BD Biosciences
CD62L	DREG-56	BV421	BD Biosciences
CD69	FN50	BV786	BD Biosciences
CD134	ACT35	PE-CF594	BD Biosciences
CD137	4B4-1	APC	BD Biosciences
CD278	DX29	PE	BD Biosciences
HLA-DR	G46-6	PE-Cy7	BD Biosciences
IgD	IA6-2	PE-CF594	BD Biosciences

CD, cluster of differentiation; HLA-DR, human leukocyte antigen-DR isotype; Ig, immunoglobulin.

**Table S2. Peripheral soluble cytokines and chemokines receptors used.**

Chemokine Panel 1	Proinflammatory Panel 1	Cytokine Panel 1
MIP-1 $\beta$	IL-6	IL-16
MDC		VEGF-A

MDC, macrophage derived chemokine; MIP-1 $\beta$ , macrophage inflammatory protein-1 $\beta$ ; IL, interleukine; VEGF-A, vascular endothelial growth factor-A.

**Table S3. Cytokine results.**

Outcomes	Parameters	Estimate	Standard Error	Wald Chi square	p	Effect size
IL-6	Intercept	-0.490	0.685	0.511	0.475	
	Treatment	-0.392	0.165	5.674	<b>0.017</b>	0.347
	Baseline	-0.993	0.095	108.968	<b>0.000</b>	
	SDS score	0.045	0.041	1.211	0.271	
	Sex	-0.341	0.238	2.054	0.152	
	Age	0.005	0.009	0.343	0.558	
IL-16	Intercept	-180.902	56.445	10.272	<b>0.001</b>	
	Treatment	2.448	17.133	0.020	0.886	0.021
	Baseline	-1.015	0.044	543.877	<b>0.000</b>	
	SDS score	2.507	3.439	0.531	0.466	
	Sex	19.886	20.454	0.945	0.331	
	Age	1.754	0.639	7.535	<b>0.006</b>	
MIP-1 $\beta$	Intercept	-87.314	24.840	12.356	<b>0.000</b>	
	Treatment	13.746	7.565	3.301	0.069	0.265
	Baseline	-0.608	0.117	27.062	<b>0.000</b>	
	SDS score	1.865	1.298	2.065	0.151	
	Sex	8.002	11.870	0.454	0.500	
	Age	0.270	0.321	0.704	0.401	
MDC	Intercept	-1404.405	291.097	23.276	<b>0.000</b>	
	Treatment	65.980	70.328	0.880	0.348	0.137
	Baseline	-0.611	0.091	44.589	<b>0.000</b>	
	SDS score	-3.439	14.564	0.056	0.813	
	Sex	76.750	89.650	0.733	0.392	
	Age	12.242	2.954	17.174	<b>0.000</b>	
VEGF-A	Intercept	-48.964	34.636	1.998	0.157	
	Treatment	-14.417	6.722	4.600	<b>0.032</b>	0.313
	Baseline	-0.567	0.163	12.130	<b>0.000</b>	
	SDS score	0.000	1.245	0.000	1.000	
	Sex	-6.442	11.633	0.307	0.580	
	Age	0.390	0.343	1.293	0.255	

IL, interleukin; MDC, macrophage derived chemokine; MIP-1 $\beta$ , macrophage inflammatory protein-1 $\beta$ ; p, p-value; SDS, severity of dependence scale; VEGF-A, vascular endothelial growth factor-A.

