Effects of Broad Spectrum Cannabidiol Oil on Behavioral Disturbances in Patients with Dementia: A Randomized Clinical Trial

Vered Hermush (vhermush@laniado.org.il)
Laniado Hospital
Liora Ore
The Max Stern Yezre'el Valley College
Noa Stern
Laniado Hospital
Nisim Mizrahi
Laniado Hospital
Malki Fried
Laniado Hospital
Marina Krivoshey
Laniado Hospital
Ella Staghon
Laniado Hospital
Violeta E. Lederman
Tikun-Olam Cannbit Pharmaceuticals
Lihi Bar-Lev Schleider
Tikun-Olam Cannbit Pharmaceuticals

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Abstract

Background: Almost 90% of patients with dementia suffer from some type of neurobehavioral symptom and there are no approved medications for these symptoms. We aimed to evaluate the safety and efficacy of Avidekel compared with a placebo for the reduction of behavioral disturbances among patients with dementia.

Methods: In this randomized, double-blind, placebo-controlled trial conducted in a medical center in northern Israel**,** male and female patients, aged at least 60, with a diagnosis of major neurocognitive disorder and associated behavioral disturbances were randomized 2:1 to receive either Avidekel oil (30% cannabidiol and 1% tetrahydrocannabinol: 295 mg and 12.5 mg per ml respectively; n=40), or a placebo oil (n=20) three times a day for 16 weeks. The primary outcome was a decrease, as compared to baseline, of four or more points on the Cohen-Mansfield Agitation Inventory score by week 16. Secondary outcomes included: mean change in the Cohen-Mansfield Agitation Inventory, the time necessary to achieve a 4-point reduction in Cohen-Mansfield Agitation Inventory, mean change in Neuropsychiatric Inventory agitation/aggression sub-score.

Results: Among 60 randomized patients (mean age, 79.4 years; 36 women [60.0%]), 52 (86.7%) completed the trial (all eight patients who discontinued treatment were from the investigational group). There was a statistically significant difference in the proportion of subjects who had a Cohen-Mansfield Agitation Inventory score reduction of ≥4 points at week 16: 24/40 (60.0%) and 6/20 (30.0%) for investigational and control groups, respectively (P<.05). The ANOVA repeated measures analysis demonstrated significantly better improvement in the investigational group compared to the control group in weeks 14 and 16 (P<.05). The Neuropsychiatric Inventory results demonstrated a significant reduction (>29%) in agitation/aggression (P<.05). There were no significant differences in the occurrence of adverse events between the two groups.

Conclusions: In this randomized controlled trial, Avidekel oil significantly reduced agitation over placebo in patients suffering from behavioral disorders related to dementia, with minimal side-effects. Further research is required involving various sub-types of dementia and a larger sample size.

Trial Registration: ClinicalTrials.gov Identifier: NCT03328676. Registered on November 1, 2017.

1. Background

Dementia, characterized by a progressive decline in cognitive and functional abilities and challenging behavioral symptoms, (1, 2) is one of the major causes of disability and dependency among older people.(3) Neuropsychiatric symptoms (NPS) occur in up to 90% of patients with dementia.(4-6) These symptoms include mood disorders, sleep disorders, psychotic symptoms, and agitation.(7-9) NPS are associated with a reduced quality of life for both patient and caregiver(s).(7, 10-12) Agitation, a common NPS in dementia, is associated with an increased rate of cognitive and functional decline,(13) rapid disease progression(14, 15) and earlier death when compared with patients with dementia without agitation. In addition, patients with agitation are more likely to be admitted to institutions,(16-19) increasing the overall cost of care.(7, 9, 10, 20-23) Agitation may also require greater use of antipsychotics and antidepressants.(20) A systematic evidence review concluded that there is a lack of clear and consistent evidence to support the use of various nonpharmacologic interventions for the treatment of behavioral symptoms of dementia. For instance, in the review of controlled studies testing cognition-oriented interventions or restorative strategies, a limited evidence for improving behaviors was found.(23) Antipsychotics are typically used off-label to treat NPS in dementia, although evidence for their efficacy is limited and usage may involve dangerous side-effects.(21, 22, 24-26) Guidelines recommend the use of antipsychotics for the treatment of NPS in patients with dementia only when symptoms are dangerous or cause significant patient distress.(22) Therefore, identifying an effective, low-risk therapeutic alternative for NPS in patients with dementia is essential.

Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most common cannabinoids found in the cannabis plant. (27) THC is the primary psychoactive ingredient.(28) In contrast, CBD is non-intoxicating;(27) and when combined with THC, may counterbalance the psychoactivity of THC.(29) CBD has anti-inflammatory, neuroprotective, antipsychotic, anxiolytic, and antidepressant properties.(30)

Several controlled studies suggest that CBD is safe and effective for the treatment of anxiety,(31-34) Parkinson's disease, (33, 35) post-traumatic stress disorder,(34) and schizophrenia.(36, 37) While each of the two main cannabinoids has been linked to clinical and physiological effects on its own, researchers have hypothesized that the main cannabinoid and minor cannabinoids operate synergistically.(38)

Some clinical data support the beneficial therapeutic effects of cannabinoids on behavioral symptoms, particularly agitation in patients with dementia,(39-41) but reviews concluded that it is uncertain whether cannabinoids have any beneficial or harmful effects on behavioral disorders related to dementia. All included studies tested THC and synthetic THC analogues; none of them examined the direct effect of CBD on agitation.(42),(43) Although treatment with cannabinoids appears to be safe in patients with dementia,(43) oncology,(44) and elderly patients;(45) overall evidence for the management of dementia-related NPS with medical cannabis has been equivocal.(46)

The primary objective of this trial was to evaluate the safety and efficacy of cannabis oil extracted from one chemovar *Avidekel* (30% CBD and 1% THC: 295 mg and 12.5 mg per ml, respectively), for behavioral disturbances in patients with dementia.

2. Methods

Study Design

This was a single-center, randomized (2:1), placebo-controlled, double-blind trial. Patients were recruited nationally by the principal investigator (VH). During enrollment written informed consent was provided, and an application for a cannabis treatment license was arranged (issuance took an average of seven weeks). Over 16 weeks of the treatment period, participants were followed every two weeks, with the option to terminate their participation. The trial took place in a tertiary medical center in northern Israel from December 2017 to September 2019.

Study procedures were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guidelines on Good Clinical Practice and followed the CONSORT reporting guideline.(47).

