Background & Preclinical Data

Alzheimer's disease (AD) is a progressive, neurodegenerative disease that impacts memory function and behavior. Approximately 60–90% of patients with AD develop neuropsychiatric symptoms (NPS)[1]. Currently, there is no FDA-approved drug to treat many of the NPS like agitation in AD patients.

Evidence suggests that THC, when used in low doses, could attenuate agitation and anxiety through the modulation of the endocannabinoid system. THC is a partial agonist of Type 1 (CB1) receptors in the brain. CB1 receptors regulate the effect of neurotransmitters involved in anxiety, including serotonin, norepinephrine, and acetylcholine. It also regulates stress hormones, such as cholecystokinin and opioid peptides. THC is also an agonist of the Type 2 (CB2) endocannabinoid receptor, which is a potent anti-inflammatory receptor found in activated microglia. Our preclinical studies demonstrated that THC at low doses mitigates Aβ aggregation, lowers Aβ levels and decreases GSK3β protein levels. In addition, low doses of THC inhibit or modulate phosphorylation of tau protein levels and increase mitochondrial function in AD model N2a/APPswe cells[2]. In-vivo studies revealed that low concentrations of THC significantly improved the spatial learning performance of aged APP/PS1 mice in a dose-dependent manner. Furthermore, brain tissue treated with low doses of THC showed significantly decreased expressions of Aβ oligomers and phosphorylated tau[4].

Melatonin has also been shown to decrease anxiety and regulate the circadian rhythm and sleep through activation of the melatonin receptors 1 and 2 (MT1 & MT2) in the suprachiasmatic nucleus in the brain. Melatonin's mechanism of action against AD is believed to be neuroprotective via activation of known G-protein-coupled melatonin receptors. Data indicates that melatonin also acts intracellularly to protect mitochondria and neurons by scavenging reactive oxygen species and reducing free radical formation[3]. Melatonin secretion decreases in AD, and published evidence shows that melatonin is a useful add-on therapeutic tool in AD. In studies Melatonin was shown to improve sleep and suppressed sundowning, independently or as an adjunct medication[4]. A key finding in our pre-clinical studies is that the combination of a) low dose of THC and b) melatonin help maintain APP levels, decrease Aβ aggregation, decrease hyperphosphorylation of tau and increase mitochondrial functioning.

Based on this evidence, IGC-AD1 is superior to THC or melatonin. This is supported by the clinical data presented here.

Methods

Phase 1 Objectives.

Primary Objectve: *To evaluate the safety and tolerability of IGC-AD1, in a double-blind multiple ascending dose (MAD) study, measured by solicited and non-solicited Adverse Events (AEs) in participants with mild to severe AD.*

Secondary: *: To compare pre and post intervention neuropsychiatric symptoms (NPS) as measured by the neuropsychiatric inventory (NPI-12).*

Exploratory: *To measure the pharmacokinetics (PK) of IGC-AD1, and the impact of polymorphisms of CYP2C9 on PK.*

IGC AD1 is an FDA approved (ClinicalTrials.gov Identifier: NCT04749563) randomized, double-blind, placebo-controlled, MAD study to evaluate the safety and tolerability of IGC-AD1 in AD participants (n = 12: AD1 n = 10; Placebo n = 2). It was completed in 2021 at SCB, Puerto Rico.

Three consecutive cohorts participated in the study, with each cohort (n=12) lasting 14 days with a wash out period of at least four days. The first cohort was administered q.d, the second b.i.d and the third t.i.d (figure 1). The demographic composition of the trial is 100% Puerto Rican. The average age and weight of the participants receiving the active medication was 81.5 years old and 138.8 lb. respectively. Of the participants 69.2% were women. The NPI data was analyzed using a two-tail t-test (df=10), results showing p< .05 were considered statistically significant. The adverse events, PK, NPI, and genotyping were analyzed using mean, IQR, and SD.

Study Design

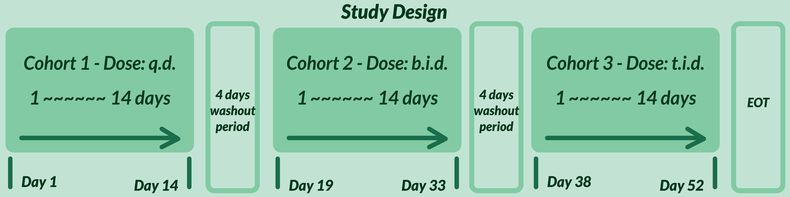

Figure 1. Study design

Demographic Characteristic (N=13)	n = number of participants	
Male	n=4	30.8%
Female	n=9	69.2%
Ethnicity, not Hispanic or Latino	None	
Ethnicity, Hispanic or Latino/ Puerto Rican	n=13 100%	
Mean (SD) age for participants on active medication.	81.5 (5.5) years	
Mean (SD) weight for participants on active medication	138.8 (24.7) lb.	

