Effect of the Combination of Tetrahydrocannabinol and Melatonin (IGC-AD1) on Blood Pressure Variability in Patients with Mild to Moderate Alzheimer's Disease

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IGCPHARMA

POSTER #: 80273

Takeaway message: A Phase I trial suggests that IGC-AD1 may not contribute to increased risk in AD associated with BP and BPV.

Background:

- Alzheimer's Disease (AD) patients experience neuropsychiatric symptoms (NPS), including agitation, depression, and apathy. These NPS are frequently treated with atypical antipsychotics, which are off-label and can affect blood pressure (BP) levels[1].
- Blood pressure variability (BPV) —fluctuations in BP over time— is recognized as a risk factor for AD given that elevated BPV may be associated with cognitive decline, progression of dementia, cerebrovascular disease, stroke, and AD pathology[2,3].
- The investigational drug IGC-AD1 is a combination that contains tetrahydrocannabinol (THC) and melatonin as its main active components and aims to address NPS such as agitation in AD patients.
- The following research explores the influence of IGC-AD1 on BP and BPV over 15 days of drug administration.
- Initial findings indicate that IGC-AD1 does not affect BP or BPV in AD patients.

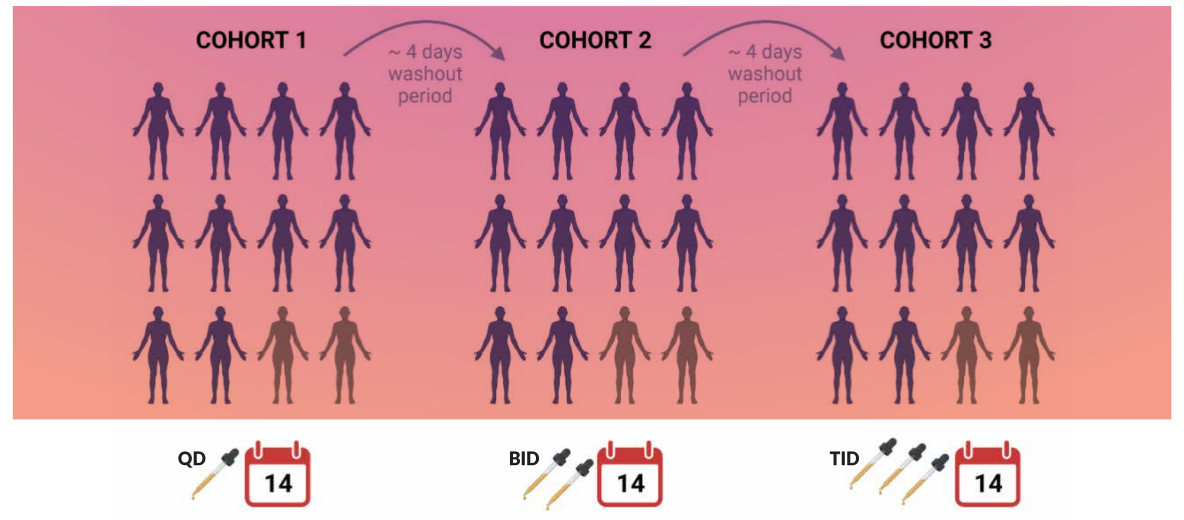
Methods:

- Study participants: In our FDA-regulated Phase 1 trial, we evaluated a study on BP measurements in AD patients (n = 13) from the Puerto Rican (PR) population as a safety measure.
- Patients were grouped as having uncontrolled systolic (SBP) and diastolic BP (DBP) when more than 20% of their SBP and DBP fell above SBP 140mmHg and DBP 80mmHg, respectively.

Table 1. Demographics

Age	Gender	Hypertension	Baseline SBP	Baseline DBP	Taking BP medication
years, mean ± SD	Females n (%)	n (%)	MmHg, mean ± SD	MmHg, mean ± SD	n (%)
81.5 ± 5.5	9 (69.2%)	13 (100%)	134 ± 18.6	71.1 ± 11.9	13 (100%)

- Inclusion criteria: diagnosed as having AD by a certified clinician according to NIA-AA criteria
- Trial details:
  - Three-Cohort Phase 1, MAD (Multiple Ascending Dose), safety and tolerability trial (IND146069, NCT04749563).
  - Daily BP recordings for all cohorts.
  - Daily evaluations of BP-associated adverse events (AEs) were conducted.



*Dosage: 1mL. Once a day (QD), Twice a day (BID), Three times a day (TID).

Statistical analysis:

- To identify the change in average blood pressure, a multiple linear regression analysis was made comparing the average change in BP by days, cohort, and treatment group.
- A chi square was made to identify if the change in uncontrolled and controlled BP was due to the medication in the treated participants[4].
- Coefficients of variation (CV), ΔDBP, and ΔSBP were calculated to evaluate SBP variability in each cohort (Δ= max-min BP measurement)[2].
- One-way ANOVA was conducted to analyze SBP-CV and DBP-CV difference among cohorts.
- Independent t-tests were used to compare active and placebo groups for each cohort.

Results:

Table 2 represents the results from the multiple regression analysis for the daily average SBP and DBP per participant. The day of measurement didn't influence the results in both SBP and DBP (Figure 1).

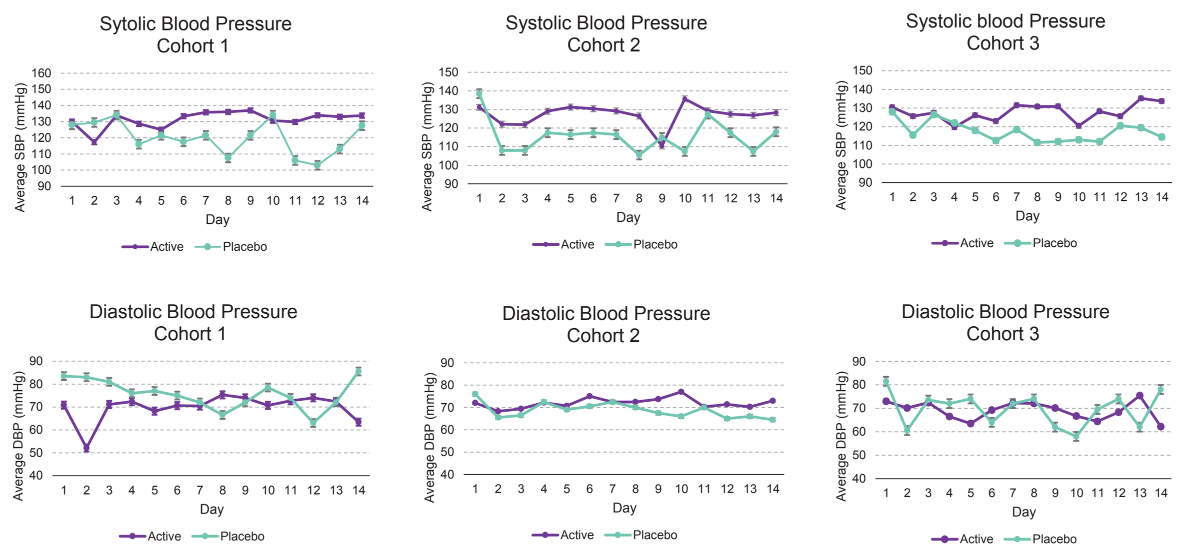


Figure 1. Average daily BP of active and placebo groups.

Table 2. SBP and DBP multiple regression coefficients.

Variable	Estimate	95%CI	p-value
Systolic BP			
Intercept	131.37	126.95, 135.79	<0.0001
Cohort 2	-4,514	-8.70, -0.33	0.035
Cohort 3	-5,169	-9.37, -0.70	0.016
Group (Placebo)	-11,974	-16.40, -7.55	<0.001
Day	0.269	-0.16, 0.7	0.215
Diastolic BP			
Variable	**Estimate**	**95%CI**	**p-val**
Intercept	72,425	69.98, 74.87	<0.001
Cohort 2	-1,321	-3.64, 0.99	0.263
Cohort 3	-2,596	-4.92, -0.27	0.029
Group (Placebo)	-0.316	-2.77, 2.13	0.8
Day	0.069	-0.17, 0.31	0.565

- **Differences between controlled and uncontrolled BP in active group:**
  There were no statistically significant differences in the active group between cohorts in participants with controlled and uncontrolled BP (X2(2) = 0.341, p = 0.843) (Figure 2).

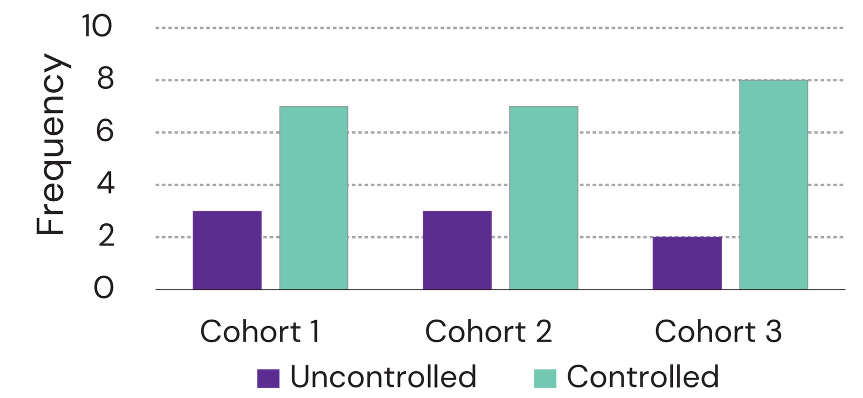


Figure 2. Patients with uncontrolled and controlled BP among cohorts.

- **IGC-AD1 effect on SBP-CV and DBP-CV:**
  No significant difference in SBP-CV and DBP-CV mean was observed among cohorts (SBP CV: F(2,27) = 0.589, p = 0.562; DBP-CV: F(2,27) = 0.388, p = 0.682) (figure 3).

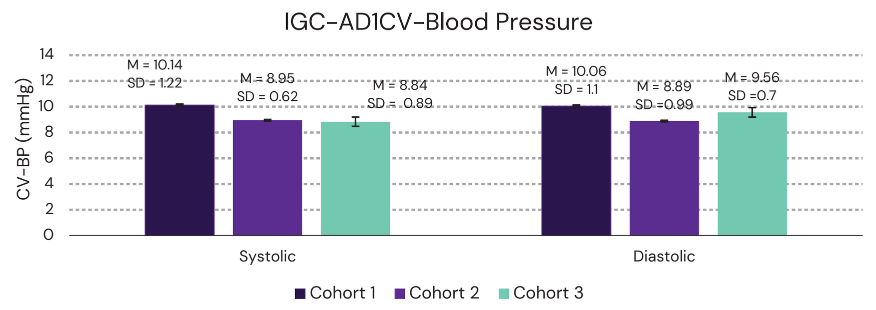


Figure 3. Effect of IGC-AD1 on SBP-CV and DBP-CV in all three cohorts.

- **Differences of ΔSBP and ΔDBP between placebo and active groups:**
  There were no significant differences between placebo and active groups in cohort 1 and 2 ΔSBP (Cohort 1: t (1.26) = 2.572, p = 0.772; Cohort 2: t (1.183) = -0.276, p = 0823; Cohort 3: t (5.096) = 2.637, p = 0.045). Similarly, ΔDBP showed no statistically significant differences between the active and placebo groups in all three cohorts (Cohort 1: t(1.228) = -0.101, p = 0.934; Cohort 2: t (2.427) = 1.587, p = 0.231; Cohort 3: t (9.606) = -1.942, p = 0.082) (figure 4).

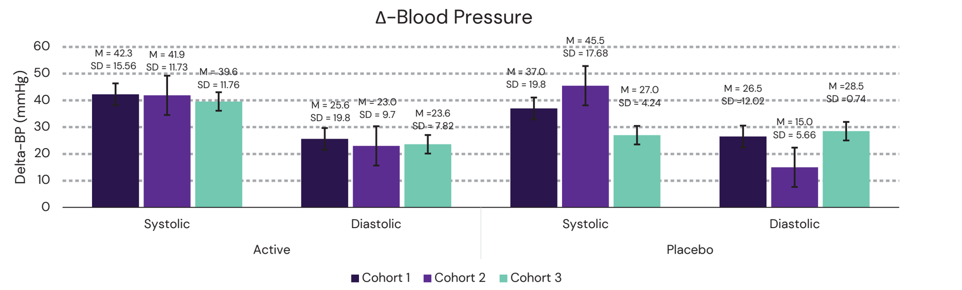


Figure 4. Average of ΔSBP and ΔDBP for active and placebo group in all three cohorts.
Error bars represented as SEM. Statistical significance markers: * p < 0.05, ** p < 0.01, *** p < 0.001.

- **BP-related AEs:**
  Several BP-related adverse events (AEs) were reported, which are not considered to be associated with the treatment (table 2).

