CB_1 Receptor Antagonist Selonabant (ANEB-001) Blocks Acute THC Effects in Healthy Volunteers: A Phase II Randomized Controlled Trial

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Emergency department visits due to cannabinoid-induced toxicity, including acute cannabinoid intoxication (ACI) have increased worldwide as more states have liberalized cannabis policy. ACI symptoms include anxiety, panic attacks, tachycardia, and psychosis, primarily mediated through cannabinoid type 1 receptor (CB_1) agonism by Δ^9-tetrahydrocannabinol (THC). This phase II randomized, double-blind, placebo-controlled study assessed the potential of CB_1 receptor antagonist selonabant (ANEB-001) to block THC-induced effects in healthy adults. In Part A of the study, 10.5 mg of THC was coadministered with 50 mg ($N = 20$) or 100 mg ($N = 20$) selonabant, or matching placebo ($N = 20$). In Part B, 21-mg THC was coadministered with 30 mg ($N = 9$) or 10 mg ($N = 7$) selonabant, or matching placebo ($N = 9$). THC-related effects were assessed using visual analogue scales (VAS) for feeling high and alertness, objective measures of postural stability, and heart rate and analyzed using a mixed effects model. Selonabant significantly reduced VAS "Feeling High" (up to −82.8% (95% CI: −91.0%, −67.2%, $P < 0.0001$) at 30-mg selonabant) and increased VAS "Alertness" (up to 10.8 mm (95% CI: 4.7, 16.8 mm, $P = 0.001$) at 30-mg selonabant) vs. placebo. Selonabant 10 and 30 mg significantly reduced body sway (up to −30.6% (95% CI: −44.1%, −13.9%, $P = 0.002$) at 30 mg selonabant) vs. placebo. Effects on heart rate were not significant. Selonabant was generally safe and no clinically meaningful changes in mood occurred. Nausea and vomiting occurred more frequently at high selonabant doses; 10-mg selonabant was both well tolerated and efficacious. Present results support further development of selonabant for emergency treatment of ACI.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The incidence of cannabinoid-induced toxicity, including acute cannabinoid intoxication is increasing due to a liberalization of cannabis policy. Currently, there are no approved treatments that specifically target the cause of acute cannabinoid intoxication.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study assessed whether CB_1 receptor antagonist selonabant blocked the acute effects of Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, in healthy volunteers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Selonabant largely blocked the acute effects of THC intoxication at oral THC doses of up to 21 mg and was safe and well tolerated.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These result provide a basis for further development of selonabant as a treatment for cannabinoid-induced toxicity, such as acute cannabinoid intoxication.

Cannabis is the most widely used recreational drug in the world.[1,2] Cannabis use has further increased worldwide following legalization and decriminalization in many states; as of November 2023, the number of cannabis users in the United States alone exceeded 60 million.[3] In parallel, the potency of cannabis has increased over time, with the average content of Δ^9-tetrahydrocannabinol

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(THC), its main psychoactive constituent, tripled between the years 1994 and 2014 in the United States.[4] Consumers now also have access to cannabis extracts, which typically contain more than triple the amount of THC compared to cannabis flowers,[5] cannabis resins, which had an average THC concentration of 24.8% in the European Union in 2022,[6] and various edible cannabis products, such as chocolates, brownies, and gummies, which are visually appealing to children and easily mistaken for regular foods.[7,8] Additionally, synthetic cannabinoids have emerged as unregulated alternatives to botanical cannabis products.[9] Synthetic cannabinoids are more potent agonists of the CB_1 receptor compared to THC and are associated with more frequent and severe toxicities.[9] As a result of these factors, the incidence of emergency department visits related to cannabinoid-related toxicity, including acute cannabinoid intoxication (ACI) and cannabis hyperemesis syndrome has continued to grow.[8,10–12] As of 2018, there were approximately 1.7 million emergency department visits in the United States associated with cannabis exposure.[13] Of these cannabis-related emergency department cases, approximately 25% are attributable to a direct effect of cannabis.[14]

Typical effects of cannabis in recreational users may include euphoria, sensory distortion, and increased appetite.[15] Common adverse effects of ACI in adults are cognitive and motor impairment, anxiety, paranoia, tachycardia, and postural hypotension.[16] In adults presenting to emergency departments, adverse effects of high cannabis doses more commonly include neuropsychiatric symptoms, such as panic attacks, depersonalization, and acute psychosis.[16] In children, unintentional exposure to THC can result in severe complications, such as profound sedation, seizures, and respiratory depression.[16] Currently, there are no approved therapies available for targeted treatment of cannabinoid-induced toxicity and management typically consists of supportive care.

THC acts primarily through partial agonism of the cannabinoid 1 receptor (CB_1)[17] and therefore antagonism of this receptor represents an opportunity for targeted treatment of cannabinoid-induced toxicity. In prior clinical studies, several CB_1 antagonists, including drinabant, surinabant, and rimonabant, were shown to reduce THC effects when administered prophylactically, several hours prior to cannabis inhalation.[18–20] However, the potential of a CB_1 antagonist as an acute treatment for established cannabinoid intoxication has not been explored to date. Although the CB_1 antagonist rimonabant was originally approved in Europe for the treatment of obesity, chronic dosing was found to be associated with long-term psychiatric adverse effects.[21] In contrast, emergency treatment of cannabinoid-induced toxicity represents an opportunity for acute use of a potent CB_1 antagonist while potentially avoiding the risk of long-term adverse effects.

Selonabant (ANEB-001; formerly V24343) is a CB_1 receptor antagonist that was originally under development as a potential treatment for obesity. In early-phase trials (unpublished), selonabant was well tolerated and significantly reduced caloric intake and body weight in healthy overweight or mildly obese subjects. To explore the potential of single oral doses of selonabant as an emergency treatment for ACI, a phase II clinical study was conducted in healthy adult volunteers, in which selonabant was coadministered with oral THC. Here, we report on the initial part of the larger study, designed to assess safety, PK, and the potential for coadministration of selonabant to block the effects of THC over a range of dose levels.

