The LiBBY Trial

LIfe's end Benefits of cannaBidiol and tetrahYdrocannabinol Trial

Double-Blind Phase Topline Results

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The LiBBY Study is funded by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) and the Alzheimer's Association. It is being conducted by the NIH-funded Alzheimer's Clinical Trial Consortium (ACTC) and coordinated by the University of Southern California's Epstein Family Alzheimer's Therapeutic Research Institute (ATRI), Medical University of South Carolina, and Georgetown University.

The Current State of our Knowledge

- Half of the patients suffering from Alzheimer's disease (AD) use hospice care in the last days of their life.
- Most present with moderate to severe agitation and effective treatments are needed.

Kramarow, E. A., & Tejada-Vera, B. (2019, March). Dementia Mortality in the United States, 2000-2017. 68(2), 1-29.
Agar, M. R., Lawlor, P. G., Quinn, S., Draper, B., Caplan, G. A., Rowett, D., Sanderson, C., Hardy, J., Le, B., Eckermann, S., McCaffrey, N., Devilee, L., Fazekas, B., Hill, M., & Currow, D. C. (2017). Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. JAMA internal medicine, 177(1), 34–42.

LIBBY Study Objective

To develop a safe and effective approach for the treatment of hospice care-eligible, agitated patients suffering from Alzheimer's disease (AD) or other types of dementia (HAD).

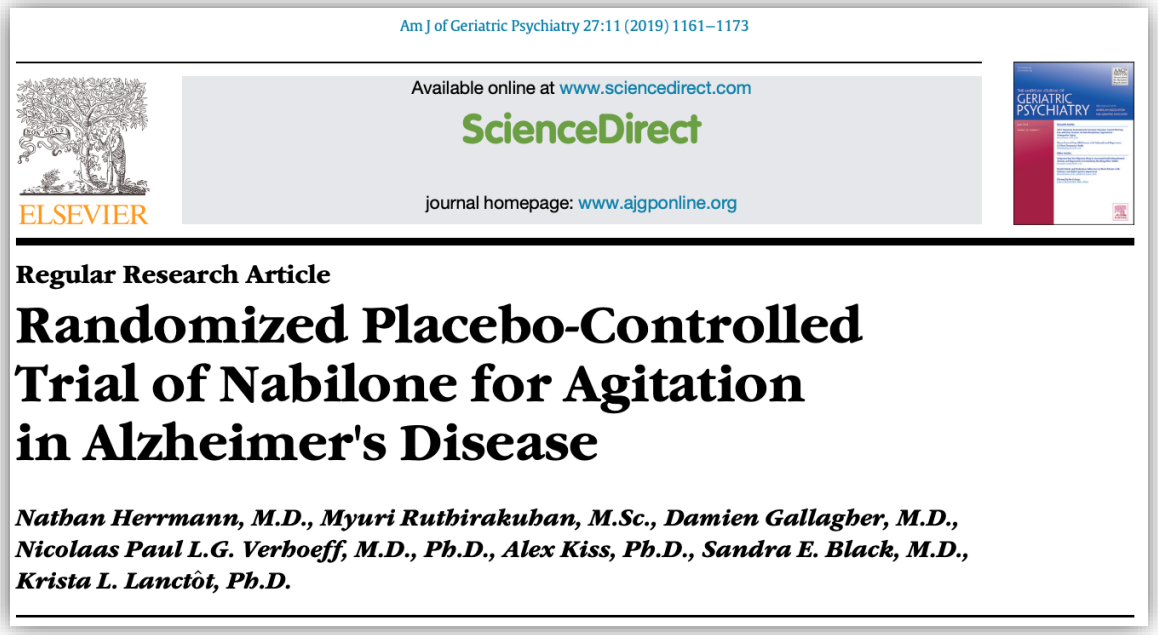
Tetrahydrocannabinol and Cannabidiol

- Tetrahydrocannabinol (THC)
  - Has well documented psychoactive activity
  - Exerts a broad effect on the regulation of emotion
  - Activates cannabinoid receptors directly
    - CB1 represses neurotransmitter release in the brain and regulates synaptic transmission
    - CB2 is a partial agonist that triggers anti-inflammatory effects

- Cannabidiol (CBD)
  - Non-psychoactive component of the marijuana plant
  - Directly activates the hydroxytryptamine (5-HT1A) serotonin receptors and triggers an inhibitory response that slows down 5-HT1A signaling, thus having positive therapeutic effects on: anxiety, appetite, sleep, and pain

Wiffen, P. J., Derry, S., & Moore, R. A. (2014). Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. The Cochrane database of systematic reviews, 2014(5), CD011056. https://doi.org/10.1002/14651858.CD011056.pub2
Hill K. P. (2015). Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA, 313(24), 2474–2483. https://doi.org/10.1001/jama.2015.6199
Tambaro S, Bortolato M. Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives. Recent Pat CNS Drug Discov. 2012 Apr 1;7(1):25-40. doi: 10.2174/157488912798842269. PMID: 22280339; PMCID: PMC3691841.
Iffland, K., & Grotenhermen, F. (2017). An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis and cannabinoid research, 2(1), 139–154. https://doi.org/10.1089/can.2016.0034
Malfitano AM, Basu S, Maresz K, Bifulco M, Dittel BN. What we know and do not know about the cannabinoid receptor 2 (CB2). Semin Immunol. 2014 Oct;26(5):369-79. doi: 10.1016/j.smim.2014.04.002. Epub 2014 May 28. PMID: 24877594; PMCID: PMC4567276.

Preliminary Data



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ELSEVIER

Regular Research Article

Randomized Placebo-Controlled Trial of Nabilone for Agitation in Alzheimer's Disease

Nathan Herrmann, M.D., Myuri Ruthirakuhan, M.Sc., Damien Gallagher, M.D., Nicolaas Paul L.G. Verhoeff, M.D., Ph.D., Alex Kiss, Ph.D., Sandra E. Black, M.D., Krista L. Lanctôt, Ph.D.