**Table S4. Monocyte results.**

Outcomes	Parameters	Estimate	Standard Error	Wald Chi square	p	Effect size
Total monocytes CD11c <sup>+</sup>	Intercept	-13.858	7.572	3.349	0.067	0.134
	Treatment	-1.547	1.682	0.845	0.358	
	Baseline	-0.726	0.105	47.605	<b>0.000</b>	
	SDS score	0.362	0.317	1.304	0.254	
	Sex	-0.829	2.316	0.128	0.720	
	Age	0.078	0.082	0.906	0.341	
Classical monocytes (CD14 <sup>+</sup> CD16 <sup>-</sup> )	Intercept	-10.500	5.933	3.132	0.077	0.127
	Treatment	-1.460	1.677	0.758	0.384	
	Baseline	-0.713	0.107	44.428	<b>0.000</b>	
	SDS score	0.275	0.276	0.991	0.319	
	Sex	-1.126	1.891	0.355	0.551	
	Age	0.063	0.070	0.794	0.373	
Intermediate monocytes (CD14 <sup>+</sup> CD16 <sup>+</sup> )	Intercept	-0.032	1.036	0.001	0.975	0.330
	Treatment	-0.468	0.207	5.082	<b>0.024</b>	
	Baseline	-0.552	0.122	20.371	<b>0.000</b>	
	SDS score	0.055	0.060	0.852	0.356	
	Sex	-0.081	0.288	0.078	0.780	
	Age	-0.017	0.010	2.644	0.104	
Non-classical monocytes (CD14 <sup>lo</sup> CD16 <sup>+</sup> )	Intercept	-0.962	0.358	7.230	<b>0.007</b>	0.187
	Treatment	0.127	0.099	1.659	0.198	
	Baseline	-0.896	0.022	1687.591	<b>0.000</b>	
	SDS score	0.045	0.023	3.795	0.051	
	Sex	0.049	0.124	0.153	0.696	
	Age	0.005	0.004	1.366	0.242	
DC	Intercept	-2.485	0.981	6.418	<b>0.011</b>	0.100
	Treatment	0.170	0.248	0.469	0.493	
	Baseline	-0.769	0.084	83.387	<b>0.000</b>	
	SDS score	0.043	0.052	0.691	0.406	
	Sex	-0.098	0.383	0.066	0.798	
	Age	0.018	0.012	2.253	0.133	
mDC	Intercept	-2.578	0.960	7.204	<b>0.007</b>	0.213
	Treatment	0.337	0.231	2.127	0.145	
	Baseline	-0.774	0.102	57.113	<b>0.000</b>	
	SDS score	0.019	0.043	0.204	0.652	
	Sex	0.351	0.258	1.842	0.175	
	Age	0.018	0.012	2.122	0.145	
mMDSC	Intercept	0.316	0.303	1.085	0.298	0.031
	Treatment	-0.026	0.123	0.045	0.833	
	Baseline	-0.403	0.196	4.216	<b>0.040</b>	
	SDS score	0.011	0.017	0.406	0.524	
	Sex	-0.149	0.209	0.507	0.476	
	Age	-0.010	0.004	6.465	<b>0.011</b>	
gMDSC	Intercept	0.334	0.762	0.193	0.661	0.034
	Treatment	0.030	0.128	0.053	0.818	
	Baseline	-0.766	0.135	32.037	<b>0.000</b>	
	SDS score	0.022	0.026	0.681	0.409	
	Sex	-0.320	0.253	1.599	0.206	
	Age	-0.011	0.007	2.579	0.108	

CD, cluster of differentiation; DC, dendritic cells; gMDSC, granulocytic myeloid derived suppressor cells; mDC, myeloid dendritic cells; mMDSC, monocytic myeloid derived suppressor cells; p, p-value; SDS, severity of dependence scale.