METHODS

Study design

This study was a phase II double-blind, randomized, placebo-controlled parallel-arm study, in which the effects of single oral doses of selonabant were compared to placebo coadministered with a single oral dose of THC. As a part of a larger study, the current report focuses on data from the coadministration of selonabant with THC. In Part A, 60 participants were randomized to three parallel treatment arms (20 participants/arm). All participants received a single oral dose of 10.5 mg THC coadministered with one of three treatments: a single oral dose of selonabant (50 or 100 mg) or matching placebo. In Part B, two sequential cohorts of participants (target $N = 15$ per cohort) each received a single oral dose of 21 mg THC, coadministered with 30-mg selonabant or placebo (2:1 active/placebo) in Cohort 1 and 10-mg selonabant or placebo in Cohort 2.

The study was conducted at the Centre for Human Drug Research in Leiden, the Netherlands. The study was approved by the Medical Ethics Committee of Stichting Beoordeling Ethiek Biomedisch Onderzoek (Assen, the Netherlands) and was conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and in compliance with all International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. This study was registered prospectively with the IRCTN registry under registration number: ISRCTN45282100 and registered to clinicaltrials.gov under NCT05282797.

Study participants

Each subject provided written informed consent before any screening procedures were performed. All participants were healthy volunteers between 18 and 45 years of age with a body mass index of 18–30 kg/m^2. Initially, only males were included; during Part A the protocol was amended to allow inclusion of females. The participants underwent a full medical screening, including patient-reported medical history, a physical examination, blood chemistry and hematology, urinalysis, and an electrocardiogram (ECG) to assess eligibility. Participants with a clinically significant known medical condition, particularly any psychotic disorder, clinically significant mood disorder, suicidal ideation in the past 5 years, or any lifetime suicide attempts, were excluded.

All included participants were occasional cannabis users for at least 1 year prior to screening, with a lifetime cannabis use of at least 10 times and recent cannabis use not exceeding once per week on average in the 6 months prior to study participation. The participants refrained from cannabis use from at least 3 weeks prior to dosing until the end of the study. Any participant who was a regular user of any illicit drugs (other than the casual use of cannabis) or had a history of drug abuse or a positive drug screen at screening, was excluded. The full list of inclusion and exclusion criteria is provided in the **Supplementary Materials S1**.

Study drugs

Selonabant was administered as oral capsules containing 10 or 50-mg selonabant. Matching placebo capsules were administered to participants randomized to placebo. THC was administered as oral tablets containing 1.5 mg THC per tablet (Namisol®, Echo Pharmaceuticals). All treatments were administered in a fasted state.

Selonabant (ANEB-001; formerly V24343) was previously studied in phase I clinical trials of safety, PK, tolerability, and efficacy as a treatment for obesity (unpublished data from Vernalis).[22] This is the first clinical study to examine selonabant when administered in combination with THC. The selonabant dose levels in Part A of the study were selected based on the selonabant doses demonstrating acceptable tolerability and efficacy in reducing body weight. The initial THC dose

of 10.5 mg was chosen based on historical data showing induction of typical psychotropic effects while being safe and well tolerated.[23] Based on results from Part A of the study, Part B subsequently evaluated lower dose levels of selonabant in combination with a higher dose level of THC.

Pharmacodynamic assessments

Pharmacodynamic assessments of THC effects were performed on the dosing day twice predose for baseline measurements and at 1, 2, 3, 4, 5, and 8 hours postdose. In order to minimize potential learning effects, all participants were acquainted with the pharmacodynamic tests within 3 weeks prior to dosing.

Primary pharmacodynamic assessments. The Bowdle visual analog scale (VAS), an instrument for evaluating subjective psychedelic effects, was performed in this study to assess the subjective outcome of "Feeling High," using a scale of 0–100 mm.[24,25] The Bond and Lader VAS was used to evaluate scores from a series of horizontal bipolar scales related to how a person feels, ranging from 0 to 100, where values of 0 and 100 represented opposing subjective states and a value of 50 represented the neutral state. From these measurements, the outcome for "Alertness" was calculated as described in previous publications.[26]

Postural stability was measured objectively using a pot string meter based on the Wright ataxiameter.[27] With a string attached to the waist, subjects were asked to stand still with their eyes closed for a period of 2 minutes. All anteroposterior body movements over time were integrated and expressed as body sway in mm.

Heart rate measurements were performed predose as baseline and at 20 minutes, 40 minutes, 1, 2, 3, 4, 5, 8, and 22–24 hours postdose using Dash 3,000, Dash 4,000, Dynamap 400, or Dynamap ProCare 400 automated devices after 5 minutes in supine position.

Secondary pharmacodynamic assessments. Secondary pharmacodynamic assessments included VAS "Internal Perception" and VAS "External Perception" according to Bowdle,[24,25] VAS "Mood" and VAS "Calmness" according to Bond and Lader,[26] saccadic and smooth pursuit eye movements,[28,29] pupillometry,[30] state–trait anxiety inventory (STAI),[31] adaptive tracking,[32,33] and N-back,[34] performed as described elsewhere.

Pharmacokinetic assessments

Venous blood samples were taken predose and 0.5, 1, 2, 3, 4, 6, and 8 hours following dosing. Plasma selonabant, THC, and 11-OH-THC concentrations were determined using a validated LC–MS/MS method (described further in the **Supplementary Material S1**).

Safety assessments

Safety and tolerability were assessed by adverse event (AE) monitoring, clinical laboratory tests, vital signs, ECGs, and physical and neurological examinations. The Beck Depression Inventory, the second edition, Dutch version (BDI-II-NL) was used to measure depressive symptoms and the Columbia Suicide Severity Rating Scale (C-SSRS) was performed throughout the study in order to monitor suicidal ideation and behavior.