- Double-blind, placebo-controlled, cross-over study in a similar population using nabilone (0.5mg – 2mg), a synthetic derivative of THC
- Showed benefit on the CMAI and trend on global measures

Herrmann, N., Ruthirakuhan, M., Gallagher, D., Verhoeff, N. P. L. G., Kiss, A., Black, S. E., & Lanctôt, K. L. (2019). Randomized Placebo-Controlled Trial of Nabilone for Agitation in Alzheimer's Disease. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 27(11), 1161–1173. https://doi.org/10.1016/j.jagp.2019.05.002

LiBBY Investigational Product - T2:C100

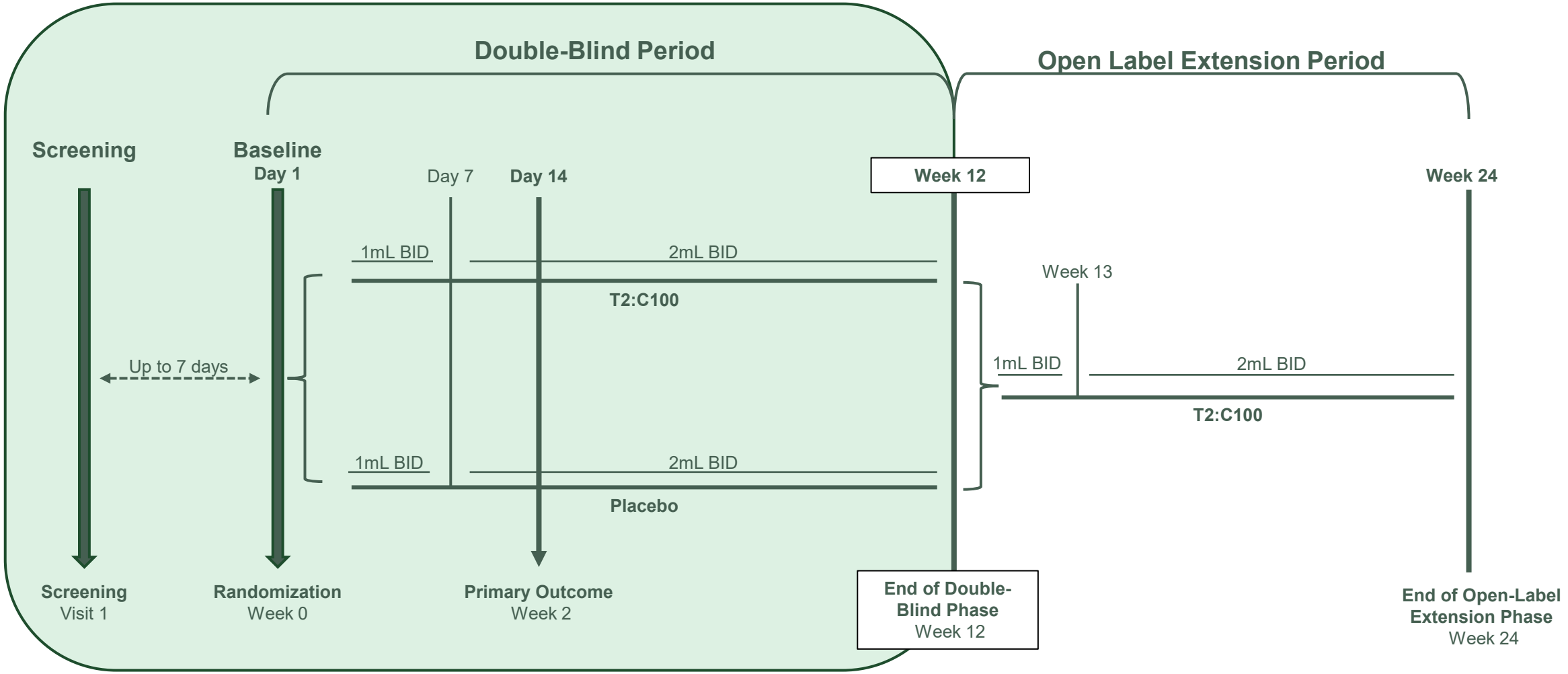
- LiBBY study compound - **T2:C100**
  - specific formulation conceived by the study team
  - 1mL solution contains 2mg THC and 100mg CBD
  - manufactured in Canada by MediPharm Labs
  - formulation is not publicly available and not currently being used for any other indication
- Divided daily dose- 8mg of THC and 400mg of CBD
  - THC bioequivalent of 1-2mg of nabilone
- Purified THC:CBD combination selected because of a more benign side effect profile compared to nabilone

The data presented today applies only to the T2:C100 purified compound at the specific dosing and delivery system used in the study and does not apply to any other form of cannabis or to any other form of publicly available marijuana.

Wiffen, P. J., Derry, S., & Moore, R. A. (2014). Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. The Cochrane database of systematic reviews, 2014(5), CD011056. https://doi.org/10.1002/14651858.CD011056.pub2
Hill K. P. (2015). Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA, 313(24), 2474–2483. https://doi.org/10.1001/jama.2015.6199
Tambaro S, Bortolato M. Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives. Recent Pat CNS Drug Discov. 2012 Apr 1;7(1):25-40. doi: 10.2174/157488912798842269. PMID: 22280339; PMCID: PMC3691841.
Iffland, K., & Grotenhermen, F. (2017). An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis and cannabinoid research, 2(1), 139–154. https://doi.org/10.1089/can.2016.0034

LiBBY Study Design

12-week, phase 2, multi-center, randomized, double-blind, parallel-group, placebo-controlled study



Key Inclusion and Exclusion Criteria

Inclusion Criteria

- 40 years of age or older
- Meets DSM-V criteria for Major Neurocognitive Disorder
- NPI-agitation subscale of 4 or above at Screening
- Meets at least one of the following requirements:
  - Currently enrolled in inpatient/outpatient hospice care
  - FAST Score of 6D or greater
  - ADEPT Score of 12 or greater
- Has a third-party clinician who is managing patient care
- Resides in a suitable environment (i.e., where research can successfully be conducted)

Exclusion Criteria

- Use of cannabinoids or other forms of marijuana in the 3 weeks prior to Baseline
- Known allergic reactions, adverse reactions, or hypersensitivity to cannabinoids and/or components of sesame oil
- Treatment with another investigational drug of other intervention within the previous 30 days or five half-lives of the investigational product, whichever is longer

