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A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group QT/QTc Study to Evaluate the Electrophysiologic Effects of THC/CBD Spray

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Abstract

Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray has proved efficacious in the treatment of spasticity in multiple sclerosis and chronic pain. A thorough QT/QTc study was performed to investigate the effects of THC/CBD spray on electrocardiogram (ECG) parameters in compliance with regulatory requirements, evaluating the effect of a recommended daily dose (8 sprays/day) and supratherapeutic doses (24 or 36 sprays/day) of THC/CBD spray on the QT/QTc interval in 258 healthy volunteers. The safety, tolerability, and pharmacokinetic profile of THC/CBD spray were also evaluated. Therapeutic and supratherapeutic doses of THC/CBD spray had no effect on cardiac repolarization with primary and secondary endpoints of QTcI and QTcF/QTcB, respectively, showing similar results. There was no indication of any effect on heart rate, atrioventricular conduction, or cardiac depolarization and no new clinically relevant morphological changes were observed. Overall, 19 subjects (25.0%) in the supratherapeutic (24/36 daily sprays of THC/CBD spray) dose group and one (1.6%) in the moxifloxacin group withdrew early due to intolerable AEs. Four psychiatric serious adverse events (AEs) in the highest dose group resulted in a reduction in the surpatherapeutic dose to 24 sprays/day. In conclusion, THC/CBD spray does not significantly affect ECG parameters. Additionally, THC/CBD spray is well tolerated at therapeutic doses with an AE profile similar to previous clinical studies.

Keywords

cannabinoids, tetrahydrocannabinol, cannabidiol, cardiotoxicity, toxic psychosis

An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, which puts patients at risk of sudden cardiac death. Current regulatory guidance emphasizes the need for clear robust data on the effect of new chemical entities on electrocardiogram (ECG) parameters,[1] with focus on cardiac repolarization, as measured by the QTc duration.

Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) spray (Sativex) is an oromucosal spray containing two principal cannabinoids, THC and CBD. These extracts are prepared from the *Cannabis sativa* L. plant and formulated into an approximate 1:1 ratio alongside minor cannabinoids and other plant components, including but not limited to the phytocannabinoids cannabigerol and cannaibicromene, as well as cannabis terpenoids.[2] There is much interest in the future development of THC/CBD spray as it has promising efficacy in several therapeutic areas and currently has approval for use in the UK, Spain, Czech Republic, New Zealand, Germany, Sweden, Denmark, and Canada for the treatment of spasticity due to multiple sclerosis (MS), and is also approved and marketed in Canada for the relief of neuropathic pain in MS and as an adjunctive treatment in

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cancer pain. THC/CBD spray has also shown positive effects on non-MS neuropathic pain,[3,4] rheumatoid arthritis,[5] and bladder dysfunction.[6]

Cannabis use may be associated with tachycardia and transient changes in blood pressure.[7–11] There was also one report of antiarrhythmic effects after large doses in subjects treated with intravenous THC.[12] Although there are few reports of cardiovascular events associated with marijuana use, it is feasible that the real incidence of arrhythmias is substantially underreported given the prohibition of cannabis use.[13] Despite this, a large cohort study showed no association between marijuana use and hospitalization or mortality associated with cardiovascular disease.[14]

Given the regulatory requirements and the potential cardiovascular effects of cannabinoids, it was felt necessary to evaluate the effects of THC/CBD spray on the QT/QTc interval in humans. As such, the effects of THC/CBD spray on ECG parameters were investigated.

Methods

This multiple-dose, randomized, double-blind, double-dummy, placebo- and active-controlled, four-arm, parallel-group study, designed to evaluate the effect of THC/CBD spray on the QT/QTc interval, was performed in 258 healthy male and female subjects aged between 18 and 45 years inclusive. It was carried out by an independent contract research organization at one study center (DecisionLine Clinical Research Corporation, ON, Canada), with all subjects enrolled on-site. It was designed in accordance with the Declaration of Helsinki, and with adherence to the principles of Good Clinical Practice (GCP), outlined by the ICH GCP guidelines, was reviewed and approved by the Ontario Institutional Review Board, and all participants provided written informed consent.

