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

David Silva-García[a], Maria Paula Naranjo[a], Evelyn Gutiérrez[a], Laura Tatiana Sánchez[a], Maria Juanita Arbelaez[a], Maria Alejandra Tangarife[a], Laura Delgado-Murillo[a], Saadia Shahnawaz[a], Varduhi Ghazaryan[a], Margarita Venegas[a], Karen Y. Pujals[b], William Julio[b], Jagadeesh Rao[a], Claudia Grimaldi[a], Krista Lanctôt[c], L. Elliot Hong[d], and Ram Mukunda[a]

[a. IGC Pharma LLC, USA, b. SCB Research Center, USA, c. Sunnybrook Health Sciences Centre, CA, d. University of Maryland School of Medicine, USA]

POSTER #: P2-694

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

Background:

- Chronic elevated blood pressure (BP) has been associated with an increased risk for cognitive decline and AD progression, given that hypertension has been associated with increased amyloid deposition and neurofibrillary tangles, both neuropathologic hallmarks of AD.[1]
- Blood pressure variability (BPV) —fluctuations in BP over time— is also recognized as a risk factor for AD given that elevated BPV may be associated with cognitive decline, progression of dementia, cerebrovascular disease, stroke, and AD pathology.[2,3]
- The investigational drug IGC-AD1 is a combination that contains tetrahydrocannabinol (THC) and melatonin as its main active components and aims to address neuropsychiatric symptoms such as agitation in AD patients.
- The following research explores the influence of IGC-AD1 on BP and BPV over 15 days of drug administration.

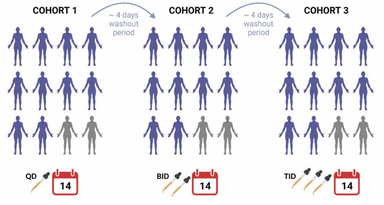
Methods:

- Study participants: In our FDA-regulated Phase I trial, we evaluated a study on BP measurements in AD patients from the Puerto Rican (PR) population as a safety measure.

Table 1. Demographics (n=12)

Age	Years, mean ± SD	81.5 ± 5.5
Gender	Females, n (%)	9 (69.2%)
Active	n (%)	10 (83.3%)
Hypertension	n (%)	12 (100%)
Baseline SBP	mmHg, mean ± SD	134 ± 18.6
Baseline DBP	mmHg, mean ± SD	71.1 ± 11.9
Taking BP medication	n (%)	12 (100%)

- Inclusion criteria: diagnosed as having AD by a certified clinician according to NIA-AA criteria
- Trial details:
  - Three-Cohort Phase I, MAD (Multiple Ascending Dose), safety and tolerability trial (IND146069, NCT04749563).
  - Daily BP recordings for all cohorts.
  - Patients were grouped as having uncontrolled BP when more than 20% of their SBP and DBP fell above SBP 140mmHg and DBP 80mmHg, respectively.
  - Daily evaluations of BP-associated adverse events (AEs) were conducted.



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

Statistical analysis:

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

Results:

The multiple regression analysis showed that daily average SBP and DBP in Cohort 2 and Cohort 3 decreased compared to Cohort 1, DBP decreased only in Cohort 3 (Table 2). The day variable did not have an impact on either SBP or DBP (**Fig. 1**).

Table 2. SBP and DBP multiple regression coefficients.

Systolic BP			Diastolic BP		
Variable	**95%CI**	**p-value**	**Variable**	**95%CI**	**p-value**
Cohort 2	-8.70,-0.33	0.035	Cohort 2	-3.64,0.99	0.263
Cohort 3	-9.37,-0.70	0.016	Cohort 3	-4.92,-0.27	0.029
Group (Placebo)	-16.40,-7.55	<0.001	Group (Placebo)	-2.77, 2.13	0.8

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

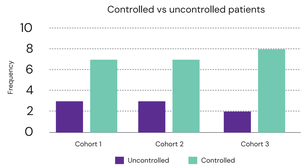


Figure 2. Patients with uncontrolled and controlled BP among cohorts.

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

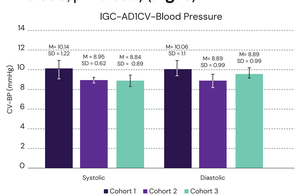


Figure 3. Effect of IGC-AD1 on SBP-CV and DBP-CV in all three cohorts. Error bars represented as SEM.

- **BP-related AEs:**
  Several BP-related adverse events (AEs) were reported, which are not considered to be associated with the treatment (**Table 3**).

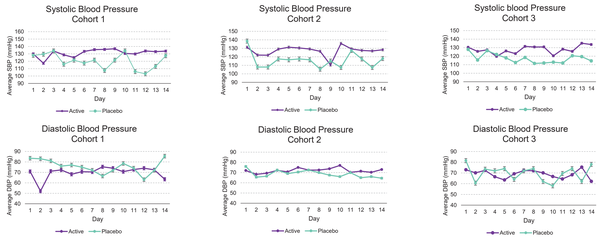


Figure 1. Average daily BP of active and placebo groups.

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

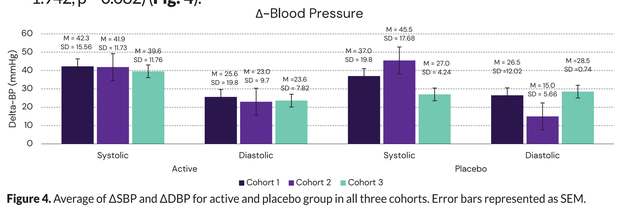


Figure 4. Average of ΔSBP and ΔDBP for active and placebo group in all three cohorts. Error bars represented as SEM.

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

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

Conclusion:

- Preliminary data from the Phase I multiple ascending dose study suggests that investigational drug IGC-AD1, does not have a significant impact on BP or BPV in AD patients with controlled and uncontrolled BP.
- Regression analysis indicates that multiple ascending doses between cohorts may have lowered average BP during the trial. However, the 15-day treatment duration did not impact BP within cohorts.
- Although a larger cohort study with a larger placebo group is warranted, this study suggests that IGC-AD1 may not impact BP or BPV-related risk for AD.

Disclosure of Funding:

This study was funded by IGC Pharma, LLC.

References:

1. Panminerva Medica, 2018, 60(1), 8-16.
2. Medicine, 2019, 98(28), e16347.
3. Scientific reports, 2022,12(1), 17197.
4. European Heart Journal, 2018, 39(33), 3021–3104.

SCAN ME