Sample size and randomization

VAS "Feeling High" was used for the sample size calculation, as it was shown previously to be sensitive to THC intoxication, as well as prophylactic inhibition of the effect by CB_1-receptor antagonists.[18–20] For Part A of the study, a sample size of 20 per group was calculated to have a power of 0.986 to detect an inhibition of 50% of the VAS "Feeling high," assuming a log-normal distribution of VAS "Feeling High," a coefficient of variation (CV%) of 55% (CV% defined as ratio of the standard deviation to the mean expressed as a percentage), and using a two-sample t-test with a 0.05 two-sided significance level. The emergent data from Part A were used for a sample size calculation for Part B of the study. Assuming a CV% of 55%, a sample size of 10 participants per treatment group had a power of 0.814 to detect an inhibition of VAS "Feeling high" of 50%. For this reason, a treatment group size of $N = 10$ was considered sufficient for Part B of the study.

Study staff and participants remained blinded until database lock. The randomization code was generated using SAS version 9.4 by a study-independent statistician. Blinded study staff assigned the randomization numbers to the participants sequentially after medical screening.

Statistical analysis

To establish whether significant treatment effects could be detected, the endpoints were analyzed with a mixed effects model with treatment, time, and treatment by time as fixed factors and subject as random factor and the average baseline measurement as covariate. Postdose measurements that were performed outside a 10% time window around the scheduled protocol time were excluded from analysis. For VAS "Feeling High," a constant value of 2 mm was added to each measurement to allow log-transformation and satisfy the model's normality assumption for residuals; subsequently, the analysis results were back-transformed for reporting. All calculations were performed using SAS for Windows V9.4 (SAS Institute Inc., Cary, NC, USA). No adjustments for multiple comparisons were employed. The incidence of treatment-emergent AEs (TEAEs), defined as AEs that occurred or worsened after study treatments, was summarized.

A prespecified interim analysis of unblinded PK, PD, and safety data was performed following the completion of Part A. In Part B, each cohort was followed by a blinded review of PK, PD, and safety data in a dose evaluation meeting.

RESULTS

Participants and demographics

The clinical phase of Part A, and Part B, cohorts 1 and 2 of the study, ran from December 2021 to September 2022. For Part A of the study, 110 participants were screened and 60 participants were dosed. For Part B, cohorts 1 and 2, 34 participants were screened and 25 participants were dosed, 5 less than the planned 15 participants per cohort due to recruitment challenges. There were no discontinuations and all dosed participants completed the study and were evaluated for pharmacodynamic, pharmacokinetic, and safety outcomes (**Figure 1**). The participant demographics are summarized in **Table S1**.

Pharmacodynamic outcomes

Primary. The statistics of the primary pharmacodynamic results are summarized in **Table 1**. All measurements fell within the 10% time window around the planned timepoints and were included in the analysis.

In Part A of the study, where a 10.5 mg THC was administered to all participants, selonabant significantly reduced mean VAS "Feeling High" compared to placebo at both 50 mg (estimated difference (ED): −63.7%, 95% confidence interval (CI): −77.3%, −41.8%, $P < 0.0001$) and 100 mg (ED: −61.8%, 95% CI: −75.8%, −39.4%, $P < 0.0001$) dose levels (**Figure 2a**). The VAS "Alertness" remained approximately at baseline throughout the study day for participants treated with selonabant, whereas a pronounced

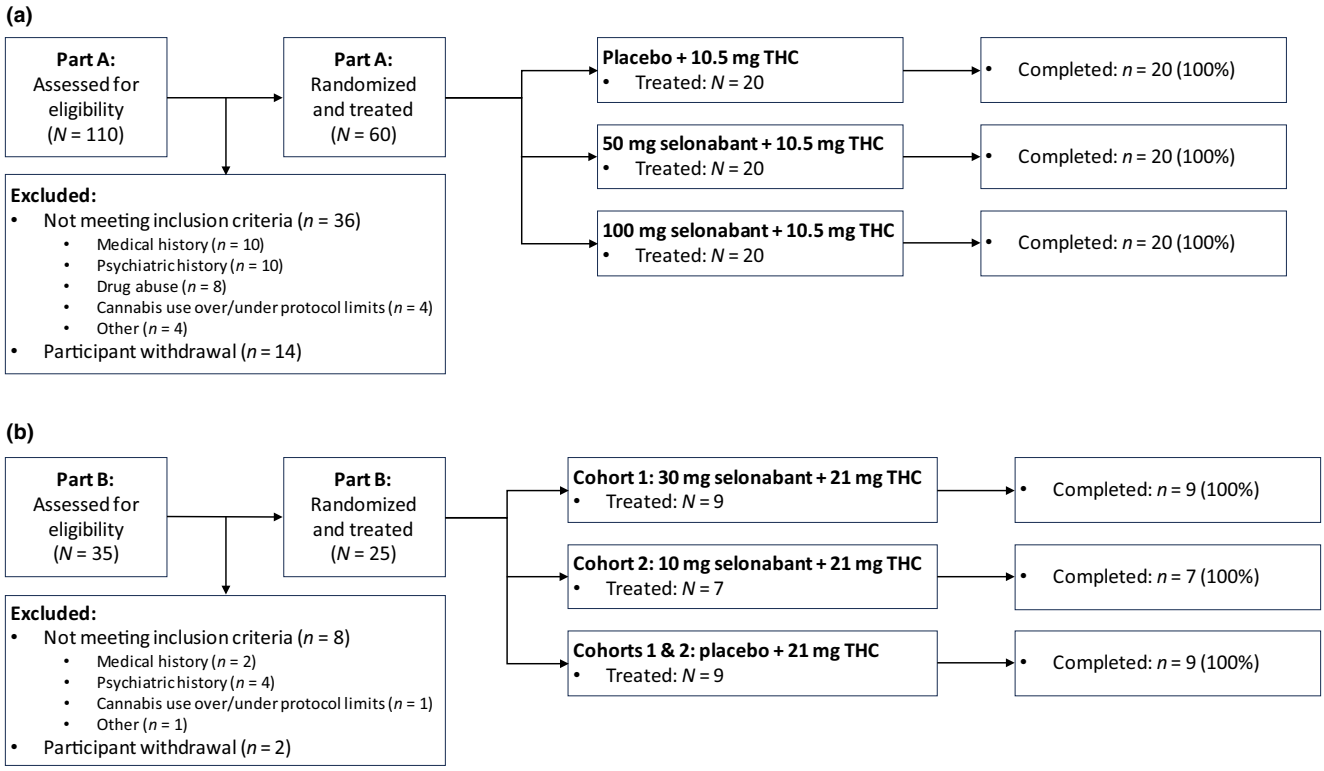

Figure 1 CONSORT study flow diagram.