Primary Objective

The primary objective was to evaluate the effects of therapeutic and supratherapeutic doses of THC/CBD spray on ECG parameters.

Secondary Objectives

Secondary objectives were to evaluate the safety, tolerability, and pharmacokinetics (PKs; CBD, THC and its metabolite 11-hydroxy-THC [11-OH-THC]) of THC/CBD spray following multiple dose administration, and to evaluate the relationship between the PKs and the QT/QTc interval.

Inclusion Criteria

Eligible subjects were English speakers aged 18–45 with a body mass index (BMI) between 19 and 29.9 kg/m^2, and a minimum weight of 50 kg at screening. Eligible subjects were non-tobacco users within 6 months of study onset, were free from clinically significant abnormalities, and had systolic and diastolic blood pressures between 90–140 and 50–90 mmHg at screening, respectively. Those of reproductive potential were required to ensure effective contraception was used within 1 month of study onset, for the study duration, and for a minimum of 60 days following study completion. Female subjects were required to have a negative pregnancy test result, were to not be lactating or planning a pregnancy for at least 60 days following study completion. All subjects also had to be willing to abide by all study requirements and restrictions.

Exclusion Criteria

Subjects with a history of significant psychiatric, renal, hepatic, gastrointestinal, endocrine, immunologic, dermatologic, oncologic, cardiovascular, or convulsive disorder or with a known hypersensitivity to the study medication were excluded. Subjects taking a non-prescription medication (within 7 days of study onset), a prescription, natural, or recreational drug (within 14 days of first dosing and throughout the study), or those who had received any investigational medicinal product within 30 days of screening were excluded, as were those with a known history of alcohol or substance abuse. Those using cannabis or a THC-containing medicine within 3 months of study entry were excluded, as were those with habituation to analgesic drugs and those unable to refrain from consuming caffeine for at least 9 days. Those who were positive for Hepatitis B, Hepatitis C, or HIV at screening were excluded, as were those with current or pending legal charges, or on probation. Subjects who had donated more than 50 mL of blood within 30 days, or more than 400 mL with 56 days of admission for treatment were excluded, as were those who were study site employees, or relatives of employees directly involved in the study.

Treatment Groups and Dosing

Subjects attended a screening visit to determine eligibility, then, within 30 days were admitted to the study site 2 days prior to Dosing (Day −1) to reassess eligibility. The following day (Day 0) triplicate (i.e., three simultaneous recordings) baseline ECG measurements were performed at 14 specified times (0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 23.5 hours post the time of the planned first dose on Days 1–5) to provide averaged time-matched baseline QT intervals for comparison with the intervals obtained later in the treatment session.

Dosing. Each 100 μL spray of THC/CBD spray contained 2.7 mg THC and 2.5 mg CBD. The therapeutic dose of THC/CBD spray chosen for the study was eight daily sprays which totaled 21.6 mg THC + 20 mg CBD, and the supratherapeutic doses of 24 or 36 daily sprays

totaled 64.8 mg THC + 60 mg CBD (24 sprays) or 97.2 mg THC + 90 mg CBD (36 sprays), respectively (36 daily sprays was the initial supratherapeutic dose, but this was later reduced to 24 daily sprays due to four subjects experiencing psychiatric serious adverse events [SAEs]). Placebo spray contained the colourants plus excipients, and placebo tablets were similar in size, shape, and color to moxifloxacin tablets but contained no active ingredient. Moxifloxacin tablets (400 mg) served as the positive control.

Subjects were randomized to one of four treatment groups according to a pre-generated randomization schedule:

Group 1: received 24 or 36 placebo sprays (divided into 12 or 18 sprays twice daily, 12 hours apart) for 5 days and a single oral moxifloxacin placebo on Day 5.

Group 2: received eight sprays of THC/CBD spray (four sprays twice daily, 12 hours apart) and 16 or 28 placebo sprays (eight or 14 sprays twice daily every 12 hours) for 5 days and a single oral moxifloxacin placebo on the morning of Day 5.