Participants

At screening, participants were evaluated for eligibility criteria, which included an age of 60 years or older**,** major neurocognitive disorder according to the DSM-5 criteria (all types of dementia)**,** Mini–Mental State Examination (MMSE)(48) score of <26 for cognitive impairment measurement**,** clinically relevant neuropsychiatric behaviors defined as Neuropsychiatric Inventory–Nursing Home Version (NPI-NH)(49-51) sub-score of agitation ≥3, a stable medication regimen for at least two weeks prior to baseline visit, and residing in either an institutionalized setting or in a non-institutionalized setting subject to 24-hour supervision**.** Exclusion criteria included severe heart disease, epilepsy, anxiety disorder; psychotic condition in the present or in the past (not related to dementia); family history of schizophrenia; current substance use disorder, recent cannabis experience, or scheduled surgery during the trial.

Randomization

Eligible participants were randomly assigned by a computerized random-number generator system in a 2:1 ratio to receive either Avidekel oil or a placebo. The 2:1 ratio was intended to encourage interest in caregivers to participate in the trial. The randomized list of patients was set before the trial was initiated; based on it, the investigational product and placebo were prepared. Patients, families, and the medical team were masked to the individual patients' treatment assignment. To ensure masking was maintained, Avidekel and placebo oils were manufactured to have identical appearances and smell.

Investigational product (IP)

The investigational product or the placebo were added to the routine medication regiment (Table 1). Subjects received the IP or the placebo as drops applied under the tongue three times a day. Participants in the investigational group received *Avidekel* (made in Israel by Tikun-Olam Cannbit Pharmaceuticals), an ethanol extraction of high-CBD (~15%), low-THC (~0.5%) cannabis

chemovar dissolved in olive oil. The IP contained 30% CBD, 1% THC, 1% Cannabichromene (CBC), 0.5% Cannabigerol (CBG), and 0.5% Cannabidivarin (CBDV). One drop ~0.04 ml contained 11.8 mg CBD and 0.5 mg THC. Patients in the control group received a placebo containing olive oil and chlorophyll. We selected this specific chemovar aiming mainly to minimize side-effects. This was based on earlier clinical experience with 39 patients with dementia (unpublished data), and with pediatric autism spectrum disorder patients suffering from behavioral disorders.(52) Patients receiving this product showed improvement in agitation.

The initial dose was one oil drop at morning, noon, and evening, for two days; then two drops, three times a day, for two more days, and so forth. The dose was titrated gradually depending on the tolerance of each patient, to a maximum dose of 21 drops per administration or until an adverse reaction occurred; the patients were then tapered down one level to a pre-adverse reaction dose. The time for each patient to "find" the therapeutic dose, a balance between maximum reduction in agitation and minimum side-effects, lasted up to six weeks. After the titration phase, patients entered a ten-week treatment phase of fixed-dose (Table 2).

Safety Assessments

For safety evaluation, serious adverse events (SAEs; defined as: death, life-threatening events, hospitalization, debilitation, or immobility), and all adverse events (AEs), with a severity score on a Likert scale of 1 to 10, were collected in all trial visits. In this population, with many comorbidities and medications, the symptom list of main AEs was also evaluated at baseline and documented as a non-IP-related AE report. An AE was defined as any unfavorable symptom, sign, syndrome, or disease that occurred during the study, having been absent at baseline, or if present at baseline, appeared to worsen. Clinical data included vital signs and physical examination in all trial visits, as well as blood chemistry and hematology every other visit.

Outcomes Measures

The primary efficacy endpoint was the proportion of subjects achieving a 4-point decrease at week 16 compared to baseline in the Cohen-Mansfield Agitation Inventory (CMAI)(53-57), with higher scores indicating greater severity. We evaluated a decrease in CMAI score to demonstrate a better outcome compared to a similar randomized controlled trial using oral THC (in which a 2.3 points reduction in the active group was deemed not significant),(58) and to set the bar above the placebo effect (two points decrease in the placebo group).(59)

Secondary outcomes included: mean change in the CMAI, the time necessary to achieve a 4-point reduction in CMAI, mean change in NPI-NH agitation/aggression sub-score. In the NPI-NH, the higher the score, the more severe and frequent the behavioral disturbances.

At each visit, a geriatrician and a trained occupational therapist examined the patients. All study questionnaires were administered and completed by the trained staff and answered by the patient's main caregiver on every visit. The following questionnaires were also administered: the Geriatric Depression Scale (GDS), the Pain Assessment in Advanced Dementia Scale (PAINAD), the Clinical Global Impression for Agitation and Aggression (CGI-S-A/A), and the MMSE.

Statistical Analysis

Sample size was calculated for a power of 80% and for two-sided α level of 0.05 to detect difference in proportion of successful reduction in CMAI score between investigational group versus control, at week 16. Success was defined as at least a 4-point reduction. For an expected difference of 35% in the proportion of success between the groups, an unbalanced sample of 42 and 22 was selected for the investigational and placebo group, respectively. Thus, 64 patients were randomly assigned to the investigational or control group (4 patients withdraw immediately after randomization, therefore 60 patients who started treatment were analyzed).

The efficacy analyses were performed according to the intention-to-treat (ITT) principle, to provide unbiased comparisons among groups. The ITT analysis was done in all patients randomized and receiving treatment, with multiple imputation of missing data of those patients who did not complete the trial (to get more accurate results than provided by a single imputation method, the

number of imputations was 5). We further performed a per protocol (PP) analysis (for 52 patients) as a sensitivity analysis, where only patients who completed the trial according to protocol were counted towards results.

Baseline characteristics between groups are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Chi-square tests and independent t-tests were performed to compare groups for categorical and continuous baseline variables, respectively.

The primary outcome was analyzed with the chi-square test including Yates' corrected chi-square (continuity correction). The baseline CMAI distribution was tested for normality using the Kolmogorov-Smirnoff test, and the Mauchly's Test of Sphericity tested whether the variances of the differences were equal.

The GLM (general linear models) Repeated Measures procedure was used to provide an analysis of variance for repeated CMAI measurements for nine visits on each subject. The analyses involve one within factor (time) and one between factor (groups). Changes over time and differences within groups were calculated (time*group), including contrasts tests to test differences among factor levels (1 factor, 9 levels), with a total significant level of 5%. The contrast was compared by method: difference; each level was compared to baseline. Analyses were performed on two sets of full data (without missing data), the ITT set (n=60) and the PP set (n=52).