decrease in VAS "Alertness" was observed in placebo participants; the difference from placebo-treated participants was significant for both 50 mg (ED: 6.0 mm, 95% CI: 1.8, 10.1 mm, $P = 0.006$) and 100-mg selonabant (ED: 5.4 mm, 95% CI: 1.3, 9.6 mm, $P = 0.011$) treatment groups (**Figure 2b**). Selonabant did not significantly reduce the overall mean body sway or heart rate when compared to placebo in Part A of the study (**Figure 2c,d**).

In Part B of the study, where the THC dose was increased to 21 mg, the lower doses of 30 mg (ED: −82.8%, 95% CI: −91.0%, −67.2%, $P < 0.0001$) and 10 mg of selonabant (ED: −80.4%, 95% CI: −90.5%, −59.5%, $P < 0.001$) significantly reduced the mean VAS "Feeling High" compared to placebo (**Figure 3a**). Similar to Part A, the VAS "Alertness" remained close to baseline for the selonabant treatment groups in Part B of the study, whereas the placebo group had a notably decreased VAS "Alertness," with the difference between selonabant and placebo being statistically significant for both 30 mg (ED: 10.8 mm, 95% CI: 4.7, 16.8 mm, $P = 0.001$) and 10 mg (ED: 9.2 mm, 95% CI: 3.1, 15.3 mm, $P = 0.005$) selonabant groups (**Figure 3b**). Both 30 mg (ED: −30.6%, 95% CI: −44.1%, −13.9%, $P = 0.002$) and 10 mg (ED: −29.3%, 95% CI: −44.3%, −10.2%, $P = 0.007$) selonabant treatments significantly reduced body sway compared to placebo in Part B of the study (**Figure 3c**). Selonabant did not significantly reduce the overall mean heart rate compared to placebo in Part B of the study (**Figure 3d**).

Table 1 Overall treatment effects on main pharmacodynamic outcome measures (estimated mean differences with 95% CI and *P*-values)

Study part	Part A (10.5-mg THC)		Part B (21-mg THC)	
Parameter	100-mg Selonabant vs. Placebo	50-mg Selonabant vs. Placebo	30-mg Selonabant vs. Placebo	10-mg Selonabant vs. Placebo
VAS "Feeling High" (%)	**−61.8% (−75.8%, −39.4%) $P < 0.0001$**	**−63.7% (−77.3%, −41.8%) $P < 0.0001$**	**−82.8% (−91.0%, −67.2%) $P < 0.0001$**	**−80.4% (−90.5%, −59.5%) $P < 0.001$**
VAS "Alertness" (mm)	**5.4 (1.3, 9.6) $P = 0.011$**	**6.0 (1.8, 10.1) $P = 0.006$**	**10.8 (4.7, 16.8) $P = 0.001$**	**9.2 (3.1, 15.3) $P = 0.005$**
Body sway (%)	−12.4% (−26.2%, 4.1%) $P = 0.129$	−6.5% (−21.3%, 11.0%) $P = 0.436$	**−30.6% (−44.1%, −13.9%) $P = 0.002$**	**−29.3% (−44.3%, −10.2%) $P = 0.007$**
Heart rate in supine position (bpm)	−0.2 (−3.0, 2.6) $P = 0.881$	−2.6 (−5.3, 0.1) $P = 0.062$	−2.2 (−8.6, 4.1) $P = 0.473$	1.1 (−5.2, 7.4) $P = 0.726$

bpm, beat per minute; CI, confidence interval; THC, THC, Δ^9-tetrahydrocannabinol; VAS, visual analog scale.The figures in bold indicate statistical significance.