Table 3. Percentage of participants with blood pressure related adverse events in all three cohorts.

Hypertension	Cohort 1		Cohort 2		Cohort 3		Total	
	"Active (N=10)"	"Placebo (N=2)"	"Active (N=10)"	"Placebo (N=2)"	"Active (N=10)"	"Placebo (N=2)"	"Active (N=30)"	"Placebo (N=6)"
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
None	5 (50 %)	-	7 (70 %)	1 (50 %)	7 (70 %)	1 (50 %)	19 (63 %)	2 (33 %)
Mild	-	1 (50 %)	-	1 (50 %)	-	1 (50 %)	-	3 (50 %)
Moderate	2 (20 %)	1 (50 %)	2 (20 %)	-	1 (10 %)	-	5 (17 %)	1 (17 %)
Severe	3 (30 %)	-	1 (10 %)	-	2 (20 %)	-	6 (20 %)	-

Conclusion:

- Preliminary data from the Phase I multiple ascending dose study suggests that investigational drug, IGC-AD1, does not have a statistically significant impact on BP or BPV in AD patients with controlled and uncontrolled BP.
- Regression analysis suggests that the multiple ascending doses may have reduced average BP during the trial. The measurement recording day did not affect SBP or DBP.
- Although a larger cohort study with a larger placebo group is warranted, this study suggests that IGC-AD1 may not impact BP or BPV-related risk for AD.

Disclosure of funding:

This study was funded by IGC Pharma, LLC.

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SCAN ME

Reduction of Neuropsychiatric Symptoms and Associated Caregiver Distress Using a Tetrahydrocannabinol and Melatonin Combination in Dementia due to Alzheimer's Disease

IGCPHARMA

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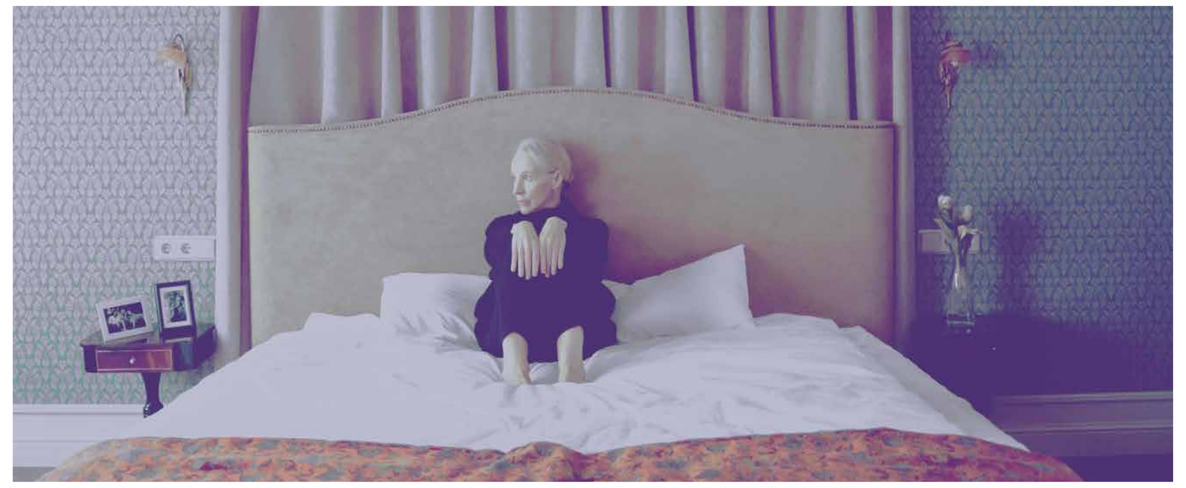
POSTER #: P3-663

Takeaway message: An oral combination of low doses of tetrahydrocannabinol (THC) and melatonin (IGC-AD1) administered to participants with Alzheimer's disease (AD) showed a significant reduction in neuropsychiatric symptoms and caregiver distress, as evaluated with the neuropsychiatric inventory (NPI-12).

Background:

Neuropsychiatric symptoms (NPS), as a feature of AD, affecting ~90% of AD patients, are a leading cause of institutionalization[1, 2]. As summarized in Figure 1, NPS, and appetite, and sleep disturbances, are characteristics of AD[2]. Even though NPS patients' cognitive decline and increases caregiver distress in 80% of cases, existing medications for NPS often have black-box warnings and detrimental side effects[3,4]. Previous clinical studies suggest that low doses of THC or melatonin may potentially manage NPS and thus improve mood reduce the severity of some behavior[5,6]. In this phase 1 study, we evaluated the safety of the combination of these two active ingredients and their effect on NPS and caregiver distress with the Neuropsychiatric Inventory-12 (NPI-12)[7].



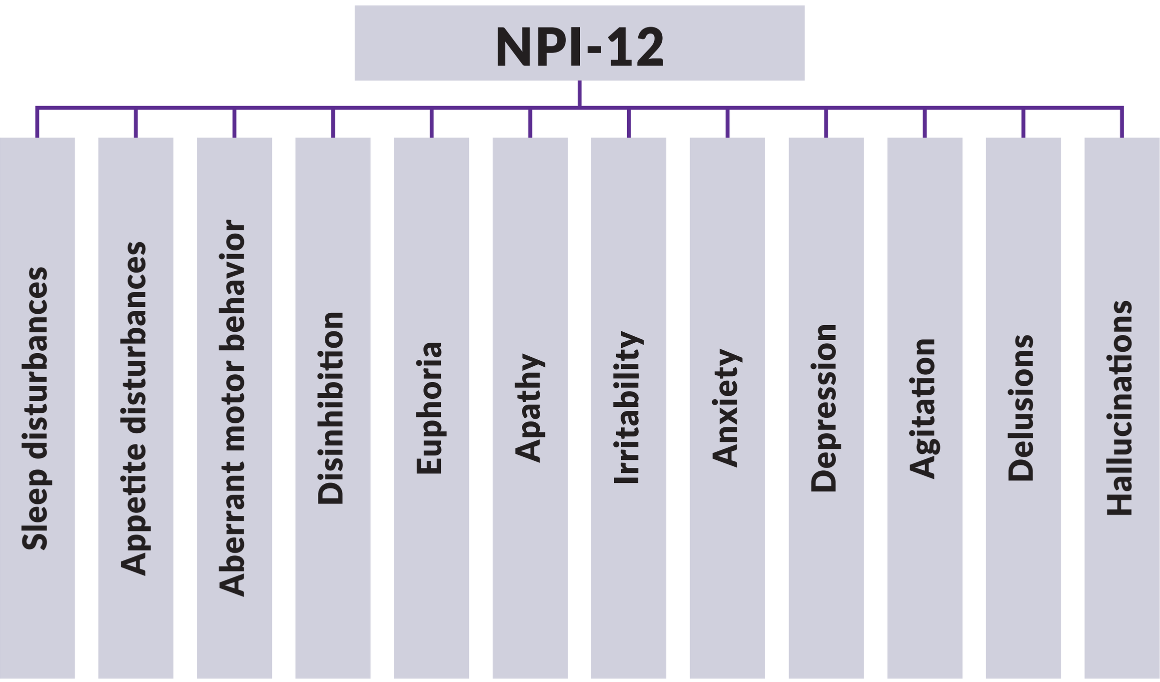


Figure 1. NPI-12 domains.

Methods:

Twelve patients diagnosed with mild (15.38%) to moderate (84.62%) AD (NIA-AA criteria and clinical history) participated in a three-cohort Phase 1 trial with MAD for safety and tolerability (10 active, 2 placebo, 81.5 ± 5.5yrs, 69.2% women). In Cohort 1, 2, and 3, onemilliliter of IGC-AD1 was administered once a day (QD), twice a day (BID), and three times a day (TID), respectively, for 14-days (EOT) (Fig. 2). There was a 4-day minimum washout period between cohorts. Solicited and non-solicited adverse events (AEs) and the vital signs of all participants were monitored during each 14-day period.

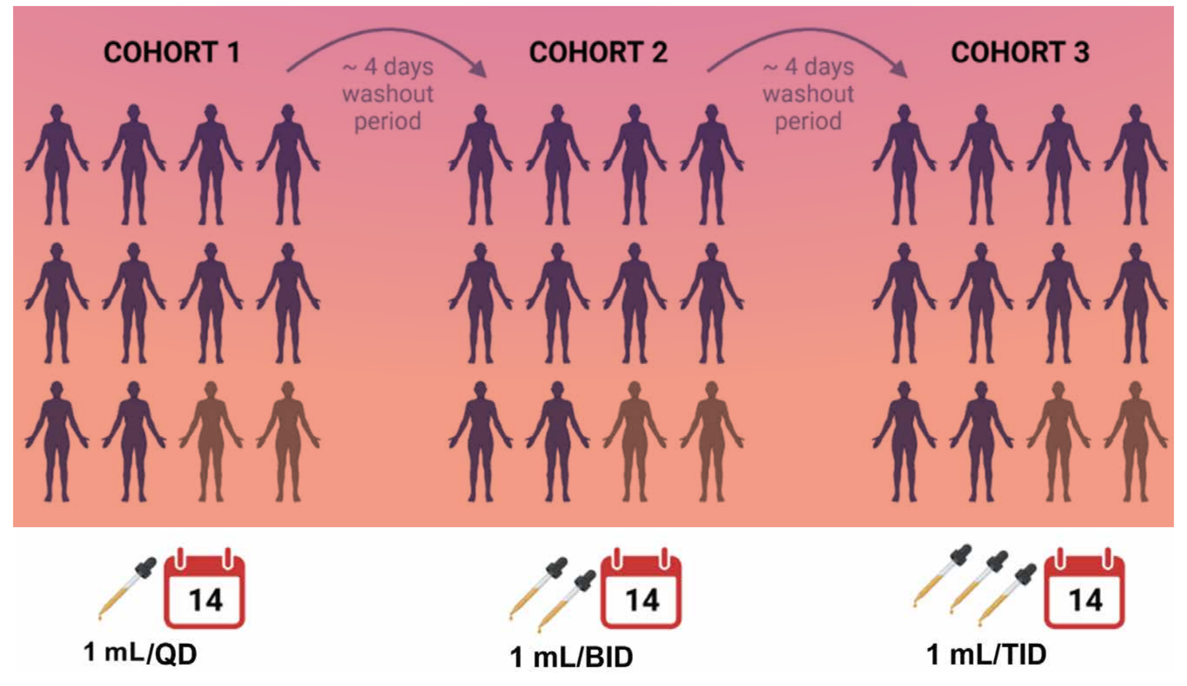


Figure 1. Phase 1 clinical trial implementation. Purple indicates the number of active participants nd gray the number of placebo participants.

Behavioral test: NPI-12 / NPI-Distress (NPI-D) were administered at baseline (Day 1) and EOT (Day 15)[7].

Statistical analysis: For all cohorts, the average score differences between Day 1 and Day 15 were determined with two-sided Wilcoxon signed-rank tests or paired t-tests. The differences between placebo and active groups were assessed with Mann-Whitney U tests or independent t-tests (R-Studio, dplyr).

Results

Change between Day 1 and 15 in the NPI-12 and NPI-D scores.

There was no statistically significant difference in the baseline between cohorts on the NPI-12 (F (1, 25) = 1.134, p = 0.297) (Fig. 3A) and NPI-D scores (F (1, 25) = 1.59, p = 0.219) (Fig. 3B).

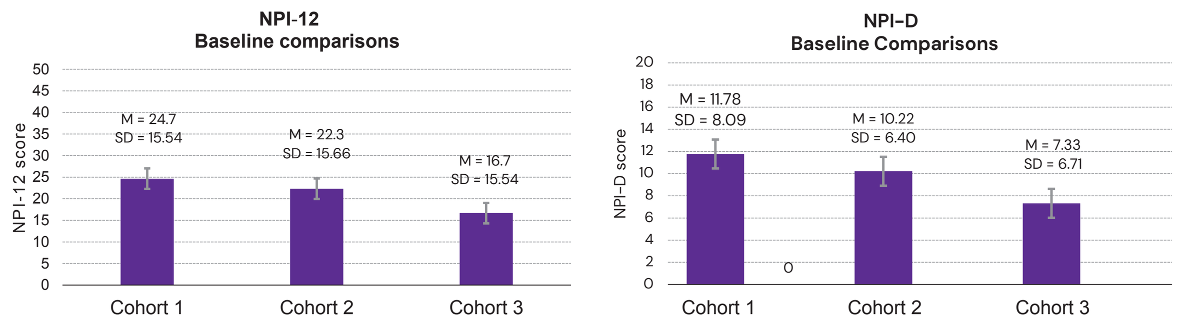


Figure 3. Average baseline scores comparisons between cohorts.
No significant differences for the A) NPI-12 and B) NPI-D. Means (M) and standard deviations (SD) are represented at the top of each bar. Error bars represented 95%CI.

