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

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

Background:

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

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

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

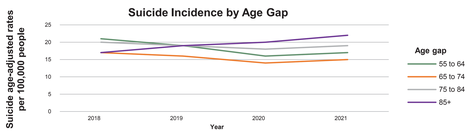

Figure 2. Suicide rates by age gap. Rate per 100.000 Individuals (6).

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

Methods:

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

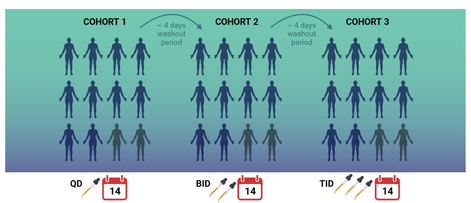

Figure 3. Phase I clinical trial timeline. Purple indicates the number of active participants and gray the number of placebo participants per cohort in the trial.

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

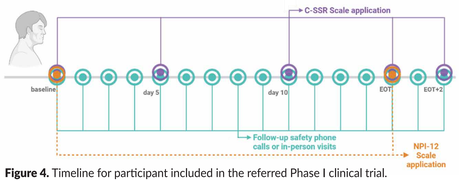

Figure 4. Timeline for participant included in the referred Phase I clinical trial.

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

Results:

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

Table 1. Cohort 1 NPI-12 depression domain.

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

Table 2. Cohort 2 NPI-12 depression domain.

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

Table 3. Cohort 3 NPI-12 depression domain.

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

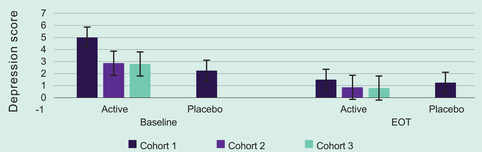

Figure 5. NPI-12 Depression domain, baseline, and EOT.

Discussion and Conclusions:

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

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