Table 1. Overall Demographic Characteristic of All Participants

IGC PHARMA

Safety and Tolerability of IGC-AD1 in Alzheimer's patients

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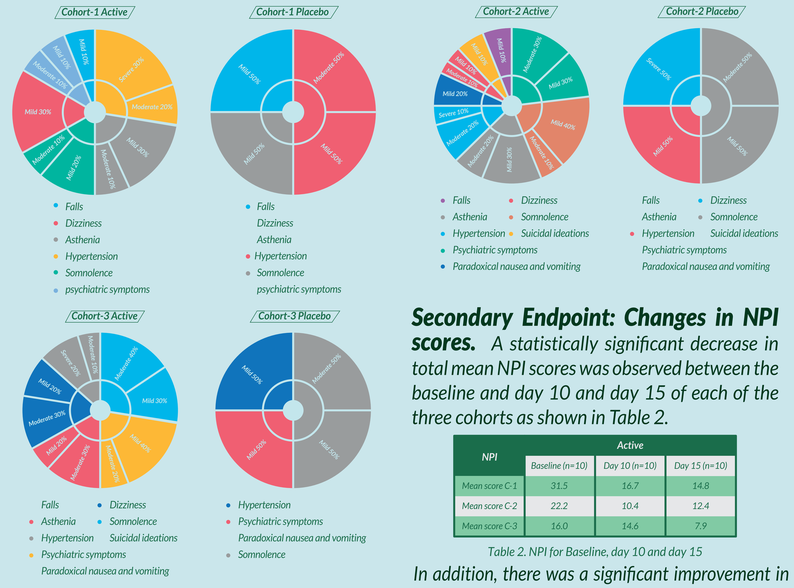
Results

Primary Endpoint: Safety & Tolerability. *Each Participant was given a log booklet in which they kept track of solicited AEs, included in the figures below. The AEs were classified as* ***mild, moderate, severe, life threatening, and serious.***

- *IGC- AD1 was well-tolerated at all three cohort levels, without any serious, life threating, or severe drug related AEs. In all three cohorts, participants reported mild to moderate AEs. It was determined that none of the AEs were drug related (figure 2).*
- *In Cohort 1, in the group that received IGC-AD1 (N=10), 50% reported hypertension, 40% reported asthenia, 30% reported somnolence and dizziness, 20% reported psychiatric symptoms and 10% reported falls. One case of dizziness was deemed by the PI to be related to IGC-AD1. In the placebo group (N=2), 100% reported hypertension, and 50% somnolence and falls.*
- *In Cohort 2 for the IGC-AD1 group, 60% reported psychiatric symptoms, 50% reported somnolence and asthenia, 30% reported hypertension, 20% reported nausea and dizziness, and 10% reported falls and suicidal ideation. In the placebo group 100% reported somnolence, and 50% reported dizziness and hypertension.*
- *In Cohort 3 for the IGC-AD1 group, 70% reported somnolence, 60% reported psychiatric symptoms, 50% reported dizziness and asthenia, and 30% reported hypertension. In the placebo group 100% reported somnolence, and 50% reported hypertension and psychiatric symptoms.*

Figure 2. Proportions of Participants with Solicited AEs by Severity for each Cohort



Domain	Cohort 1 (n=7)			Cohort 2 (n=6)			Cohort 3 (n=5)		
Agitation	Baseline Day 0	Day 10	Day 15	Baseline Day 0	Day 10	Day 15	Baseline Day 0	Day 10	Day 15
Mean Score	4.7	3.3	3	4.3	2.1	1.5	4.2	3.2	1.4
Mean Change%	-	37%	48%	-	53%	67%	-	23%	67%
p-values P(T<=t) two-tail	-	0.058	0.045	-	0.085	0.05	-	0.29	0.045

Table 3. Statistical results for NPI-Agitation, IGC-AD1 Phase-1 trial

Secondary Endpoint: Changes in NPI scores. *A statistically significant decrease in total mean NPI scores was observed between the baseline and day 10 and day 15 of each of the three cohorts as shown in Table 2.*

NPI	Active		
	Baseline (n=10)	Day 10 (n=10)	Day 15 (n=10)
Mean score C-1	31.5	16.7	14.8
Mean score C-2	22.2	10.4	12.4
Mean score C-3	16.0	14.6	7.9

Table 2. NPI for Baseline, day 10 and day 15

In addition, there was a significant improvement in individual NPI domains such as Agitation, Depression, and Anxiety in the means of the participants that presented the symptoms at the baseline.