There were statistically significant differences in the mean NPI-12 scores between Day 1 and 15 in all the Cohorts, per the Wilcoxon signed-rank test results (Cohort 1: mean difference = -16.7 (±16.07), V = 55, p=0.005; Cohort 2: mean difference= -9.8 (10), V = 42, p = 0.024; Cohort 3: mean difference=-8.1± 8.08, V = 35, p = 0.021) (Fig. 4A). Similarly, the distress scores were significantly decreased on Day 15 as compared to Day 1 in all the Cohorts (Cohort 1: mean difference = -7 (±6.53), V = 44, p = 0.01; Cohort 2: mean difference = -6.40 (±5.82), V = 45, p = 0.009; Cohort 2: mean difference = - 3.10 ±3.81, V = 26.5, p = 0.034) (Fig. 4B).

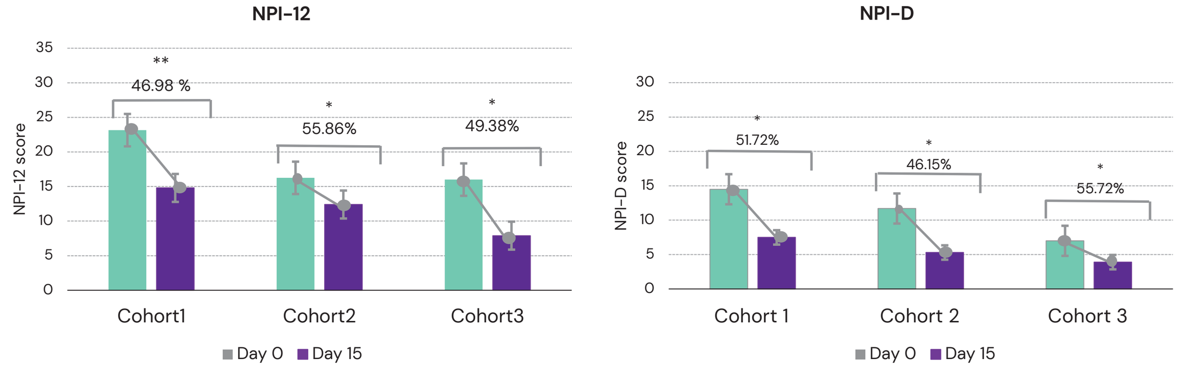


Figure 4. Average scores comparisons for Day 1 and Day 15 in Cohort 1, Cohort 2, and Cohort 3 **A)** NPI-12 and **B)** NPI-D. Percentage reduction from baseline is presented above. Error bars represented 95%CI. Statistical significance markers: * p < 0.05, ** p < 0.01, ***p < 0.001.

Active vs. placebo comparisons at Day 15

Comparisons of NPI-12 scores between the placebo (N = 2) and the active groups (N = 10) showed significant difference for Cohort 3 (U=35, p = 0.017) but not for Cohort 1 & 2 (Fig. 5A). Caregiver distress showed no statistically significant differences between groups for all three Cohorts (Fig. 5B).

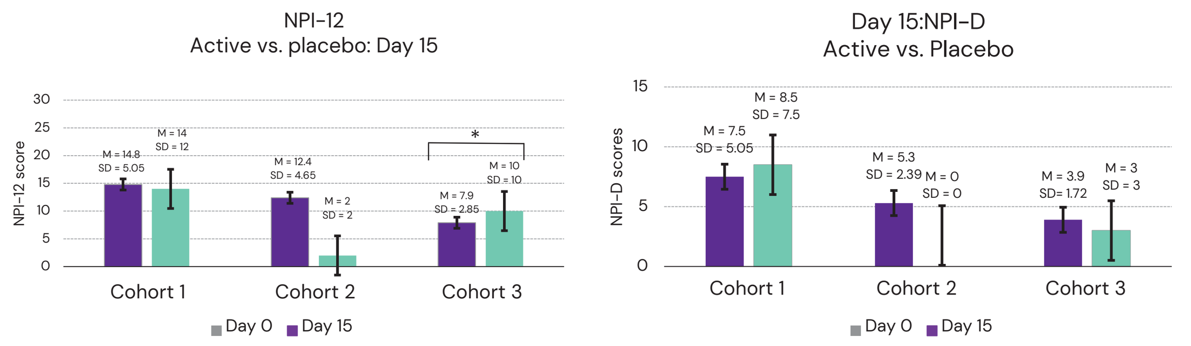
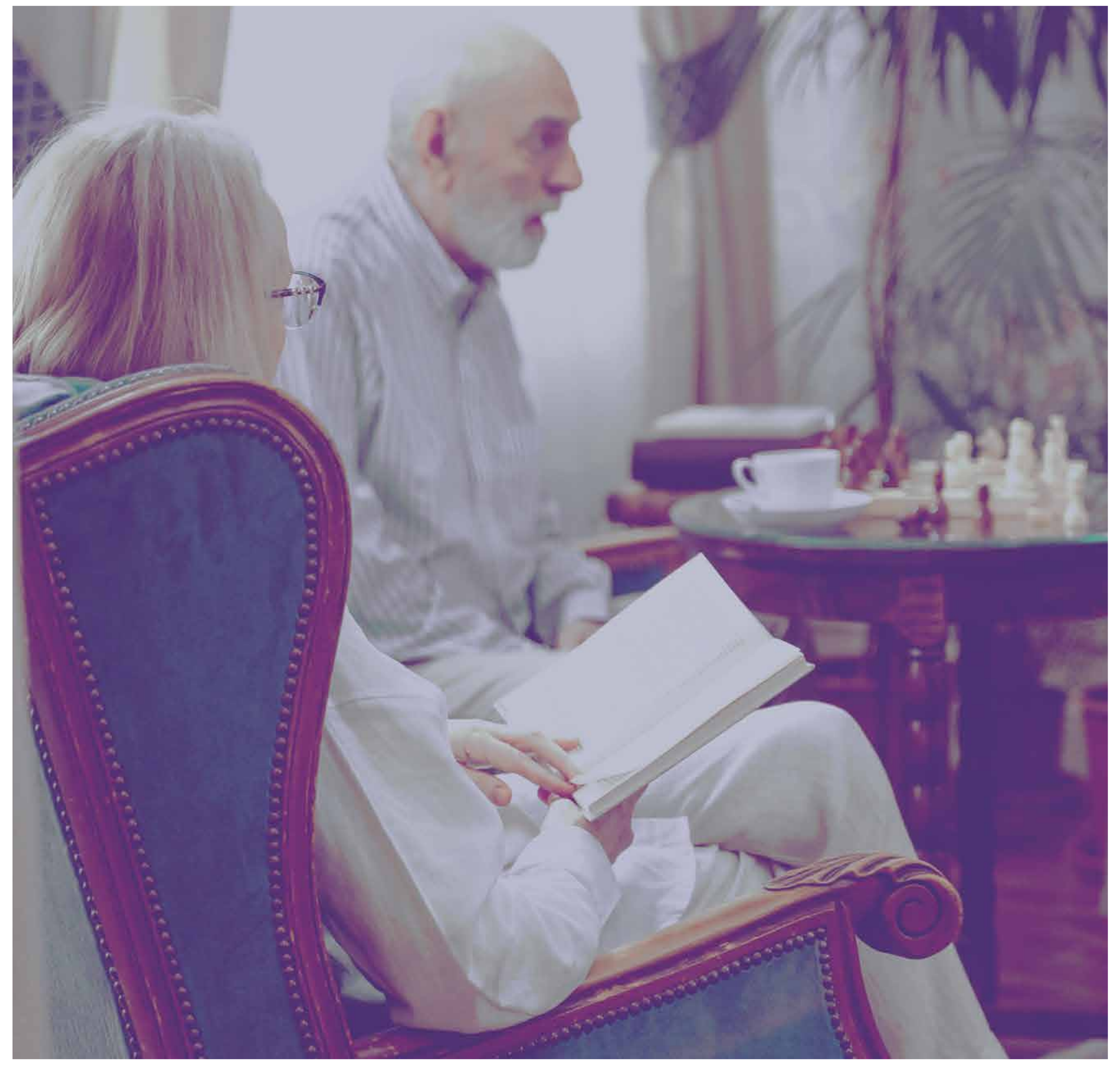


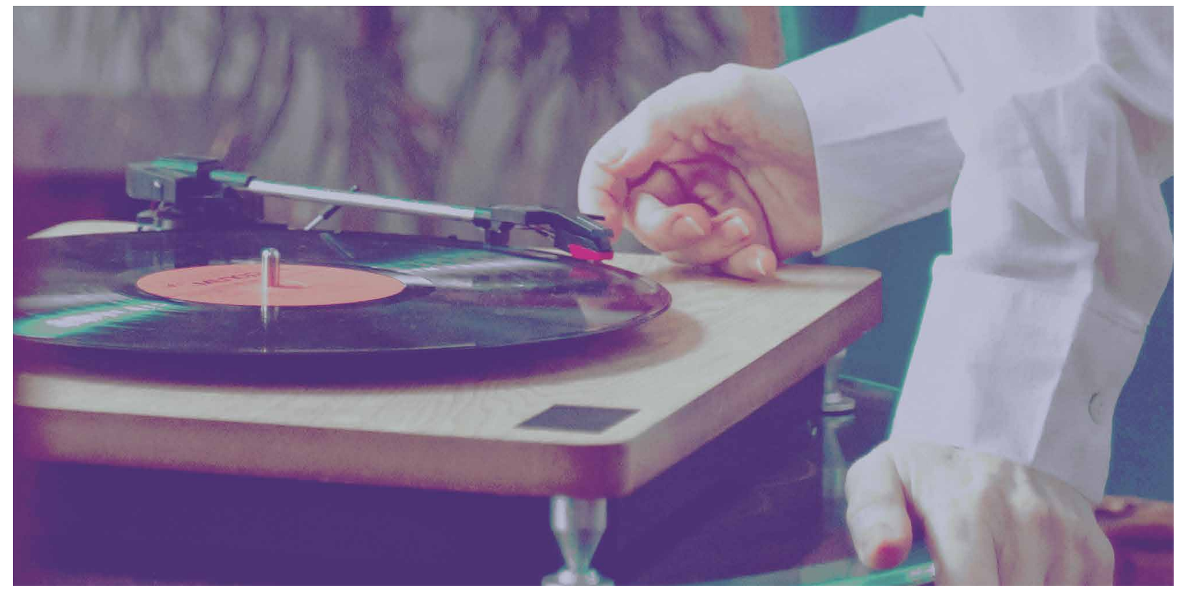
Figure 5. Active vs. placebo average scores comparisons Day 15 in A) NPI-12, B) NPI-D. Means (M) and standard deviations (SD) are represented at the top of each bar. Error bars represented as 95%CI. Statistical significance markers: * p < 0.05, ** p < 0.01, ***p < 0.001.



Conclusion:

At all three dosages, the IGC-AD1 led to a clinically and statistically significant reduction in NPS in AD patients and distress among their caregivers. This study's active and placebo score comparison provided a non-inferential glimpse into the difference between the treatments. However, a larger placebo group could facilitate more concrete comparisons in future trials.

A phase 2 trial is underway to test the ICG-AD1 efficacy at reducing NPS in AD patients with a larger sample.



Disclosure of funding:

This study was funded by IGC Pharma, LLC.

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SCAN ME

Reduction of Agitation and Associated Caregiver Distress using a Combination of Tetrahydrocannabinol and Melatonin in Participants with Dementia Due to Alzheimer's Disease.

IGCPHARMA

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POSTER #: P3-660

Takeaway message: IGC AD1, an oral solution combining low doses of Tetrahydrocannabinol (THC) and melatonin, showed safety, tolerability, and clinically significant reduction in NPI Agitation and Caregiver Distress scores as measured by the NPI-12.

Introduction

Agitation is a common neuropsychiatric symptom in Alzheimer's Disease (AD) patients[1]. It affects roughly 40% to 76% of AD patients[2,5]. The International Psychogeriatric Association (IPA) defines it as recurrent emotional distress associated with excessive motor activity, verbal aggression, or physical aggression that is severe enough to impair personal relationships, social functioning, and/or daily activities[4].

Agitation is a determining factor with a direct influence on patients' quality of life not only because of its direct effect on the patient, but also because it, along with aggression and disinhibition, significantly contributes to caregiver distress[6]. As these behaviors persist, the caregiver burden increases and intensifies, resulting in potential consequences such as depression, sleep disturbances, and various emotional and behavioral disorders. Consequently, the patient-caregiver relationship is compromised, resulting in an elevated risk of providing inadequate care and potential mistreatment of the patient[6]. Moreover, this situation contributes to a decline in the quality of patient care and exacerbates the persistence of agitation.