**Table S5. Lymphocyte results.**

Outcomes	Parameters	Estimate	Standard Error	Wald Chi square	p	Effect size
Total NK	Intercept	-4.794	3.029	2.505	0.113	0.210
	Treatment	-1.003	0.698	2.062	0.151	
	Baseline	-0.774	0.124	38.949	<b>0.000</b>	
	SDS score	0.125	0.154	0.660	0.417	
	Sex	0.916	0.805	1.297	0.255	
	Age	0.015	0.034	0.194	0.660	
NK CD56 <sup>dim</sup> CD16 <sup>hi</sup>	Intercept	-3.435	2.583	1.768	0.184	0.060
	Treatment	-0.254	0.618	0.168	0.681	
	Baseline	-0.899	0.145	38.184	<b>0.000</b>	
	SDS score	0.064	0.147	0.186	0.666	
	Sex	0.930	0.677	1.888	0.169	
	Age	0.010	0.025	0.165	0.685	
NK CD56 <sup>hi</sup> CD16 <sup>neg</sup>	Intercept	-0.351	0.209	2.818	0.093	0.247
	Treatment	0.088	0.052	2.804	0.094	
	Baseline	-0.502	0.134	14.143	<b>0.000</b>	
	SDS score	-0.016	0.011	2.226	0.136	
	Sex	0.090	0.050	3.282	0.070	
	Age	0.004	0.003	2.296	0.130	
NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	Intercept	-0.899	0.817	1.211	0.271	0.643
	Treatment	-0.736	0.167	19.552	<b>0.000</b>	
	Baseline	-0.430	0.072	35.759	<b>0.000</b>	
	SDS score	0.033	0.030	1.169	0.280	
	Sex	0.058	0.208	1.169	0.782	
	Age	0.003	0.012	0.064	0.800	
Total B cells	Intercept	-2.136	2.534	0.711	0.399	0.123
	Treatment	-0.490	0.579	0.716	0.397	
	Baseline	-0.457	0.069	44.359	<b>0.000</b>	
	SDS score	-0.015	0.100	0.023	0.879	
	Sex	-1.245	0.701	3.155	0.076	
	Age	-0.004	0.032	0.014	0.906	
Early B cells	Intercept	-7.950	4.807	2.735	0.098	0.221
	Treatment	-2.010	1.329	2.287	0.130	
	Baseline	-0.875	0.056	241.367	<b>0.000</b>	
	SDS score	0.156	0.230	0.462	0.497	
	Sex	-1.025	1.373	0.557	0.455	
	Age	-0.013	0.036	0.130	0.719	
Late B cells	Intercept	-4.250	4.050	1.101	0.294	0.232
	Treatment	2.088	1.313	2.529	0.112	
	Baseline	-0.874	0.056	245.400	<b>0.000</b>	
	SDS score	-0.159	0.233	0.469	0.494	
	Sex	1.055	1.342	0.617	0.432	
	Age	0.007	0.035	0.043	0.835	
Total T cells	Intercept	-10.539	10.037	1.103	0.294	0.117
	Treatment	1.595	1.982	0.648	0.421	
	Baseline	-0.690	0.089	59.481	<b>0.000</b>	
	SDS score	-0.091	0.382	0.057	0.812	
	Sex	1.173	2.606	0.203	0.653	
	Age	-0.110	0.096	1.305	0.253	
CD4 <sup>+</sup> T	Intercept	3.540	5.118	0.479	0.489	0.131
	Treatment	1.101	1.222	0.812	0.368	
	Baseline	-0.901	0.048	355.014	<b>0.000</b>	
	SDS score	-0.507	0.273	3.441	0.064	
	Sex	-0.322	1.180	0.075	0.785	
	Age	-0.064	0.053	1.445	0.229	
CD8 <sup>+</sup> T	Intercept	-10.415	4.383	5.646	<b>0.017</b>	0.238
	Treatment	1.840	1.130	2.653	0.103	
	Baseline	-0.942	0.047	394.806	<b>0.000</b>	
	SDS score	0.459	0.261	3.097	0.078	
	Sex	-0.266	1.053	0.064	0.801	
	Age	0.028	0.045	0.386	0.534	

CD, cluster of differentiation; NK, natural killer; p, p-value; SDS, severity of dependence scale.

**Table S8. Anti-inflammatory drugs used by participants at least once during the trial.**

Anti-inflammatory drugs, n (%)	Treatment group	
	CBD (n=24)	Placebo (n=24)
Inhaled corticosteroid	1 (4.2)	2 (8.3)
Topical corticosteroid	2 (8.3)	3 (12.5)
Nasal corticosteroid spray	2 (8.3)	0 (0.0)
Oral corticosteroid	0 (0.0)	0 (0.0)
Nonsteroidal anti-inflammatory drugs	3 (12.5)	3 (12.5)
Monoclonal antibody therapy	0 (0.0)	1 (4.2)
Total*	6 (25.0)	6 (25.0)

\*Some participants took many anti-inflammatory drugs which explains why the total does not correspond to the sum. CBD, cannabidiol; n, number of participants.