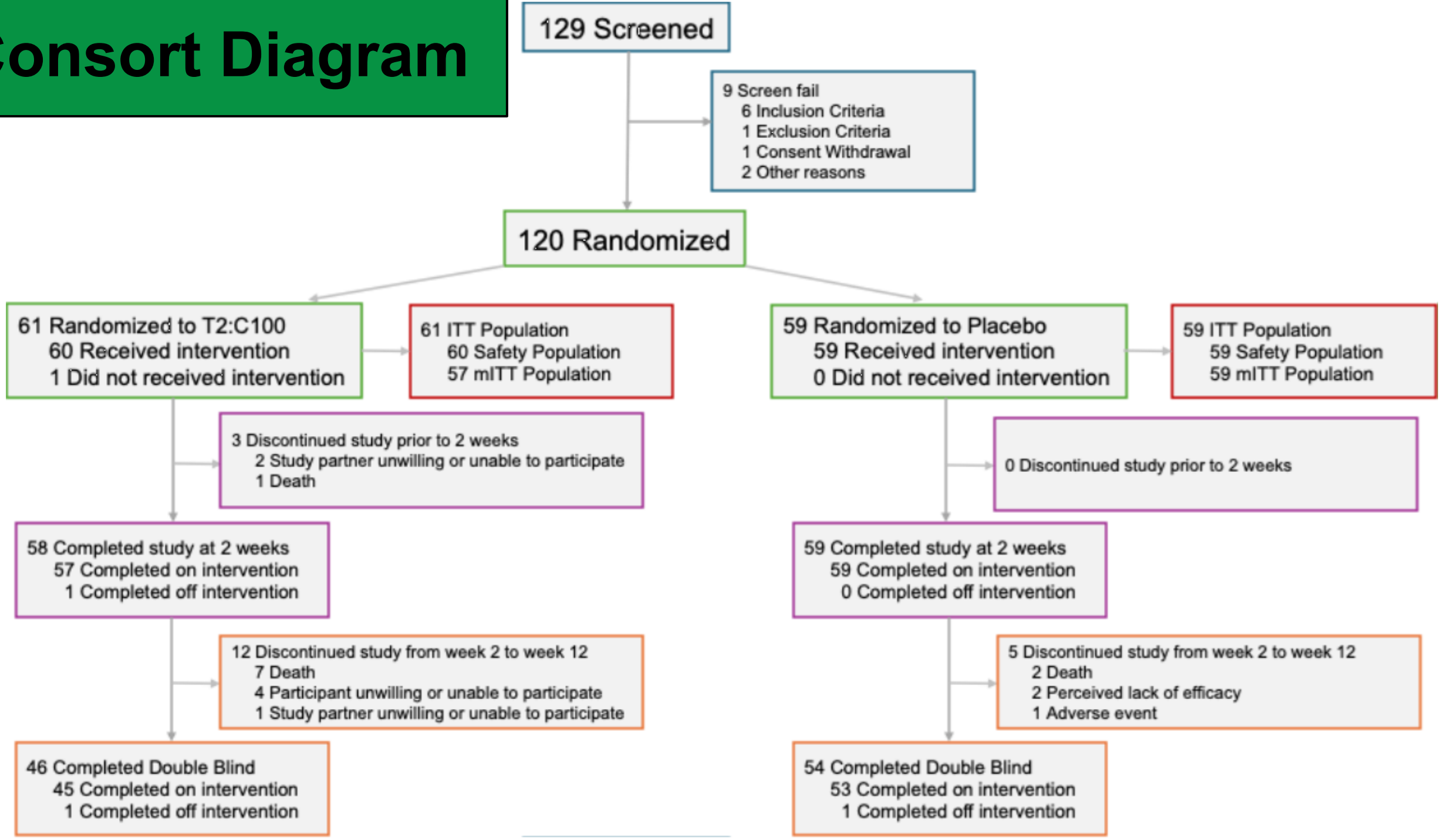
FAST= Functional Assessment Staging Tool
ADEPT = Advanced Dementia Prognostic Tool

Study Endpoints

	Endpoints
Primary	• CMAI Frequency: Week 2 change from baseline
Key Secondary	• CMAI Frequency: Week 12 change from baseline • CGIC-B at Week 2 • CGIC-B at Week 12
Secondary	• CMAI-Disruptiveness: Week 2 and week 12 change from baseline • PAINAD score: Week 2 and week 12 change from baseline • NPI-Q Caregiver Distress score: Week 2 and week 12 change from baseline • NPI-Q Severity score: Week 2 and week 12 change from baseline • SSS score: Week 2 and week 12 change from baseline • BSFC-S score: Week 2 and week 12 change from baseline

CMAI = Cohen-Mansfield Agitation Inventory
CGIC-B = Clinical Global Impression of Change in Behavior
PAINAD = Pain Assessment in Advanced Dementia Scale
NPI-Q = Neuropsychiatric Inventory-Questionnaire
SSS = Standford Sleepiness Scale
BSFC-S = Burden Scale for Family Caregiver-Short Version

Consort Diagram



Baseline characteristics (ITT)

	T2:C100 N = 61	Placebo N = 59	Overall N = 120
Age in years, Mean (SD)	80 (8)	80 (9)	80 (8)
Education in years, Mean (SD)	12.3 (4.8)	12.9 (4.4)	12.6 (4.6)
Participant Sex at birth, Female, N (%)	29 (48%)	37 (63%)	66 (55%)
Race			
Asian	0 (0%)	1 (1.7%)	1 (0.8%)
Black or African American	10 (16%)	8 (14%)	18 (15%)
Caucasian or White	51 (84%)	50 (85%)	101 (84%)
Hispanic or Latino Ethnicity, n(%)	28 (46%)	26 (44%)	54 (45%)
Living Situation, n(%)			
House/Apartment	43 (70%)	47 (80%)	90 (75%)
Lives with family	8 (13%)	6 (10%)	14 (12%)
Senior Residence/Retirement Community/Assisted Living/Nursing Facility	10 (17%)	6 (10%)	16 (13%)
Study Partner Relationship, n(%)			
Spouse	23 (35%)	20 (32%)	43 (33%)
Other relative (Adult Child, Child-in-law, Sibling)	28 (42%)	23 (36%)	51 (39%)
Paid caregiver	11 (17%)	13 (21%)	24 (19%)
Other (Friend, Other)	4 (6%)	7 (11%)	11 (9%)
Study Partner Sex at Birth, Female, n(%)	48 (73%)	50 (79%)	98 (76%)
Study Partner Lives with participant, n(%)	39 (59%)	42 (67%)	81 (63%)

Treatment Discontinuations

	Baseline to Week 2			Baseline to Week 12		
	T2:C100 N = 61	**Placebo** N = 59	p value*	**T2:C100** N = 61	**Placebo** N = 59	p value*
Treatment discontinuations	4 (6.6%)	0 (0%)	0.119	16 (26.2%)	6 (10.2%)	0.033
Adverse Event	1	0		1	1	
Death	1	0		8	3	
Unwilling or unable to participate	2	0		7	2	

* Fisher's exact test

Deaths

	From Baseline to Week 2		
	T2:C100 N = 61	**Placebo** N = 59	Difference of proportion* (95% CI)
# of participants	1 (1.6%)	0 (0%)	1.6% (1.5%, 4.8%)

	From Baseline to Week 12		
	T2:C100 N = 61	**Placebo** N = 59	Difference of proportion* (95% CI)
# of participants	8 (13.1%)	3 (5.1%)	8% (3.8%, 19.6%)

Arm	AE related to cause of Death
T2:C100	Sepsis
	Pulmonary embolism
	Dementia
	Dementia
	Creutzfeldt-Jakob disease
	Dementia
	Malnutrition
	Urinary tract infection
Placebo	Respiratory distress
	Dementia
	Respiratory distress