This condition is thought to arise from dysfunction of CB1 receptor, neurotransmitter imbalance, and neuroinflammatory processes[7,8,9]. Unfortunately, the current drugs used for managing agitation in dementia patients are prescribed off-label and are associated with undesirable side effects. However, IGC Pharma is addressing this issue by developing IGC-AD1, an oral combination of low doses of THC, acting as a CB1 receptor agonist addressing neurotransmitter imbalance, along with melatonin, which is known for its ability to modulate neurotransmitters like acetylcholine and glutamate[9,10]. IGC-AD1 has the potential to provide neuromodulatory and neuroprotective effects, reducing oxidative stress, and mitigating neuroinflammation[11].

Here, we report the preliminary data from the IGC-AD1 Phase 1 trial on the reduction of NPI Agitation and Caregiver Distress scores as measured by the NPI-12. Agitation and the associated caregiver distress as measured in the NPI-12.

Methods:

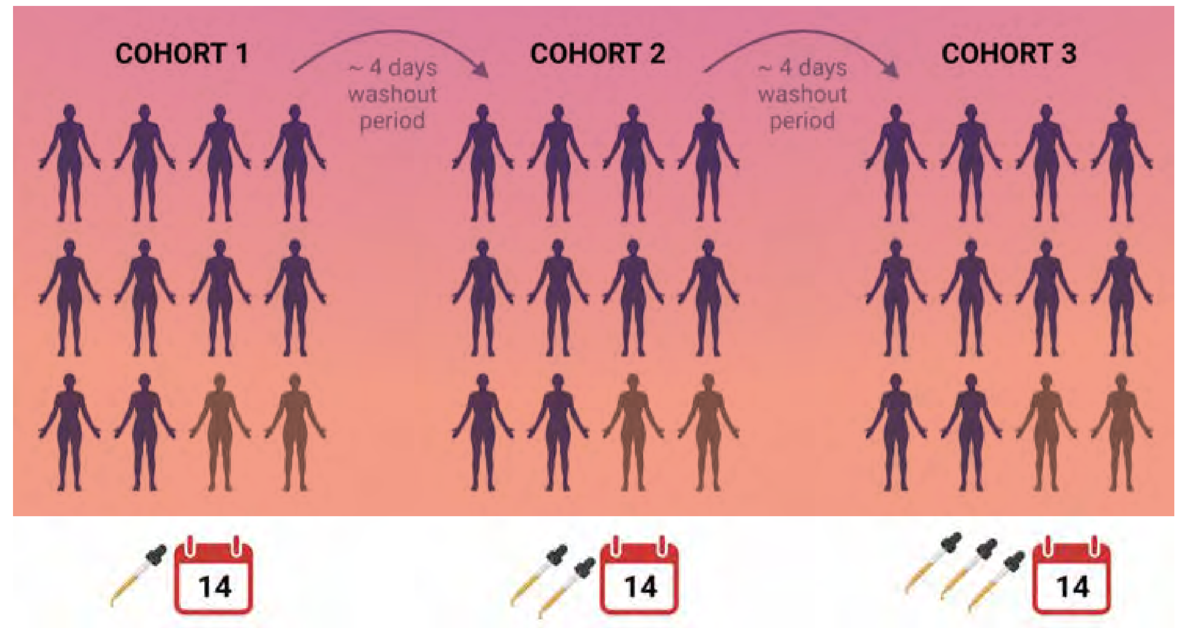

Figure 1. Phase 1 representation of all cohorts. Purple are active participants and placebo participants.

- 13 patients diagnosed with mild to moderate AD were included in this phase 1, three-cohort MAD trial to evaluate the safety and tolerability of IGC-AD1 (IND146069, NCT04749563). Participants mean age was 81.5 ± 5.5 years. 9 women and 4 men.
- In Cohorts 1, 2, and 3, 1ml of IGC-AD1 was administered QD, BID, and TID, respectively, for 14-days (EOT) with a 4-day minimum washout period between cohorts (Fig. 1). In all three cohorts, 7 participants from active group had agitation at baseline, while only 1 participant from placebo group had agitation in Cohort 1. NPI agitation / NPI-D were administered at baseline (Day 1) and EOT (Day 15). Solicited adverse events, unsolicited adverse events (AEs) and vital signs were monitored daily.
- The difference between NPI-agitation and NPI-D score means comparing Baseline and EOT were analyzed using a Wilcoxon signed-rank test or paired t-test. An independent t-test was used to compare active and placebo group.

Results:

Table 1. NPI Agitation Mean and NPI Caregiver (CG) Distress Mean Scores for All Cohorts on Day 0 and Day 15, Difference between Day 15 and Day 0, Percentage of Reduction, and Statistical Analysis of the Reduction.

Cohort	N	Intervention	NPI	DAY 0	DAY 15	D15-D0	% Red	P value	A vs P
1	7	**Active**	**Agitation**	4.71 ± 3.50	**3** ± 3.22	**-1.71** ± 1.8	**36.31**	V = 10 p = 0.063	t = 0.891 p = 0.407
	1	**Placebo**		3 ± 0	3 ± 0	0 ± 0	**0**	-	
	6	**Active**	**CG Distress**	3.67 ± 1.21	1.83 ± 1.47	-1.83 ± 1.17	**50.14**	V = 15 **p = 0.041**	t = 0.660 p = 0.538
	1	**Placebo**		3 ± 0	2 ± 0	-1 ± 0	**33.33**	-	
2	7	**Active**	**Agitation**	3.71 ± 2.36	1.29 ± 2.36	-2.43 ± 2.69	**65.23**	V = 10 p = 0.066	-
	7	**Active**	**CG Distress**	2.57 ± 1.27	0.86 ± 1.46	-1.71 ± 1.70	**66.54**	V = 10 p = 0.066	-
3	7	**Active**	**Agitation**	3 ± 2.45	1 ± 1.73	-2 ± 2.24	**66.67**	V = 10 p = 0.066	-
	7	**Active**	**CG Distress**	2.40 ± 0.89	1 ± 1.41	-1.40 ± 1.14	**58.33**	V = 10 p = 0.066	-

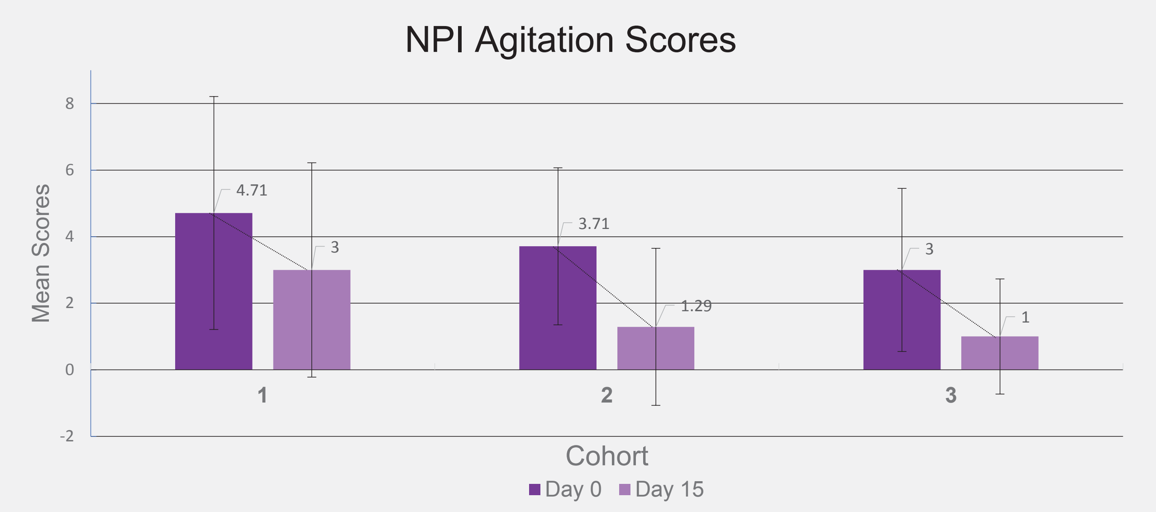

Figure 2. NPI Agitation Mean Scores for Day 0 and Day 15 for All Cohorts.

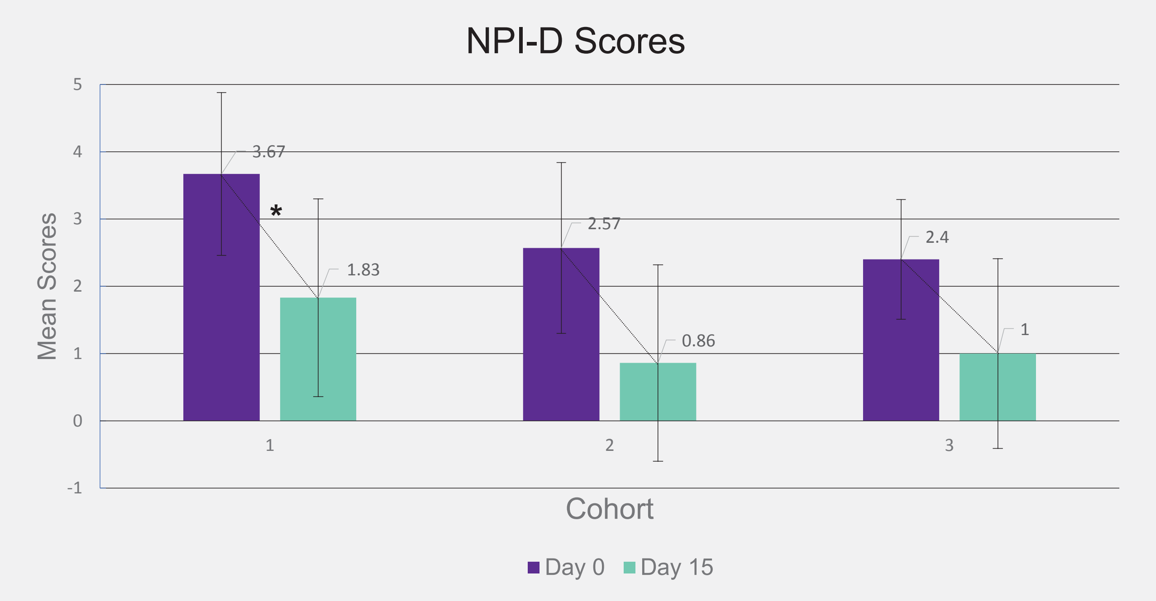

Figure 3. NPI-D Scores for Day 0 and Day 15 for all Cohorts.

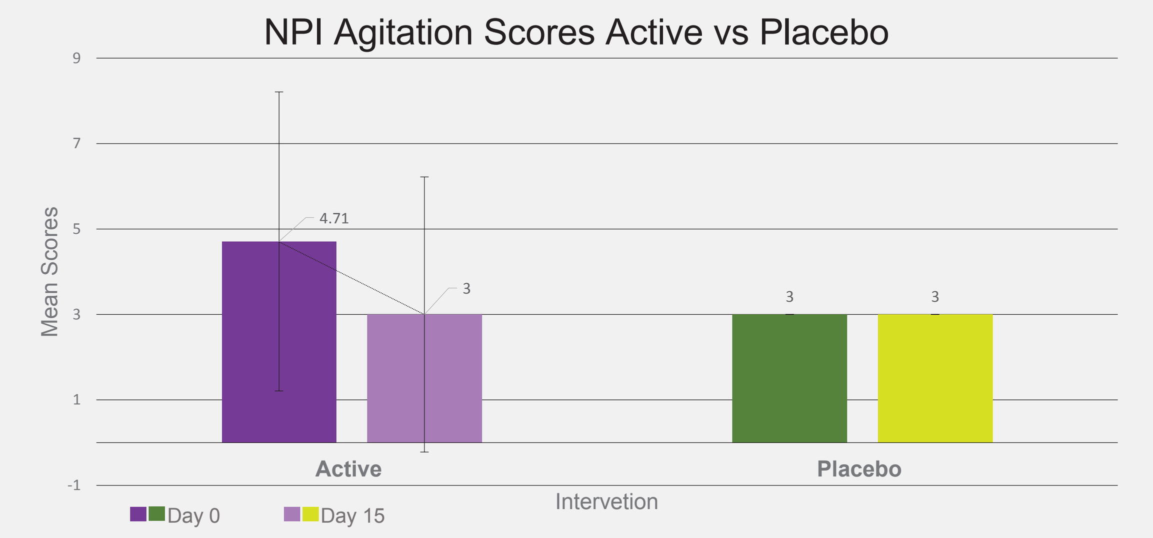

Figure 4. NPI Agitation Mean Scores for Day 0 and Day 15 for active vs placebo. Cohort 1.