**Table S9. Sensitivity analysis without participants taking anti-inflammatory drugs.**

Outcomes	Parameters	Estimate	Standard Error	Wald Chi square	p	Effect size
IL-6	Treatment	-0.392	0.165	5.674	<b>0.017</b>	0.347
	Treatment without participants taking anti-inflammatory drugs	-0.466	0.161	8.402	<b>0.004</b>	0.423
VEGF-A	Treatment	-14.417	6.722	4.600	<b>0.032</b>	0.313
	Treatment without participants taking anti-inflammatory drugs	-12.146	9.376	1.678	0.195	0.189
Intermediate monocytes (CD14 <sup>+</sup> CD16 <sup>+</sup> )	Treatment	-0.468	0.207	5.082	<b>0.024</b>	0.330
	Treatment without participants taking anti-inflammatory drugs	-0.258	0.213	1.470	0.225	0.177
NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	Treatment	-0.736	0.167	19.552	<b>0.000</b>	0.643
	Treatment without participants taking anti-inflammatory drugs	-0.673	0.182	13.682	<b>0.000</b>	0.539
CD25 <sup>+</sup> CD4 <sup>+</sup> T	Treatment	0.689	0.256	7.220	<b>0.007</b>	0.393
	Treatment without participants taking anti-inflammatory drugs	0.511	0.308	2.760	0.097	0.242

CD, cluster of differentiation; IL, interleukine; NK, natural killer; p, p-value; VEGF-A, vascular endothelial growth factor-A.

**Table S10. Sensitivity analysis with anti-inflammatory drug use added as a binary covariate.**

Outcomes	Parameters	Estimate	Standard Error	Wald Chi square	p	Effect size
IL-6	Intercept	-0.480	0.697	0.475	0.342	0.346
	Treatment	-0.392	0.165	5.608	<b>0.018</b>	
	Baseline	-0.993	0.094	111.527	<b>0.000</b>	
	SDS score	0.045	0.040	1.283	0.257	
	Sex	-0.347	0.244	2.024	0.155	
	Age	0.005	0.008	0.347	0.556	
	Anti-inflammatory drug use	0.023	0.240	0.009	0.923	
VEGF-A	Intercept	-47.149	33.890	1.936	0.164	0.311
	Treatment	-14.462	6.792	4.535	<b>0.033</b>	
	Baseline	-0.564	0.160	12.497	<b>0.000</b>	
	SDS score	0.025	1.254	0.000	0.984	
	Sex	-7.540	12.204	0.382	0.537	
	Age	0.342	0.339	1.018	0.313	
	Anti-inflammatory drug use	4.370	8.145	0.288	0.592	
Intermediate monocytes (CD14 <sup>+</sup> CD16 <sup>+</sup> )	Intercept	-0.006	1.024	0.000	0.996	0.330
	Treatment	-0.467	0.207	5.111	<b>0.024</b>	
	Baseline	-0.554	0.124	19.946	<b>0.000</b>	
	SDS score	0.056	0.060	0.862	0.353	
	Sex	-0.097	0.297	0.107	0.744	
	Age	-0.017	0.010	2.984	0.084	
	Anti-inflammatory drug use	0.090	0.202	0.200	0.655	
NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	Intercept	-0.928	0.820	1.279	0.258	0.649
	Treatment	-0.736	0.166	19.784	<b>0.000</b>	
	Baseline	-0.427	0.073	34.490	<b>0.000</b>	
	SDS score	0.032	0.030	1.132	0.287	
	Sex	0.075	0.211	0.128	0.720	
	Age	0.004	0.012	0.096	0.757	
	Anti-inflammatory drug use	-0.074	0.158	0.218	0.641	
CD25 <sup>+</sup> CD4 <sup>+</sup> T	Intercept	-2.456	0.801	9.397	<b>0.002</b>	0.386
	Treatment	0.685	0.259	6.999	<b>0.008</b>	
	Baseline	-0.759	0.069	120.789	<b>0.000</b>	
	SDS score	0.035	0.051	0.467	0.494	
	Sex	0.164	0.366	0.202	0.653	
	Age	0.016	0.010	2.471	0.116	
	Anti-inflammatory drug use	-0.114	0.285	0.161	0.688	

CD, cluster of differentiation; IL, interleukine; NK, natural killer; p, p-value; SDS, severity of dependence scale; VEGF-A, vascular endothelial growth factor-A.

**Table S11. Correlations between weight and inflammatory markers levels.**

Inflammatory markers	Pearson r	t	df	p
IL-6	-0.060	-0.284	22	0.390
VEGF-A	-0.397	-2.029	22	<b>0.027</b>
Intermediate monocytes	-0.198	-0.949	22	0.177
NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	0.102	0.480	22	0.682
CD25 <sup>+</sup> CD4 <sup>+</sup> T	0.149	0.706	22	0.756

CD, cluster of differentiation; df, degree of freedom; IL, interleukine; NK, natural killer; p, p-value; r, correlation coefficient; t, Student t; VEGF-A, vascular endothelial growth factor-A.