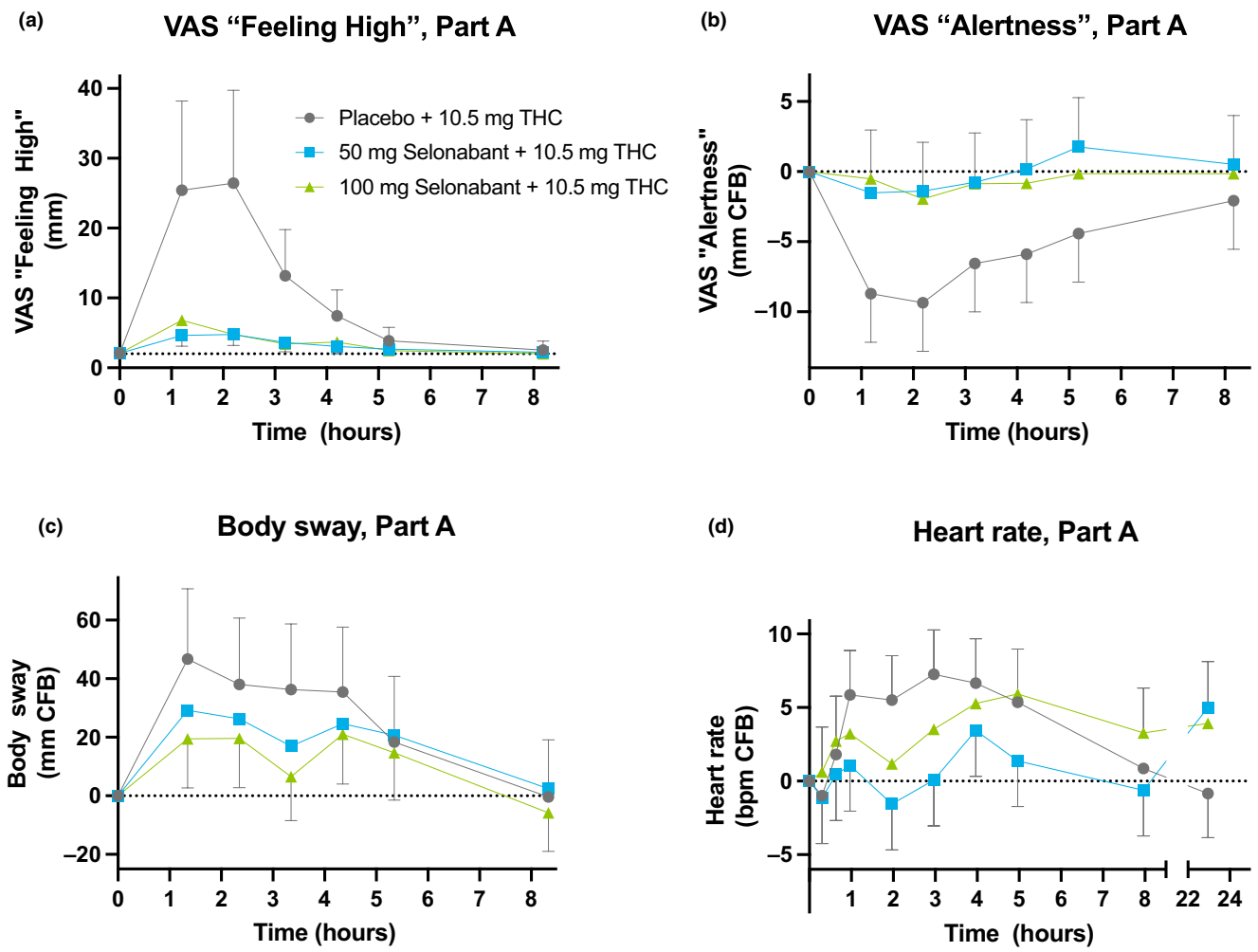

Figure 2 Least Square Means of (**a**) VAS "Feeling High" (absolute values in mm), (**b**) VAS "Alertness" (change from baseline in mm), (**c**) Body sway (change from baseline in mm), (**d**) Heart rate (change from baseline in bpm), Part A of the study. Means are displayed with 95% confidence intervals.

Secondary. Selonabant significantly reduced VAS "External Perception" compared to placebo at all dose levels, and VAS "Internal Perception" in Part B only (**Table S2**). Selonabant significantly improved the adaptive tracking performance compared to placebo in Part B, but not Part A (**Table S2**). For the remaining secondary pharmacodynamic outcome measures (VAS "Mood," VAS "Calmness," STAI, saccadic and smooth pursuit eye movements, pupillometry, and n-back), significant treatment effects were either absent, or identified at a single dose level only, and are not reported here further.

Pharmacokinetics

The concentration–time profiles of selonabant are shown in **Figure 4** and those of THC and 11-OH-THC in **Figure S3**. An overview of the pharmacokinetic parameters for all analytes is provided in **Table S4**.

Peak concentrations of selonabant occurred at a median (min, max) T_{max} of 1–2 hours (0.67, 3) postdose. The C_{max} increased approximately dose-proportionally, whereas the AUC_{last} was approximately dose proportional at 30 mg and higher and slightly greater than proportional at the 10-mg dose level. The terminal half-life of selonabant could not be calculated due to the limited plasma sampling time frame. Moderate variability was observed for the C_{max} and AUC_{last} of selonabant, with coefficient of variations (CV%) ranging from 27.8% to 35.5%.

Peak concentrations of THC occurred at a dose-independent median (min, max) T_{max} of 0.67 to 1 hour (0.33 to 3.0) postdose. Moderate to high variability was observed for the C_{max} and AUC_{last} of THC, with CV% ranging from 36.8% to 75.4%.

Safety

No serious adverse events occurred during the study. All TEAEs were mild in severity, except for vomiting and nausea in one participant treated with 50-mg selonabant, and dizziness in two participants treated with placebo in Part B, all of which were considered moderate. An overview of TEAEs that were reported at least twice is provided in **Table 2** (full overview available in **Table S5**).

At the highest dose level of selonabant (100 mg), 40% of participants reported nausea and 30% reported vomiting, whereas only