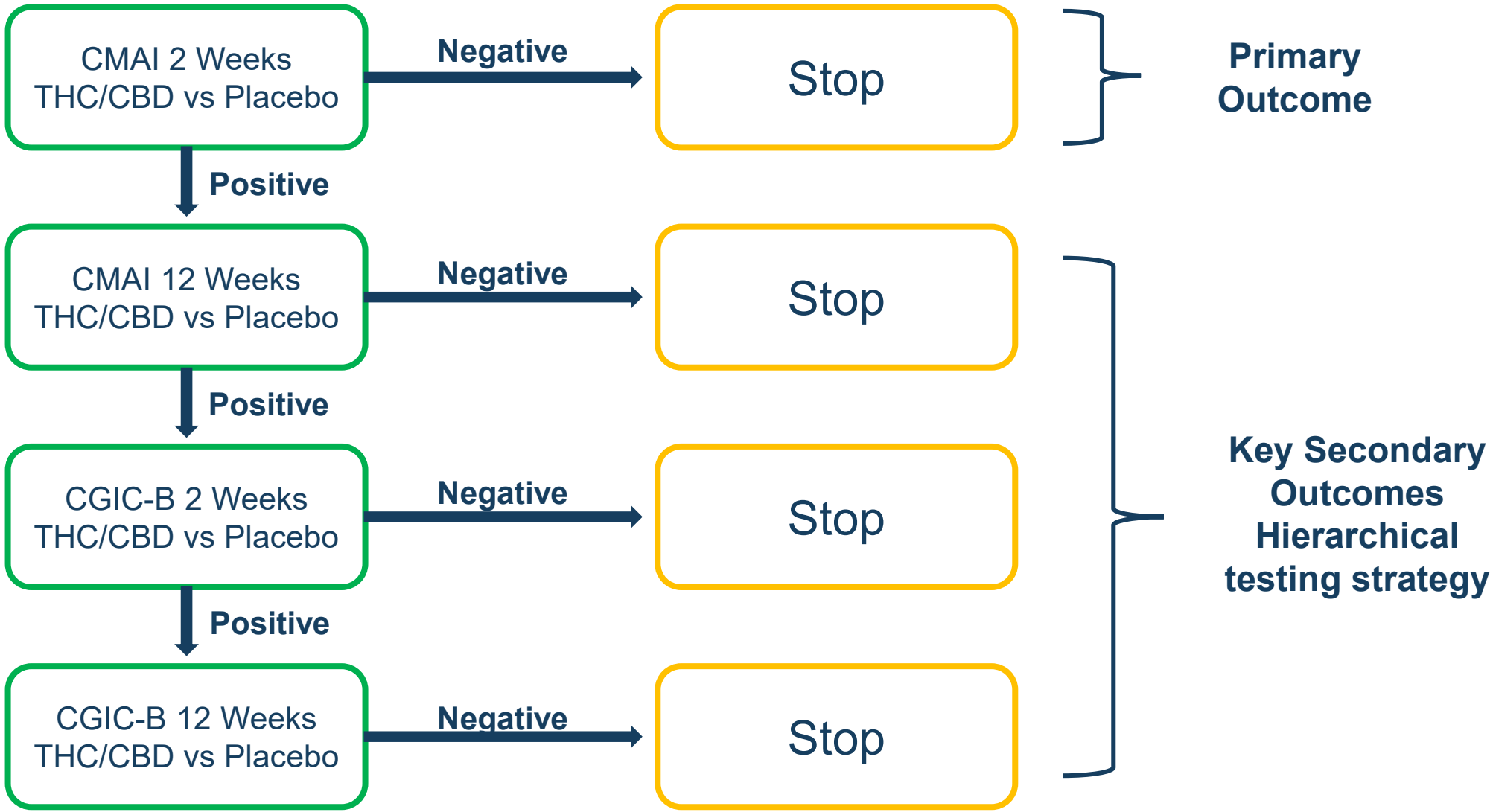
None reported as related to IP

Treatment Emergent Adverse Events Overall and by MedDRA SOC

	From baseline to week 2		From baseline to week 12	
	T2:C100 N = 60	**Placebo** N = 59	**T2:C100** N = 60	**Placebo** N = 59
Number of subject who experienced at least one AE	10 (16.7%)	11 (18.6%)	28 (46.7%)	25 (42.4%)
Nervous system disorders	5 (8.3%)	3 (5.1%)	10 (16.7%)	10 (17%)
Infections and infestations	2 (3.3%)	2 (3.4%)	10 (16.7%)	5 (8.5%)
Gastrointestinal disorders	1 (1.7%)	1 (1.7%)	6 (10%)	5 (8.5%)
Injury, poisoning and procedural complications	1 (1.7%)	2 (3.4%)	5 (8.3%)	4 (6.8%)
Skin and subcutaneous tissue disorders	1 (1.7%)	1 (1.7%)	4 (6.7%)	4 (6.8%)
General disorders and administration site conditions	0 (0%)	2 (3.4%)	3 (5%)	3 (5.1%)
Number of subject who experienced at least one SAE	3 (5%)	0 (0%)	14 (23.3%)	7 (11.9%)
Infections and infestations	0 (0%)	0 (0%)	7 (11.7%)	1 (1.7%)
Nervous system disorders	1 (1.7%)	0 (0%)	3 (5%)	3 (5.1%)