Kaplan Meier survival analysis was performed to compute the time to achieve a CMAI ≥4-point reduction (success) for each group and tested the group difference using the log rank chi-square test. Comparison of CMAI mean score between the two groups was analyzed by the independent t-test.

Comparison between groups in NPI-NH frequencies of all sub-categories (as dichotomous variables: yes/no) were analyzed by the Fisher’s exact test for baseline and end of study. NPI-NH factors scores, total NPI-NH, and all other variables were tested by independent t-test. Frequency of AEs and medications consumption between the two groups was compared by using the Fisher's exact test.

Data were analyzed with IBM SPSS statistics software version 27.0 (SPSS Inc. Headquarters, Illinois, USA). Significance levels were set at 0.05.

3. Results

Of 67 patients screened for a possible enrollment, three patients were not eligible and four opted not to participate in the trial. Among 60 randomized patients initiating treatment, the mean age was 79.4±9.4 years; 36 (60.0%) were female and 52 (86.7%) completed 16 weeks of trial (Figure 1).

Upon enrollment, no meaningful differences were found. At baseline, all recruited patients presented MMSE scores of ≤25 (Table 1). In the repeated measures analysis, there was no difference in MMSE change from baseline to week 16 between the two groups (F=1.58, *P*=.21). Overall, 32 of 40 participants in the investigational group (80.0%) and all participants in the control group completed 16-week treatment. Two patients died of non-product-related causes; for the remaining six patients, attrition seemed due to personal and caregiver difficulties. AEs were not reported as a reason to leave the trial. At baseline, there were no statistically significant differences between completers and those who did not completed the trial.

Participants in the active and control groups consumed on average 14.9 and 17.9 drops per administration, respectively (44.7 and 53.7 drops per day, respectively) (Figure 2). Mean CBD and THC consumption per administration was 175.8 mg and 7.4 mg, respectively (527.5 mg and 22.3 mg per day, respectively) (Figure 3). Dose was not correlated with age (r=-0.17, *P*=.28), nor with the outcome both for the continuous change in CMAI (r=-0.23, *P*=.21), and for reduction of ≥4 point, (t=0.21, *P*=.83).

Primary Outcome

The primary endpoint of the trial was the proportion of subjects achieving a CMAI ≥4-point decrease during the treatment period. For the ITT set, the proportions observed were 24/40 (60.0%) and 6/20 (30.0%) for investigational and control groups, respectively (χ^2*=4.80, P*<.05; with continuity correction χ^2=3.67, *P*=.06). For the PP set (52 completers), the proportions observed

were 22/32 (68.7%) and 6/20 (30.0%) for investigational and control groups, respectively ($\chi^2=7.44$, $P<.01$; with continuity correction $\chi^2=5.96$, $P<.05$).

Secondary Outcomes

The main hypothesis that the consumption of the IP will reduce behavioral disorders and restlessness in elderly patients with dementia was tested by the CMAI reduction over time, between groups (Figure 4). The CMAI baseline measures were slightly skewed, but we could not observe significant skewedness distribution when splitting data to groups (Kolmogorov-Smirnoff $P>.05$). We compared the CMAI reduction from baseline to week 16 in both ITT and PP sets. Both demonstrate significant greater reduction in the investigational group, compared to the control group.

In the ITT set, reduction in CMAI were 12.4±15.5 and 2.5±9.4 (t=-3.07, $P<.01$), and in the PP set reduction were 13.3±15.3 and 2.5±9.4 (t=-2.85, $P<.01$), for the investigational and control group, respectively. Sub-score of CMAI aggressive behavior showed significantly better improvement as well ($P<.05$ for the PP set).

To test the reduction of CMAI over time, we used two full data sets: an ITT set, and a PP set of completers. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated ($\chi^2(35)=353.4$, $P<.001$ for ITT and $\chi^2(35)=299.4$, $P<.001$ for PP), meaning the F-statistic is positively biased rendering it invalid and increasing the risk of Type I error. To overcome this problem, we corrected the degrees of freedom using the Greenhouse-Geisser correction to obtain a valid critical F-value.

CMAI measurements over time for the ITT data demonstrate a significant decrease over time in the multivariate test for both groups (within-subject effect F=4.74, $P=.001$); and a trend of significant different reduction between the two groups (F=0.39, $P=.53$). In the same analyses, we defined within-subject contrasts to compare CMAI differences from each time point to baseline, between groups. Analysis demonstrated significantly greater improvement in the investigational group compared to the control group, for tests of week 14 (F=6.13, $P=.01$), and week 16 (F=7.07, $P=.01$). The same analysis for the PP data demonstrates similar results to the ITT data, with a significant decrease over time (F=6.45, $P<.001$), and with different reduction trend between the two groups (F=3.18, $P=.02$). Tests of difference between groups at week 14 (F=4.83, $P=.03$), and at week 16 (F=4.84, $P=.03$) were significantly different.

For patients in the investigational group who achieved a ≥4-point decrease in CMAI (60.0%), it took a mean of 8.8 weeks (95% CI: 6.7-11.1 weeks), whereas for patients who received placebo and achieved a ≥4-point decrease in CMAI (30.0%), it took 12.9 weeks (95% CI: 10.2-15.6). This difference was significant (log rank $\chi^2=5.19$, $P=.02$).

Table 3 demonstrates the differences between groups in clinical parameter scores for completers at baseline and end of trial. NPI-NH results demonstrate a significant reduction (29.4%) in agitation/aggression ($P<.05$) and a significant reduction (31.9%) in sleep disturbances ($P<.05$) in the investigational group compared to the control group, as well as a significant reduction in the mean NPI-NH Agitation/Aggression factor score from 12.1±5.8 to 6.7±6.9 in the investigational group and from 15.5±7.8 to 11.4±8.7 in the control group ($P<.05$). There was no statistically significant difference in the GDS, PAINAD, CGI-S-A/A and MMSE questionnaires.

There was no statistically significant difference in medications used between groups and over time, demonstrating stable medication consumption throughout the trial in both groups (Table 4).

Adverse events

All withdrawals occurred in the investigational group. The reported reasons for withdrawals were: four patients discontinued treatment due to difficulty commuting to the study appointments (one patient completed baseline visit, two patients completed 2 weeks, and one completed 4 weeks in the study); one patient left after 4 weeks due to the ideological concerns of her son; one patient withdrew after the baseline visit due to a deterioration in his condition (dialysis patient).

