Effect of CYP2C9 Polymorphism on Neuropsychiatric Symptoms in Alzheimer's Dementia

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Takeaway message: CYP2C9 gene polymorphism does not influence the effect of the medication IGC-AD1, a combination of THC and melatonin, in the reduction of the NPI-12 scores in patients with Alzheimer's.

Background:

Alzheimer's Disease (AD) is a neurodegenerative disease that affects millions of people worldwide[1]. Individuals with AD are often prescribed medications to manage comorbidities, but Inter-individual variability in medication response may lead to adverse drug reactions. Many drugs are metabolized by the enzyme CYP2C9[2,3].

CYP2C9 gene is highly polymorphic and impacts how a drug is metabolized[4] and affects the drug's concentration in blood, leading to different drug effects[3,4]. CYP2C9 contributes to the metabolism of many compounds, including Δ-9-tetrahydrocannabinol (THC)[2]. We present data on the influence of CYP2C9 polymorphism in reducing the total scores of the Neuropsychiatric Inventory (NPI-12) following the administration of IGC-AD1, which comprises of THC and melatonin, in participants with

Methodology:

Participants: 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, IGC-AD1 was administered once a day (QD), twice a day (BID), and three times a day (TID), respectively, for 14 days (EOT) (Fig. 1). There was a 4-day minimum washout period between cohorts.

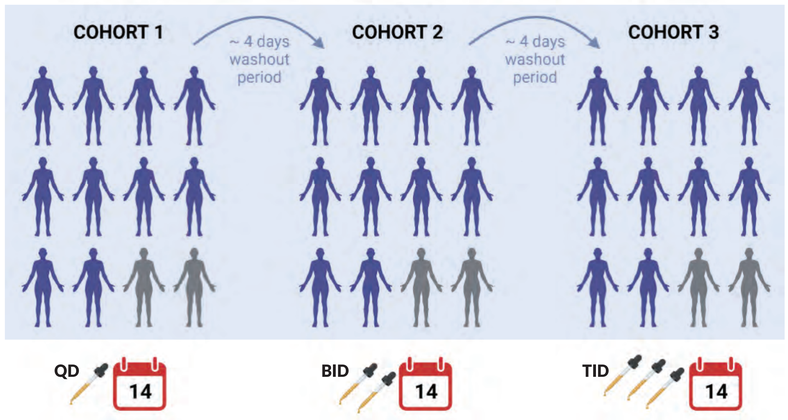


Figure 1. Phase 1 clinical trial implementation. Purple indicates the number of active participants and gray the number of placebo participants.

Genotyping: All participants were evaluated for CYP2C9 polymorphism and grouped based on their respective phenotypes. Blood samples were shipped and evaluated at Invitae Corporation, CA., USA. The assay was performed on a Mass ARRAY Analyzer 4 Instrument to determine the polymorphic sites of interest. A MALDI-TOF mass spectrometry was used to identify the distinct mass of the extended primer that identifies the single nucleotide polymorphisms alleles in the samples.

Statistical analysis: Wilcoxon matched-pairs signed-rank test and student t-tests were used to independently compare differences between mean NPI-12 scores at baseline and EOT for each CYP2C9 (normal or intermediate) metabolizer Phenotype. For all three cohorts, active participants NPI-12 scores differences were grouped depending on whether the reduction was clinically significant (≥ 30% from baseline) or not. Odds ratios were calculated odds to evaluate the strength of the association between the CYP2C9 metabolizers and the score reductions.

Results:

Altogether, there were statistically significant reductions from baseline to EOT in the IGC-AD1 active groups (Cohort 1: t(9) = 3.256, p = 0.01, 46.98% reduction; Cohort 2: V= 42, p = 0.024, 55.86% reduction; Cohort 3: V = 35, p = 0.042, 49.38% reduction).

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 or 2.

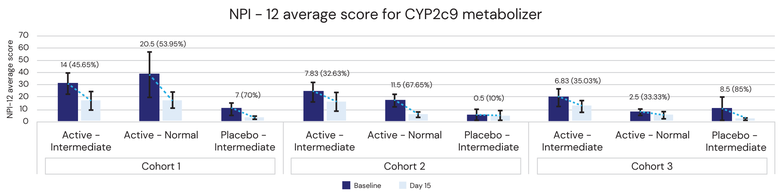
Separated by CYP2C9 Phenotype: Genotyping revealed that 40% of active participants expressed *1/*1 normal CYP2C9 variant, 40% expressed *1/*2 intermediate CYP2C9 variant, and 20% expressed *1/*3 intermediate variant. Placebo participants, on the other hand, all expressed the intermediate CYP2C9 variants *1/*11, *1/*2, and *1/*3.

Participants with normal (*1/*1) and intermediate (*1/*2, *1/*3, and *1/*11) CYP2C9 variants were grouped into their metabolizer phenotypes. No placebo participants presented normal metabolizer phenotypes (table 1).

Table 1. NPI Agitation Scores for All Cohorts on Day 0 and Day 15. Difference between Day 15 and Day 0, Percentage of Reduction and statistical tests by CYP2C9 metabolizer.

Cohort	Treatment	CYP2C9 Phenotype	N	Day 0 ± SD	Day 15 ± SD	Difference ± SD	95% CI Difference	% Reduction	Test: Normal vs Intermediate	Test Intermediate: Active vs Placebo
1	Active	Intermediate	6	30.67 ± 20.78	16.67 ± 18.74	14 ± 6.57	(9.2, 18.8)	45.65%	W = 10, p = 0.761	W = 9.5, p = 0.314
	Placebo	Intermediate	2	10 ± 7.07	3 ± 1.41	7 ± 5.66	(1.46, 12.54)	70%		
	Active	Normal	4	38 ± 36.87	17.5 ± 12.87	20.5 ± 25.95	(-1.53, 42.53)	53.95%		
2	Active	Intermediate	6	24 ± 19.24	16.17 ± 18.32	7.83 ± 12.14	(-1.03, 16.07)	32.63%	t (7.81) = 0.549, p = 0.599	t (5.09) = 1.472, p = 0.199
	Placebo	Intermediate	2	5 ± 7.07	4.5 ± 6.36	0.5 ± 0.71	(-0.19, 1.19)	10%		
	Active	Normal	4	17 ± 10.49	5.5 ± 4.12	11.5 ± 8.96	(3.89, 19.11)	67.65%		
3	Active	Intermediate	6	19.5 ± 17.74	12.67 ± 10.69	6.83 ± 12.24	(-2.11, 15.77)	35.03%	t (6.953) = 0.782, p = 0.46	t (1.76) = -0.17, p = 0.883
	Placebo	Intermediate	2	10 ± 14.14	1.5 ± 2.12	8.5 ± 12.02	(-3.28, 20.28)	85%		
	Active	Normal	4	7.5 ± 5.07	5 ± 6.16	2.5 ± 4.8	(-1.57, 6.57)	33.33%		

Active - Normal vs. Intermediate CYP2C9: Normal metabolizers had a higher total NPI reductions than intermediate metabolizers in Cohort-1 (NPI: Normal = 53.95%, Intermediate = 45.65%) and Cohort-2 (NPI: Normal = 67.65%, Intermediate = 32.64%) but not Cohort-3, were intermediate metabolizers had a similar score reduction compared to normal metabolizers (NPI: Normal = 33.33%, Intermediate = 35.04%) (Fig. 2). However, there were no statistically significant associations between the CYP2C9 active normal and intermediate metabolizers on the NPI-12 scores difference from baseline to EOT (Cohort 1: W = 10, p = 0.7611; Cohort 2: t(7.81) = 0.549, p = 0.599; Cohort 3: t(6.953) = -0.782, p = 0.46).



CYP2C9 Intermediate metabolizers Active vs. Placebo: There were no differences in the score reduction between the active and the placebo participants at any cohort (Cohort 1: W = 9.5, p = 0.314; Cohort 2: t(5.09) = 1.472, p = 0.199; Cohort 3: t(1.76) = 0.17, p = 0.883) (figure 3).

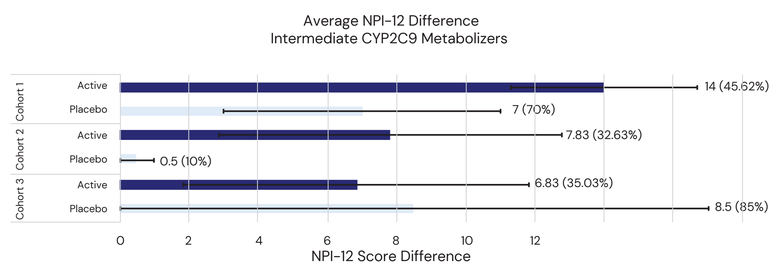


Figure 2. NPI Agitation score differences for CYPC9 intermediate metabolizer active and placebo participants. The labels represent the score reduction and the percentage of reduction. Error bars represent the SE.

Odds ratios

Table 3. Odds ratio for the active group normal and intermediate CYP2C9 metabolizers separated by NPI-12 total score clinically (30%) and not clinically significant reductions.

CYP2C9 Metabolizer	Yes	No	Odds ratio (95%CI)
Cohort 1 – Normal Cohort 1 – Intermediate	3 4	1 2	OR = 0.67 (0.04–11.29)
Cohort 2 – Normal Cohort 2 – Intermediate	3 4	1 2	OR = 0.67 (0.04–11.29)
Cohort 3 – Normal Cohort 3 – Intermediate	2 4	2 2	OR = 2 (0.15–26.73)

Cohort 1 and 2 showed that the odds ratio of an intermediate metabolizer in clinically significantly reducing the NPI-12 was about 0.67 times the odds of normal metabolizers reducing the NPI-12, however, this result is not statistically significant (95%CI = 0.04–11.29). For cohort 3, the odds ratio of an intermediate metabolizer clinically significantly reducing the NPI-12 was 2 times (95%CI = 0.15 – 26.73) the odds of a normal Metabolizer reducing the NPI-12 from baseline to day 15 Nevertheless, this result was not statistically significant (figure 3).

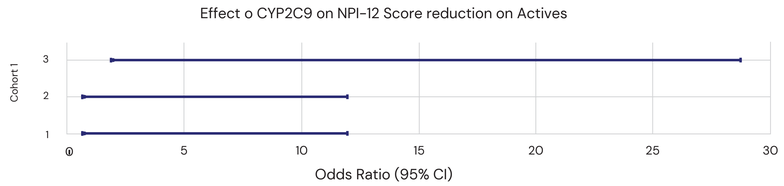


Figure 3. Odds ratio and confidence intervals of the active group normal and intermediate CYP2C9 metabolizers separated by NPI-12 total score clinically (30%) and not clinically significant reductions.

Conclusions:

IGC-AD1 was well tolerated and is potentially efficacious in reducing NPS in AD as measured by the NPI-12. The results indicated that normal metabolizers obtained higher total NPI-12 reductions than intermediate metabolizers after 1 mL and 2 mL administrations; however, with 3 mL, the reduction was similar. A greater number of participants obtained clinically significant reductions in the NPI-12 (≥30%) for all cohorts compared to those who did not. However, when comparing these reductions by metabolizer in the active group, it is not likely that changes in NPI score reductions is due to the CYP2C9 metabolizer profile. The metabolizer effect should be further explored with a larger sample.

Disclosure:

This study was funded by IGC Pharma, LLC.

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SCAN ME

Exploring the Safety and Tolerability of IGC-AD1 in Alzheimer's Patients: Insights from CYP2C9 Polymorphism Assessment

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Takeaway message: IGC-AD1 is safe and well tolerated. No Serious Adverse Events occurred and there were no significant differences in the incidence of AEs between the two CYP2C9 phenotypes (Intermediate metabolizers and normal metabolizers).

Background:

Alzheimer's disease (AD) affects millions of Americans, with potential future increases without breakthroughs in treatment. IGC-AD1 is a novel formulation currently in Phase 2 trial as a treatment for agitation in Alzheimer's dementia.