Only SOC with overall percentages greater than 5% are presented

Efficacy Outcomes - Order of Testing



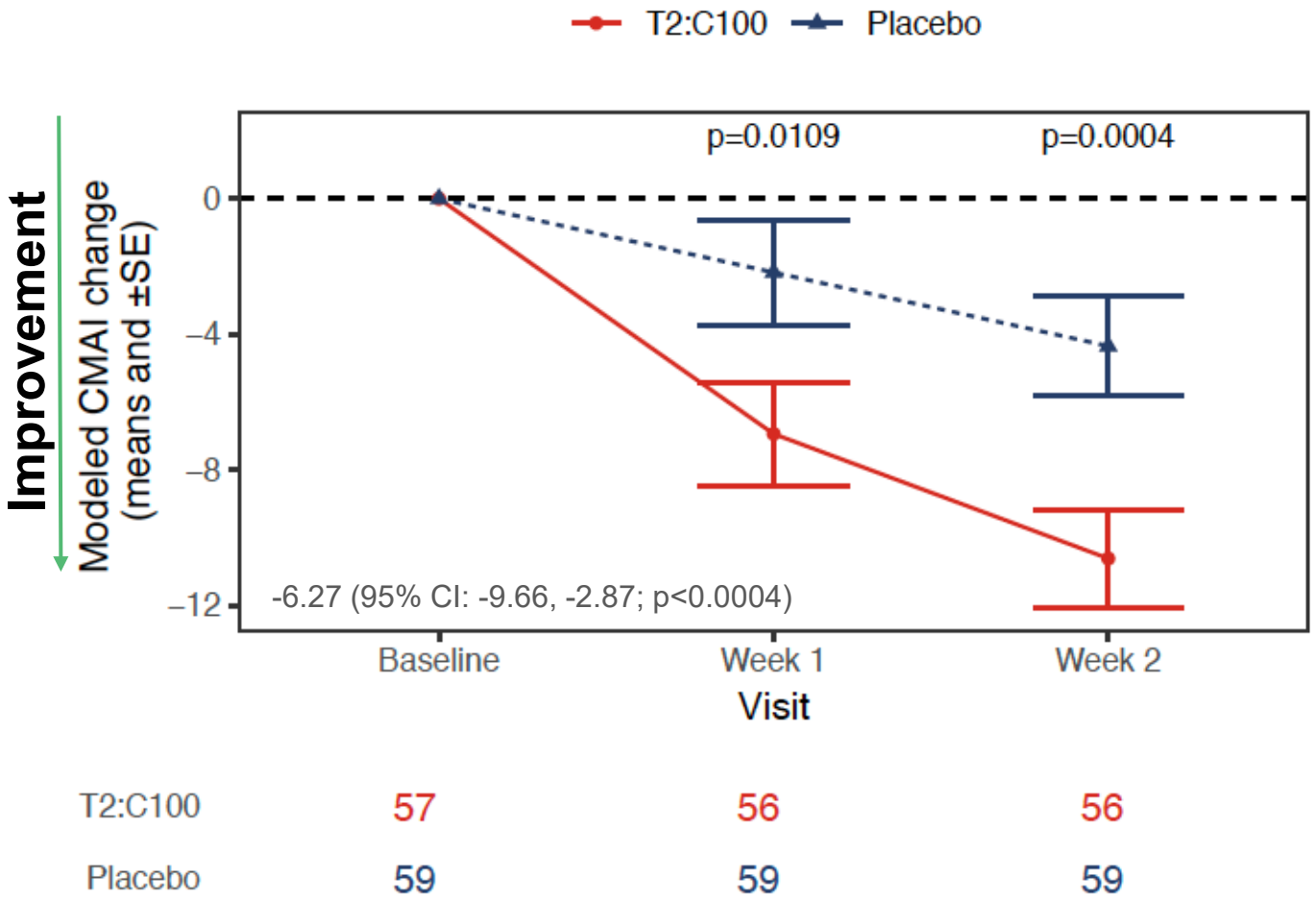
Statistical Methods - Outcomes

Outcome	Population*	Methods	Sensitivity Analysis
CMAI Frequency 2 weeks	mITT	Mixed-Method Repeated Measures (MMRM)	Analysis of Covariance (ANCOVA) using Multiple Imputation
CMAI Frequency 12 weeks	mITT	Area Under the Curve (AUC) derived from a MRMM model	Complier Population: AUC derived from a MMRM model
CGIC-B 2 weeks, 12 weeks	mITT	General Linear Model for Binary Data using Logit link (MMRM)	General Linear Model for Binary Data using Logit link using Multiple Imputation

mITT = modified Intention-to-treat

- MMRM model was adjusted for hospice (Y/N), treatment location, site, baseline score and baseline score*time.
- ANCOVA model was adjusted for hospice (Y/N), treatment location, site and baseline
- Generalized Linear Model was adjusted for hospice (Y/N), treatment location, site

Primary Outcome: CMAI Frequency at week 2



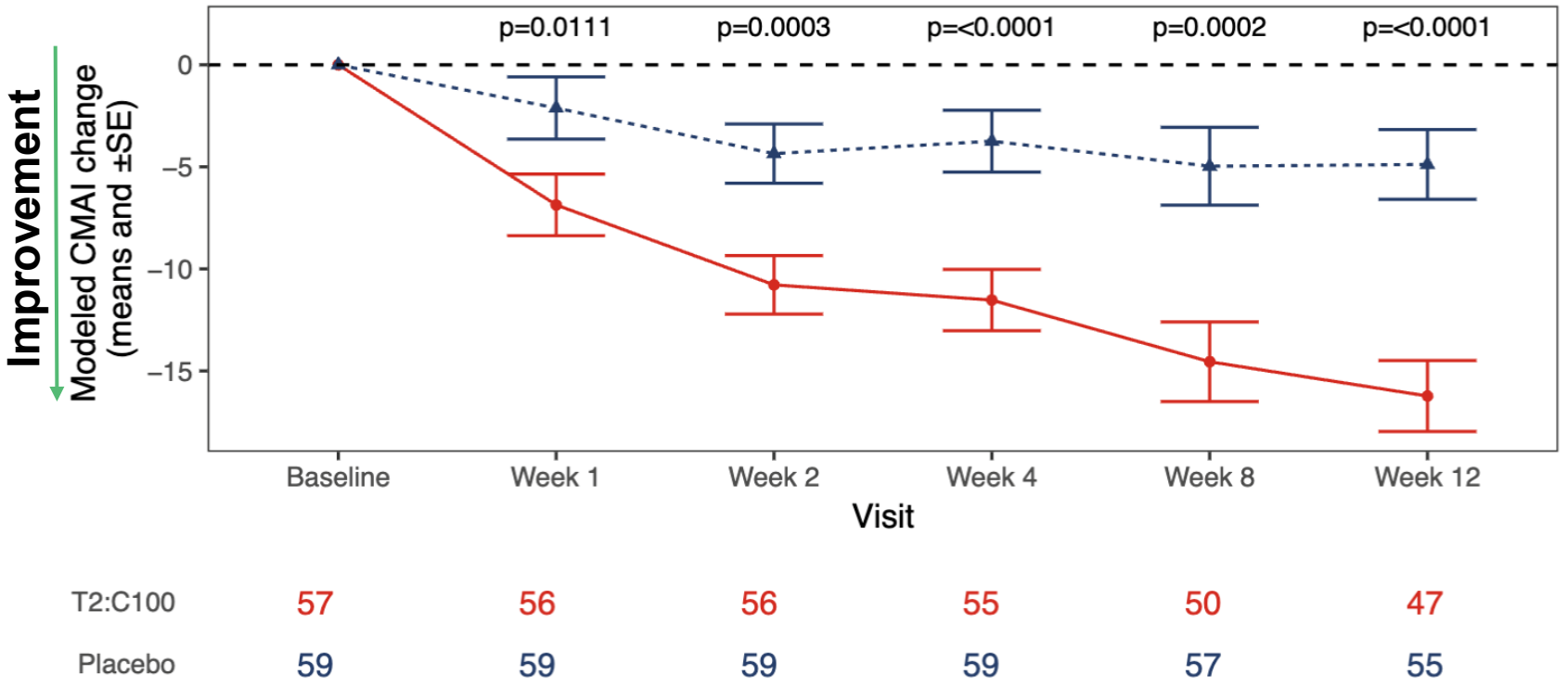
Positive

MMRM Modeled CMAI Frequency
Change from baseline

Visit	Arm	Estimate (SE)	P value
Week 1	T2:C100	-6.94 (1.52)	0.0109
	Placebo	-2.18 (1.54)	
Week 2	T2:C100	-10.61 (1.45)	0.0004
	Placebo	-4.35 (1.47)	