Thirteen SAEs included two deaths and eleven hospitalizations (Table 5). There were no significant differences in the occurrence of SAEs (9 and 4 in the investigational and control groups, respectively). The two deaths were in the investigational group. The

first patient, 94-year-old, suffering from colonic cancer and chronic renal failure, died from septic shock after completion of 4 weeks in the study. The second patient, 87-year-old, experienced recurrent hospitalizations due to severe hyponatremia and anemia, for which he was recurrently intubated, and died from breathing difficulties (only baseline results were recorded). There was no statistically significant differences in the death rate between the two groups (active group 6.25% versus placebo group 0.0%, χ^2=1.28, *P*>.52). We did not see a direct link between the SAEs and the IP.

Sleepiness (48.6%), confusion and disorientation (45.9%), and decreased memory (32.4%) were the most frequent complaints among participants in the investigational group. No significant differences were observed in the occurrence of AEs between groups (Table 5). However, in the investigational group there were notable higher rates of decreased memory (*P*=.06), hallucinations (*P*=.08), sleepiness (*P*=.17), and confusion and disorientation (*P*=.18). No change in pulse and blood pressure were observed throughout the study.

4. Discussion

In this randomized placebo-controlled trial, we aimed to test the hypothesis that broad-spectrum high-CBD medical cannabis oil differs from placebo in alleviating behavioral disturbances in patients with dementia. Patients in the investigational group experienced significantly greater reduction in agitation, aggression and in sleep disturbances over placebo, with minimal side-effects. These findings suggest that high-CBD cannabis oil can alleviate behavioral disturbances in this population.

A recent meta-analysis found increased odds of cerebrovascular events, fracture and death associated with antipsychotics; increased odds of falls associated with dextromethorphan-quinidine; and increased odds of death associated with anticonvulsants.(21) Meta-analyses on the reasons patients with dementia are placed in nursing homes confirm the significant role played by NPS symptoms(60, 61) that are ineffectively managed. High CBD cannabis oils are becoming increasingly available and should therefore be further evaluated as a possible treatment option for agitation.

Our four-month treatment period perhaps allowed behavioral changes, especially given that the treatment is based mainly on CBD. Unlike treating agitation with THC, where a patient can experience a rather immediate response, treatment with a high CBD product takes a longer period and requires patience. Consistent with this, the difference in average CMAI between groups reached significance only at week 14.

Thirty-one percent of the patients in the investigational group reached the maximum allowed dose of 21 drops (10.5 mg THC) and another 15.6% reached 20 drops (10 mg THC) per administration. Although not statistically significant, the higher rates of decreased memory and hallucinations in the investigational group may indicate that the dose of 10 mg THC or more per administration is too high for patients with dementia, even when combined with an increased presence of CBD. To prevent AEs, a slow and gradual titration process with the maximal attention to AEs is important, reducing the dose to the pre-adverse reaction dose, if necessary.

Limitations

Our trail has several limitations. All eight patients who discontinued the treatment belonged to the investigational group. Although we did not find a link between the IP and the study discontinuation, we cannot exclude the option that the IP might have a tolerability barrier, and should be explored in further studies. Outcome measures did not include measures that would rule out functional impairment following treatment with a product containing THC. However, it is worth noting that the IP consumption does not appear to be related to increased apathy, as there were no differences between the groups in the NPI-NH apathy scores.

The sample size of 60 participants for our main outcome in an ITT analysis has a power of only 60%. The small number of participants, recruited in a single medical center, with no comparison between sub-types of dementia, provides limited ability to define the safety profile of the IP and threats generalizability. Pharmacokinetic indices of the IP were not collected in this trial.

5. Conclusions

This trial suggest that Avidekel oil is a safe and effective treatment for behavioral disturbances in patients with dementia. We recommend conducting a larger scale randomized controlled trial to evaluate the efficacy and side-effects of broad-spectrum CBD in behavioral disturbances related to dementia and to compare clinical sub-types of dementia.

Declarations

Ethics approval and consent to participate: The legal representatives of all participants provided informed consent prior to participation. The trial, registered NCT03328676, was approved by the Laniado Hospital Ethics Committee (project LND 0111-16) and the clinical trials department at the Israel Ministry of Health (project 20173138).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: Lihi Bar-Lev Schleider and Violeta Lederman report employment at Tikun-Olam Cannbit Pharmaceuticals Ltd with stock options in the company. Lihi Bar-Lev Schleider reports consulting role with TO Pharmaceuticals LLC; as a consultant of the company, she is registered as an inventor on a patent on the investigational product for behavioral disturbance in patients with dementia. All other authors have no competing interests.

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Authors' contributions: VH, LBLS; conceived the study, wrote the protocol, and drafted the manuscript. All authors acquired, analyzed, or interpreted the data. All authors critically revised the manuscript for important intellectual content. VH is the corresponding author and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. VH is the guarantor.

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Tables

Table 1. Characteristics of the patient population at baseline.

Characteristic	Avidekel oil (n=40)	Placebo oil (n=20)
Age (years), mean±SD	78.8±9.3	80.5±9.6
Gender, n (%)		
Females	22 (55)	14 (70)
Males	18 (45)	6 (30)
Country of birth, n (%)		
Israel	12 (30)	6 (30)
Other	28 (70)	14 (70)
Residence, n (%)		
Institution	7 (17)	2 (10)
Home	33 (83)	18 (90)
Years since diagnosis, mean±SD	4.24±2.91	3.27±2.42
Comorbidities, n (%)		
Cardiovascular diseases	33 (83)	17 (85)
Hypertension	17 (43)	9 (45)
Diabetes-type 2	11 (28)	6 (30)
Neurologic	10 (25)	8 (40)
Endocrine	5 (13)	2 (10)
Eye/ear	5 (13)	2 (10)
Depression	3 (8)	1 (5)
Renal	2 (5)	2 (10)
Other	16 (40)	9 (45)
Medication, n (%)		
Antihypertensive	21 (53)	12 (60)
Antidepressant	21 (53)	7 (35)
Antipsychotic	17 (43)	9 (45)
Relaxing	12 (30)	10 (50)
Other	31 (78)	20 (100)
Questionnaires, mean±SD		
MMSE[a] score	12.4±6.8	15.2±6.2
CMAI[b] score	59.3±20.3	58.7±22.3
NPI-NH[c] score	41.7±19.1	42.5±20.1
GDS[d] score	4.9±3.3	2.8±3.1
PAINAD[e] score	0.1±0.4	0.1±0.4

CGI-S-A/A[f] score	2.6±3.3	2.9±3.3

Data are presented as mean ± standard deviation for continuous data and No. (%) for categorical data.