Delta-9-Tetrahydrocannabinol ("THC"), one of its active pharmaceutical ingredients is metabolized predominantly by CYP2C9.[1] This enzyme is involved in the metabolism of nearly 25% of clinically used drug such as some antihypertensives and Nonsteroidal anti-inflammatory drugs.[2,3]

Due to its genetic polymorphisms, this enzyme has multiple phenotypes classified as normal ("IM"), intermediate ("NM") and poor metabolizers ("PM"). The differences between phenotypes can result in the alteration of the expected effect and potency of certain drugs.[4]

Some polymorphisms are more frequent in some ethnicities as shown in table 1:

Table 1. Ethnicities with the highest frequency of main CYP2C9 alleles[5]

Allele	CYP2C9*2	CYP2C9*3	CYP2C9*5	CYP2C9*8
Ethnicity	American Caucasian	South Asians	African American	
Frequency	14.7%	11.7%	1.6%	4.7%

Note: The functional status of mentioned alleles is decreased enzymatic function

Similarly, phenotype frequency varies depending on the region. For instance Puerto Rico has a broadly mixed population including European, Native American and African ancestries.[6] It is characterized by having a greater African contribution than other Hispanics, making it a special population that may harbor some rare genetic variants at CYP2C9.[7] As shown in **Figure 1**, Puerto Rico is one of the ethnogeography groups in the American Continent with a greater percentage of IM (over 14%).

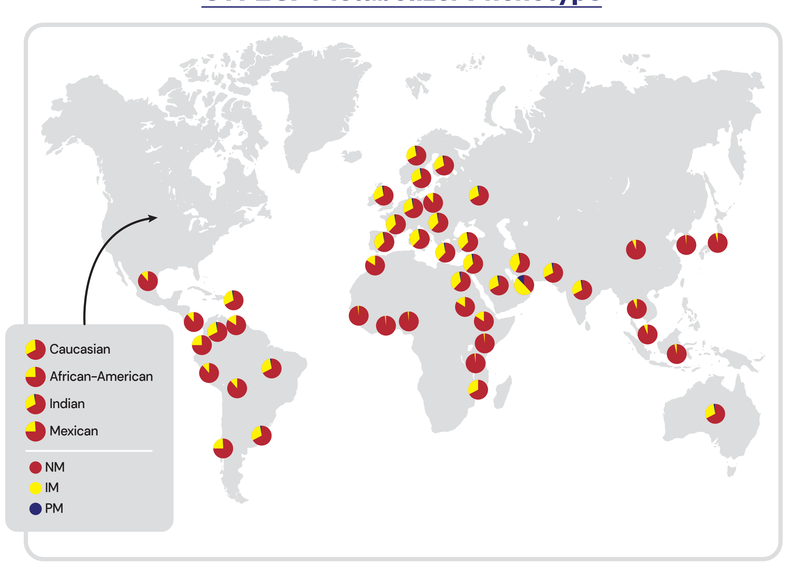


Figure 1. Regions distribution of CYP2C9 metabolizer phenotypes[8]
Note: Pie charts display the percentage of normal metabolizer (green), intermediate metabolizer (orange) and poor metabolizer (red) for representative countries.
Figure adapted from Zhou et al with permission from Yitian Zhou[8]

The results of the CYP2C9 genotyping from the Phase 1 MAD trial Puerto Rican participants, and its phenotype relationship with the incidence of Adverse Events are presented next.

Methods:

Thirteen Puerto Rican AD patients participated in a three-cohort MAD, Phase-1 safety, and tolerability trial (IND146069, NCT04749563). In Cohorts 1, 2, and 3, one mL of IGC-AD1 was administered QD, BID, TID, respectively, for 14-days, with a minimum washout period of 4-days between cohorts **(Figure 2)**. For each cohort constituted by 10 active and 2 placebo participants.

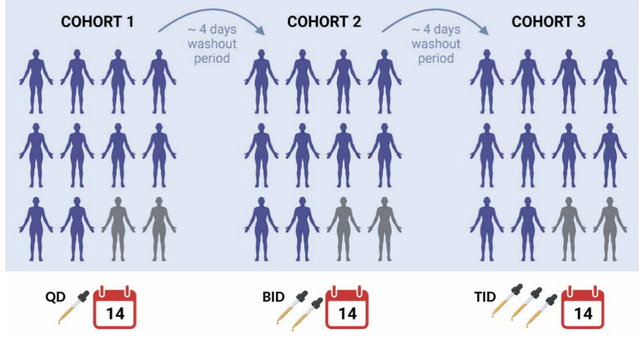


Figure 2. Phase I clinical trial timeline. Purple indicates the number of active participants, and gray indicates placebo participants per cohort in the trial.

Blood samples taken at screening were shipped to Invitae Corporation, CA., USA. They were analyzed using Mass ARRAY Analyzer 4 instrument, a locus-specific polymerase chain reaction followed by mass-modified dideoxynucleoside terminators of an oligonucleotide primer annealing just upstream of the polymorphic site of interest. MALDI-TOF mass spectrometry was used to determine the unique mass of the extended primer that identifies the allele of the single nucleotide polymorphism.

Genotyping results from active participants of all Cohorts were grouped by phenotype (PM, IM, and NM) following CYP2C9 Diplotype Phenotype table published by Clinical Pharmacogenetics Implementation Consortium.[9] **Table 2** shows the main Diplotypes found in Latins and Africo-Caribeans.

Table 2. Phenotypes of the main Diplotypes in Latin and Africo-Caribbean biogeographical groups[9]

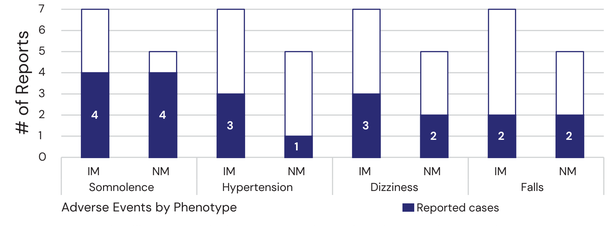
Phenotype	Diplotype							
Poor metabolizers	*2/*3	*2/*6	*2/*15	*2/*25	*2/*42	*3/*3	*3/*4	*3/*5
	*3/*6	*3/*8	*3/*11	*3/*12	*3/*13	*3/*15	*3/*25	*3/*42
	*3/*44	*3/*45	*4/*6	*4/*13	*4/*15	*4/*25	*42/*44	*42/*45
		*44/*45				*45/*45		
Intermediate metabolizers	*1/*2	*1/*3	*1/*4	*1/*5	*1/*6	*1/*8	*1/*11	*1/*12
	*1/*13	*1/*15	*1/*25	*1/*42	*1/*44	*1/*45	*2/*2	*2/*4
	*2/*5	*2/*8	*2/*9	*2/*11	*2/*12	*2/*44	*3/*9	*4/*4
	*4/*5	*4/*8	*4/*9	*4/*11	*4/*12	*5/*5	*5/*8	*5/*9
	*5/*11	*5/*12	*5/*44	*6/*9	*8/*8	*8/*9	*8/*11	*8/*12
	*8/*44	*9/*11	*9/*12	*9/*13	*9/*15	*9/*25	*11/*11	*11/*12
		*11/*44			*12/*12		*44/*44	
Normal metabolizers		*1/*1			*1/*9		*9/*9	

The Incidence of Solicited Adverse Events (somnolence, hypertension, dizziness and falls) was assessed by phenotype group. Chi-squared was used to compare differences between them (SPSSv.28).

Results:

Out of twelve active participants, seven were IM (diplotype *1/*2 = 4, diplotype*1/*3 =3) and five were NM (diplotype *1/*1 = 5). Both groups presented Adverse Events ("AEs") as follows: somnolence (IM: 57%; NM: 80%, p=0.63), hypertension (IM: 43%; NM: 20%, p=0.50), dizziness (IM: 43%; NM: 40% p=0.94) and falls (IM: 29%; NM: 40% p=0.74). **Figure 3** shows the number of reports of the Solicited AEs by phenotype and **Table 3** summarizes the obtained results.

Figure 3. Frequency of Solicited Adverse Events by Phenotype



Note: The silhouettes of the bars represent the total number of patients per phenotype and the filled part the frequency of each Solicited AEs per phenotype.

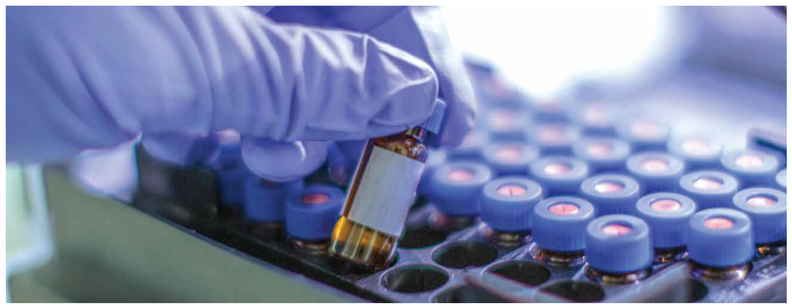
Table 3. AEs incidence rated by phenotype

Phenotype	Diplotype	Number of patients	Incidence of Solicited AEs (count)%							
			Somnolence		Hypertension		Dizziness		Falls	
			Count	%	Count	%	Count	%	Count	%
Intermediate metabolizers (N=7)	*1/*2 *1/*3	4 3	4	57.1%	3	42.9%	3	42.9%	2	28.6%
Normal metabolizers (N=5)	*1/*1	5	4	80.0%	1	20.0%	2	40.0%	2	40.0%
p-value	N/A	N/A	0.63		0.50		0.94		0.74	

Conclusion:

There were 58.3% intermediate metabolizers, and 41.7% normal metabolizers. Out of the 7 intermediate metabolizers, 4 presented *1/*2 diplotype and 3 presented *1/*3. There were no significant differences in the incidence of AEs between the two IM and NM CYP2C9 phenotypes. This suggests that IGC-AD1 is safe, well tolerated, and its safety profile remains stable between these two CYP2C9 phenotypes.

This study has a limited sample size. It is recommended to continue studying the possible impact of the CYP2C9 polymorphism on the THC metabolism, and its safety profile in a larger trial. IGC Pharma is addressing this through its ongoing Phase 2 trial assessing the safety and efficacy of IGC-AD1 in treating agitation in Alzheimer's dementia.



Disclosure of Funding:

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Blood samples were processed by Invitae Corporation, CA., USA.

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SCAN ME

Pharmacokinetic Effects of combination therapy of Delta-9-Tetrahydrocannabinol and Melatonin compared to monotherapy in Elderly Population

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Takeaway message: Relative bioavailability and peak plasma concentrations of Delta-9-tetrahydrocannabinol and melatonin in the elderly population increase when administered together compared to separate administration.

Background:

THC-based therapies have gained interest in treating different ailments in the elderly population, including severe or chronic pain, sleep disturbances, and more recently Alzheimer's Disease1. This raises the importance of understanding the influence of age on the pharmacokinetics ("PK") of Delta-9-tetrahydrocannabinol ("THC").

IGC-AD1 comprises THC at a low concentration combined with melatonin. In this sense, the PK of THC/Melatonin co-administration acquires importance since employing both drugs might affect the baseline PK, which is critical to understanding possible changes because of renal or hepatic failures and accurately adjusting doses to ensure the safety of those drugs.

No literature available has studied any drug interaction between THC and melatonin and the influence over the drugs' absorption, or their pharmacokinetics profiles. However, it has been reported that Melatonin is absorbed mainly by the transcellular route, and in less extension through paracellular or P-gp mediated absorption2. On the other hand, cannabinoids are thought to be absorbed primarily in a transcellular way, however, limited information is found regarding this behavior3, while some suggest reflux pumps influence the molecules' systemic absorption.

Methods:

Data on combination therapy IGC-AD1 is presented from a Phase 1 Multiple Ascending Dose ("MAD") study (n=10 active; Puerto Rican), cohorts 1 and 2 on AD patients. Pharmacokinetic parameters Cmax and Area under the curve (AUC) were analyzed by Northeast Biolabs. To obtain data regarding monotherapy of THC and Melatonin, a literature review was performed, as described in Table 1.