MMRM model was adjusted for the following covariates: hospice (Y/N), treatment location, binary site, baseline score and baseline score*time. The p value reflects the treatment group contrast at week 2

Key Secondary: CMAI Frequency at week 12

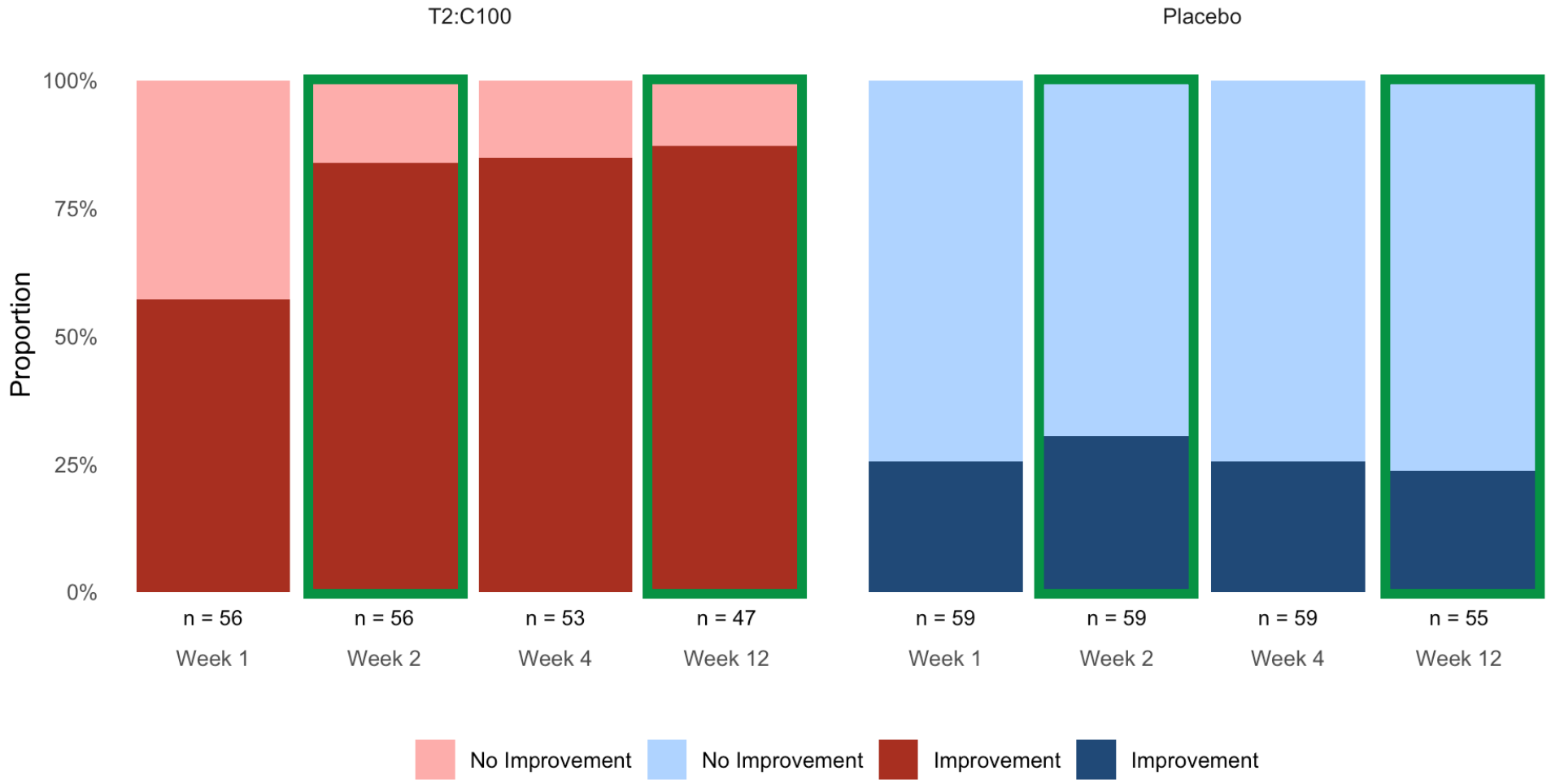


Positive

Mean AUC contrast between arms:
-8.23 (95% CI: -11.6, -4.86; p*<0.0001)

The mean AUC is derived from a MMRM model adjusted for the following covariates: hospice, treatment location, binary site, baseline score and baseline score*time. The p value reflects the mean area under the curve (AUC) contrast between intervention arms at week 12

Key Secondary: CGIC-B at Week 2 and Week 12



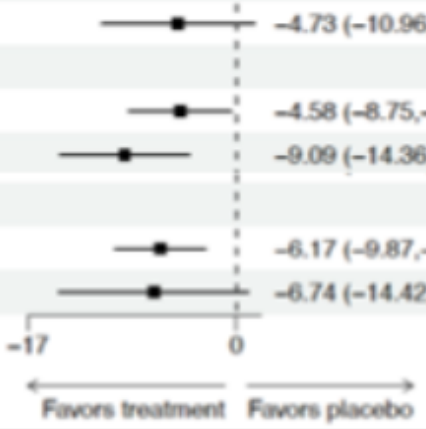
- 2 weeks: 83.9% vs 30.5% (p<0.0001)
- 12 weeks: 87.2% vs 23.6% (p<0.0001)

Positive

CMAI at Week 2 and Week 12: (Forest Plot with Prespecified Subgroup Analyses)