Abbreviations: SD, Standard Deviation.

[a] MMSE - Mini–Mental State Examination. Range and scaling: 0–30 points (≤9 meaning severe cognitive impairment).

[b] CMAI - Cohen-Mansfield Agitation Inventory. Range and scaling: 29–203 points (29 meaning no symptoms).

[c] NPI-NH - Neuropsychiatric Inventory–Nursing Home Version. Range and scaling: 0–144 points (0 meaning no symptoms).

[d] GDS - Geriatric Depression Scale. Range and scaling: 0–30 points (0 meaning no symptoms).

[e] PAINAD - Pain Assessment in Advanced Dementia Scale. Range and scaling: 0–10 points (0 meaning no symptoms).

[f] CGI-S-A/A - Clinical Global Impression for Agitation and Aggression. Range and scaling: 0–10 points (0 meaning no symptoms).

Table 2. Schedule of events.

Visits	1	2	3	4	5	6	7	8	9	10
Time Point	**Enrolment**	**Day 0 Baseline**	**Week 2 ± 3 days**	**Week 4 ± 3 days**	**Week 6 ± 3 days**	**Week 8 ± 3 days**	**Week 10 ± 3 days**	**Week 12 ± 3 days**	**Week 14 ± 3 days**	**Week 16 ± 4 days**
Informed Consent	X									
Inclusion/ Exclusion Criteria	X									
Demographics	X									
Medical History + Dementia history	X									
Physical Examination	X	X	X	X	X	X	X	X	X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
Assessments										
MMSE[b]		X			x			X		X
CMAI[c]	X	X	X	X	X	X	X	X	X	X
NPI-NH[d]	X	X	X	X	X	X	X	X	X	X
GDS[e]	x	X			X			X		X
PAINAD[f]		X	X	X	X	X	X	X	X	X
CGI-S-A/A[g]	X	X	X	X	X	X	X	X	X	X
Adverse Events	x	X	X	X	X	X	X	X	X	X
Blood Tests										
Hematology Panel	X		X		X		X		X	
Chemistry Panel	X		X		X		X		X	
IP Administration										
Randomization	X									
IP Accountability			x	x	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Titration	X	X	X	X	X					
Stable Dose						X	X	X	X	X

[a] Vital signs - the following parameters will be collected: temperature, pulse, blood pressure, height (only screening visit) and weight.

[b] MMSE - Mini–Mental State Examination. Range and scaling: 0–30 points (≤9 meaning severe cognitive impairment).

[c] CMAI - Cohen-Mansfield Agitation Inventory. Range and scaling: 29–203 points (29 meaning no symptoms).

[d] NPI-NH - Neuropsychiatric Inventory–Nursing Home Version. Range and scaling: 0–144 points (0 meaning no symptoms).

[e] GDS - Geriatric Depression Scale. Range and scaling: 0–30 points (0 meaning no symptoms).

[f] PAINAD - Pain Assessment in Advanced Dementia Scale. Range and scaling: 0–10 points (0 meaning no symptoms).

[g] CGI-S-A/A - Clinical Global Impression for Agitation and Aggression. Range and scaling: 0–10 points (0 meaning no symptoms).

Table 3. Effects on neuropsychiatric signs and symptoms for completers, at baseline and end of trial.

Variable	Baseline - Week 0			End of Trial – Week 16		
	Avidekel (n=32)	Placebo (n=20)	*P*	Avidekel (n=32)	Placebo (n=20)	*P*
NPI-NH[a] Sub-categories, n (%)						
Delusion	16 (50)	9 (45)	.78	6 (19)	6 (30)	.35
Hallucinations	12 (38)	6 (32)	.77	6 (19)	5 (25)	.59
Agitation/Aggression	32 (100)	20 (100)		21 (66)	19 (95)	.01
Depression/Dysphoria	24 (75)	15 (75)	.26	18 (56)	9 (45)	.43
Anxiety	21 (66)	14 (70)	.89	14 (44)	11 (55)	.43
Elation/Euphoria	2 (6)	7 (35)	.02	2 (6)	2 (11)	.61
Apathy/Indifference	25 (78)	14 (70)	.53	21 (66)	14 (74)	.55
Disinhibition	11 (34)	12 (60)	.09	9 (28)	11 (55)	.08
Irritability/Lability	25 (78)	15 (75)	.87	21 (66)	13 (65)	.96
Aberrant Motor Behavior	19 (59)	11 (55)	.78	19 (59)	8 (40)	.17
Sleep Disturbances	21 (66)	15 (75)	.55	9 (28)	12 (60)	.03
Appetite and Eating Disturbances	18 (56)	10 (50)	.78	9 (28)	8 (40)	.37
NPI-NH Factors Scores, mean±SD						
Agitation/Aggression	12.1±5.8	15.5±7.8	.08	6.7±6.9	11.4±8.7	.03
Depression	7.1±4.8	8.0±6.2	.56	4.1±4.7	5.8±6.1	.26
Psychosis	5.4±7.3	3.4±4.3	.27	1.3±2.3	2.7±4.5	.14
Psychomotor Agitation	7.9±6.3	9.1±6.6	.51	3.6±4.1	6.5±6.7	.06
Apathy	8.7±5.8	6.7±5.1	.21	5.8±5.5	4.9±3.8	.52
NPI-NH Total Score, mean±SD	41.2±18.4	42.5±20.1	.81	21.4±16.9	31.2±22.0	.08
CMAI[b] Sub-cores, mean±SD						
Aggressive Behavior	14.0±4.4	14.7±5.0	.60	12.0±3.2	16.0±8.6	.02
Physically Nonaggressive Behavior	23.7±9.1	22.9±9.1	.76	17.3±7.4	21.0±9.7	.13
Verbally Agitated Behavior	19.7±9.9	21.1±10.4	.63	14.7±6.8	19.2±10.6	.07
CMAI Total Score, mean±SD	57.4±17.4	58.7±22.3	.81	44.0±13.2	56.2±25.5	.03
GDS[c] Total Score, mean±SD	5.5±3.3	2.8±3.1	.01	4.9±4.0	3.3±4.4	.18
PAINAD[d] Total Score, mean±SD	0.1±0.4	0.1±0.4		0.0±0.0	0.1±0.2	
CGI-S-A/A[e] Total Score, mean±SD	2.8±3.5	2.9±3.3	.84	1.3±2.4	2.0±2.9	.35
MMSE[f] Total Score, mean±SD	12.2±6.3	15.2±6.2	.10	10.4±6.8	13.7±7.5	.21

Abbreviations: SD, Standard Deviation.