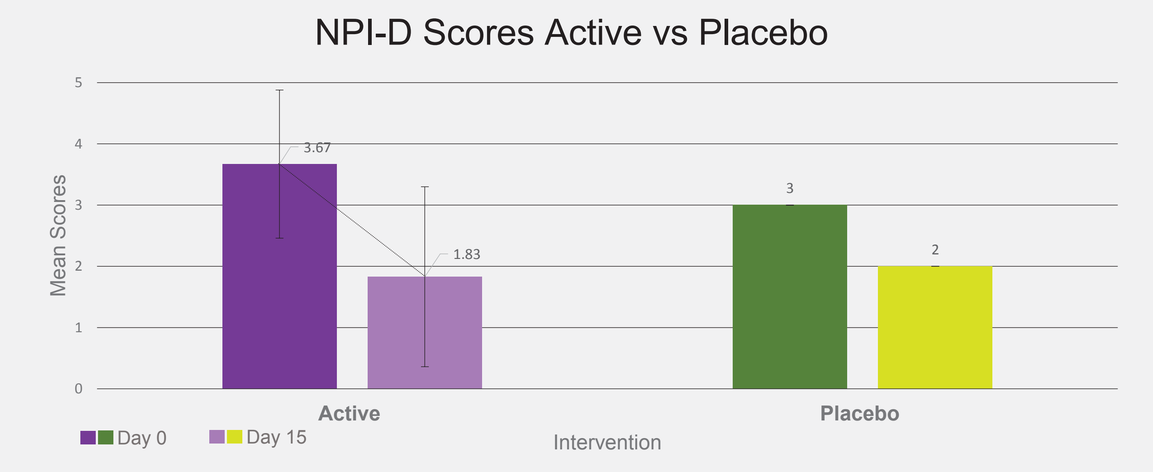

Figure 5. NPI-D Mean Scores for Day 0 and Day 15 for active vs placebo. Cohort 1.

- Despite the no statistical significance (p>0.05), the P values for the difference between Day 0 and Day 15 in the NPI Agitation Scores for the 3 cohorts were between 0.063 – 0.066. Thus, larger follow-up studies are expected to yield statistically significant improvements in reducing agitation. The reduction in caregiver Distress scores for Cohort 1 showed statistical significance. However, in Cohort 2 and Cohort 3, the reductions were 66.54% and 58.33%, respectively, with p-values of 0.063, which is likely attributed to the small sample size.
- All cohorts demonstrated a clinically significant reduction in NPI Agitation and NPI-D score surpassing the threshold of a 30% reduction.
- n the Placebo group, there was no significant difference in the NPI agitation score between Day 0 and Day 15. However, the active treatment group showed a clinical reduction of 55% in NPI-D scores, compared to 33% in the placebo group. A larger, comparable control sample size is required. No serious AEs, deaths, or dropouts due to AEs were reported. No major changes in concomitant medications were observed.

Conclusion:

IGC-AD1, a THC-melatonin combination, was safe, well-tolerated, and had no serious adverse events. NPI agitation and NPI-D scores showed promising results that indicate IGC-AD1 may be efficacious at reducing agitation due to AD and associated caregiver distress. A study with a larger sample size and comparable active/control groups is needed to confirm these results. Currently, IGC Pharma is conducting a Phase 2 clinical trial to investigate IGC-AD1's efficacy in treating agitation in AD patients.

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SCAN ME

Effect of Tetrahydrocannabinol and Melatonin Combination on Suicidal Ideation and Behavior in Dementia due to Alzheimer's Disease

IGCPHARMA

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POSTER #: P3-657

Takeaway message: Low doses of THC + melatonin (IGC-AD1) did not create a risk of developing suicidal ideation or behavior as assessed by the C-SSRS in mild to moderate AD participants taking active medication. This finding might be associated with the decreased score of the NPI-12 depression domain during the 6-week Phase I clinical trial.

Background:

- Alzheimer's disease (AD) is a progressive neurodegenerative disorder that primarily affects the elderly population. AD is the most common cause of dementia, accounting for 60% to 80% of all cases (1).
- AD's severity can be evaluated by NIA-AA criteria, and common symptoms in mild, moderate, and severe stages of AD are summarized in **Fig. 1** (1).

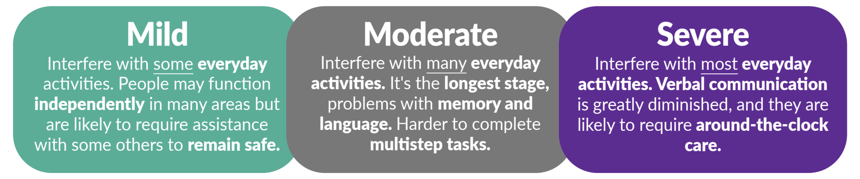

Figure 1. AD severity evaluated by NIA-AA criteria (1).

- Individuals with dementia in early stages of cognitive decline more commonly show suicidal ideations and/or attempts, wherein patients have more negative thoughts related to cognitive disability awareness (2). AD patients have low prevalence of suicidal ideation (3).
- The specific relationship between age, dementia, and suicide is not as straightforward as a linear increase (**Fig. 2**). Suicide has been defined as an intentional act that has the purpose of causing self-harm and death (4).
- Depression is one of the most significant risk factors for developing suicidal ideation in the elderly (5), and dementia likely increases the risk of developing depression. Thus, there has been a significant research interest in understanding the complex relationship between AD and suicidal ideation/behaviors.

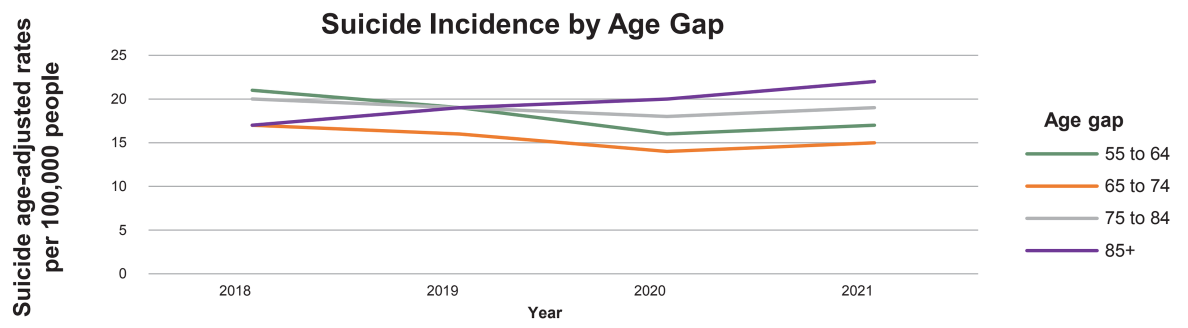

Figure 2. Suicide rates by age gap. Rate per 100.000 Individuals (6).

- IGC Pharma conducted a Phase I multiple ascending dose (MAD) clinical trial that explored the safety of the investigational drug IGC-AD1 for AD patients.
- The active pharmaceutical ingredients (APIs) of our investigational drug are tetrahydrocannabinol (THC) and melatonin. This study investigated the effect of IGC-AD1 on the risk of developing suicidal ideation and behavior in AD patients.
- THC is a component of cannabis with psychoactive and analgesic properties (7), with potential as an alternative pharmacologic treatment for AD (8). It showed how to improve cognitive function, behavioral and psychological symptoms in dementia (BPSD) (9). However, long-term exposure to THC in adolescence is reported to be associated with an increased risk of depression, psychosis, and suicidality in humans (10).
- The other API, melatonin, has a significant impact on emotional well-being by promoting sleep and regulating the circadian rhythm (11). Although further research is needed to establish the relationship between melatonin and suicidal ideation and behavior, sleep disturbances may increase the risk of developing SI and SB in AD patients.
- Accordingly, this study evaluated the effect of IGC-AD1 on Columbia-Suicide Severity Rating Scale (C-SSRS) in AD patients.

Methods:

- Twelve patients with mild (15.4%) to moderate (84.6%) AD according to NIA-AA criteria (10-active, 2-placebo (**Fig. 3**), 81.5 ± 5.5yrs, 69.2% women).
- In cohort 1, IGC-AD1 was administered once daily (QD) at 1ml for 14-days (end of treatment (EOT)).
- In cohorts 2 and 3, one ml twice daily (BID) and three times daily (TID) were administered respectively with a minimum of 4-days washout between cohorts.

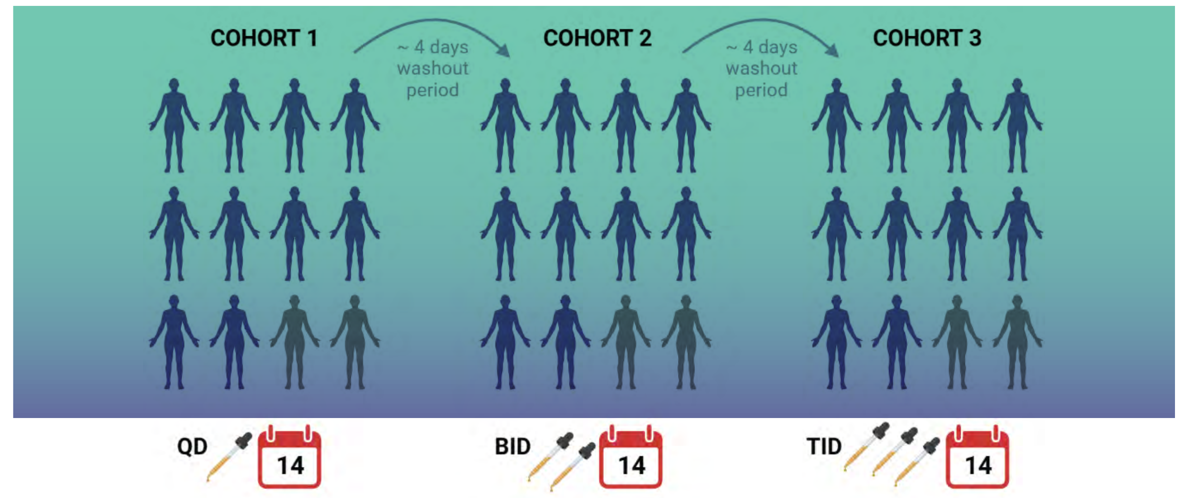

Figure 3. Phase I clinical trial timeline. Purple indicates the number of active participants and gray the number of placebo participants per cohort in the trial.

- C-SSRS was applied at baseline and on days 5, 10, EOT, and EOT + 2 days at each cohort by a neuropsychologist (**Fig. 4**).
- Safety follow-up phone calls, or in-person follow-up visits, were done for the 14 days of dosing at each cohort (**Fig. 4**), where a review of adverse events was performed (including suicidal ideation).

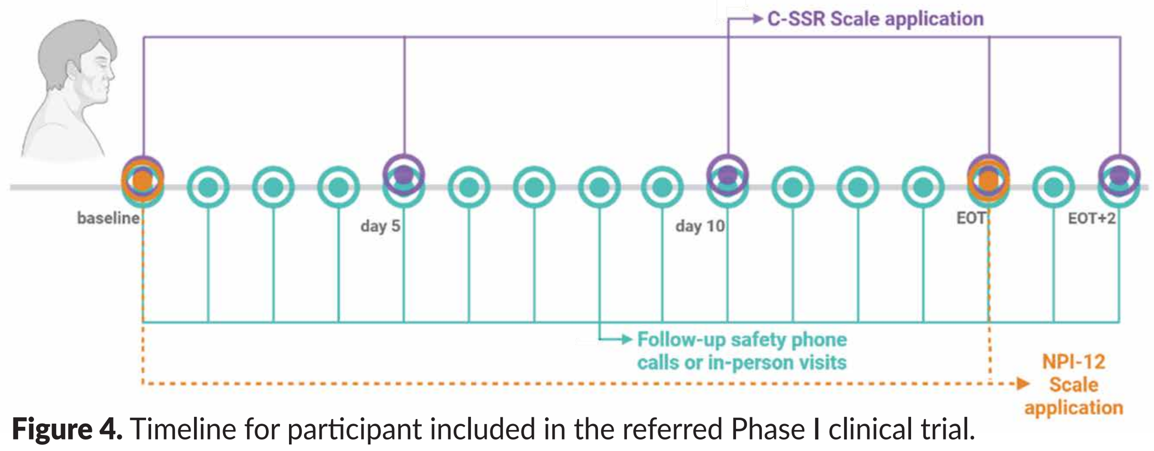

Figure 4. Timeline for participant included in the referred Phase I clinical trial.

- Depression was evaluated through the NPI-12. This scale was administered at baseline and EOT (**Fig. 4**). A Shapiro-Wilk test was used to determine data's normality. Based on this, a Wilcoxon signed-rank test (V) was applied to compare the difference between scores at baseline and EOT for each cohort. In addition, the difference between placebo and active groups was assessed with an independent t-test (t) (R-Studio, dplyr).
- The same rater performed evaluations to promote more cohesive results and minimize inconsistencies.