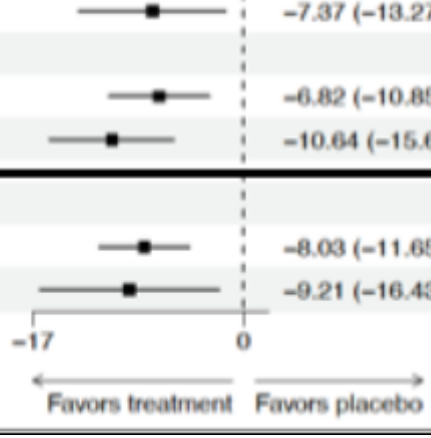
2 weeks

mITT Population	T2:C100	Placebo	Contrast (95% CI)	Pvalue
Age				
<81	28	28	-6.85 (-11.61,-2.09)	0.0052
>=81	29	31	-5.76 (-10.33,-1.19)	0.0139
Ethnicity				
No	29	33	-6.3 (-10.87,-1.72)	0.0075
Yes	28	26	-5.95 (-10.68,-1.23)	0.0140
Gender				
Male	30	22	-4.32 (-9.23,0.58)	0.0835
Female	27	37	-7.98 (-12.49,-3.47)	0.0006
Hospice status				
No	42	44	-6.81 (-10.68,-2.94)	0.0007
Yes	15	15	-4.73 (-10.96,1.5)	0.1357
NPI-Agitation				
<8	36	35	-4.58 (-8.75,-0.41)	0.0314
>=8	21	24	-9.09 (-14.36,-3.83)	0.0009
Treatment Location				
Home	46	50	-6.17 (-9.87,-2.47)	0.0013
Institution	11	9	-6.74 (-14.42,0.95)	0.0852



12 weeks

mITT Population	T2:C100	Placebo	Contrast (95% CI)	Pvalue
Age				
<81	28	28	-8.33 (-12.9,-3.75)	0.0005
>=81	29	31	-8.18 (-12.58,-3.78)	0.0003
Ethnicity				
No	29	33	-7.71 (-12.1,-3.31)	0.0007
Yes	28	26	-8.44 (-12.96,-3.92)	0.0003
Gender				
Male	30	22	-6.63 (-11.33,-1.93)	0.0061
Female	27	37	-9.79 (-14.13,-5.44)	<0.0001
Hospice status				
No	42	44	-8.54 (-12.33,-4.75)	<0.0001
Yes	15	15	-7.37 (-13.27,-1.47)	0.0148
NPI-Agitation				
<8	36	35	-6.82 (-10.85,-2.78)	0.0011
>=8	21	24	-10.64 (-15.65,-5.63)	<0.0001
Treatment Location				
Home	46	50	-8.03 (-11.65,-4.4)	<0.0001
Institution	11	9	-9.21 (-16.43,-1.98)	0.0129



Medications of Special Interest (MSI) at baseline

Visit	Medication of Special Interest	T2:C100 N=57	Placebo N=59	Overall N=116
Baseline	Antipsychotic agents	21 (36.84%)	23 (38.98%)	44 (37.93%)
	Benzodiazepines and sedatives	16 (28.07%)	27 (45.76%)	43 (37.07%)
	Other medications used to treat agitation	8 (14.04%)	8 (13.56%)	16 (13.79%)
	Opiates/opioids	0 (0%)	2 (3.39%)	2 (1.72%)

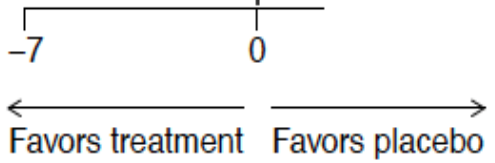
Number of participants with at least one reported MSI

No changes in use of medication of special interest over time

Other Secondary Outcomes

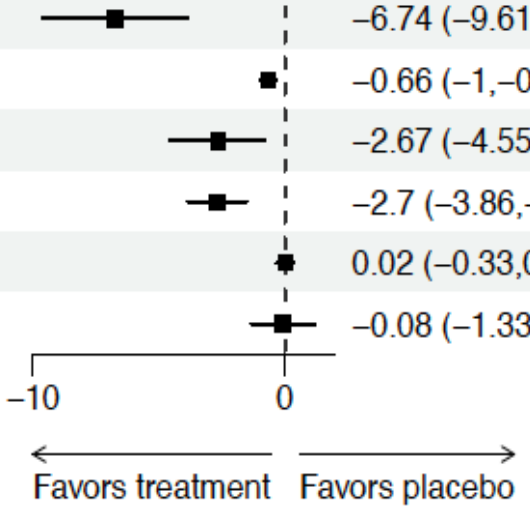
2 weeks

outcome	T2:C100	Placebo	Contrast (95% CI)	Adj.pvalue
CMAI–Disruptivness	57	59	–4.24 (–6.98,–1.49)	0.0167
Pain Assessment in Advanced Dementia	57	59	–0.34 (–0.81,0.12)	0.4306
NPI–Q Caregiver Distress	57	59	–3.25 (–5.51,–0.99)	0.0262
NPI–Q Severity	57	59	–2.27 (–3.67,–0.88)	0.0115
Stanford Sleepiness Scale	57	59	0.15 (–0.28,0.58)	0.7022
Burden Scale for Family Caregiver	57	59	–0.62 (–1.93,0.69)	0.7022



12 weeks

outcome	T2:C100	Placebo	Contrast (95% CI)	Adj.pvalue
CMAI–Disruptivness	57	59	–6.74 (–9.61,–3.86)	<0.0001
Pain Assessment in Advanced Dementia	57	59	–0.66 (–1,–0.33)	0.0009
NPI–Q Caregiver Distress	57	59	–2.67 (–4.55,–0.78)	0.0179
NPI–Q Severity	57	59	–2.7 (–3.86,–1.54)	<0.0001
Stanford Sleepiness Scale	57	59	0.02 (–0.33,0.36)	>0.9999
Burden Scale for Family Caregiver	57	59	–0.08 (–1.33,1.17)	>0.9999



Conclusions

- First randomized, placebo-controlled trial performed in HAD patients. One of the few randomized, controlled clinical trials testing purified natural THC and CBD
- Established the feasibility of conducting randomized, controlled studies in this population
- Met all primary and key secondary endpoints; results were consistent across sensitivity analyses and pre-specified subgroups
  - Demonstrated efficacy on the CMAI at 2 weeks and 12 weeks overall
  - Demonstrated improvement on the CGIC-B at 2 weeks and 12 weeks overall
- THC and CBD intervention was well tolerated by a majority of participants
- Numerical increase in deaths in the THC and CBD intervention arm
  - Data review showed no pattern in the cause of death in either group

The data presented today applies only to the T2:C100 purified compound at the specific dose and delivery system used in the study and does not apply to any other form of cannabis or any other form of publicly available marijuana.

Next Steps

We intend to extend these findings in a larger study in a broader study population.

Libby Sofar's Last Few Weeks of Life

- Treated by the Charleston Hospice Care Team
- Received standard hospice end-of-life care:
  - Haloperidol
  - Valium
  - Morphine
- With treatment:
  - Her agitation and confusion increased
  - She developed severe pruritus and constipation
  - She died in despair

Acknowledgments

A special thanks to our study participants, caregivers, and study partners
The LiBBY Study was funded by the National Institute on Aging (R01AG068324) and the Alzheimer's Association and conducted through the Alzheimer's Clinical Trials Consortium (ACTC).