Group 3: received 24 or 36* THC/CBD sprays (12 or 18 sprays twice daily 12 hours apart) for 5 days and a single oral moxifloxacin placebo on the morning of Day 5.

*It should be noted that during the study, the supratherapeutic dose was reduced from 36 sprays to 24 sprays THC/CBD spray following SAEs in four subjects (in 162 exposures, 2.5%) who received THC/CBD sprays at 36 sprays. ECG data were analyzed for the two supratherapeutic doses combined (n = 52 total; 29 of these subjects received THC/CBD spray at 24 sprays, and 23 subjects received THC/CBD spray at 36 sprays).

Group 4: received 24 or 36 placebo sprays (12 or 18 sprays twice daily 12 hours apart) for 5 days and a single oral moxifloxacin 400 mg tablet on the morning of Day 5.

Blinding was maintained by using two vials of spray. At each dose, four THC/CBD spray or placebo sprays were administered from Vial 1 and the remaining eight THC/CBD spray or placebo sprays were administered from Vial 2.

THC/CBD spray or placebo administration was started on Day 1 and continued for 5 days. On the morning of Day 5, subjects received either moxifloxacin 400 mg (Group 4) or moxifloxacin placebo (Groups 1, 2, and 3) in addition to the THC/CBD spray/placebo sprays.

On Days 1–4, vital signs and safety ECG measurements were collected pre-dose and at 2 hours post-dose. Triplicate ECG measurements, PK samples and vital signs measurements were collected on Day 5 at exactly the same time points as the ECG measurements taken on Day 0. In addition, a safety EGC was performed pre- and approximately 2 hours post-dose.

Adverse events (AEs) were recorded throughout the study period. The last post-dose procedures were completed 23.5 hours after the last dose and then a final safety follow-up visit was performed 7–14 days later.

Study Design

The study was designed to take into account the long terminal elimination half-life of THC/CBD spray and the potential for lower tolerability of THC/CBD spray in healthy, drug naïve subjects.

Despite sampling of plasma concentration levels during chronic THC/CBD spray dosing suggesting that significant accumulation does not occur, and although a crossover design is often recommended for these studies,[1] it was not appropriate in this instance for several reasons. Firstly, the distribution and slow release of THC and active metabolites from adipose tissue results in a prolonged terminal elimination half-life. Secondly, since high doses of THC/CBD spray were used, a crossover design would increase the risk of subject withdrawals, which would hinder data collection for the lower THC/CBD spray dose and moxifloxacin. As such, a parallel-group multiple-dose trial design was selected to evaluate the effects of THC/CBD spray on QT/QTc intervals.

In accordance with ICH guidelines moxifloxacin tablets (400 mg) served as the positive control to establish assay sensitivity since it is known to have an effect on the mean QT/QTc interval of about 5 milliseconds (ms).[1] The study was performed in healthy volunteers to eliminate variables known to change ECG parameters such as concomitant drugs, diseases etc. All subjects were either cannabis-naïve or had not taken cannabis or THC-containing medicines for at least 3 months prior to study entry.

Assay for the Measurement of Moxifloxacin

Assay method. The assay was developed and validated by Quotient Bioresearch Limited (Cambridge, UK), who measured moxifloxacin in human plasma (100 flL) by liquid chromatography-tandem mass spectrometry (LC–MS/MS) following protein precipitation and reference to a calibration line over the range 50–5,000 ng/mL, extracted with each batch. Quality control (QC) samples at three concentrations were interspersed with the test samples at 150, 1,000, and 4,000 ng/mL for moxifloxacin. The internal standard used in the assay was lomefloxacin.

Data processing. Data collection and peak area integration were performed using Analyst software

(versions 1.4.1 and 1.4.2) associated with the mass spectrometer. Standard regression and quantification were performed using Watson L1MS (version 7.0). The mass spectrometer response (peak area ratio of analyte to internal standard) of each calibration standard was plotted against the theoretical (prepared) concentrations. This plot was subjected to least squares regression analysis using a linear fit (weighted 1/x2) to provide values for correlation coefficient and back-calculated concentrations.