Results:

- In 420 person-days (10 patients on active x 14 days x 3 cohorts) of dosing, there was one day on which a participant on active medication self-reported suicidal ideation as part of the solicited AEs.
- The participant has a medical history of mild AD and intermittent depressive episodes, among other underlying conditions.
- The subject reported mild (severity grade 1) suicidal ideation on a subjective assessment one day in cohort 2. The event self-resolved the next day and the C-SSRS did not reveal any positive results. At the next in-person visit, the participant denied having suicidal ideas.
- The participant continued participating in the study as cohort 3, where no suicidal ideation events were reported.
- The subject was on some psychoanaleptics, including sertraline (a selective serotonin reuptake inhibitor drugs (SSRI)). No major changes in concomitant medications were reported for this or any patient.
- There was a total of 50 administrations of the C-SSRS to the participants on active medication across all three cohorts. None showed signs of suicide ideation or behavior.
- Across the 30 administrations in the placebo group, there were no suicide ideations or behaviors either.
- No serious AEs, deaths, nor dropouts due to AEs were reported.
- Depression scores between EOT and baseline in all three cohorts (**Table 1, 2, 3**) showed a clinically significant reduction, but only cohort 2 (**Table 2**) demonstrated a statistically significant result (**Fig. 5**).

Table 1. Cohort 1 NPI-12 depression domain.

COHORT 1		DAY 0	DAY 15	D15-DO Difference	% Reduction	Test I P	Active vs Placebo
Active N=8	Depression NPI	5 ± 4.24	1.50 ± 2.12	-1 ± 1.85	70	V = 21.5	t = 0.211 p = 0.838
Placebo N=2	Depression NPI	2.25 ± 1.04	1.25 ± 1.39	-3.5 ± 2.12	44	p = 0.200	

Table 2. Cohort 2 NPI-12 depression domain.

COHORT 2		DAY 0	DAY 15	D15-DO Difference	% Reduction	Test I P
Active N=7	Depression NPI	2.86 ± 0.69	0.86 ± 1.46	- 2 ± 1.16	69.9	V = 21 p = 0.026

Table 3. Cohort 3 NPI-12 depression domain.

COHORT 3		DAY 0	DAY 15	D15-DO Difference	% Reduction	Test I P
Active N=5	Agitation NPI	2.8 ± 2.39	0.80 ± 1.79	-2 ± 2.55	71.4	V = 6 p = 0.109

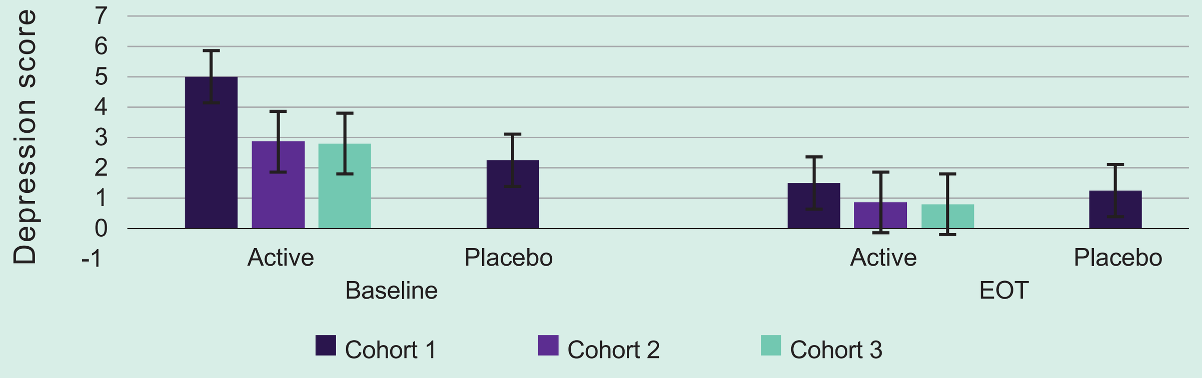

Figure 5. NPI-12 Depression domain, baseline, and EOT.

Discussion and Conclusions:

- The principal investigator (PI) determined that the suicidal ideation reported event was unrelated to IGC-AD1 administration.
- Low doses of THC and melatonin in IGC-AD1 did not create a risk of developing suicidal ideation or behavior as assessed by the C-SSRS in the mild to moderate AD population during the 6-week Phase I trial.
- Previous reports have shown harm caused by prolonged exposure to THC, this study, while only 6-weeks long, showed no effect of low doses of THC on suicidal ideation and behaviors during the trial.
- Most existing studies have a cross-sectional design, limiting our ability to draw causal conclusions or assess the long-term effects of THC exposure on suicidal ideation in older individuals. Longitudinal studies tracking individuals over time would provide more robust evidence.
- SSRIs are a pharmacological alternative for treating depression with fewer secondary effects. However, some studies have found greater suicidal risk associated with SSRIs in elderly patients. IGC-AD1 while warranting further study, appears to be a promising pharmaceutical option for the treatment of depression.
- Clinically significant decreases in NPI-12 (depression domain) were observed in all three cohorts. However, statistical significance was only observed in cohort 2. This could be related to the small sample size. The medication reduced depression, a major risk factor for suicide.
- Further studies are needed to test the conjecture on a larger population. IGC Pharma's ongoing Phase II trial plans to collect more data.

Disclosure of Funding:

This study was Funded by IGC Pharma, LLC.

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SCAN ME

Reduction of Apathy and the Associated Caregiver Distress using a Combination of Tetrahydrocannabinol and Melatonin in Participants with Dementia due to Alzheimer's Disease

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IGCPHARMA

POSTER #: P3-662

Takeaway message: IGC-AD1, a Tetrahydrocannabinol (THC) and melatonin combination, has the potential to treat Apathy in Alzheimer's disease.

Background:

Apathy is one of the most frequent and long-lasting neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD).[1] Studies reported a prevalence of apathy in AD ranging from 19% to 88%, with an overall mean prevalence of 49%, related to caregiver distress, decreased quality of life, and increased morbidity.[2] Apathy is defined as loss of or diminished motivation in at least two of three domains, including goal-directed behavior, cognitive activity, and emotion, sufficiently causing significant impairment in everyday life.[2]

There is no FDA-approved drug to treat apathy in AD. While some off-label medications and behavioral interventions are used to treat apathy, the effects are often limited and lack in-depth research to support these approaches.[3,4] Thus, apathy is emerging as a treatment target for pharmacological and non-pharmacological interventions.

Brain amyloid-β (Aβ) deposition, one of the hallmarks of AD, has been reported to be correlated with apathy.[5] Tetrahydrocannabinol (THC) and melatonin showed preclinical data supporting its effect to decrease Aβ40 levels in N2a/APPswe cells in a dose-dependent manner, through direct interaction with Aβ peptide and aggregation inhibition.[6,7] In addition, an in vivo study in aged APP/PS1 transgenic mice revealed that low-dose THC treatment significantly decreased the expression of Aβ oligomers.[8] Preclinical data suggest the potential effect of THC and melatonin on apathy management through an Aβ-associated mechanism.

Thus, this study investigated the effect of our investigational drug, IGC-AD1, a combination of THC and melatonin, on the reduction in NPI-Apathy scores and NPI Caregiver Distress (NPI-D) scores in Phase I clinical trial.

Methods:

Thirteen Participants diagnosed with mild (15.4%) to moderate (84.6%) AD (NIA-AA criteria and clinical history) participated in a three-cohort Phase 1 trial with MAD for safety and tolerability (10 Active, 2 Placebo per cohort, 81.5 ± 5.5yrs, 69.2% women). In Cohorts 1, 2, and 3, 1ml of IGC-AD1 was administered QD, BID, and TID, respectively, for 14-days (EOT) (**Fig. 1**). There was a 4-day minimum washout period between cohorts. Solicited and non-solicited adverse events (AEs) and the vital signs of all participants were monitored during each 14-day period.

In each cohort, seven Participants (5-Active, 2-Placebo) had apathy at baseline, as rated by the NPI-Apathy.

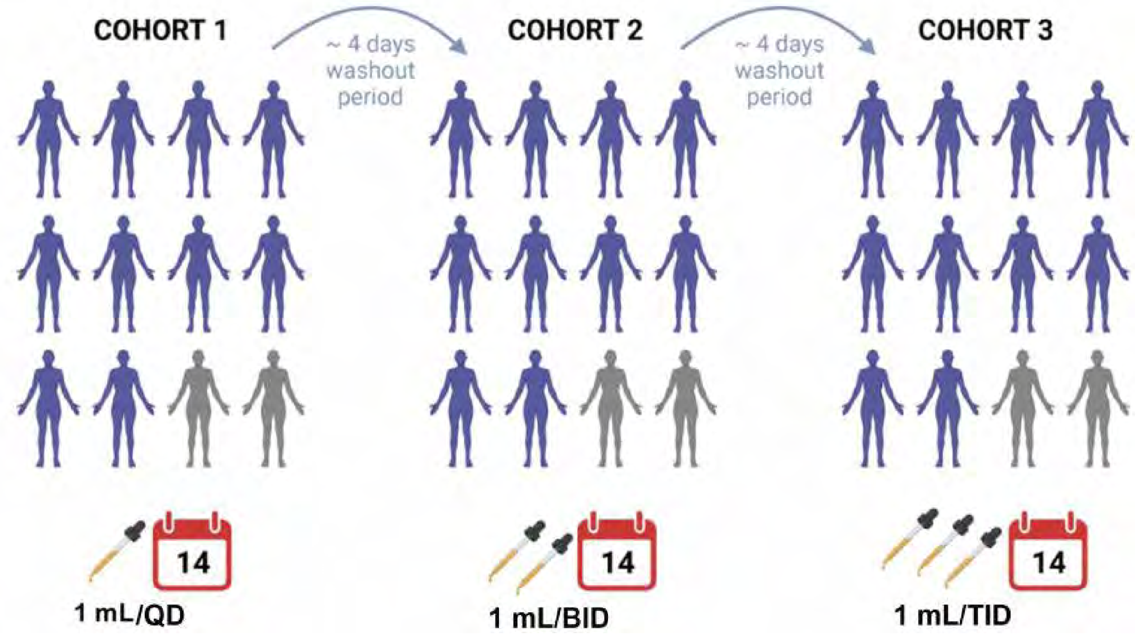

Figure 1. Phase I clinical trial design.
Purple: Active Participants, gray: Placebo Participants

Behavioral test: NPI-Apathy / NPI-Distress (NPI-D) were administered at baseline (Day 1) and EOT (Day 15).

Statistical analysis: The average score differences between Day 1 and Day 15 were calculated using either two-sided Wilcoxon signed-rank tests or paired t-tests, depending on the data distribution. The differences between placebo and active groups were assessed with Mann-Whitney U tests or independent t-tests (R-Studio, dplyr).

Results:

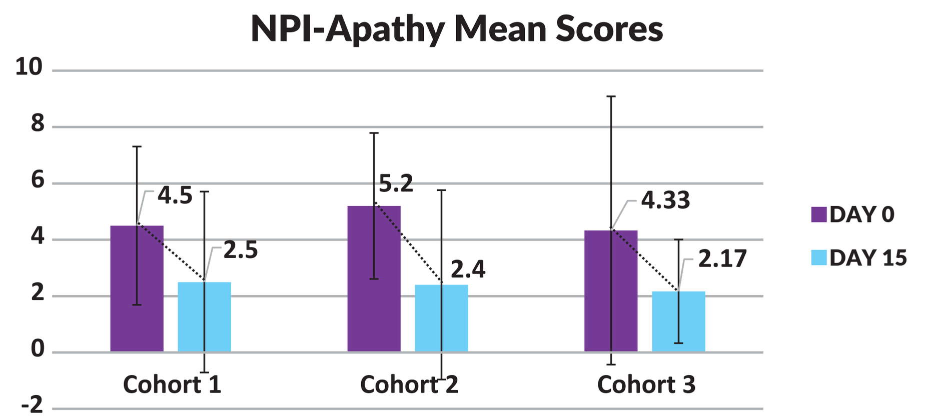

Figure 2. Phase I clinical trial NPI-Apathy mean scores for all cohorts on Day 0 and Day 15