Table 1. Parameters employed for literature review to obtain pharmacokinetic data for THC and Melatonin monotherapy.

Databases	Search terms	Inclusion criteria
•ScienceDirect •PubMed •CAS •SpringerLink •Google Scholar	•"Absorption" •"Pharmacokinetics" •"Transporter" •"Intestinal" •"Elderly" •"Melatonin" •"Cannabinoid" •"THC" or "Tetrahy-drocannabinol"	•Nature of the research: PK analysis •Languages: English and Spanish •Age of participants: >49 years old •No temporal inclusion-exclusio criteria were considered. •Disclosure of the following data: ◦ Dose ◦ Cmax ◦ AUC

Given that pharmacokinetic parameters such as Cmax, are related to the maximum reached concentration, and the area under the curve (AUC), that provides a clear notion about the THC bioavailability. These parameters were normalized relative to the dose $\left(\frac{C_{max}}{dose\ (mg)}\right)$ and $\left(\frac{AUC}{dose\ (mg)}\right)$ respectively.

To assess the effect of combination therapy of THC and melatonin compared to monotherapy of both API, a regression analysis was performed comparing the trend of bioavailability (measured as the area under the curve (AUC)).

Additionally, a t-test was performed between the peak plasma concentration reached after oral administration of THC and Melatonin administered alone (literature) and in combination (IGC-AD1).

Results:

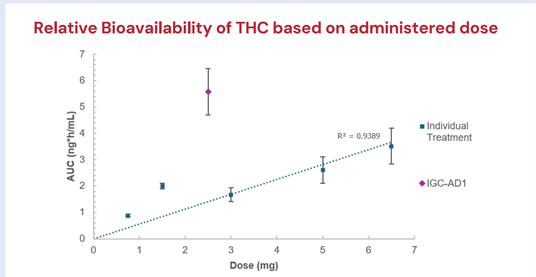
A total of 2 studies were found to disclose key melatonin PK parameters, and 2 studies were found to disclose key THC PK parameters in Elderly patients healthy and with dementia. The results are summarized in table 2.

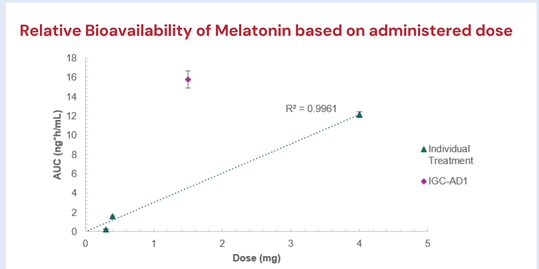
Table 2. Pharmacokinetic parameters of delta-9-THC and Melatonin, administered together and alone.

THC				
Study	**Dose (mg)**	**AUC (h*ng/mL)**	**C_{max} (ng/mL)**	**Sample Size**
IGC-AD1	2.5	5.58 (±2.78)	2.01 (±1.19)	n = 10
Ahmed A. I. A. et al. (2014).	0.75	0.88 (±0.46)	0.41 (±0.23)	n = 98
	1.5	2.01 (±1.04)	1.01(±0.42)	
Ahmed A.I. et al. (2015).	3	1.67 (±0.87)	1.42 (±0.89)	n = 11
	5	2.61 (±1.64)	3.15 (±1.61)	
	6.5	3.51 (±2.25)	4.57 (±2.46)	
Melatonin				
IGC-AD1	1.5	10.04 (±1.19)	15.77(±8.78)	n = 10
Gooneratne N. S. et al. (2012).	0.4	1.60 (±0.37)	0.41(±0.09)	n = 7
	4.0	12.12(±0.2.27)	4.00 (±0.70)	
Zhdanova I. V. et al. (1998).	0.3	0.25 (±0.21)	0.26 (±0.15)	n = 10

Considering the data found, the regression analysis was performed for Melatonin relative bioavailability in elderly patients taking oral melatonin, and elderly patients taking IGC-AD1; for THC relative bioavailability, data from healthy elderly patients and elderly patients with dementia taking oral THC, and elderly patients with dementia taking IGC-AD1 was considered. The regression analysis shows that joint administration of THC and Melatonin in IGC-AD1 increases the relative bioavailability when compared to single administration of both active ingredients, as evidenced with figures 1 and 2.

Figures 1 and 2. Relative bioavailability of THC and Melatonin administered alone or together (IGC-AD1).



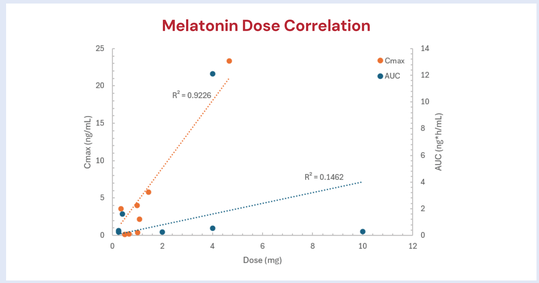


THC data suggests that the AUC values for IGC-AD1 are significantly higher when considering the administered dose. Unlike THC, melatonin does not evidence a strong correlation between AUC and dose, even for results taken from the same study.

Among the data collected, no clear correlation is found between the Area Under the Curve (AUC) data, while it is on Peak Serum Concentrations. This variation may be due to common changes in serum concentrations due to the influence of endogenous melatonin, but C_{max} is directly related to the exogenous administered dose.

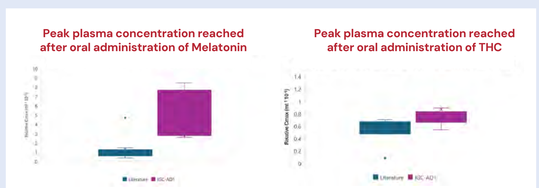
Thus, suggesting C_{max} as a key parameter to understand de relationship between the absorption and the dose for melatonin.

Figure 3. Correlation between administered dose, and C_{max} or AUC based on literature available data for melatonin therapy.



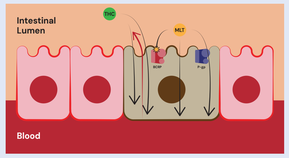
When considering the relationship between the administered dose and $\left(\frac{C_{max}}{dose\ (mg)}\right)$ of the co-administered THC, 0.0008, is significantly higher than other reported PK data for oral cannabis administration 0.0003 (p = 0.0103). Co-administered melatonin (6.95) is significantly higher than other reported PK data for oral melatonin administration 0.954 (p=0.0129).

Figures 4 and 5. Relative peak plasma concentrations of THC and Melatonin administered alone (Literature) and together (IGC-AD1).



When administered jointly, the observed behavior is probably related to many factors that may influence the pharmacokinetic profile of melatonin and THC. On the one hand, THC absorption is reportedly affected by the BCRP (Breast Cancer Related Protein) transporter, which may induce THC molecule efflux.[4] Besides it, has been demonstrated in vitro that melatonin induces reduced expression of BCRP transporters, while also affecting its function through epigenetic mechanisms.[5]

Figure 6. Intestinal transporter BCRP interaction scheme for THC and Melatonin coadministration[2,3]



Another important factor is the changes in gastrointestinal motility since THC has been reported to induce delayed gastric emptying, delayed colonic transit, and diminished post-prandial colonic tone, which elevates the drugs' intestinal transit (exerted through the BC1 receptors located in intestinal epithelial cells). Additionally, melatonin is reported to reduce the contraction forces on the ileum, by inhibiting among others, enteric sympathetic neurons, and stimulating the activity of cholecystokinin. Those factors enhance both drugs' absorption.

Figure 7. Gastrointestinal motility changes due to the active compounds administration.

Conclusion:

The analysis suggests that melatonin when administered jointly with THC could play a significant role in THC absorption and PK. We hypothesize that the higher reported dose-dependent absorption of THC may be related to the effect of melatonin in gastrointestinal transporters and efflux pumps.

Additionally, melatonin absorption may be improved by joint administration because of gastrointestinal motility pattern alterations induced by THC.

To overcome the limitations of the current study, more studies are warranted, including a more ethnically diverse population, and a greater study group. Additionally, the effect of concomitant medication and basal gastrointestinal diseases were not considered.

Disclosure of funding:

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SCAN ME

Exploring the Impact of IGC-AD1 on Serum Potassium Levels in Alzheimer's Disease: Insights from a Phase I Trial

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POSTER #: 95358

Takeaway message: Serum Potassium levels can serve as a blood-based diagnostic tool for Alzheimer's disease ("AD"). We present a theory that by identifying the reduction of this biomarker in blood serum post-treatment, IGC-AD1 may be prospectively considered to be a potential disease-modifying medication.

Background:

Alzheimer's disease is a progressive neurodegenerative disorder that primarily affects the elderly population.[1] There are several medications that can modify the disease progression or treat symptoms, but as of now, Alzheimer's has no cure.[2]

Physicians currently determine if a patient suffers from AD by combining diagnostic tools such as medical history, neurological, cognitive, functional, and behavioral tests, computerized cognitive exams and devices, brain imaging (MRI, CT, PET), and cerebrospinal fluid (CSF) or blood tests.[3]

IGC Pharma conducted a Phase I multiple ascending dose ("MAD") clinical trial (ClinicalTrials.gov ID NCT04749563) that explored the safety of the investigational drug IGC-AD1 for AD patients. The investigational drug's active pharmaceutical ingredients ("API"s) are delta-9-tetrahydrocannabinol ("THC") and melatonin.

This study investigates the impact of the liquid oral formulation IGC-AD1 (Figure 1), a combination comprising of low concentrations of THC and melatonin, on blood serum potassium levels in patients with AD.

Figure 1. Bottles of IGC-AD1 liquid formulation

IGC-AD1 and blood-potassium level:

Studies in non-rodent animal models showed a reduction in the serum potassium level following a 13-day subcutaneous administration (3 - 100 mg/kg daily) of THC to rabbits.[4] After THC oral administration in baboons (0.275 g – 1.38 g daily for four months), serum potassium level also decreased.[5]

Clinical studies have shown that after administering 5 mg of melatonin orally daily, for four days, plasma potassium level was not altered compared to the control group.[6]

Loss of intracellular compartmentalization of potassium is a characteristic of AD pathology, with supporting studies indicating significantly lower potassium level in intracellular compartments of AD brains and an associated increase in serum potassium level in AD subjects. Here, we present preliminary data from a Phase I trial of AD patients administered with IGC-AD1.[7]

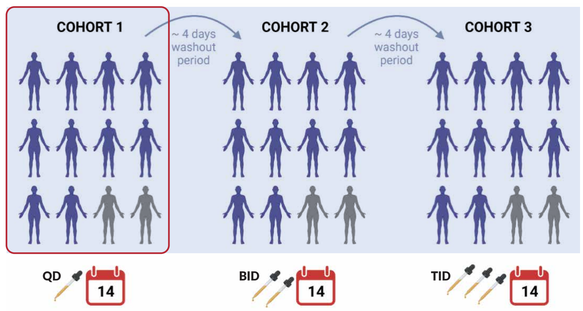
Neuropathological AD hallmarks include accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles.[8] Studies have shown that Aβ accumulation in a brain area induces K+ efflux in cortical cultures of double-transgenic APP/PS1 Göttingen minipigs.[9] This correlates with the decreased potassium levels in AD brains as A β accumulation progresses in the disease.

Methods:

Thirteen Puerto Rican patients (mean age: 80.18 ± 6.22 years, 70% women) diagnosed with mild (15.38%) to moderate (84.62%) AD (NIA-AA criteria and clinical history) participated in a three-cohort Phase I trial with MAD for safety and tolerability. Cohorts 1, 2, and 3 received 1 mL of IGC-AD1 once a day, twice a day, or thrice a day, respectively, for 14 days ("EOT"), followed by a washout period between each cohort, as observed in Figure 2. Blood draws occurred at baseline, day 5, day 10, and day 14, as shown in Figure 3. Blood chemistry analysis was made in central lab Marie-E, Bayamón, Puerto Rico, US.