Acceptability of analytical batches. The acceptability of each batch of test samples depended on the data from the calibration standards and the QC samples fulfilling the following requirements:

- At least 75% of calibration samples being within ±15% (±20% at the Lower Limit of Quantification [LLOQ]) of their target concentration.
- At least four of the six QC samples being within ±15% of their respective target values.
- Two of the six QC samples may be outside the ±15% limit but not at the same concentration.

Assay for the Measurement of THC, 11-OH-THC, and CBD

The assay was developed and validated by Quotient Bioresearch Limited. Each study sample was initially analyzed using an assay with a LLOQ of 0.5 ng/mL for THC, 11-OH-THC, and CBD. Following the first phase of analysis, a more sensitive analytical method with a LLOQ of 0.1 ng/mL was developed and was used to reanalyze specific samples which were originally Below the Limit of Quantification.

Original assay (LLOQ of 0.5 ng/mL) method. Human plasma samples (200 µL) were analyzed for THC, 11-OH-THC, and CBD by LC–MS/MS after supported liquid extraction, and referenced to a calibration line over the range 0.5–100 ng/mL for THC, 11-OH-THC, and CBD, extracted with each batch. QC samples at three concentrations were interspersed with the test samples at 1.5, 40, and 75 ng/mL for THC, 11-OH-THC, and CBD. The respective internal standards used in the assay were d3-THC, d3-11-OH-THC, and d3-CBD.

More sensitive assay (LLOQ of 0.1 ng/mL) method. Human plasma samples (500 µL) were analyzed for THC, 11-OH-THC, and CBD by LC–MS/MS after solid-phase extraction and referenced to a calibration line over the range 0.1–100 ng/mL for THC and 0.1–30 ng/mL for 11-OH-THC and CBD, extracted with each batch. QC samples at three concentrations were interspersed with the test samples at 0.3, 45, and 80 ng/mL for THC, and at 0.3, 15, and 23 ng/mL for 11-OH-THC and CBD. The respective internal standards used in the assay were d3-THC, d3-11-OH-THC, and d3-CBD.

Analysis sequence. Each batch of samples was injected as follows: serum separator tube, wash solvent, blank, zero, calibration standards, extracted carryover blank, unknown samples interspersed with QC samples, duplicate calibration standards at LLOQ, and Upper Limit of Quantification levels. Each batch consisted of 96 samples or less.

Data Processing and acceptability of analytical batches. Data processing was carried out as for moxifloxacin, and the acceptability of analytical batches was also the same.

Statistical Considerations

Sample size. The sample size was based on the non-inferiority of THC/CBD spray against placebo in the primary analysis. A sample size of 60 subjects per group was selected to provide at least 80% power to show that the upper limit of the 90% confidence interval (CI; two-sided) for the comparison of THC/CBD spray and placebo would fall below 10 ms.[15]

Triplicate ECG analysis. The primary analysis was a time-matched analysis performed at all 14 time points to investigate whether anyone had a placebo corrected mean change from baseline in QTcI in which the upper two-sided 90% (i.e., one-sided upper 95%) CI exceeded 10 ms. Placebo correction was calculated as the difference from the mean change of the same time point in the subjects on placebo.

Change from mean of all baseline ECGs to the mean of all on-treatment ECG values for a given subject for each of: heart rate and PR, QRS, QT, QTc intervals were calculated. Time-averaged analysis (i.e., mean of all time points at baseline and steady state [Day 5]) was also included to provide a context for other historical drug data. New ECG morphological changes (present on treatment but not baseline ECGs) were also evaluated.

Correction formulae. QTcI was the individually determined QT correction, and the goal was to find β such that QTcI was a constant, where $QTcI = QT/(RR)^{\beta}$ where RR is the interval from the onset of one QRS complex to the onset of the next QRS complex.