[a]NPI-NH - Neuropsychiatric Inventory–Nursing Home Version. Range and scaling: 0–144 points (0 meaning no symptoms).

[b]CMAI - Cohen-Mansfield Agitation Inventory. Range and scaling: 29–203 points (29 meaning no symptoms).

[c]GDS - Geriatric Depression Scale. Range and scaling: 0–30 points (0 meaning no symptoms).

[d]PAINAD - Pain Assessment in Advanced Dementia Scale. Range and scaling: 0–10 points (0 meaning no symptoms).

[e]CGI-S-A/A - Clinical Global Impression for Agitation and Aggression. Range and scaling: 0–10 points (0 meaning no symptoms).

[f]MMSE - Mini–Mental State Examination. Range and scaling: 0–30 points (≤9 meaning severe cognitive impairment).

Table 4. Concomitant medications over time for patients completing the trial per protocol (Avidekel, N=32; Placebo, N=20).

Timeline	No. %									
	Antihypertensive		Antidepressant		Antipsychotic		Relaxing		Other	
	Avidekel	Placebo	Avidekel	Placebo	Avidekel	Placebo	Avidekel	Placebo	Avidekel	Placebo
Baseline	21 (65.6)	12 (60.0)	21 (65.6)	7 (35.0)	17 (53.1)	9 (45.0)	12 (37.5)	10 (50.0)	31 (96.9)	20 (100)
Week 2	21 (65.6)	12 (60.0)	18 (56.3)	8 (40.0)	16 (50.0)	9 (45.0)	12 (37.5)	10 (50.0)	31 (96.9)	20 (100)
Week 4	21 (65.6)	14 (70.0)	18 (56.3)	7 (35.0)	15 (46.9)	9 (45.0)	12 (37.5)	9 (45.0)	30 (93.8)	20 (100)
Week 6	18 (56.3)	14 (70.0)	17 (53.1)	7 (35.0)	14 (43.8)	8 (40.0)	13 (40.6)	9 (45.0)	30 (93.8)	20 (100)
Week 8	18 (56.3)	14 (70.0)	21 (65.6)	7 (35.0)	16 (50.0)	8 (40.0)	13 (40.6)	8 (40.0)	31 (96.9)	20 (100)
Week 10	18 (56.3)	14 (70.0)	19 (59.4)	4 (20.0)	15 (46.9)	9 (45.0)	13 (40.6)	10 (50.0)	31 (96.9)	20 (100)
Week 12	19 (59.4)	13 (65.0)	18 (56.3)	4 (20.0)	19 (59.4)	10 (50.0)	14 (43.8)	10 (50.0)	31 (96.9)	20 (100)
Week 14	19 (59.4)	13 (65.0)	19 (59.4)	4 (20.0)	19 (59.4)	11 (55.0)	15 (46.9)	11 (55.0)	31 (96.9)	20 (100)
Week 16	19 (59.4)	12 (60.0)	16 (50.0)	4 (20.0)	19 (59.4)	11 (55.0)	14 (43.8)	11 (55.0)	31 (96.9)	20 (100)

Table 5. Patients experiencing Adverse Events[a].

Variable	Avidekel (n=32)	Placebo (n=20)	*P*
Serious Adverse Events, n (%)			
Hospitalization	7 (19)	4 (20)	0.74
Death	2 (5)	0 (0)	
Adverse Events, n (%)			
Decreased Memory	12 (32)	2 (10)	0.06
Hallucinations	8 (22)	1 (5)	0.08
Sleepiness	18 (49)	6 (30)	0.17
Dry Mouth	5 (14)	5 (25)	0.17
Confusion and Disorientation	17 (46)	6 (30)	0.18
Fear	9 (24)	3 (15)	0.34
Restlessness	10 (27)	7 (35)	0.39
Blurred Vision	4 (11)	1 (5)	0.41
Dizziness	6 (16)	2 (10)	0.47
Weakness	8 (22)	5 (25)	0.54
Red/Irritated Eyes	2 (5)	1 (5)	0.61
Increased Heart Rate	3 (8)	1 (5)	0.65
Psychoactive Effects	3 (8)	1 (5)	0.65
Headaches	3 (8)	2 (10)	0.66
Slurred Speech	6 (16)	3 (15)	0.99
Decreased Concentration	0 (0)	1 (5)	
Other	21 (57)	9 (45)	0.29

[a]The analysis was performed on an ITT population. In three patients, there were no visits after treatment initiation and side-effect reports were not available.