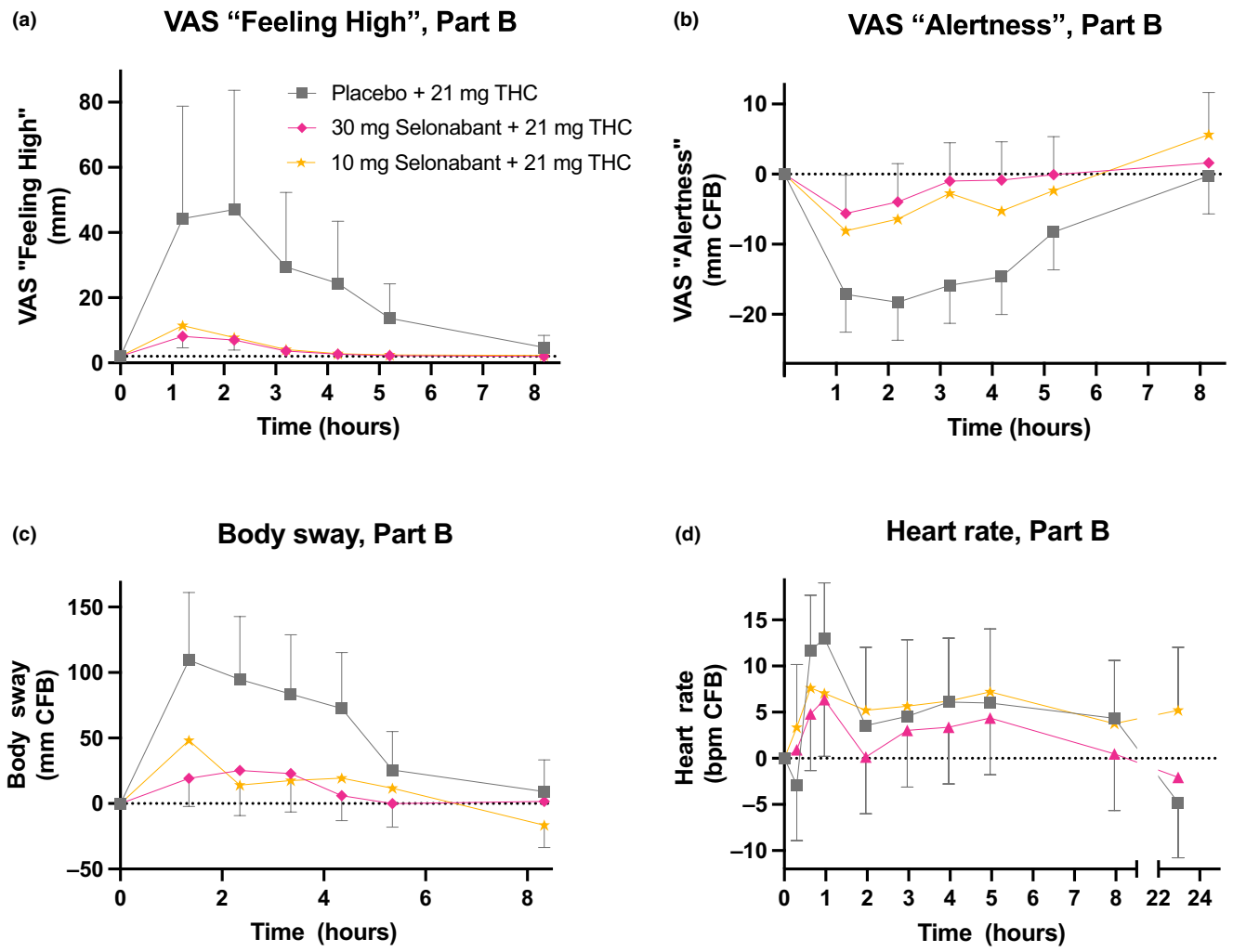

Figure 3 Least Square Means of (**a**) VAS "Feeling High" (absolute values in mm), (**b**) VAS "Alertness" (change from baseline in mm), (**c**) Body sway (change from baseline in mm), (**d**) Heart rate (change from baseline in bpm), Part B of the study. Means are displayed with 95% confidence intervals.

10% of placebo-treated participants in Part A reported nausea and none reported vomiting. Incidence of nausea and vomiting were dose-dependent, and at the lowest dose level of selonabant (10 mg), no vomiting occurred, and the incidence of nausea (42.9%) was similar to the placebo group of Part B (44.4%). Furthermore, hyperhidrosis and feeling hot were reported by approximately 20–30% of participants treated with 30-mg to 100-mg selonabant, but were absent at the 10-mg selonabant dose level and in both placebo groups. TEAEs typically associated with THC, for example, euphoric mood, dizziness, bradyphrenia, paresthesia, and dry mouth, generally occurred more frequently in the placebo groups compared to the selonabant groups, and more frequently in the placebo participants receiving 21-mg THC compared to 10.5 mg THC.

Events of depressed mood were infrequent (two events in the 100-mg selonabant group and one event in the 50-mg selonabant group), transient, and mild and were not considered clinically meaningful by the investigators. There was no suicidal ideation in any of the participants at any time during the study, as assessed by the Columbia Suicide Severity Rating Scale. Beck Depression Inventory scores were similar in the selonabant and placebo groups (Figure S6).

There were no clinically relevant group differences in blood pressure, hematology, biochemistry, urinalysis, or ECG parameters between selonabant and placebo-treated participants. In one participant treated with 100-mg selonabant and 10.5-mg THC, a systolic blood pressure increase of up to 32 mmHg from baseline occurred, peaking at 162 mmHg at 3 hours postdose and returning to baseline at 24 hours postdose.

DISCUSSION

This study was designed to evaluate the potential of selonabant, a CB_1 receptor antagonist, to block the clinical effects of oral THC in healthy volunteers when administered simultaneously. Single doses of selonabant almost completely blocked the typical subjective effects of THC, that is, VAS "Feeling High" and VAS "Alertness," and significantly reduced the impairment of postural stability caused by the administration of 21-mg THC. Selonabant had an approximately equal efficacy in blocking the

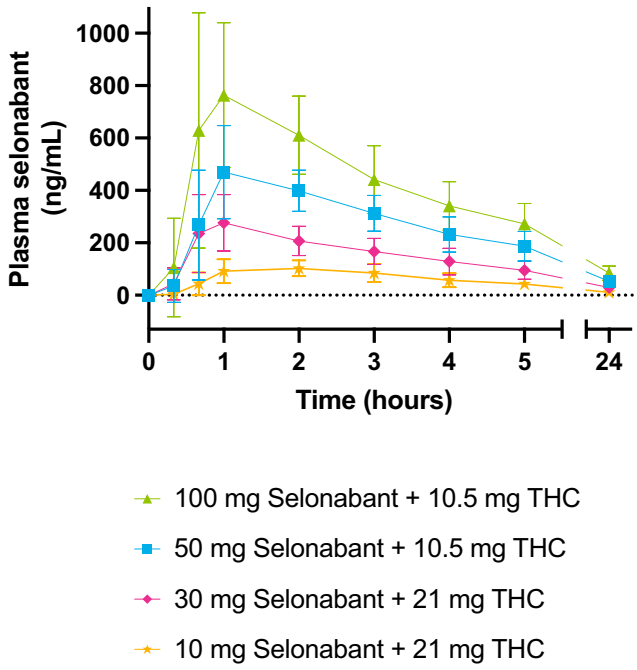

Figure 4 Concentration–time profiles of selonabant following oral administration, displayed as means with standard deviation.