**Table S12. Correlations between cannabidiol plasma concentration and inflammatory markers levels.**

Inflammatory markers	Pearson r	t	df	p
IL-6	-0.032	-0.148	22	0.442
VEGF-A	0.041	0.191	22	0.575
Intermediate monocytes	0.199	0.951	22	0.824
NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	-0.134	-0.634	22	0.266
CD25 <sup>+</sup> CD4 <sup>+</sup> T	-0.199	-0.954	22	0.175

CD, cluster of differentiation; df, degree of freedom; IL, interleukine; NK, natural killer; p, p-value; r, correlation coefficient; VEGF-A, vascular endothelial growth factor-A.

**Table S13. Linear regressions analysis of inflammatory markers on drug-cue induced craving by treatment group.**

Model	Variables	Estimate	Standard Error	t	p
IL-6	Intercept	3.498	3.621	0.966	0.340
	Treatment	-0.823	1.577	-0.522	0.604
	IL-6	0.838	0.887	0.944	0.351
	Baseline	-1.217	0.746	-1.632	0.111
	SDS score	-0.108	0.187	-0.576	0.568
	Sex	0.962	1.181	0.814	0.420
	Age	0.017	0.042	0.408	0.686
	Treatment*IL-6	1.118	0.980	1.140	0.261
VEGF-A	Intercept	4.550	3.689	1.233	0.225
	Treatment	2.383	2.753	0.865	0.392
	VEGF-A	-0.005	0.018	-0.308	0.760
	Baseline	0.014	0.015	0.947	0.349
	SDS score	-0.133	0.199	-0.669	0.508
	Sex	0.028	1.441	0.019	0.985
	Age	-0.008	0.047	-0.166	0.869
Treatment*VEGF-A	-0.018	0.025	-0.728	0.471	
Intermediate monocytes	Intercept	5.066	3.766	1.345	0.186
	Treatment	1.358	1.344	1.010	0.318
	Intermediate monocytes	0.218	0.484	0.451	0.655
	Baseline	0.339	0.515	0.658	0.514
	SDS score	-0.139	0.196	-0.708	0.483
	Sex	-0.053	1.353	-0.039	0.969
	Age	-0.016	0.046	-0.339	0.737
	Treatment*Intermediate monocytes	-0.398	0.803	-0.495	0.623
NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	Intercept	4.100	3.814	1.075	0.289
	Treatment	-0.140	1.808	-0.078	0.939
	NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	-0.362	0.925	-0.391	0.698
	Baseline	0.032	0.535	0.061	0.952
	SDS score	-0.114	0.205	-0.555	0.582
	Sex	0.739	1.241	0.595	0.555
	Age	0.009	0.045	0.196	0.845
	Treatment*NK CD56 <sup>neg</sup> CD16 <sup>hi</sup>	0.660	1.233	0.536	0.595
CD25 <sup>+</sup> CD4 <sup>+</sup> T	Intercept	3.345	4.000	0.836	0.408
	Treatment	1.231	1.764	0.698	0.489
	CD25 <sup>+</sup> CD4 <sup>+</sup> T	-0.639	0.520	-1.230	0.226
	Baseline	0.523	0.355	1.475	0.148
	SDS score	-0.096	0.192	-0.499	0.620
	Sex	0.833	1.212	0.687	0.496
	Age	0.007	0.044	0.152	0.880
Treatment*CD25 <sup>+</sup> CD4 <sup>+</sup> T	0.075	0.429	0.174	0.863	

The dependent variable for all models was the difference between pre and post self-reported drug-cue induced craving scores (using a visual analogue scale ranging from 0 to 10). The five main significant inflammatory markers by treatment group were the independent variables in their respective model. Baseline inflammatory marker's level, SDS score, sex and age were added as covariates in all models. CD, cluster of differentiation; IL, interleukine; NK, natural killer; p, p-value; SDS, severity of dependence scale; t, Student t; VEGF-A, vascular endothelial growth factor-A.