Wilcoxon and t-tests (two-tailed) were used to analyze the serum potassium levels in the active (n=9) and placebo participants (n=2), comparing results from baseline and EOT in cohort 1 of the Phase I trial.

Figure 2. Phase I clinical trial timeline.



Note. Purple indicates the number of active participants, and gray indicates placebo participants per cohort in the trial.

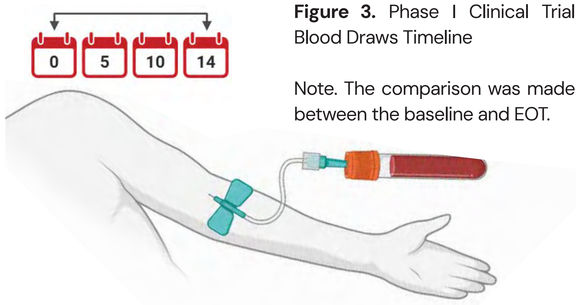


Figure 3. Phase I Clinical Trial Blood Draws Timeline

Note. The comparison was made between the baseline and EOT.

Results:

The analysis showed that participants from active (n=9) and placebo (n=2) groups began the study with no significant differences in serum potassium level at baseline (Active: 4.38 mmol/L, Placebo: 4.65 mmol/L, W = 6.5, p= 0.63) (Table 1, Figure 4).

After an independent comparison of the serum potassium levels in the active and placebo groups in cohort 1, a statistically significant decrease was observed in levels from baseline (4.38 mmol/L) to EOT (4.16 mmol/L) on active medication (V = 44, p=0.013), while no differences were identified in participants on placebo (Baseline: 4.65 mmol/L and EOT: 4.70 mmol/L; t(1) = -0.2, p=0.874) (Table 1, Figure 5 and 6).

At EOT, participants from active (n=9) showed a significantly lower level of serum potassium compared to placebo (n=2) (Active: 4.16 mmol/L, Placebo: 4.70 mmol/L, t(5.84) = -3.18, p = 0.019) (Table 1, Figure 7).

Figure 4. Serum Potassium Level at Baseline comparing Active (n=9) vs Placebo (n=2).

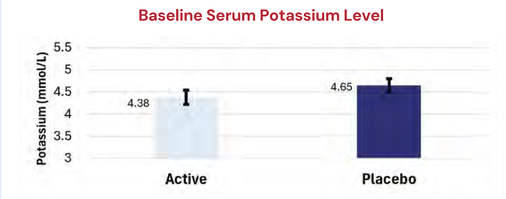


Figure 5. Serum Potassium Level in Active Group (n=9) comparing Baseline vs EOT.

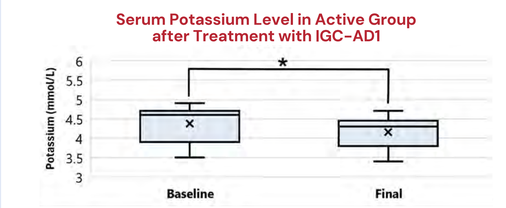


Figure 6. Serum Potassium Level in Placebo Group (n=2) comparing Baseline vs EOT.

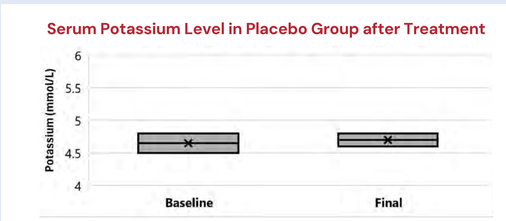


Figure 7. Serum Potassium Level at EOT comparing Active (n=9) vs Placebo (n=2).

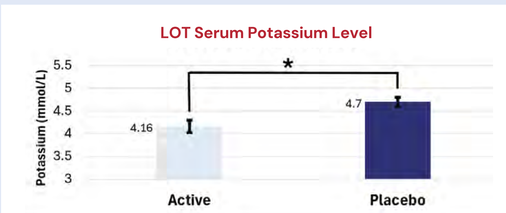


Table 1. Cohort 1 Serum Potassium Levels

Cohort 1		Baseline	EOT	EOT-Baseline Difference	Test / p-value
Active (n=9)	Blood Serum Potassium	4.38 ± 0.49	4.16 ± 0.42	0.22 ± 0.17	V = 44/ p = 0.013
Placebo (n=2)	Blood Serum Potassium	4.65 ± 0.21	4.70 ± 0.14	-0.05 ± 0.35	t(1) = -0.2/ p = 0.874

Discussion and Conclusions:

Findings for this Phase I study postulate potassium as a potential blood-based AD diagnosis biomarker that could provide a more robust overview for diagnosing AD from blood. Future imaging studies using radioactive potassium tracers could be explored for diagnosis, as well as the relationship with other blood-based biomarkers such as plasma p-tau217, which is the current valid blood-based biomarker that can accurately identify biological AD, comparable to CSF biomarker.[10]

The study provides insights into the potential of IGC-AD1 as a disease-modifying medication, given the preliminary data showing a reduction in serum potassium level in AD subjects post-treatment and considering the relationship between Aβ accumulation and decreased potassium levels in AD brains.

-We expect the ongoing Phase II and the subsequent Phase III of the clinical trial, with a larger sample size and a longer duration, will provide a more comprehensive understanding of the relationship between serum potassium level and the administration of IGC-AD1, as well as the medication's possible correlation with AD.

Disclosure of funding:

This study was funded by IGC Pharma, LLC.

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SCAN ME

Assessing Sleep Hours in Participants with Alzheimer's Disease: Findings from a Phase I MAD Study with IGC-AD1

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POSTER #: 95667

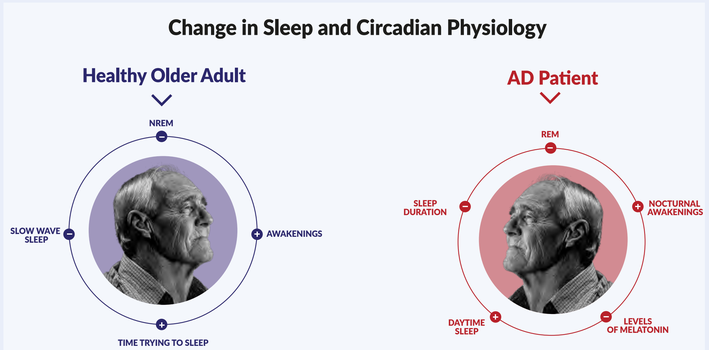
Takeaway message: Sleep disturbances are highly prevalent in the Alzheimer's disease (AD) population, and melatonin is a commonly used treatment. However, higher doses of melatonin may cause side effects such as drowsiness and sleepiness. Evidence regarding THC is inconclusive, with current dosing limitations. IGC-AD1 a combination of THC and melatonin, did not induce excessive sleepiness across three doses. Instead, with two doses, patients tended to fall closer to the recommended sleep range without additional sleepiness.

Background:

Sleep Disturbances

- Sleep disturbances are prevalent in AD, affecting up to 45% of patients according to research[13,14]. Frequent sleep problems in AD include waking up often (23%), waking up too early (11%), feeling very sleepy during the day (10%), and taking long daytime naps (over 1 hour, 14%)[15]. Advanced sleep phase disorder ("ASPD") is also common in this population, characterized by difficulty staying awake until the desired bedtime and maintaining sleep until the desired wake time[15].
- Worsening sleep disruption along the disease course is associated with greater cognitive decline, negatively impacts quality of life, increases caregiver burden, and causes early institutionalization[4].

Figure 1 Sleep Disturbances in elderly and AD patients



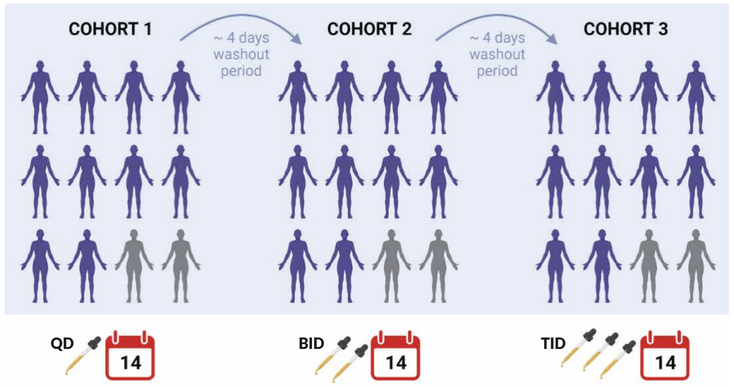
IGC-AD1 and Sleep

- IGC-AD1 comprising delta-9 tetrahydrocannabinol ("THC") and melatonin has not been studied before for sleep disturbances, but there are studies for each of the two active pharmaceuticals.
- Changes in melatonin levels are linked to sleep disruptions and sundowning in AD patients. Melatonin shows promise in improving sleep, sundowning symptoms, likely due to its protective effects against Aβ-mediated neurodegeneration[11,12], but higher doses might cause drowsiness, sleepiness, feelings of vigor, among other side effects[5,6].
- While cannabis may initially improve sleep onset[9], these benefits might disappear with chronic use and disrupt REM sleep[10]. These effects are not well documented for specific cannabinoids like THC in AD patients, though some evidence suggests short-term sleep improvements[9].

Methods:

- Data is presented from a Phase 1 Multiple Ascending Dose ("MAD") trial. The trial enrolled thirteen patients with mild (15.4%) to moderate (84.6%) AD according to NIA-AA criteria (10-active, 2-placebo (Fig. 2), 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 with a minimum of 4-days washout between cohorts.

Figure 2 Phase I clinical trial Cohorts and Doses



- Sleep duration (time elapsed between sleep onset and wake up) and nocturnal awakenings were assessed via caregiver reports in the Study Partner Log every day along with daily safety phone calls to ensure safety and compliance.
- Average sleep hours and nighttime awakenings for each cohort were calculated over the 14-day drug intake, then by cohort and treatment group. The data were analyzed through statistical methods including normality tests (Shapiro-Wilk), the Friedman test for within-group comparisons of sleep duration medians across days, and Mann-Whitney U tests to compare sleep duration between active and placebo groups on each day.

Discussion and Conclusion:

- Despite the sleep-promoting properties of melatonin (a component of IGC-AD1), this study did not observe a consistent increase in sleep duration across cohorts following IGC-AD1 administration compared to placebo. Notably, one cohort even displayed a decrease in sleep duration. These findings suggest that IGC-AD1's impact on sleep patterns requires further investigation.
- The analysis showed an average sleep duration between 7.9 and 8.9 hours across all cohorts for the active groups. Established sleep duration categories (short: ≤6 hours, normal: 7-8 hours, long: ≥9 hours)17 by the National Sleep Foundation can be used as a reference for further analysis, indicating that most of our participants fall into the normal and long sleep duration categories. Public health recommendations advise 7 to 8 hours of sleep for older adults[16]. While further investigation is necessary to determine the impact of IGC-AD1 on sleep duration, the current data show a trend where participants in the active group tend to fall closer to the recommended sleep range compared to the placebo group in cohorts 2 and 3.
- Although significant results were not found for nighttime awakenings, the active groups across cohorts showed fewer awakenings. This finding requires further exploration due to the impact of sleep fragmentation on both AD patients and their caregivers.
- This is a small phase 1 trial, and the findings may not generalize to larger populations. Future studies should include objective measures of sleep, such as polysomnography or actigraphy, to gain a more comprehensive understanding of IGC-AD1's effects on sleep.

Disclosure of Funding: This study was Funded by IGC Pharma, LLC.

Results:

Variations in average sleep duration across cohorts were observed.

- Cohort 1 showed average sleep hours of (8.97) (±SD 1.50) (active) and (8.77) (±SD 0.22) (placebo). Cohort 2 was (8.11) (±SD 0.79) (active) and (9.43) (±SD 0.86) (placebo). And Cohort 3 averages of (7.90) (±SD 0.72) (active) and (9.24) (±SD 0.85) (placebo). In Cohorts 2 and 3, the active group consistently sleeps less than the placebo group on average. However, in cohort 1 the two groups appear to be sleeping almost the same amount, witch the placebo group averages slightly less sleep.