THC effects across the entire dose range studied. Selonabant was generally safe; most adverse events were mild and transient and no SAEs occurred during the study. Nausea, vomiting, and hyperhidrosis, the main adverse events related to selonabant in this study, were dose-dependent and were absent at the well-tolerated, but equally efficacious, 10-mg dose level. This study provides a successful proof of concept and supports future research into selonabant as a potential emergency treatment for cannabinoid-induced toxicity.

The duration of effect for single oral doses of selonabant was favorable; THC effects were blocked for the duration of the observation period. The actual effect duration of selonabant is likely even longer, but could not be established precisely due to wearing off of THC effects 5–8 hours postdose at the THC doses used. Selonabant effectively blocked the effects of THC across the entire dose range tested, without a noticeable decline in efficacy at the lower dose levels, even while the THC dose was increased in Part B of the study. This confirms that selonabant is a potent CB_1 antagonist in vivo, and its efficacy was further evidenced by a lower incidence of typical THC-related adverse effects (e.g., euphoric mood, dizziness, paresthesia, bradyphrenia) in participants treated with selonabant compared to those treated with placebo.

Although selonabant had highly significant treatment effects on VAS "Feeling High" and "Alertness," this was not consistently observed for body sway and heart rate. For body sway, the difference between selonabant and placebo was significant in Part B, but not Part A, of the study. This is most readily explained by the relatively low THC dose (10.5 mg) administered in Part A, which had only modest effects on postural stability. When a higher THC dose of 21 mg was administered in Part B of the study, the effects on postural stability in placebo-treated participants were greater, allowing a significant treatment effect of selonabant vs. placebo to be detected, despite administration of lower selonabant doses than in Part A. Coadministration of selonabant did not show a statistically significant effect of heart rate after coadministration with up to 21 mg of THC. A possible explanation lies in the modest and brief heart rate increases induced by the THC doses administered against a background of high intersubject variability. The study was not powered to detect treatment effects on heart rate, and a larger sample size might have been required to detect a significant difference vs. placebo. Selonabant was observed to be generally safe in the healthy participants in this study. Although selonabant-related adverse events at the higher dose levels included nausea, vomiting, and hyperhidrosis, the 10-mg dose level was well tolerated and equally effective. Psychiatric symptoms associated with rimonabant, another CB_1 antagonist, notoriously led to its withdrawal from the market. In this study, however, only a minimal number of mood symptoms occurred. Three mild and transient events of depressed mood in selonabant-treated participants were not considered clinically significant by the investigator, and Beck Depression Inventory scores were comparable between treatment groups. Indeed, it appears plausible that single doses of CB_1 antagonists administered in the context of ACI treatment should have a favorable safety profile compared to rimonabant, which was dosed chronically for weight loss. The safety of selonabant in patients presenting to the emergency department with ACI remains to be established.

Strengths of this study include the randomized and placebo-controlled design, adequate population size for the most sensitive outcome measure, the wide dose range of selonabant studied, and the use of pharmacodynamic measures that have been shown to be sensitive to both THC effects and mitigation of THC effects by prophylactic treatment with other CB_1 antagonists.[18–20,23,35] The main limitation of this study is the limited range of THC doses investigated. High THC doses capable of inducing severe neuropsychological symptoms were not administered in this study out of ethical considerations, but patients presenting to the emergency department with such symptoms may have higher THC blood concentrations than we observed in this study. Coadministration of selonabant with higher THC doses will be the subject of future publications. Although from a mechanistic point of view, a CB_1 receptor antagonist such as selonabant should be able to counteract the effects of any CB_1 receptor agonist, synthetic agonists that differ from THC in potency, receptor binding, and pharmacokinetics may require different selonabant doses and/or dosing regimens and warrant future investigation. It could be considered a limitation that this study lacked a treatment arm for selonabant placebo without the THC coadministration. However, the main study aim was to evaluate the blocking of THC effects by selonabant, which did not require an arm without THC, and the effects of THC compared to placebo have been abundantly described by our institute and others.[23,35] Even though the two

Table 2 Summary of TEAEs by treatment, SOC, and PT (PTs with >1 event only)