Figures

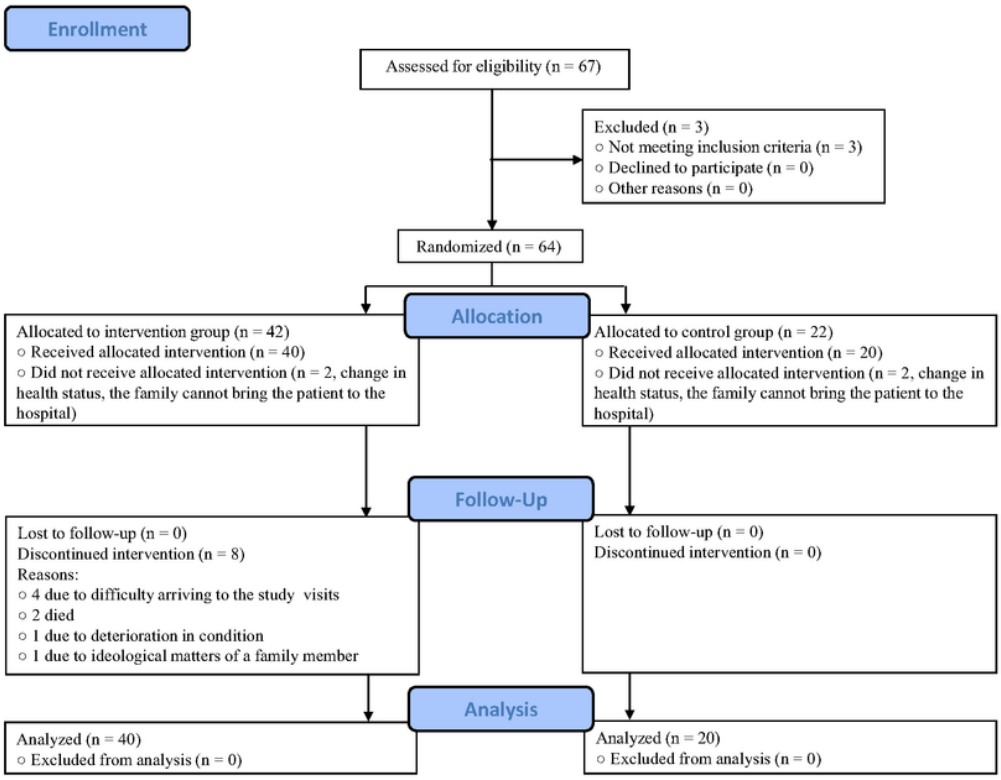

Figure 1

CONSORT Diagram.

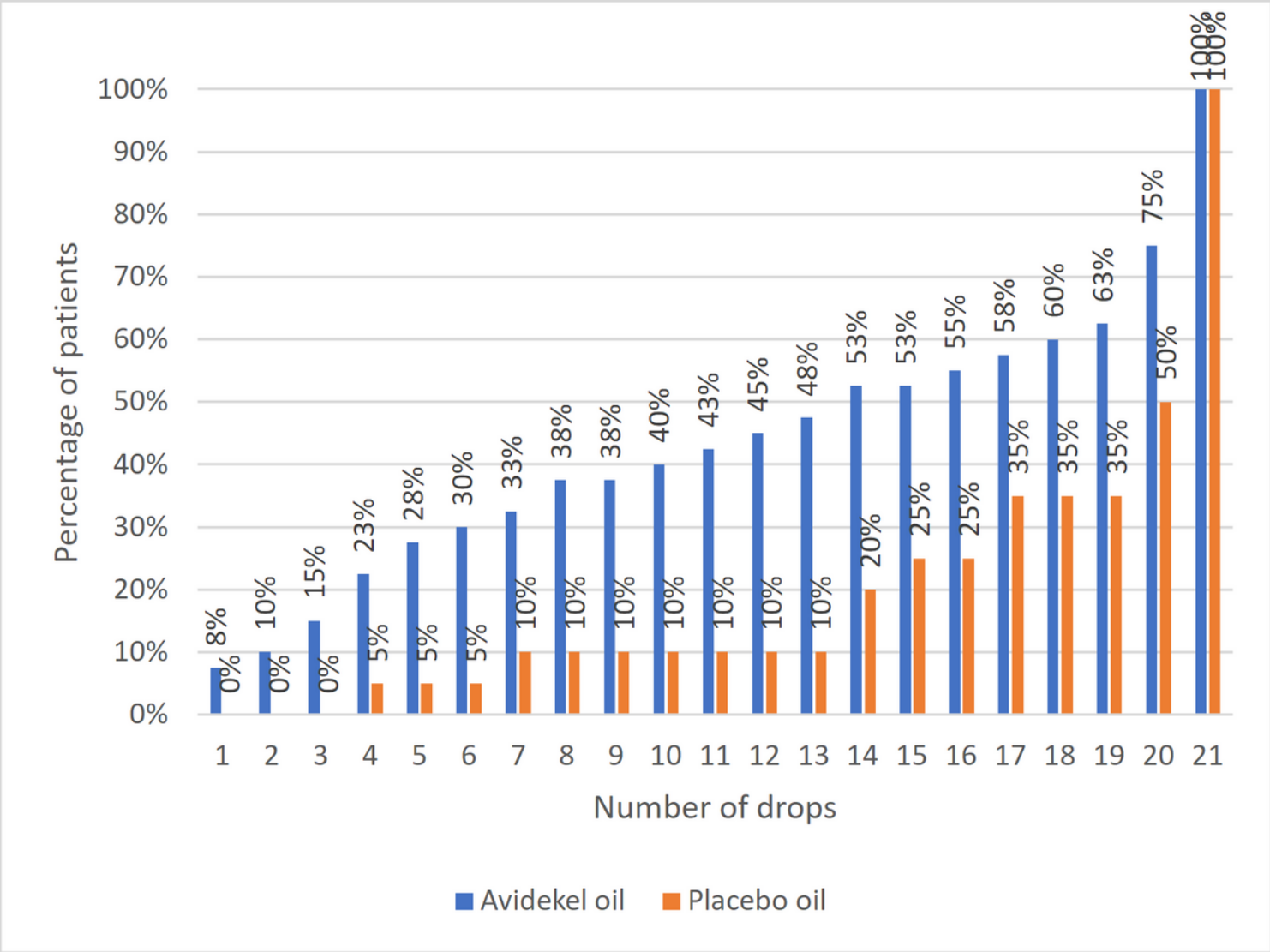

Figure 2

Cumulative frequency of doses consumed, Avidekel oil and placebo oil. The number of drops consumed after titration by 52 patients who completed the trial, receiving Avidekel oil or placebo oil during a single administration (there were three daily sublingual administrations). The investigational group and the placebo group consumed on average 14.9 and 17.9 drops per administration, respectively (44.7 and 53.7 drops per day, respectively). During titration in both groups, there were 13 cases of dose reduction and 10 cases of dose increase not according to the protocol guidelines. After titration in both groups, there were two cases of dose reduction, one case of dose increase. During the study, there were 35 cases where doses were skipped.