Figure 3 Cohort 1 Estimated Marginal Means

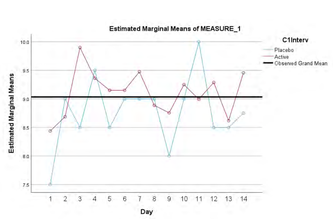


Figure 4 Cohort 2 Estimated Marginal Means

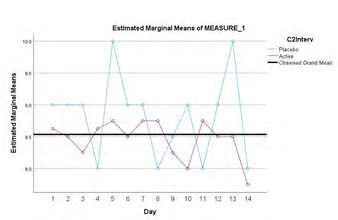
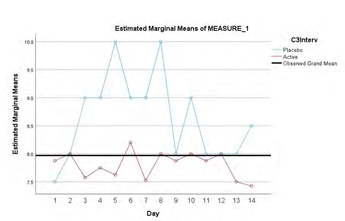


Figure 5 Cohort 3 Estimated Marginal Means



Sleep data Within Cohorts

- **Cohort 1:** Sleep duration in the active group (8.97) showed slightly greater variability compared to the placebo group (8.77). Neither the Friedman test (p=0.279) nor the Mann-Whitney U tests (all p>0.05) revealed significant differences in sleep duration between active and placebo groups across the 14 days for QD.
- **Cohort 2:** In Cohort 2 the active group (8.11) showed a lower average sleep duration compared to placebo (9.43 . The Mann-Whitney U tests identified no significant differences between groups on most days (all p>0.05, except one).
- **Cohort 3:** Similar to Cohort 2, the active group (7.90) averaged less sleep compared to placebo (9.24). The Friedman test (p=0.685) and the Mann-Whitney U tests (all p>0.05) revealed no significant differences in sleep duration between groups across the 14 days,

Nighttime awakenings were also registered throughout the 14-days of the study. The impact of the intervention on waking probability varies over time, suggesting daily fluctuations but no significant differences between interventions in all three cohorts. There's insufficient evidence of a time-varying effect of the intervention.

- In Cohort 1, the active group averaged (6.7) awakenings per night compared to (7.5) for placebo.
- Cohort 2 in the active group displayed a lower average number of nightly awakenings (4.5) compared to placebo (5.0).
- Similarly, Cohort 3 showed an average of (7) awakenings per night in the active group and (8.5) awakenings in the placebo group.

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SCAN ME

Evaluation of the Impact of IGC-AD1 on Hepatic Biomarkers in a Phase I Clinical Trial for the Treatment of Agitation in Alzheimer's Disease

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[a. IGC Pharma LLC, Potomac, USA, b. SCB Research Center, USA, CA,]

POSTER #: 95744

Takeaway message: The treatment with the oral solution IGC-AD1, a combination of THC and Melatonin, in patients with Alzheimer's disease does not exert adverse effects on liver function.

Background:

IGC-AD1 comprises of Delta-9-Tetrahydrocannabinol ("THC") and melatonin in a liquid formulation. IGC-AD1 is currently in a Phase 2 trial (clinicaltrials.gov: NCT04749563). The two active pharmaceuticals have been studied for their neuroprotective properties. In this analysis we studied multiple dosing of IGC-AD1 in Alzheimer's ("AD") populations vulnerable to hepatic complications. We present the impact of three different doses on hepatic functions, offering insights into dosage-dependent safety and potential therapeutic implications.

Introduction:

The evaluation of liver functions through biomarkers such as aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and bilirubin levels, is important in clinical trials to ensure the safety of pharmacological treatments[1]. Drug-induced liver injury (DILI) is a leading cause of drug withdrawal from the market and clinical failures, making it imperative to monitor hepatic effects when administering any new medication.

In neurodegenerative diseases such as AD, patients are particularly susceptible to adverse effects due to their age, comorbidities, and the polypharmacy often required to manage their symptoms[3]. Given this vulnerability, rigorous monitoring of liver health becomes crucial. The biomarkers AST, ALT, ALP, and bilirubin are particularly significant as they provide a quantifiable measure of liver health and are sensitive indicators of liver injury, a common concern with many drugs[4]. These enzymes and biochemicals are released into the bloodstream when liver cells are damaged, serving as an early warning system to detect potential toxic effects before serious harm occurs.

The Drug-Induced Liver Injury Network (DILI) developed a 5-point scale for grading the severity of liver injury. The grades for the severity of liver test abnormalities of liver injury have been developed and standardized and are used in many publications of clinical trials and studies of new medications. Grade 1 indicates mild, Grade 2 moderate, and Grade 3 severe and Grade 4 life-threatening. However, it should be stressed that these terms usually overestimate the severity of drug-induced liver injury, as ALT levels of 5 to 20 times the upper limit of normal (~400 to 800 U/L) without symptoms or jaundice cannot be considered severe hepatotoxicity and should instead be referred to as "Grade 3 ALT elevations"[5].

Hepatocellular injury, detected by increased serum alanine aminotransferase (ALT) activity, is found in subjects participating in clinical trials, if serum ALT activity is greater than 5 times the upper limit of the normal range (3ULN) or if >33ULN with total bilirubin concentration (TBL) >23 LSN. In the absence of other causes, the finding can probably be considered to be induced by the investigational medication.[6]

Methods:

This Phase I, three-cohort, multiple-ascending-dose (MAD) clinical trial involved 13 patients diagnosed with mild (15.4%) to moderate (84.6%) Alzheimer's disease (AD). The study aimed to evaluate the safety and tolerability of IGC-AD1 (IND146069, NCT04749563). The participants' mean age was 81.5 ± 5.5 years, 9 women and 4 men.

For each of the three cohorts the trial participants were 10 patients on active medication and 2 on placebo.

In cohorts 1, 2, and 3, one milliliter of IGC-AD1 was administered once daily (QD), twice daily (BID), and three times daily (TID), respectively, over a 15-day treatment period with a minimum of 4 days washout between cohorts.

Laboratory testing:

For each of the three cohorts, blood samples were collected at baseline, day 10, and at day 15 (EOT). Each sample was analyzed for hepatic biomarkers.

Statistical analysis:

Using Microsoft Excel, descriptive statistics were calculated for each biomarker (ALT, AST, ALP, BT) including standard error with 95% confidence intervals. These were then grouped by cohort and intervention.

Results and discussion:

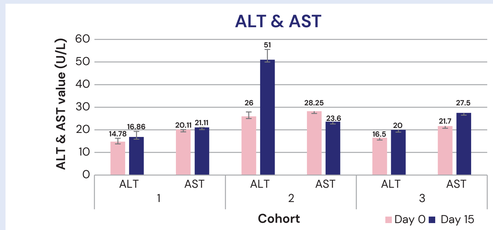
Differences between baseline and Day 15 by enzyme

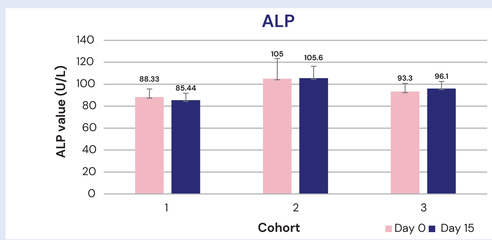
			Cohort 1 (n=9)					Cohort 2 (n=5)					Cohort 3 (n=10)				
	Enzyme	Reference value*	Day 0 Mean (SD)	Day 15 Mean (SD)	Difference (D15 - D0) Mean (Change %)	SD	95% CI	Day 0 Mean (SD)	Day 15 Mean (SD)	Difference (D15 - D0) Mean (Change %)	SD	95% CI	Day 0 Mean (SD)	Day 15 Mean (SD)	Difference (D15 - D0) Mean (Change %)	SD	95% CI
ACTIVE	ALT	7.0-50.0 (U/L)	14.78 (4.52)	16.86 (7.36)	2.11 (21.71)	6.01	(-5.81, 1.59)	26 (0)	51(0)	25 (17.83)	4.79	(-5.88, 1.38)	16.5 (6.08)	20 (14.48)	3.5 (17.86)	9.73	(-9.22, 2.22)
	AST	9.0-40 (U/L)	20.11 (5.28)	21.11 (4.76)	1 (12.7)	2.74	(-2.69, 0.69)	28.25 (23.93)	23.6 (13.26)	4.65 (11.99)	11.9	(-4.09, 10.09)	21 (8.33)	25.9 (16)	4.2 (15.38)	9.89	(-10.01, 1.61)
	ALP	35-130 (U/L)	88.33 (21.96)	85.44 (19.08)	2.89 (4.76)	4.34	(0.21, 5.56)	105 (41.36)	105.6 (24.06)	0.6 (8.53)	18.5	(-14.83, 13.63)	93.3 (23.52)	96.1 (20.11)	2.8 (6.22)	5.57	(-6.08, 0.48)
	Total Bilirubin	0.1-1.2 (mg/dL)	0.43 (0.13)	0.4 (0.19)	0.03 (23.84)	0.14	(-0.06, 0.11)	0.37 (0.12)	0.42 (0.14)	0.05 (22.56)	0.13	(-0.13, 0.03)	0.37 (0.12)	0.42 (0.14)	0.05 (35.51)	0.13	(-0.13, 0.03)

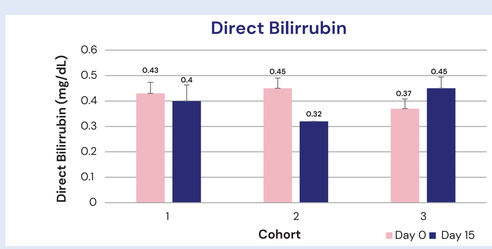
			Cohort 1 (n=2)					Cohort 2 (n=1)					Cohort 3 (n=2)				
	Enzyme	Reference value*	Day 0 Mean (SD)	Day 15 Mean (SD)	Difference (D15 - D0) Mean (Change %)	SD	95% CI	Day 0 Mean (SD)	Day 15 Mean (SD)	Difference (D15 - D0) Mean (Change %)	SD	95% CI	Day 0 Mean (SD)	Day 15 Mean (SD)	Difference (D15 - D0) Mean (Change %)	SD	95% CI
PLACEBO	ALT	7.0-50.0 (U/L)	16.5 (4.95)	17 (4.24)	0.5 (3.85)	0.71	(-1.19, 0.19)	26 (0)	34 (0)	8 (15.38)	0	(-8.0, -8.0)	19 (5.66)	26 (14.14)	7 (31.59)	8.49	(-15.32, 1.32)
	AST	9.0-40 (U/L)	22.5 (6.36)	22.5 (6.36)	0 (0)	0	(0.0, 0.0)	22 (0)	21 (0)	1 (2.27)	0	(1.0, 1.0)	21.5 (3.54)	27.5 (3.54)	6 (31.03)	7.07	(-12.93, 0.93)
	ALP	35-130 (U/L)	81.5 (45.96)	58 (36.77)	3.5 (8.17)	7.78	(-4.12,11.12)	89 (0)	94 (0)	5 (2.80)	0	(-5.0, -5.0)	64.5 (44.55)	67.5 (51.62)	3 (7.19)	7.07	(-9.93, 3.93)
	Total Bilirubin	0.1-1.2 (mg/dL)	0.55 (0.07)	0.5 (0.04)	0.05 (8.83)	0.03	(0.02, 0.08)	0.32 (0)	0.34 (0)	0.02 (3.12)	0	(-0.02, -0.02)	0.39 (0.06)	0.28 (0)	0.07 (10)	0	(0.07, 0.07)

*Taken from: ABIM Laboratory test Reference Ranges-January 2024. American Board of Internal Medicine.

Summary of the tables showing mean values by enzyme







Cohort 1: The findings showed that for Cohort 1, ALT, AST, ALP, and total bilirubin decreased in all participants (active and placebo) between Day 0 and Day 15, but this change was neither clinically nor statistically significant.