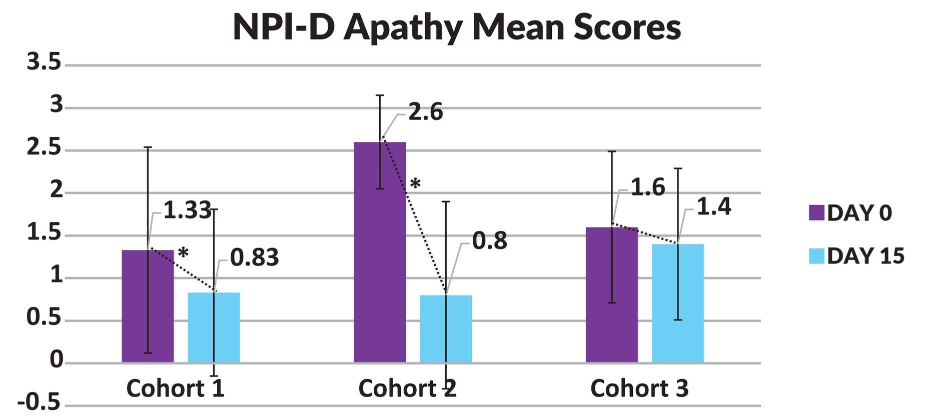

Figure 3. Phase I clinical trial Apathy, NPI-D mean scores for all cohorts on Day 0 and Day 15
*Statistically significant (p<0.05)

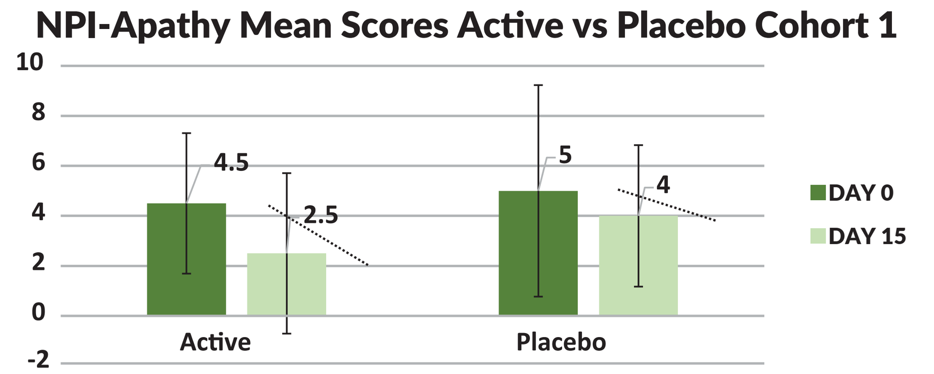

Figure 4. Phase 1 clinical trial NPI-Apathy Mean Scores, Active vs Placebo Cohort 1

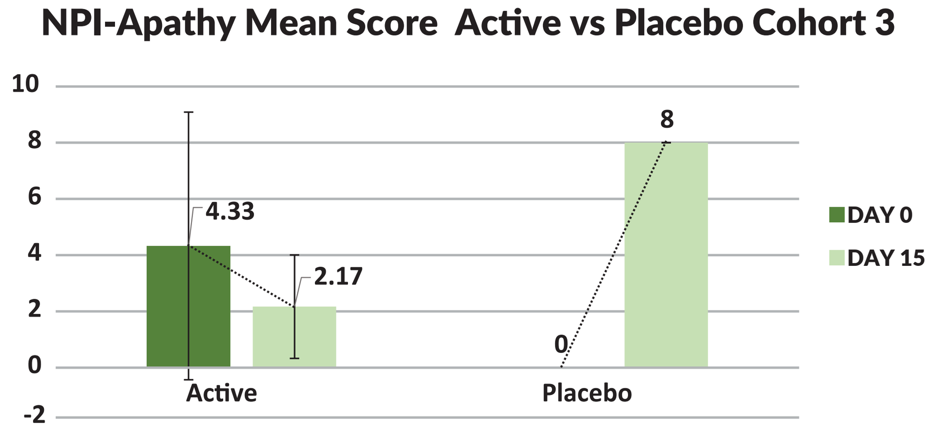

Figure 5. Phase 1 clinical trial NPI-Apathy Mean Scores, Active vs Placebo Cohort 3

Table 1. NPI-Apathy and NPI-D mean scores and statistical analysis between Day 0 and Day 15

Cohort	N	Intervention	NPI	DAY 0	DAY 15	D15-D0	% Reduction	P value	A vs P
1	6	Active	NPI-Apathy	4.5 ± 2.81	2.50 ± 3.21	-2 ± 2.53	**44.4**	t = -1.936 p = 0.111	t = 0.514 p = 0.625
	2	Placebo		5 ± 4.23	4 ± 2.83	-1 ± 1.41	**20.0**	t = -1 p = 0.5	
	6	Active	NPI-D	1.33 ± 1.21	0.83 ± 0.98	-0.50 ± 0.55	**37.6**	V = 26.5 **p = 0.028**	V = 0.300 p = 0.584
	2	Placebo		3 ± 0	2 ± 1.41	-1 ± 1.41	**33.3**	t = -1 p = 0.5	
2	5	Active	NPI-Apathy	5.2 ± 2.59	2.40 ± 3.36	-2.80 ± 3.27	**53.8**	V = 6 p = 0.102	-
	5	Active	NPI-D	2.60 ± 0.55	0.80 ± 1.1	-1.80 ± 0.84	**69.2**	V = 15 **p = 0.041**	-
3	6	Active	NPI-Apathy	4.33 ± 4.76	2.17 ± 1.84	-2.17 ± 3.87	**49.9**	t = -1.372 p = 0.228	t = 2.433 p = 0.059
	1	Placebo		0 ± 0	8 ± 0	8 ± 0	**800**	-	
	5	Active	NPI-D	1.60 ± 0.89	1.40 ± 0.89	-0.20 ± 1.1	**12.5**	V = 2 p = 0.655	t = 1.833 p = 0.141
	1	Placebo		0 ± 0	2 ± 0	2 ± 0	**200**	-	

In Cohort 1, the mean NPI-Apathy at baseline and EOT were 4.5 and 2.5, respectively (mean difference=-2, p=0.091). In Cohort 2, the mean NPI-Apathy at baseline and EOT were 5.2 and 2.4, respectively (mean difference=-2.8, p=0.087). In Cohort 3, the mean NPI-ap at baseline and EOT were 4.33 and 2.17, respectively (mean difference=-2.17, p=0.228).

Results for NPI-D: (Cohort-1: mean difference=-0.5, 37.6%, p=0.028; Cohort 2: mean difference=-1.8, 69.2%, p=0.041; Cohort 3: mean difference=-0.2, 12.5%, p =0.655). No serious AEs, no deaths, and no dropouts due to AEs were reported. No major changes in concomitant medications were observed.

Conclusion:

As IGC-AD1 contains THC, the results are intriguing. In previous studies, cannabis use has been associated with increased apathy.[9] In Cohort 1, Cohort 2, and Cohort 3, apathy as measured by NPI-Apathy reduced by 44.44%, 53.84%, and 49.88% respectively. These results were not statistically significant (p>0.05) but were clinically significant[10] (reduction in NPI-Apathy ≥30%).

A larger multi-site, placebo-controlled, double blind, randomized, Phase-2 study is currently underway wherein the NPI-12 will be used to measure among other neuropsychiatric symptoms, Apathy.

Disclosure of Funding:

This study was Funded by IGC Pharma, LLC.

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SCAN ME

Cytochrome P450 2C9 Polymorphism in Puerto Rican Alzheimer's Disease Patients and its role in the Pharmacokinetics of IGC-AD1, an Investigational Drug

IGCPHARMA

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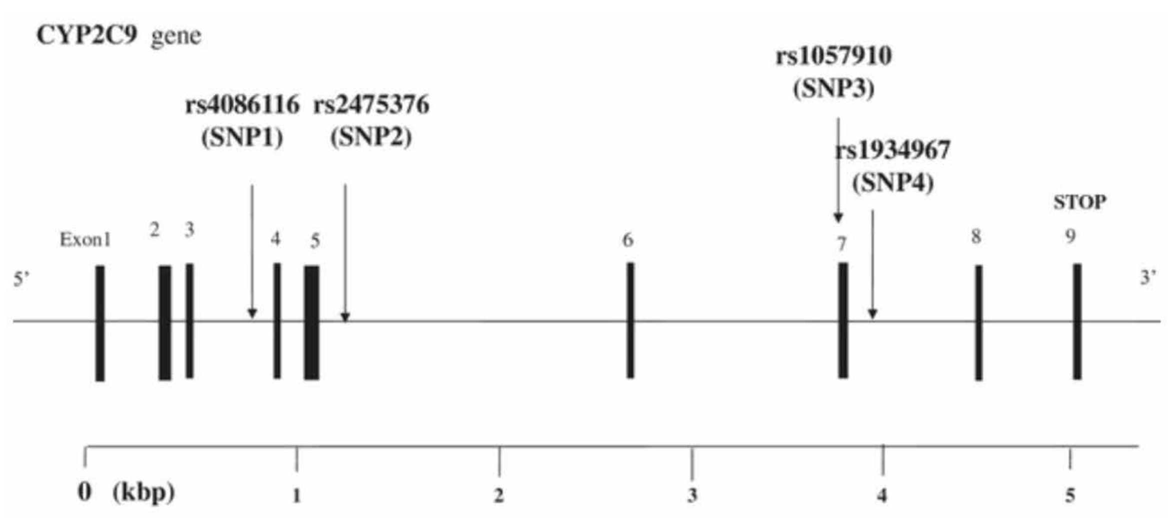
POSTER #: P3-648

Takeaway message: Polymorphisms of CYP2C9 affect the PK of THC and is a factor in determining dosing in patients with AD.

Introduction

- Alzheimer's disease (AD) is a complex and chronic neurodegenerative illness. Patients with AD are on many medications to manage their symptoms and their comorbidities.
- Cytochromes P450 (CYPs) are a superfamily of enzymes (1, 2, and 3 types) that play a key role in the metabolism of a wide range of substances, including endogenous molecules and clinical drugs. The most common CYPs-mediated pathways include CYP3A4/5, CYP2C9, CYP2D6, and CYP2C19, which are accounted for approximately 79% of the drugs' oxidation. In particular, cytochrome 2C9 (CYP2C9) is highly expressed in the liver, contributing to >25 % of the metabolism of most clinical drugs.[1] In addition, it is responsible for the metabolic clearance of several clinically used drugs with a narrow therapeutic index.
- Four polymorphism sites have been identified on the CYP2C9 gene (**Figure 1**), which lead to inter-individual variability in the phenotype of CYP2C9 protein expression. CYP2C9 variability may impact the efficacy and safety of drug treatment.[1-2]
- In this study different metabolizing phenotypes of CYP2C9 were considered, such as poor (PM), intermediate (IM), normal (NM), and ultra-rapid (UM)[3] (**Table 1 and Figure 2**).

Figure-1. Polymorphism sites that have been identified on CYP2C9 gene.



- IGC-AD1 is an oral formulation of tetrahydrocannabinol (THC) and Melatonin. CYP2C9 is the main enzyme involved in the metabolism of THC, converting THC into the active metabolite 11-hydroxy-delta-9-THC metabolite.[2] In contrast, melatonin is primarily metabolized by CYP1A2 and CYP2C19 enzymes, with CYP2C9 being found to be less important[3].
- In this study, the CYP2C9 polymorphism in AD patients was examined and its influence on the pharmacokinetics of THC was determined.