Leadership and ACTC Teams

Principal Investigators	Jacobo Mintzer, Brigid Reynolds
ACTC Leadership	Paul Aisen, Reisa Sperling, Ron Petersen, Laurie Ryan
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Biomarker	Robert Rissman, Sara Abdel-Latif
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Clinical Operations	Alison Belsha, Neelam Kaul, Yuliana Cabrera, Harriett Davey, Melissa Ruiz
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Project Administration	Arianne Zokas Fritts, Sarah Walter
Regulatory:	Elizabeth Shaffer, Cat Nguyen-Barrera
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Georgetown University	Margaret Bassett
Howard University	Thomas Obisesan
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Pennington University	Jeffrey Keller
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University of Kentucky	Gregory Jicha
University of Maryland	Raya Kheirbek
University of S. Florida	Mark Kindy
Vanderbilt University	Patricia Andrews

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Data and Safety Monitoring Board

Daniel Weintraub, Chair
Joseph Quinn
Andrew Feigin
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Richard Kryscio
Melissa Armstrong
Valerie Cotter

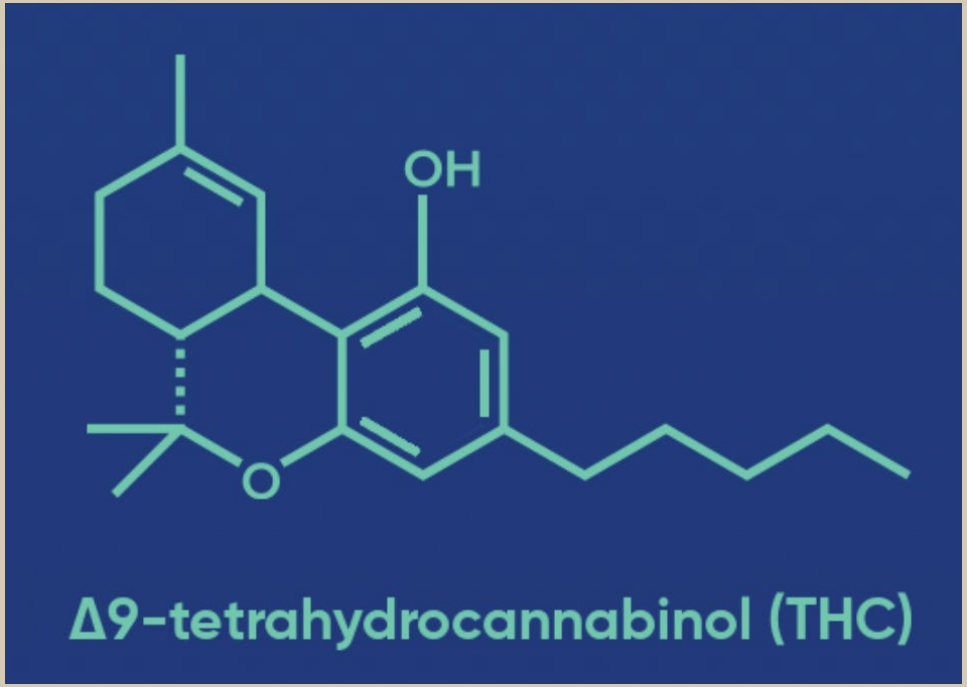
LiBBY Open-Label Extension Study Results will be presented here at AAIC

Session: P16342
Date: Tomorrow, July 15, 2026
Time: 8:00am
Location: ICC Auditorium

BACK UP SLIDES

Tetrahydrocannabinol (THC)

- Has well documented psychoactive activity
- Activates cannabinoid receptors directly (mainly CB1 type)
  - CB1 represses neurotransmitter release in the brain and regulates synaptic transmission.
- Exerts a broad effect on the regulation of emotion
- THC use has been reported to:
  - Decrease or modulate anxiety and fear-related behaviors in some people
  - Alleviate death cognition by preventing “death-related thoughts from entering consciousness”



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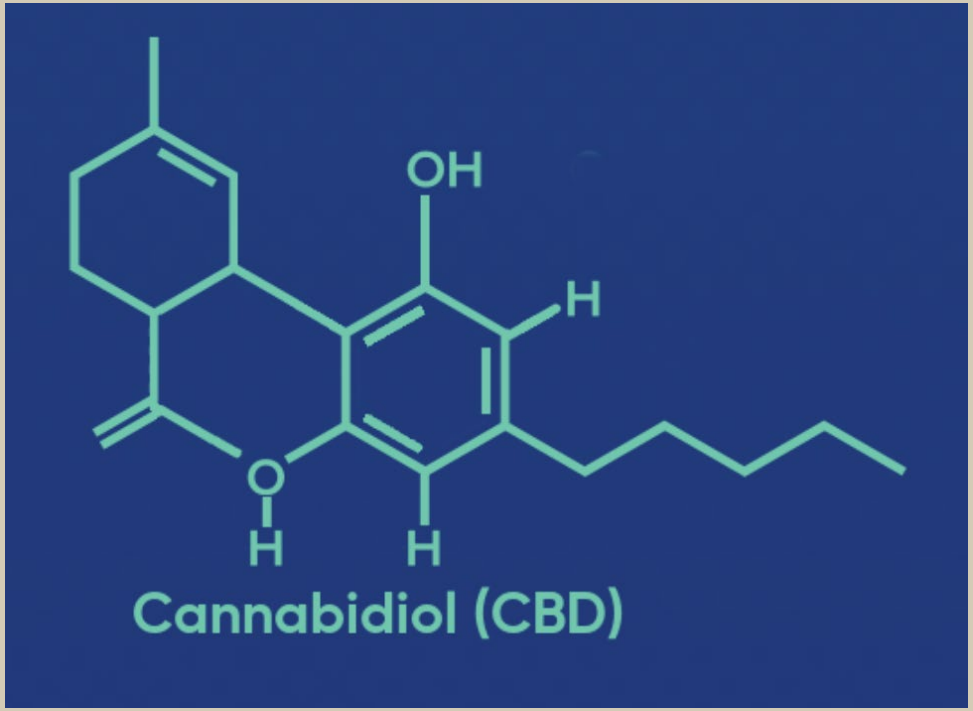
Cannabidiol (CBD)

- Non-psychoactive component of the marijuana plant
- Indirectly modulates CB1 receptors, increasing CB1 activation and reducing pain
- Binds to the transient receptor potential cation channel subfamily V, known to mediate pain perception, inflammation, and body temperature
- Opposes the action of THC, thereby muting the psychoactive effects of THC.
- Directly activates the hydroxytryptamine (5-HT1A) serotonin receptors and triggers an inhibitory response that slows down 5-HT1A signaling, thus having positive therapeutic effects on:

Anxiety	Appetite	Sleep
Pain Perception	Nausea	Vomiting



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