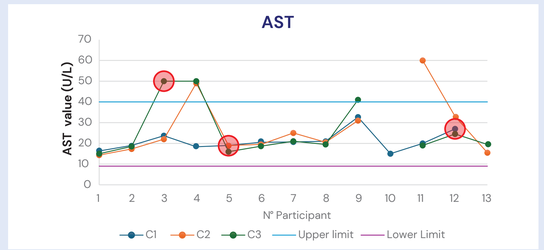
Cohort 2: For Cohort 2, the mean value of ALP showed a significant variation that began on Day 0 and persisted until Day 15 in both the active and placebo groups, exceeding the upper limit in the active group.

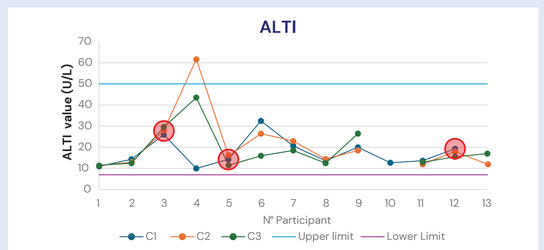
Cohort 3: In Cohort 3, the variation returned to normal values (Cohort 2, Active = 105.6 U/L, Placebo = 94 U/L; Cohort 3, Active = 96.1 U/L, Placebo = 67.5 U/L). The other biomarkers did not show significant changes, and the population in this cohort was reduced to n=5 for the active group and n=1 for the placebo group. For Cohort 3, the mean value of the difference between Day 15 and Day 0 increased for all biomarkers (ALT, AST, ALP, and total bilirubin); however, this increase was not significant and did not exceed the upper limit in any case, with the increase being more pronounced in the placebo group than in the active group.

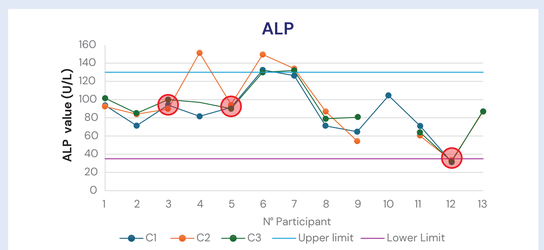
Comparing Cohorts 1 and 3, all biomarkers (ALT, AST, ALP, and total bilirubin) showed a slight increase in both active and placebo groups without exceeding the upper limit, and these increases were not significant.

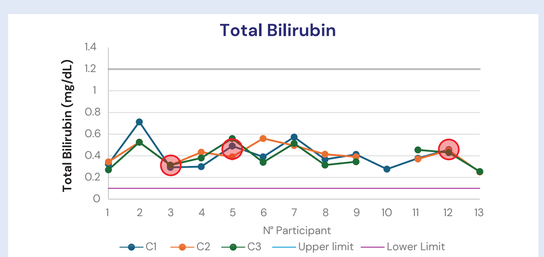
All data show that both the placebo and active groups increased across cohorts in all biomarkers (ALT, AST, ALP, and total bilirubin) without exceeding the upper limit value, except for the mean ALP in the active group in Cohort 2 (Cohort 2, Active = 105.6 U/L). Although it exceeded the upper limit, it stabilized again in Cohort 3 and was never clinically high since it never exceeded three times the upper limit value, which is the reference indicating DILI to determine if any of these biomarkers' values are clinically high.

Graphs values per enzyme between upper and lower limit









The behavior of AST values for both active and placebo groups across the three cohorts were consistent within the reference limit values, except for patient 4 in Cohort 2 (C2-P4 = 50 U/L) and patients 3 and 4 in Cohort 3 (C3-P3 = 50 U/L, P4 = 49 U/L), who exceeded the upper limit. The ALT values for both active and placebo groups across the three cohorts showed a slight increase; however, they did not exceed the reference limit values, except for patient 4 in Cohort 2 (C2-P4 = 151.3 U/L). The ALP values for both active and placebo groups across the three cohorts were consistent within the reference limit values, except for patients 4 and 6 in Cohort 2 (C2-P4 = 151.3 U/L, P6 = 149 U/L), who exceeded the upper limit without significant impact. The total bilirubin values were consistent between the active and placebo groups across all three cohorts and remained within the reference values. Despite two patients exceeding the upper reference values for AST, ALT, and ALP in Cohort 2, they did not exceed three times the reference value, which according to DILI specifications, does not classify as clinically high AST.

Therefore, all the values obtained for all biomarkers (ALT, AST, ALP, and total bilirubin) during this study are considered normal, and no significant differences were observed between the active and placebo groups.

Conclusion:

According to this safety clinical trial, the findings suggest that treatment with IGC-AD1 in patients with Alzheimer's disease does not exert adverse effects on liver function. Although two patients showed values for the biomarkers AST, ALP, and ALT slightly above their respective reference limits, these values were not three times higher than the reference values, and thus, according to DILI, they are not considered high. Based on this, albeit limited, trial, it is concluded that all biomarkers had values within ranges considered normal and remained stable across the three cohorts of the study, with no significant differences between the placebo and active groups. This supports the safety of this medication in elderly patients with AD. IGC Pharma continues to monitor this data in the larger (n=146) Phase 2 trial.

Disclosure of Funding:

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SCAN ME

Effect of IGC-AD1 on Delusions and Hallucinations as Positive Psychosis Symptoms in Alzheimer's Disease Participants: Phase 1 MAD Trial Results

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POSTER #: Sunday-789

Takeaway message: IGC-AD1, an oral solution combining THC and melatonin, demonstrated safety and tolerability in AD participants, along with a clinically significant reduction in positive psychotic symptoms, such as hallucinations and delusions as measured by the NPI-12.

Introduction:

Psychosis is a set of symptoms or experiences that disrupts the connection with reality and the ability to distinguish what is real.[1] These symptoms are categorized into two groups: positive and negative symptoms. Positive symptoms add to the typical human experience, such as disorganized speech or thoughts, delusions and hallucinations.[1] Negative symptoms diminish aspects of normal functioning, such as lack of motivation, reduced expression of emotion, social withdrawal or a decline in role functioning.[1]

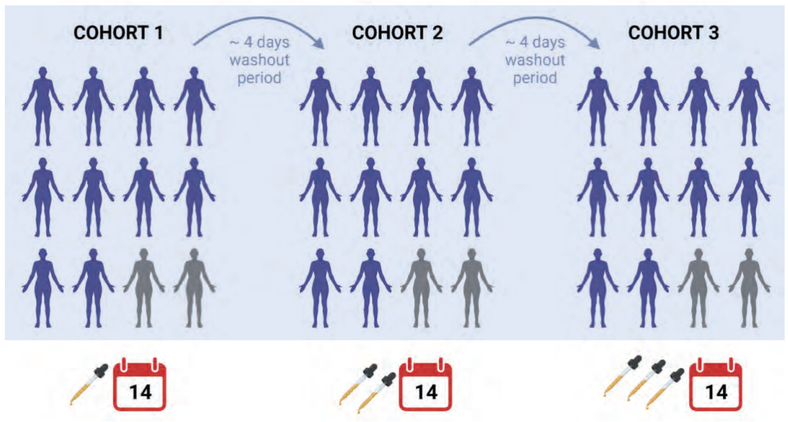
Psychosis is a common neuropsychiatric symptom in patients with Alzheimer's disease (AD), affecting approximately 30% to 50% of patients.[2,3] Psychosis in AD consists of hallucinations and delusions that appears following cognitive impairment.[4,5] These symptoms are associated with hospitalization or institutionalization, cognitive and functional impairment, accelerated cognitive decline, increased mortality, and caregiver distress.[2]

Research in young people suggests that cannabis use increases the risk of psychotic episodes.[1] Multiple case reports indicate that individuals may develop psychotic symptoms or disorders after using cannabis.[6,7] Most psychoses were preceded by the ingestion of a large dose of cannabis, with amnesia reported for the period between ingestion and hospitalization.[6] In a meta-analysis, heavy cannabis users had a 4 times higher risk, and average cannabis users had a 2 times higher risk of developing psychotic symptoms compared with nonusers.[1,7]

This association between cannabis use and psychotic symptoms raises safety concerns regarding the use of THC in AD patients, potentially worsening AD-related psychosis or producing psychotic symptoms. Here, we explore preliminary data from the Phase 1 trial of IGC-AD1, an oral solution combining THC and melatonin, on psychiatric symptoms as measured by the NPI delusions and hallucinations domain in participants with AD.

Methods:

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



• 13 patients (81.5±5 years, 69.2% female) diagnosed with mild to moderate Alzheimer's disease were included in a three-cohort, phase-1 Multiple-Ascending-Dose (MAD) trial to evaluate the safety and tolerability of IGC-AD1 (IND146069, NCT04749563).

• In Cohorts 1, 2, and 3, one milliliter of IGC-AD1 was administered QD, BID, and TID, respectively, for 14-days (EOT) with a 4-day minimum washout period between cohorts (Figure 1). For each cohort there were 10 active and 2 placebo participants.

• For each cohort, only participants who had scores greater than 0 in the delusions or hallucinations domains of the NPI-12 at baseline were considered, with these domains taken as symptoms of psychosis. Active participants with delusions/hallucinations at baseline were as follows: 5 in Cohort-1, 2 in Cohort-2, and 3 in Cohort-3. In Cohort-2, one placebo participant experienced hallucinations on Day 10. NPI-12 was administered at baseline (Day 1), at Day 10 and at EOT (Day 15). Solicited Adverse Events, Unsolicited Adverse Events, and vital signs were monitored daily.

• Descriptive statistics summarized the data. The Shapiro-Wilk Test was used to determine normality. A paired t-test or a Wilcoxon signed-rank test were used to compare the difference between Baseline-Day 10 and Baseline-EOT for each cohort (SPSS v.28).

Results:

Both the delusions and hallucinations domains did not increase, they showed a significant reduction across all cohorts, although this reduction was not statistically significant. The difference in NPI Delusions scores between Day 0 and Day 15 for all three cohorts was clinically significant (>30%), detailed in Table 1. Similarly, cohorts 1 and 2 demonstrated a clinically significant reduction in NPI Hallucinations scores. Cohort 3 showed stable hallucination scores throughout, with an increase on day 10 returning to baseline by EOT, as detailed in Table 2.

Patients with psychosis symptoms at baseline did not experience worsening of delusions or hallucinations; instead, a clinically significant reduction was mostly observed. In cohort 2, one placebo patient had scores differing from 0 on day 10 but returned to 0 at EOT. Patients not included in this analysis did not exhibit hallucinations or delusions throughout the study (NPI = 0 in those domains).

No serious adverse events, deaths, or dropouts due to adverse events were reported. No major changes in concomitant medications were observed. The results suggest that IGC-AD1 is safe and well-tolerated; likewise, it could be safe in AD patients with delusions or hallucinations, as it does not increase the severity or frequency of these symptoms.

Table 1. Descriptive Statistics and Results for NPI Delusions Domain Scores.

DELUSIONS								
Cohort	N	Day	Mean (SD)	Mean Δ (SD)	95% CI	p-value	% Reduction	Cohen's d
1	5	Baseline	6.6 (3.58)	*	*	*	*	*
		Day 10	4.8 (4.55)	-1.8 (2.49)	(-4.9, 1.3)	0.181	-27	-0.72
		EOT	2.8 (1.64)	-3.8 (2.78)	(-7.3, -0.4)	0.038	-58	-1.37
2	2	Baseline	3.5 (0.71)	*	*	*	*	*
		Day 10	0 (0)	-3.5 (0.71)	(-9.85, 2.85)	0.09	-100	-4.95
		EOT	1.5 (2.12)	-2 (1.41)	(-14.71, -10.71)	0.295	-57	-1.41
3	3	Baseline	4.3 (3.22)	*	*	*	*	*
		Day 10	1.3 (2.31)	-3 (1)	(-5.48, 0.52)	0.035	-55	-3
		EOT	0 (0)	-4.33 (3.22)	(-12.32, 3.65)	0.145	-79	-1.348

Figure 2. NPI Delusion Domain Scores at baseline, Day 10 and EOT for All Cohorts.