- *As shown in Table 3. the analysis shows that in Cohort 2 (BID), it is observed the largest absolute change in the mean Agitation score between Day one and Day ten (53% drop, p=.085) as well as between Day one and Day 15 (67% drop, p=.05).*
- *As shown in Table 4, the analysis shows that in Cohort 2 (BID), again the largest absolute change in the mean Depression score between Day one and Day 10 (61% drop, p= .017) as well as between Day one and Day 15 (75% drop, p=.004)*
- *As shown in Table 5, we observed a slight deviation for Anxiety as higher dosage and more time, Cohort 3 (TID), appear to show better results as the largest absolute change in the mean Agitation score between Day one and Day 10 (89% drop, p= .035) as well as between Day one and Day 15 (100% drop, p=.093).*

Domain	Cohort 1 (n=7)			Cohort 2 (n=7)			Cohort 3 (n=4)		
Depression	Baseline Day 0	Day 10	Day 15	Baseline Day 0	Day 10	Day 15	Baseline Day 0	Day 10	Day 15
Mean Score	2.6	1.1	1.2	2.8	1.3	0.8	3.5	2.2	1
Mean Change%	-	62%	67%	-	61%	75%	-	-25%	75%
p-values P(T<=t) two-tail	-	0.016	0.005	-	0.017	0.004	-	0.495	0.155

Table 4. Statistical results for NPI-Depression, IGC-AD1 Phase-1 trial

Domain	Cohort 1 (n=7)			Cohort 2 (n=7)			Cohort 3 (n=3)		
Anxiety	Baseline Day 0	Day 10	Day 15	Baseline Day 0	Day 10	Day 15	Baseline Day 0	Day 10	Day 15
Mean Score	3.4	1.7	1.8	3.1	1.3	2.3	3.6	1.5	0
Mean Change%	-	67%	43%	-	68%	36%	-	89%	100%
p-values P(T<=t) two-tail	-	0.017	0.091	-	0.004	0.407	-	0.035	0.093

Table 5. Statistical results for NPI-Anxiety, IGC-AD1 Phase-1 trial

Exploratory Endpoint: CYP2C9 Genotyping and Pharmacokinetics.

- *The PK data was collected for the overall group as well as the impact of polymorphisms of PK4502C9 on PK. As shown in Table 6, 62% of the study population had a polymorphism of CYP2C9.*
- *As shown in Table 7, THC half-life increased significantly for intermediate metabolizers over normal metabolizers.*
- *Table 8 shows the PK for OH-THC the active metabolite of THC.*
- *Table 9 shows the PK for melatonin.*

Participant	CYP2C9 Genotype	CYP2C9 Phenotype	Sex
1001	*1/*2	Intermediate Metabolizer	Female
1002	*1/*2	Intermediate Metabolizer	Female
1003	*1/*3	Intermediate Metabolizer	Female
1004	*1/*3	Intermediate Metabolizer	Female
1005	*1/*2	Intermediate Metabolizer	Female
1006	*1/*3	Intermediate Metabolizer	Male
1007	*1/*1	Normal Metabolizer	Male
1008	*1/*1	Normal Metabolizer	Female
1009	*1/*1	Normal Metabolizer	Female
1010	*1/*1	Normal Metabolizer	Female
1011	*1/*2	Intermediate Metabolizer	Male
1012	*1/*11	Intermediate Metabolizer	Male
1013	*1/*1	Normal Metabolizer	Female
Sex	69.2% Female, 30.8% Male		
Polymorphisms	61.5%		

Table 6. Genotype and phenotype for participants

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)
$T_{1/2}$ (h)	3.60	1.73	3.75	7.10
T_{max} (h)	2.15	2.38	2.13	1.75
C_{max} (ng/ml)	2.01	2.60	1.46	1.93
AUC_{last} (h*ng/ml)	5.58	6.72	4.20	6.06
AUCinf (h*ng/ml)	8.92	9.04	7.24	11.22

Table 7. PK analysis for THC based on Genotyping

OH-THC	$T_{1/2}$ (h) from T=0	T_{max} (h)	C_{maTx} (ng/ml)	AUC_{last} (h*ng/ml)	AUC_{inf} (h*ng/ml)
Arithmetic mean	3.30	1.90	4.30	17.03	21.60
Range	1.05 to 5.70	1.0 to 4.0	1.69 to 13.70	5.16 to 65.90	8.96 to 70.06

Table 8. PK for OH-THC

Melatonin	$T_{1/2}$ (h) from T=0	T_{max} (h)	C_{max} (ng/ml)	AUC_{last} (h*ng/ml)	AUC_{inf} (h*ng/ml)
Arithmetic mean	1.10	1.00	10.42	21.66	23.32
Range	0.56 to 1.73	1.0	3.9 to 35.0	7.3 to 74.6	7.8 to 75.0

Table 9. Pharmacokinetics for Melatonin

Conclusions

IGC- AD1 was well-tolerated at all three dose levels, without severe AEs. In addition, reduction in total NPI score, as well as decreases in scores for specific domains such as agitation, anxiety, depression, and caregiver distress as measured by the NPI were observed. We also observed a significant increase in the half-life of THC for CYP2C9 intermediate metabolizers as compared to normal metabolizers.

Currently we are working on investigating IGC-AD1 on NPS including Agitation in a vastly expanded Phase 2 trial.

IGC-AD1 shows potential efficacy that is quite different from those observed with high doses of THC and holds the promise of a low-cost medication to treat NPS in AD with minimal side effects. Based on this preliminary evidence, we hypothesize that IGC-AD1 can reduce Agitation and other NPS associated with dementia due to AD.

References.

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Disclosures.

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