	Part A (10.5 mg THC)						Part B, Cohorts 1 and 2 (21 mg THC)					
	50-mg Selonabant (*n* = 20)		100-mg Selonabant (*n* = 20)		Placebo (*n* = 20)		30-mg Selonabant (*n* = 9)		10-mg Selonabant (*n* = 7)		Placebo (*n* = 9)	
System organ class/ preferred term	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)
Any events	61	17 (85.0)	55	16 (80.0)	46	20 (100.0)	26	9 (100.0)	16	7 (100.0)	36	9 (100.0)
Eye disorders	–	–	1	1 (5.0)	2	2 (10.0)	–	–	–	–	–	–
Dyschromatopsia	–	–	1	1 (5.0)	2	2 (10.0)	–	–	–	–	–	–
Gastrointestinal disorders	26	14 (70.0)	19	12 (60.0)	4	4 (20.0)	14	6 (66.7)	5	3 (42.9)	7	5 (55.6)
Abdominal discomfort	–	–	–	–	–	–	1	1 (11.1)	1	1 (14.3)	–	–
Diarrhea	4	3 (15.0)	1	1 (5.0)	–	–	–	–	–	–	–	–
Dry mouth	–	–	–	–	2	2 (10.0)	–	–	1	1 (14.3)	3	3 (33.3)
Nausea	18	14 (70.0)	8	8 (40.0)	2	2 (10.0)	4	4 (44.4)	3	3 (42.9)	4	4 (44.4)
Retching	1	1 (5.0)	1	1 (5.0)	–	–	–	–	–	–	–	–
Vomiting	3	2 (10.0)	9	6 (30.0)	–	–	9	3 (33.3)	–	–	–	–
General disorders and administration site conditions	16	10 (50.0)	13	10 (50.0)	8	6 (30.0)	4	4 (44.4)	5	4 (57.1)	8	7 (77.8)
Asthenia	1	1 (5.0)	–	–	1	1 (5.0)	–	–	–	–	–	–
Fatigue	6	6 (30.0)	6	6 (30.0)	5	4 (20.0)	2	2 (22.2)	4	3 (42.9)	5	5 (55.6)
Feeling abnormal	1	1 (5.0)	1	1 (5.0)	1	1 (5.0)	–	–	1	1 (14.3)	–	–
Feeling cold	1	1 (5.0)	–	–	–	–	–	–	–	–	1	1 (11.1)
Feeling hot	7	6 (30.0)	4	4 (20.0)	–	–	2	2 (22.2)	–	–	–	–
Feeling of relaxation	–	–	2	2 (10.0)	1	1 (5.0)	–	–	–	–	–	–
Sluggishness	–	–	–	–	–	–	–	–	–	–	2	2 (22.2)
Infections and infestations	1	1 (5.0)	1	1 (5.0)	1	1 (5.0)	–	–	–	–	1	1 (11.1)
COVID-19	1	1 (5.0)	1	1 (5.0)	1	1 (5.0)	–	–	–	–	1	1 (11.1)
Metabolism and nutrition disorders	1	1 (5.0)	2	2 (10.0)	–	–	–	–	–	–	–	–
Decreased appetite	1	1 (5.0)	2	2 (10.0)	–	–	–	–	–	–	–	–
Musculoskeletal and connective tissue disorders	–	–	–	–	1	1 (5.0)	–	–	1	1 (14.3)	–	–
Limb discomfort	–	–	–	–	1	1 (5.0)	–	–	1	1 (14.3)	–	–
Nervous system disorders	5	4 (20.0)	4	3 (15.0)	13	8 (40.0)	2	2 (22.2)	1	1 (14.3)	11	6 (66.7)
Dizziness	–	–	–	–	5	5 (25.0)	2	2 (22.2)	–	–	5	4 (44.4)
Headache	4	4 (20.0)	3	2 (10.0)	4	4 (20.0)	–	–	–	–	2	2 (22.2)
Paresthesia	–	–	–	–	3	3 (15.0)	–	–	1	1 (14.3)	3	3 (33.3)
Presyncope	–	–	–	–	1	1 (5.0)	–	–	–	–	1	1 (11.1)
Tremor	1	1 (5.0)	1	1 (5.0)	–	–	–	–	–	–	–	–
Psychiatric disorders	5	4 (20.0)	7	6 (30.0)	17	15 (75.0)	3	3 (33.3)	4	3 (42.9)	9	7 (77.8)
Bradyphrenia	–	–	1	1 (5.0)	4	4 (20.0)	1	1 (11.1)	1	1 (14.3)	2	2 (22.2)

(Continued)

Table 2 (Continued)

	Part A (10.5 mg THC)						Part B, Cohorts 1 and 2 (21 mg THC)					
	50-mg Selonabant (*n* = 20)		100-mg Selonabant (*n* = 20)		Placebo (*n* = 20)		30-mg Selonabant (*n* = 9)		10-mg Selonabant (*n* = 7)		Placebo (*n* = 9)	
System organ class/ preferred term	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)	Events *n*	Subjects *n* (%)
Depressed mood	1	1 (5.0)	2	2 (10.0)	–	–	–	–	–	–	–	–
Euphoric mood	4	3 (15.0)	3	3 (15.0)	12	11 (55.0)	2	2 (22.2)	3	3 (42.9)	5	5 (55.6)
Inappropriate affect	–	–	–	–	–	–	–	–	–	–	2	2 (22.2)
Time perception altered	–	–	1	1 (5.0)	1	1 (5.0)	–	–	–	–	–	–
Respiratory, thoracic and mediastinal disorders	1	1 (5.0)	1	1 (5.0)	–	–	–	–	–	–	–	–
Hiccups	1	1 (5.0)	1	1 (5.0)	–	–	–	–	–	–	–	–
Skin and subcutaneous tissue disorders	6	6 (30.0)	7	6 (30.0)	–	–	3	3 (33.3)	–	–	–	–
Hyperhidrosis	6	6 (30.0)	7	6 (30.0)	–	–	3	3 (33.3)	–	–	–	–

Abbreviations: *n*, number; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; THC, Δ^9-tetrahydrocannabinol.

cohorts of Part B of the study were not fully enrolled to the targeted 15 participants per cohort due to recruitment difficulties, the achieved sample size was sufficient, as evidenced by the highly significant reductions of VAS "Feeling High," VAS "Alertness," and body sway.

The current study involved simultaneous coadministration of selonabant and THC. The results presented here supported subsequent clinical testing of delayed administration of selonabant, and the use of higher doses of THC, as the next steps in the development of selonabant for emergency treatment of patients suffering from ACI or related disorders.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

K.C.C. is Chief Scientific Officer and a shareholder of Anebulo Pharmaceuticals. J.F.L. is a shareholder of Anebulo Pharmaceuticals. D.S. is a former Chief Executive Officer of Anebulo Pharmaceuticals and a shareholder. L.E.K. is a paid consultant for Anebulo Pharmaceuticals. M.T. and L.E.K. are employees of Verdient Science. All other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

A.A.G, J.A.A.C.H., K.C.C., L.E.K, and G.J.G. wrote the manuscript. A.A.G, J.A.A.C.H., M.T., J.F.L, D.S., K.C.C., L.E.K, and G.J.G. designed the research. A.A.G, J.A.A.C.H., and G.J.G. performed the research. M.J., E.K., and M.T. analyzed the data.

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