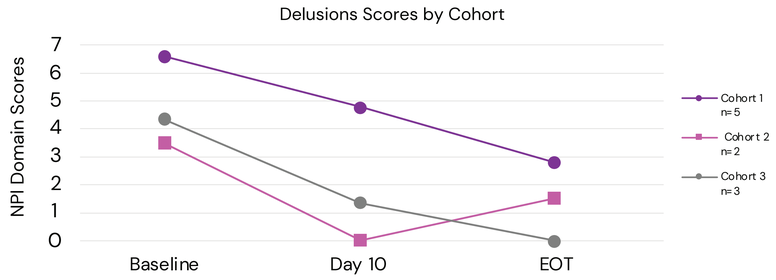
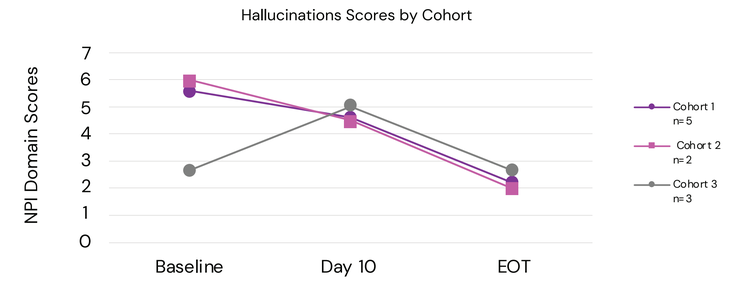


Table 2. Descriptive Statistics and Results for NPI Hallucinations Domain Scores

HALLUCINATIONS								
Cohort	N	Day	Mean (SD)	Mean Δ (SD)	95% CI	p-value	% Reduction	Cohen's d
1	5	Baseline	5.6 (4.78)	*	*	*	*	*
		Day 10	4.6 (5.18)	-1 (2.66)	(-4.29, 2.29)	0.446	-18	-0.38
		EOT	2.2 (2.05)	-3.4 (2.97)	(-7.08, 0.28)	0.062	-61	-1.15
2	2	Baseline	6 (2.83)	*	*	*	*	*
		Day 10	4.5 (2.12)	-1.5 (0.71)	(-7.85, 4.85)	0.205	-25	-2.12
		EOT*	2 (2.83)	-4 (0)	0	0.157	-67	-
3	3	Baseline	2.7 (4.62)	*	*	*	*	*
		Day 10	5 (2.65)	-2.33 (2.08)	(-2.84, 7.50)	0.192	87	1.12
		EOT*	2.7 (4.62)	0	0	1	0	-

Figure 2. NPI Hallucinations Domain Scores at baseline, Day 10 and EOT for All Cohorts.



Conclusions:

IGC-AD1, a combination of THC and melatonin for oral administration, was safe, well-tolerated, and did not cause serious or severe adverse events. The delusions and hallucinations scores, as measured by the NPI, indicate that IGC-AD1 may be safe for Alzheimer's patients with positive psychotic symptoms such as hallucinations and delusions. It did not increase or worsen the severity of these symptoms in patients who had them at baseline and did not cause these symptoms in patients who did not have them at the beginning of the study.

Contrary to other findings related to cannabis use, we observed a clinically significant reduction in both NPI domains, hallucinations and delusions, approaching statistical significance in some cases. These results warrant further analysis in a larger trial. Currently, IGC Pharma is conducting a multicenter, randomized, double-blind, placebo-controlled Phase 2 clinical trial to address those needs and investigate the efficacy of IGC-AD1 in treating agitation in Alzheimer's patients.

Disclosure of Funding:

This study was funded by IGC Pharma, LLC.

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SCAN ME

Neurobiological Alterations in Agitation in Alzheimer's Disease and potential therapeutic intervention

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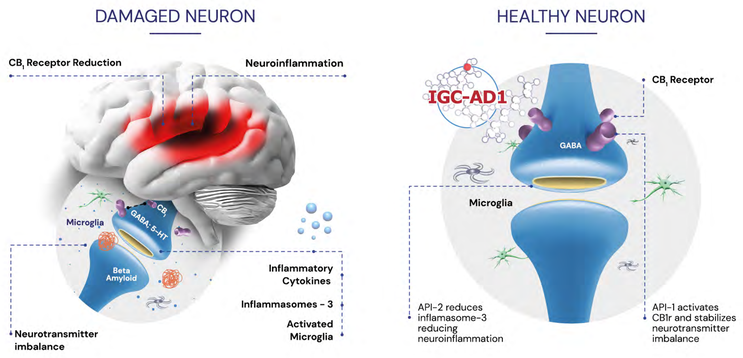
POSTER #: 0000

Takeaway message: IGC-AD1 was safe and well tolerated. No Serious Adverse Events occurred and there were no significant differences in AE incidence between the two CYP2C9 phenotypes IM and NM.

Background:

- Agitation in Alzheimer's disease is a complex behavioral phenomenon that significantly impacts the health care system and has a negative impact on people with Alzheimer's disease (AD).
- According to reports, 60% of people with mild cognitive impairment experience agitation, and 76% are prevalent in AD (Mussele et al., 2015).
- The underlying mechanism of agitation in AD is not well understood. However, several preclinical and clinical studies support the idea that several altered cellular processes have been linked to it.
- **Agitation Pathology:**
  These include increased neuroinflammation in particular AD brain regions (Yasuno et al., 2023), the participation of inflammasomes -3 (Yu et al., 2023), decreased cannabinoid receptor (CB1r) functionality, and gamma amino butyric acid (GABA) neurotransmitter imbalances in the brain (Lindenmayer, 2000).
- **Preclinical studies:**
  Several preclinical studies have indicated that CB1r, a partial agonist, delta-9-tetra cannabinol (D-9 THC), and melatonin have neuroprotection against animal models of aggressive behavior. These compounds target pathways that are known to alter agitation/ aggressive behavior.
- Studies have demonstrated that deficits in the GABAergic and serotonergic functions are associated with agitation in AD (Lindenmayer, 2000). CB1r agonists regulate the release of GABA by activating the CB1r in rats (Gonzalez et al., 2009) as well as may stabilize the impaired functionality of 5-HT1A and 5-HT2A/C receptors reported in CB1r KO mice (Mato et al., 2007).
- Animal aggression has been linked to the inflammatory response triggered by the NLRP3 inflammasome (Yu et al., 2023). An investigation conducted on animals revealed that the inflammatory response triggered by the NLRP3 inflammasome played a role in the aggressive behavior that the resident intruder paradigm elicited in mice (Yu et al., 2023). Melatonin and THC, CB1r partial agonists, that suppress the NLRP -3 activity in vitro models (Suryavanshi et al., 2022; Arioz et al., 2021). Thus, suggesting a potential path for therapeutic interventions.
- CB1r knockout mice display aggressive behaviors, but the administration of the CB1r agonist Arachidonyl-2' - chloroethylamide (ACEA; 2 mg/kg) to these mice has been shown to decrease their aggression behavior significantly (Rodriguez-Arias et al., 2013). It is also important to note that studies on AD patients have shown decreased hippocampal CB1r density (Manuel et al., 2014). Activation of CB1r by its agonist could be a potential therapeutic intervention for aggressive behavior (Figure-1).
- **Clinical evidence:**
  Several off-label studies on synthetic D-9 THC revealed a significant reduction in agitation behavior in AD patients (Walther et al., 2011; Woodward et al., 2014; Hermann et al., 2019). Further, collected off-label clinical trial studies on melatonin doses between 3 mg to 10mg for 10 days to 35 months treatments showed beneficial effects against agitation (Joseph BlaisMonica et al., 2014).
- Currently, repurposed antipsychotic drugs have been approved to treat these conditions. However, it is associated with the BlackBox warning. There is an urgent need for newer therapeutic drugs are necessary, to address the unmet agitation condition in AD.

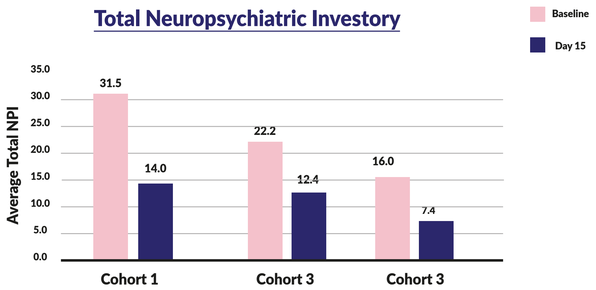


Methods:

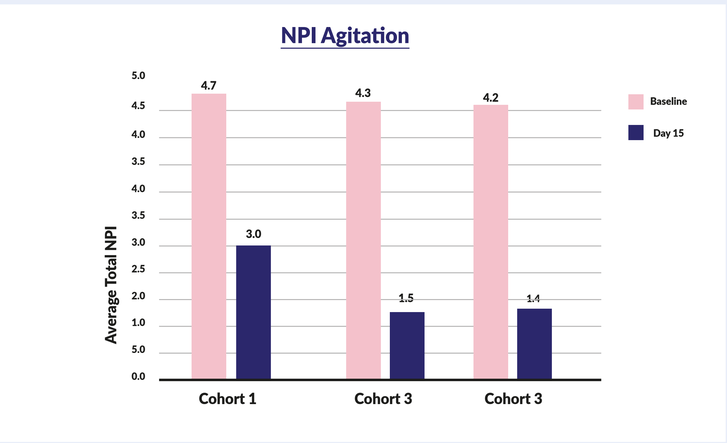
Twelve Puerto Rican patients (mean age: 80.18 ± 6.22 years, 70% female) with mild (15.38 percent) to moderate (84.62 percent) AD (based on clinical history and NIA-AA criteria) took part in a three-cohort Phase I trial using MAD to test safety and tolerability. Cohorts 1, 2, and 3 were administered 1 mL of IGC-AD1 once, twice, or three times daily, respectively, for a period of 14 days. The investigational drug (IGC-AD1)contains active ingredients D-9 THC and melatonin. The formulation was developed based on the proof of the concept derived from preclinical studies and clinical observations. We explored a pilot study on neuropsychiatric symptoms measured by neuropsychiatric Inventory scales (NPI) and agitation behavior in AD patients (n=10). We studied three different doses of IGC-AD1 against the NPI scores.

Results:

Neuropsychiatric Symptoms Measured by NPI Scores



Patients taking IGC-AD1 intervention showed an overall improvement in NPS, and specifically in agitation, anxiety, and depression domains. Caregiver distress improved as well



At three different doses, agitation improved both clinically and statistically ($p < .05$)

Conclusions

IGC-AD1 may bring beneficial effects against agitation in AD by acting on different pathways;

- Activating the CB1r receptor by THC and correcting neurotransmitter balance
- Reducing the neuroinflammation by THC and melatonin.
- Combinational drugs containing THC and melatonin significantly reduced the agitation behavior IN AD patients in two weeks period.
- Future studies involve the mode of action of IGC –AD1 in animal models of aggression and explore neurotransmitter imbalance, inflammation, and CB1r role.

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SCAN ME

Unraveling the complexities of educational and socioeconomic factors in cognitive decline with an AI model.

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POSTER #: 00000

Takeaway message: Socioeconomic risk factors for Alzheimer's Disease (AD) have been extensively studied, with lack of education being recognized as a major contributor. Utilizing AI/ML techniques, we analyzed a Mexican database and identified several corroborated factors, including education, income, rural household status, social contacts, and an unexpected one—the number of grandchildren. The latter appears to be unique, as previous research has identified the number of grandchildren as protective rather than a risk factor.