Figure-2. Effect of CYP450 Polymorphism on Drug Metabolism

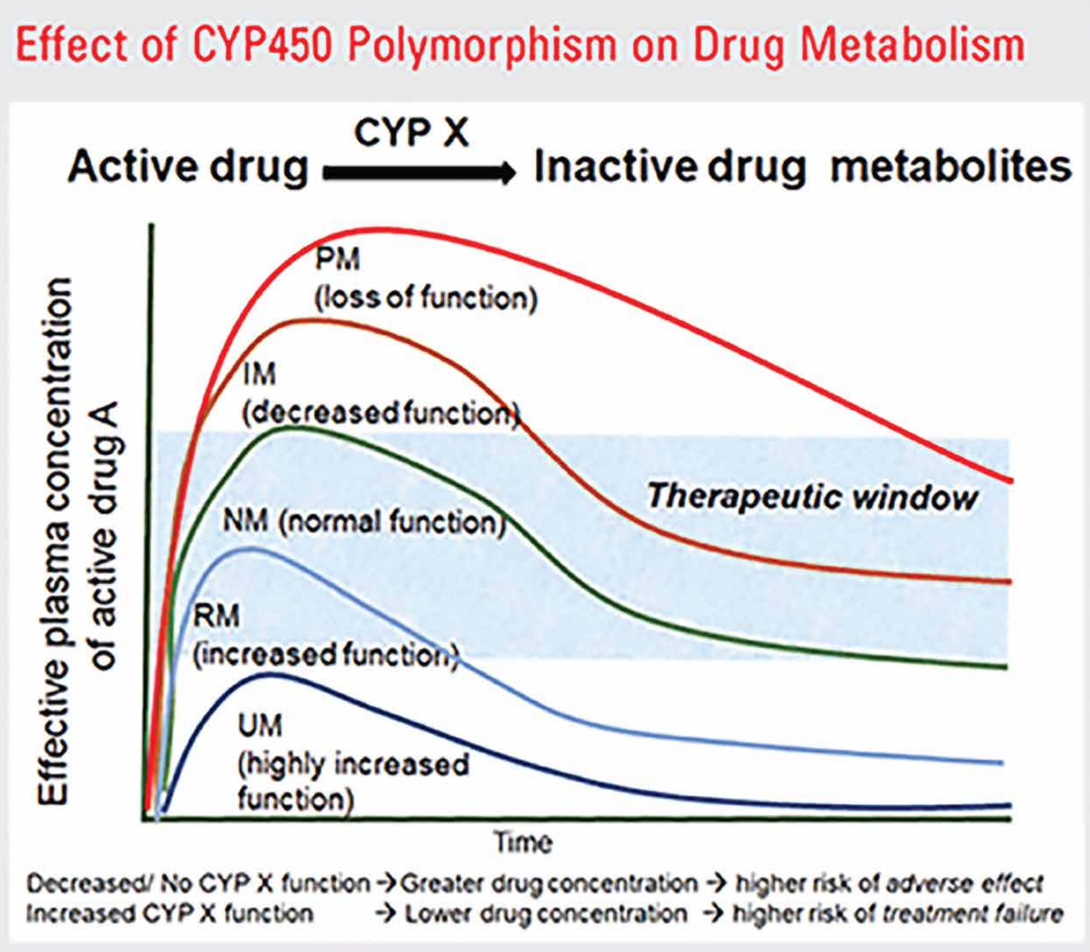


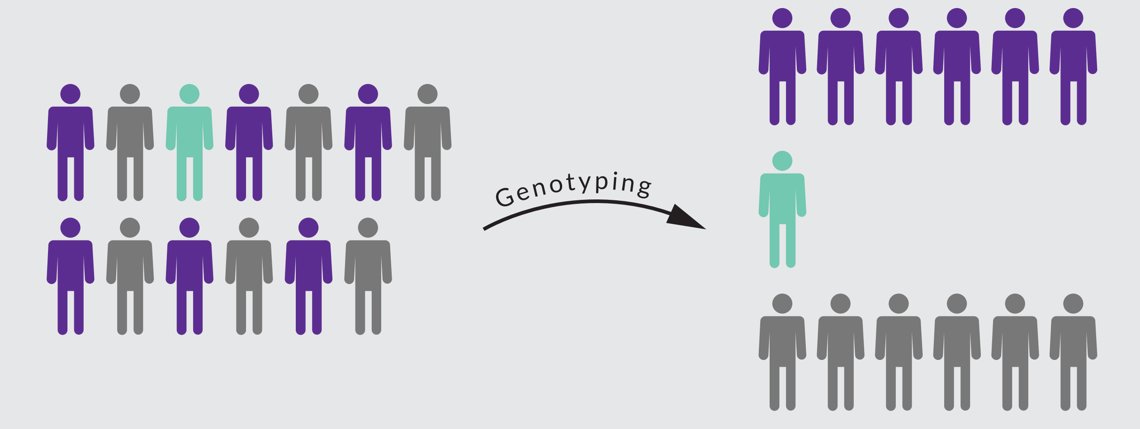
Table 1. Genotypes of CYP2C9 and Phenotypes

Genotype	Phenotype	Function
CYP2C9*1/*1	Normal Metabolizer	Homozygous for wild type
CYP2C9*1/*2	Intermediate Metabolizer	Heterozygous for reduced function
CYP2C9*1/*3	Intermediate Metabolizer	Heterozygous for no function
CYP2C9*2/*2	Intermediate Metabolizer	Homozygous for wild type
CYP2C9*2/*3	Poor Metabolizer	Heterozygous for reduced and no function
CYP2C9*3/*3	Poor Metabolizer	Homozygous for no function

Methods:

- The Phase-1 trial (n = 13) was conducted in Puerto Rican population to assess the CYP2C9 polymorphisms and their impact on THC pharmacokinetics in AD patients.
- CYP2C9 polymorphisms (alleles: *2, *3, *4, *5, *6, *8, *11, *13, *15) were determined using the Mass Array Analyzer 4 instrument (Invitae Inc., MAA4, Agena, San Diego, CA).
- Pharmacokinetics (PK) were analyzed using LC-MS/MS method at the Northeast Biolabs, Hamden, CT, USA.

Genotyping by Mass Array Analyzer

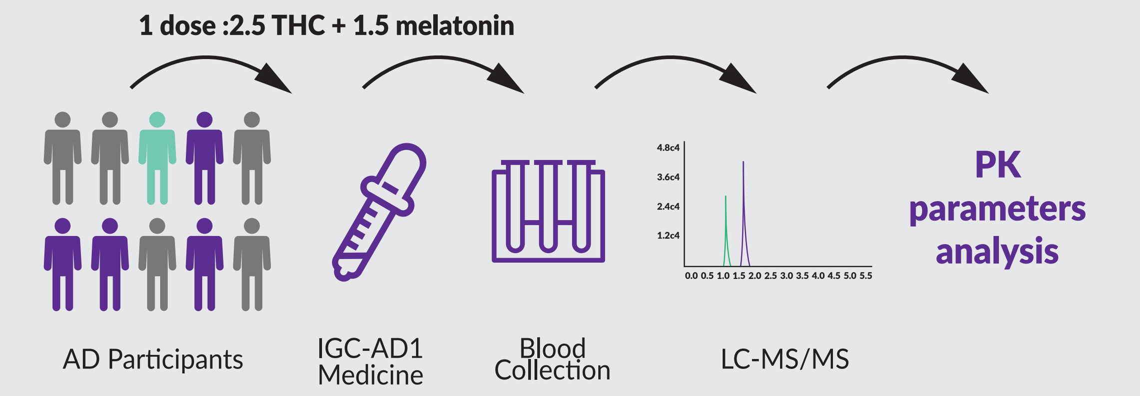


IGC-AD1 PK Studies

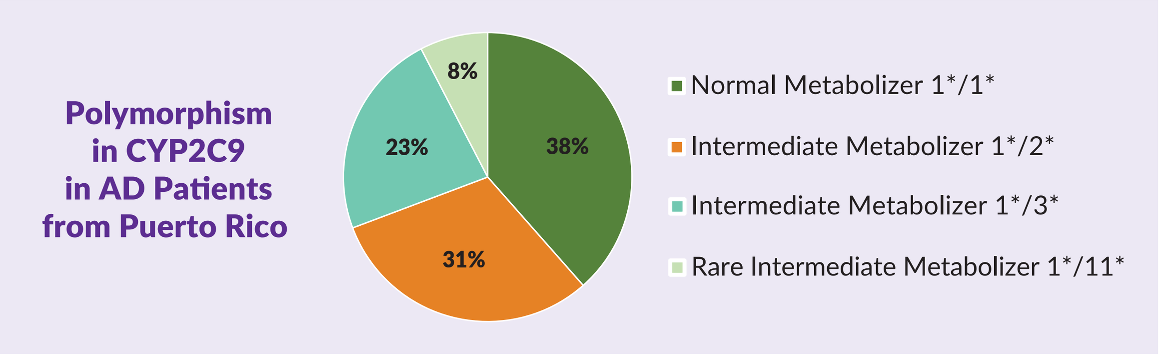
Table 2. PK Blood draws over Cohort 1 and Cohort 2

Cohort 1: IGC-AD1 (2.5mg THC & 1.5mg melatonin) Administered at or about T=8:00 p.m. (after dinner, time is for illustration)								
Draws (the next day) (hrs.)	T+12 (8:00 am)	T + 14	T + 16	T + 24				
Cohort 2: IGC-AD1 (2.5mg THC & 1.5mg melatonin) Administered at or about T=8:00 a.m. (after breakfast, time is for illustration)								
Draws same day (hrs.)	T-15 minutes	T + 1	T + 2	T + 2.5	T + 3	T + 3.5	T + 4	T + 5

PK Studies



Results:



Effects of polymorphism of CYP2C9 on PK of THC Metabolism

THC	Mean over All	Mean over *1/*1	Mean over *1/*2	Mean over *1/*3
No. Patients	N=10	Normal (n=4)	Intermediate (n=4)	Intermediate (n=2)
T1/2(h)	3.60	1.73	3.75	7.10
Tmax(h)	2.15	2.38	2.13	1.75
Cmax(ng/ml)	2.01	2.60	1.46	1.93
AUClast (h*ng/ml)	5.58	6.72	4.20	6.06
AUCinf (h*ng/ml)	8.92	9.04	7.24	11.22

Effects of polymorphism of CYP2C9 on PK of OH-THC Metabolism

OH-THC	Mean over	Mean over *1/*1	Mean over *1/*2	Mean over *1/*3
No. Patients	N=10	Normal (n=4)	Intermediate (n=4)	Intermediate (n=2)
T1/2 (h)	3.30	2.98	3.35	3.84
Tmax(h)	1.90	1.75	2.00	2.00
Cmax(ng/ml)	4.30	3.53	3.35	7.73
AUClast (h*ng/ml)	17.03	12.30	12.51	35.53
AUCinf (h*ng/ml)	21.60	16.40	17.73	39.75

- Puerto Rican AD patients had 62% CYP2C9 polymorphism; 54% were intermediate metabolizers (*1/*3 and *1/*2) and 38% were normal metabolizers.
- Intermediate metabolizers (*1/*3 and *1/*2) had altered THC metabolism leading to longer THC half-lives compared with normal metabolizers (*1/*1).

Conclusion:

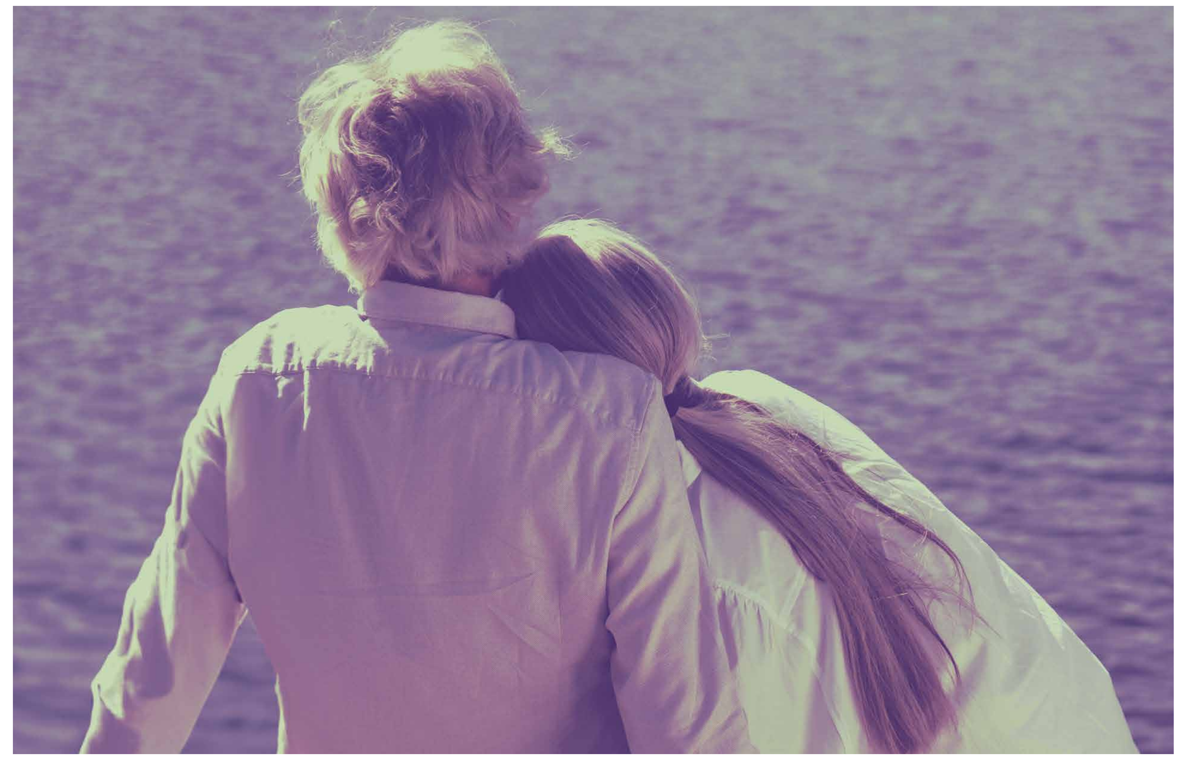
Puerto Rican population have high incidence of intermediate metabolizers compared to normal metabolizers.

Polymorphisms in CYP2C9 can lead to accumulation of THC and its' active metabolite as well as prolonging its' elimination.

There is a need for future studies to explore the presence of CYP2C9 polymorphisms in diverse populations. And to explore further impact on the pharmacokinetics.

Disclosure of Funding:

This study was Funded by IGC Pharma, LLC.



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