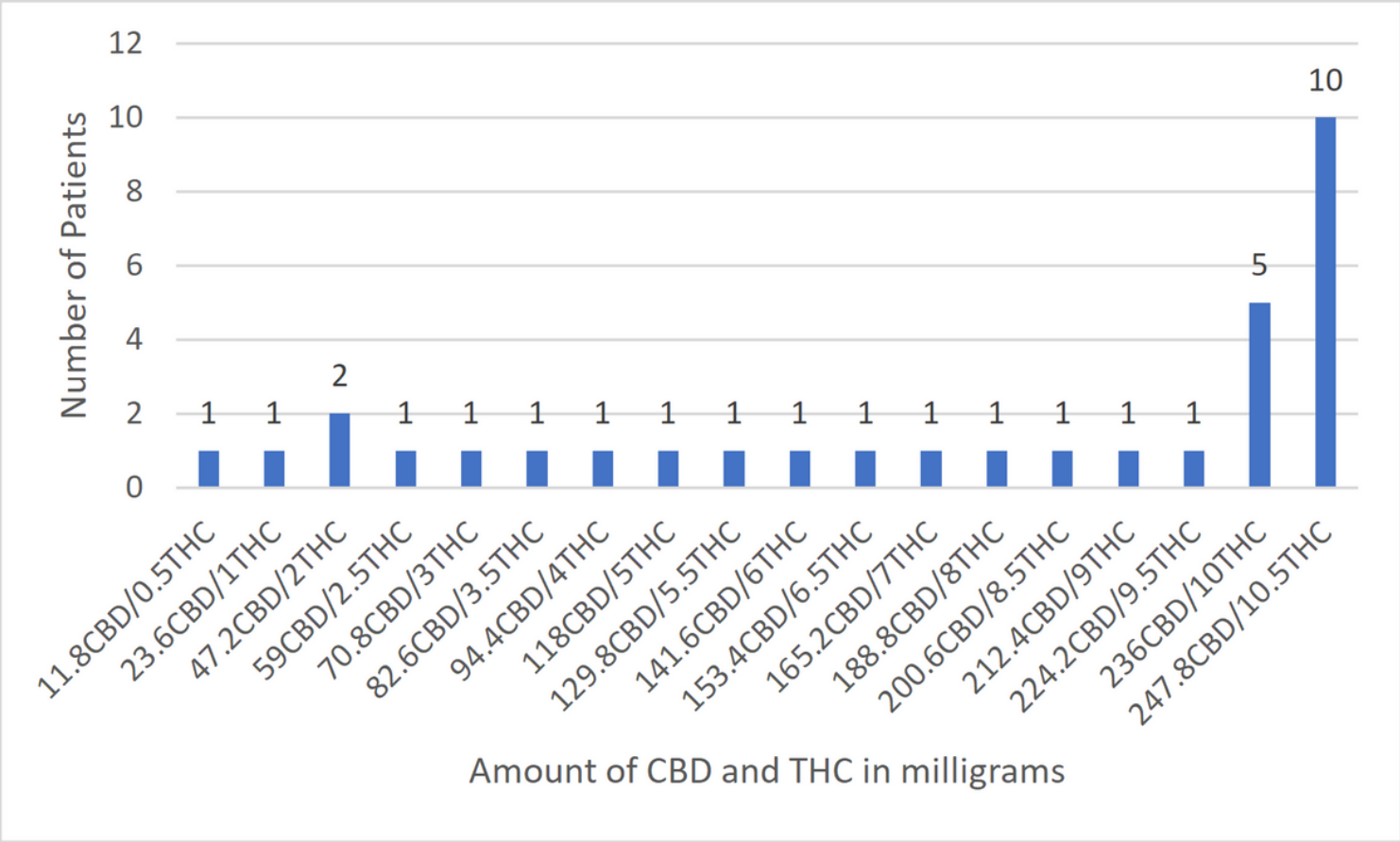

Figure 3

CBD and THC consumption. After titration, the consumption in mg of CBD and THC in Avidekel oil by the 32 patients who completed the trial at each administration (there were three equal daily administrations). Mean CBD and THC consumption per administration was 175.8 and 7.4 mg, respectively (527.5 mg and 22.3 mg per day, respectively). One drop is equivalent to approximately 0.04 ml and contains approximately 11.8 mg CBD and 0.5 mg THC. The number of bottles each patient received at each visit was documented by the research team. During the titration stage, patients increased their dose according to protocol guidelines. After reaching the therapeutic dose, very few doses were skipped or deviated from the therapeutic dose, which remained relatively stable.

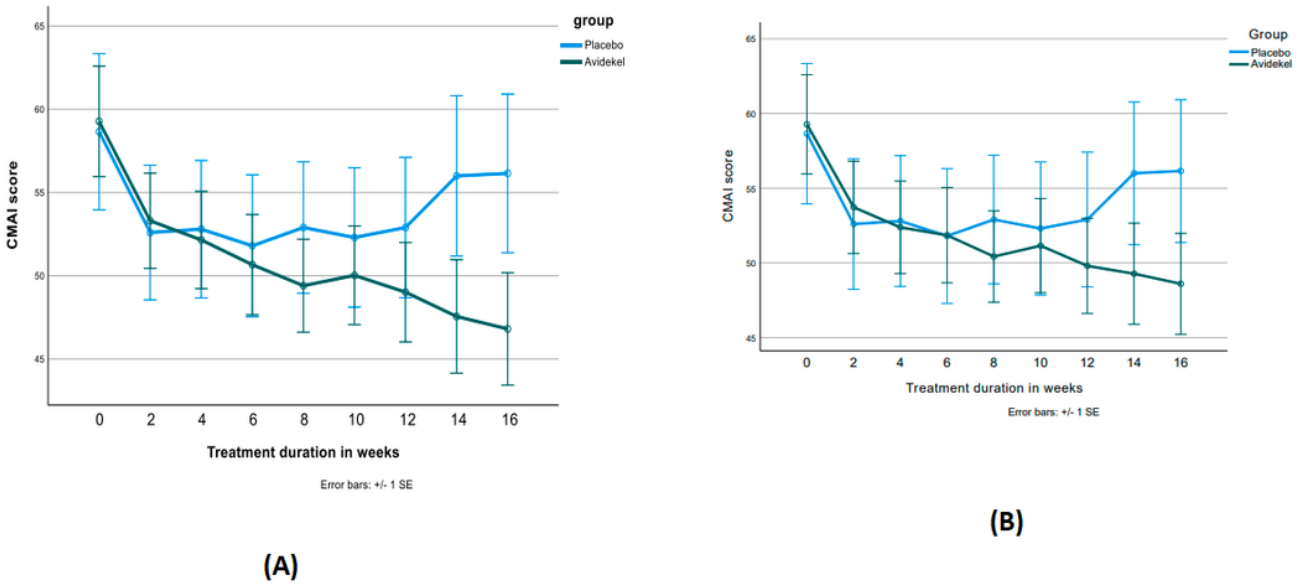

Figure 4

The CMAI score reduction over time between groups. Panels A-B present mean CMAI scores in the two groups, throughout the trial visits both in intention-to-treat analysis of all randomized patients that initiated treatment (N=60), and per protocol analysis of patients who completed the trial according to protocol (N=52).