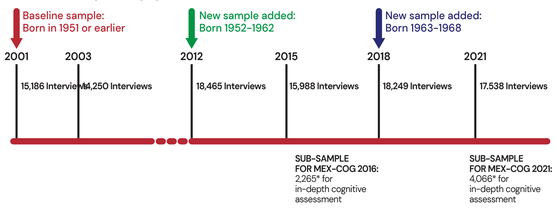
Background:

High formal education level is widely recognized as a protective factor against cognitive decline, influenced by the reserve hypothesis[1]. However, education level is highly related to cultural and socioeconomic status[2]. Low socioeconomic status (SES) has been considered a risk factor for cognitive dysfunction, increasing the risk of developing cognitive impairment by around 24%[3,4]. Therefore, identifying additional factors within SES that predominantly impact cognitive decline can improve early detection of AD and guide implementations of public health policies, aiming to provide increased support for those population groups at higher risk[4]. Artificial Intelligence (AI) has been broadly beneficial in multiple biomedical research areas and finds a particularly advantageous setting in AD. This benefit arises from the global effort dedicated to data collection, not specific to AD, but to the overall aging process. Since AD is a condition intricately linked with aging, it benefits immensely from these rich datasets. Specifically, machine learning (ML) techniques allow for in-depth analyses of large databases to uncover hidden patterns in multidomain data. Longitudinal studies like ELSA[5], MHAS[6], CHARLS[7], LASI[8], HAALSI[9], and HRS[10] that have in-depth cognitive studies enable the assessment of the interplay between social and environmental factors, lifestyle choices, and some health conditions for the development of AD by comparing subjects with similar backgrounds but different diagnosis. Analyzing these datasets through ML might enable the distinction between pathological aging and normal aging with unprecedented precision, allowing the identification of socioeconomic risk factors for AD onset. This research uses Random Forest and Transformer architectures to analyze data from the Mexican Health and Aging Study (MHAS) and the Mexican Cognitive Aging Ancillary Study (Mex-Cog), extracting insights into the most important factors in cognitive decline as measured by the Mini-Mental State Examination (MMSE)[9].

Methods:

The Mexican Health and Aging Study (MHAS) provides longitudinal national-level data on individuals aged 50 and over across six waves from 2001 to 2021, including detailed cognitive assessments (Mex-Cog) in 2016 and 2021 for a subset of the population[9]. MHAS provides information on demographics, health status, insurance, finance and wealth, family structure, employment, retirement and pension, caregiving, stress, end-of-life planning, psychosocial status, and basic cognition. Mex-Cog contains an in-depth cognitive study with the MMSE as one of its principal scores. Mex-Cog has 4245 unique participants, with 796 respondents participating in all five waves of MHAS and both waves of Mex-Cog; we selected this subset to perform our analysis[9].

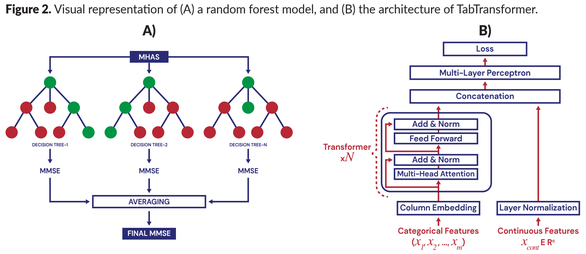
Figure 1. Data collection timeline of the Mexican Health and Aging Study and it's Mexican Cognitive Aging Ancillary Study.



As AI/ML architectures, we used a Random Forest and a Tab transformer:

Random Forest (RF), shown in Figure 2.A is an ensemble learning method composed of the following components: Root Node (Forest Level): The entire dataset is used to grow multiple decision trees, creating a 'forest' of decision trees. Tree Splitting (Tree Level): Each decision tree individually follows the process of dividing nodes into two or more sub-nodes based on certain conditions unique to each tree. Decision Node (Tree Level): When a sub-node in any individual tree divides further into other sub-nodes, it becomes a decision node. Leaf/Terminal Node (Tree Level): Nodes within each decision tree that do not split further, representing the final output or decision for that particular tree. Aggregation (Forest Level): The predictions or decisions of each decision tree are aggregated. For regression tasks, the predictions are averaged[11].

Figure 2. Visual representation of (A) a random forest model, and (B) the architecture of TabTransformer.



Tab Transformer (TabT), shown in Figure 2.B comprises a column embedding layer for categorical features, a stack of N Transformer layers, and a multilayer perceptron. Each Transformer layer consists of a multi-head self-attention layer followed by a position-wise feed-forward layer12. The attention mechanism of the transformer layer allows the model to learn how to accurately associate the input features (variables of each participant) to correctly predict the MMSE value. In this way, the model identifies the most important factors and the relationships between them.

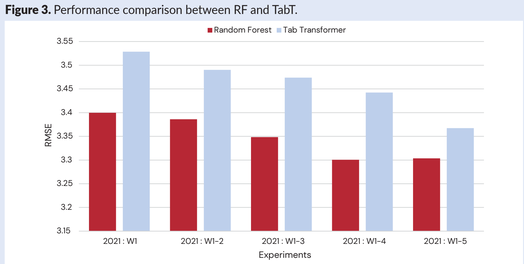
Both models were optimized under a regression framework, optimizing for Root Mean Squared Error (RMSE), equation 1. Data was partitioned in standard ways: 80% of participants for training and 20% for testing. We use Shapley values to assess the importance of each input feature in the prediction of the MMSE value. These values enable to identify the contribution of each individual feature to the output by considering all possible combinations between features' values. If one feature contributes more than another, either in a positive or negative way, its Shapley values will be of greater magnitude. This helps not only to track the general impact of the feature but also the impact of its possible values, e.g., if age is the most important factor when predicting MMSE, then Shapley values also allow to identify if higher or lower ages increase or decrease the score.

$$RMSE = \sqrt{\sum_{i=1}^{n} \frac{(\hat{y}_i - y_i)^2}{n}} \quad (1)$$

Results:

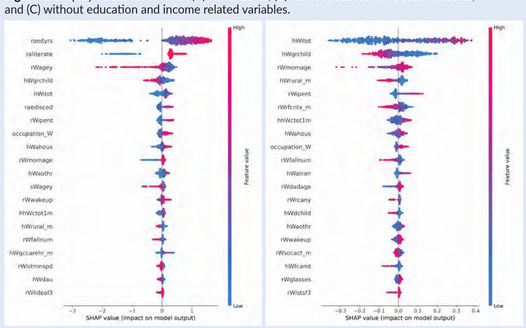
The RF and TabT models predict the MMSE with an error in the range [3.30–3.52] points in RMSE, as shown in Figure 3. In both cases, adding data of multiple waves to predict the MMSE slightly improves the performance; however, it is important to note that using data from 20 years prior, our model can predict the MMSE value with an average error of 3.39 points. The RF outperformed TabT in all experiments. TabT's attention mechanism should identify more precisely the relationships between the features that mainly affect the MMSE and, therefore, achieve higher precision. However, its lower performance compared to the RF can be a consequence of the small dataset size compared to datasets normally used to train these models. For this reason, it would be useful to test pretraining techniques to evaluate its impact on the predictions.

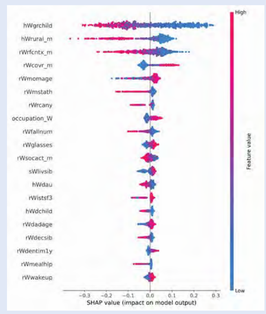
Figure 3. Performance comparison between RF and TabT.



Given the RF's inherent interpretability and superior performance, we utilized this architecture to analyze feature importance. Our analysis reveals that our model accurately identifies crucial variables that have already been identified as risk factors for cognitive decline. For instance, education-related variables emerge as the most important features of the model, as illustrated in Figure 4.A. These features alone can predict the MMSE with an RMSE of 3.485 (Figure 5). However, the addition of more variables slightly enhances the prediction accuracy.

Figure 4. Shapley values for RF with (A) all variables, (B) without education related variables, and (C) without education and income related variables.





By removing the participant's age and education-related variables from the dataset, we aimed to identify additional risk factors. The model identified total income as the next most important factor. The importance of income is further validated by the fact that education and income-related variables together are better predictors of the MMSE score than education alone (Figure 5).

Since low socioeconomic status has already been studied as a risk factor, we proceeded to remove income-related variables from the data and identified the number of grandchildren, household location, and frequency of contact with friends and relatives as the next most important factors. We further used a correlation matrix to verify if those variables have some relationship with both the education and income levels. We found that the three factors have a weak inverse relation to years of education and income, being coefficients lower than 0.38.

The selection of these features by the model could be due to two main reasons. On the one hand, although their correlations with education are not very high, they might still be the highest, and therefore, the model relies on them once education is removed. On the other hand, they might be significant factors for cognitive decline on their own due to the following reasons:

Rural or urban household: Previous research has identified that rural inhabitants may be subject to multiple factors affecting their cognitive condition. Specifically, they may have less intellectually demanding occupations, delayed screening and diagnosis of chronic illnesses, and subsequent poor disease management. Additionally, social activities are generally less prevalent in rural regions, which negatively impacts the cognitive reserve[13].

Frequency of contact with friends and relatives: Our model identified that lower frequencies of contact with friends and relatives result in lower MMSE scores, while higher frequencies result in higher MMSE scores. Previous works show that older populations that participate consistently in social activities are less prone to experience cognitive decline. This can be explained due to the development of a sense of meaning which then results in active self-care activities that help prevent cognitive decline[14]. Also, weak social interactions are a comparable risk factor to AD such as low education[15].

Number of grandchildren: Grandparenting has been studied as a protective factor against cognitive decline in some populations, including the US and Chinese. It is hypothesized that meaningful social interactions and relationships can mitigate age-related cognitive decline. *Therefore, it is unclear why the model associates a higher number of grandchildren with a lower MMSE score. Further analysis of this variable is necessary before drawing conclusions*[16].

Figure 5. Performance comparison using different set of variables for the MMSE prediction with data from wave 1 through 5.

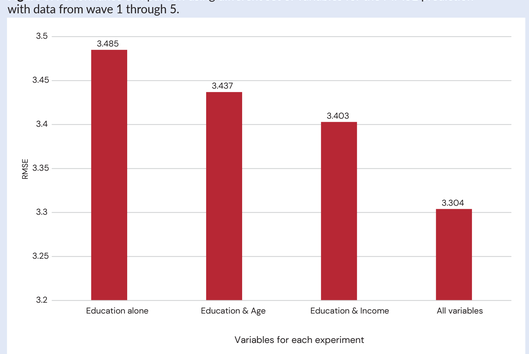
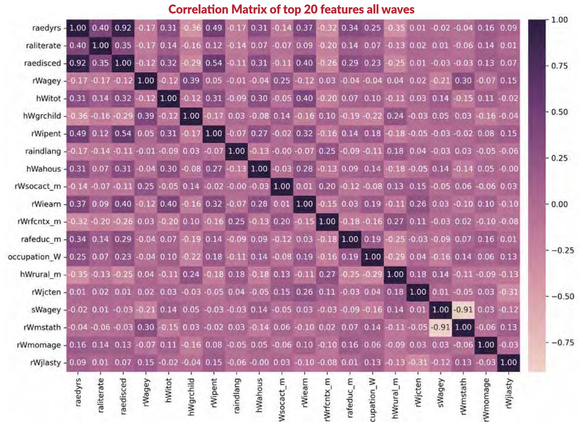


Figure 6. Correlation Matrix of top 20 features used for 2021 MMSE score prediction.



Conclusion:

We developed an AI model that is able to identify risk factors for cognitive decline, by identifying the factors that have more impact on the MMSE score in a Mexican population. Our models' findings align with established literature, independent of any prior knowledge of it. A more in-depth analysis of the features is ongoing to determine whether the model selected values solely due to their relationship with education or if they independently present an increased risk factor for cognitive decline. As future work, we plan to conduct an experiment by removing all variables that exceed a certain correlation threshold with education and income. This will allow us to evaluate what other factors the model uses to predict the MMSE, potentially identifying additional risk factors that are not related to the more commonly studied ones. Additionally, to leverage the transformer's attention mechanism, a pretraining strategy is being developed to compensate for the size of the dataset. This approach would allow the TabT architecture to provide insights into other factors and their relationships in our future work.

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