Additional correction formulae that were included but considered secondary were QTcF and QTcB, and were defined as:

- QTcF was the length of the QT interval corrected for heart rate by Fridericia's formula:

$$QTcF = \frac{QT}{(RR)^{1/3}}$$

- QTcB was the length of the QT interval corrected for heart rate by Bazett's formula:

$$QTcB = \frac{QT}{(RR)^{1/2}}$$

Pharmacokinetics. PKs for CBD, THC and its metabolite 11-OH-THC included C_{max}, T_{max}, AUC_{0-t}, and AUC_{0-inf} (derived using non-compartmental data analysis).

Methods Employed to Control for Variability

To control for variability in the study, a number of methods were employed. Inclusion into the study was limited to those aged between 18 and 45 due to the potential association between increasing age and QTc prolongation. The BMI of subjects enrolled was also limited to between 19 and 29.9 kg/m^2, since increasing BMI has been associated with increases in the QTc interval in healthy subjects, potentially leading to ventricular hypertrophy and myocardial action potential prolongation.[16] Further measures to reduce variability in the results included blinding ECG analysts and cardiologists to the treatment allocation, and having the same trained analyst reading individual subjects' ECGs, with interval durations further verified by a cardiologist.

Results

Subject Disposition and Demographics

A total of 258 eligible subjects were randomized with 257 receiving at least one dose of study drug and 229 completing the study. Of the subjects randomized to each treatment group, 98.3% for placebo (59 of 60 subjects), 98.4% for THC/CBD 8 sprays (60 of 61 subjects), and 98.4% for moxifloxacin (60 of 61 subjects) completed the study. A total of 65.8% of subjects (50 of 76 subjects) completed the study in the combined THC/CBD 24/36 sprays group: 80.0% (28 of 35 subjects) in the THC/CBD 24 sprays group and 53.7% (22 of 41 subjects) in the THC/CBD 36 sprays group. Twenty-nine subjects (11.2%) withdrew from the study prior to completion; one subject each in the placebo, THC/CBD spray 8 sprays, and moxifloxacin groups (1.7%, 1.6%, and 1.6%, respectively) and 26 subjects (34.2%) in the combined THC/CBD spray 24/36 sprays group (seven subjects taking 24 sprays and 19 subjects taking 36 sprays). The subjects in the placebo and THC/CBD spray at eight sprays groups withdrew consent, the subject in the moxifloxacin group and 19 subjects in the THC/CBD spray 24/36 sprays group withdrew due to intolerable AEs, and the remaining seven subjects in the THC/CBD spray 24/36 sprays groups withdrew consent. No subjects discontinued due to marked prolongation of QT/QTc interval alone. Two subjects were withdrawn due to AEs of QT interval prolonged in addition to other AEs and therefore were counted in the category of discontinuations due to intolerable AEs rather than marked prolongation of the QT/QTc interval. Both subjects were in the 36 spray dose group. One subject experienced toxic psychosis which resolved upon treatment cessation and led to their withdrawal from the study, and the other experienced intolerable AEs of mild abdominal pain upper, dizziness, anxiety, fatigue, left upper quadrant pain, and vomiting, with led to their withdrawal from the study (their mild AE of prolonged QT resolved within 7 hours).

Baseline medical history and physical and oral examinations revealed little of clinical significance.

There was a greater proportion of male (64.2%) to female (35.8%) subjects overall in the study, with no marked differences between treatment groups. The average age of study participants was approximately 32 years, again with little variation between treatment groups. The ethnic origins of subjects varied overall, but were similar between groups.

Primary Objective Results

Triplicate ECG results. The time-matched analysis for the QTcI endpoint revealed that assay sensitivity criteria were met (Fig. 1). The placebo-corrected, time-matched change in QTcI from baseline for moxifloxacin was greater than 5 ms at all 14 time points (range of 6.1–18.2 ms), including those time points pre-specified for determination of assay sensitivity (1, 1.5, 2, 2.5, 3, and 4 hours), where differences ranged from 14.8 to 18.2 ms. All upper bounds of the 90% CIs exceeded 10 ms ($\geq$10.4 ms) and those at the pre-specified time points ranged from 19.1 to 22.5 ms.

For THC/CBD spray, most placebo-corrected changes from baseline values were less than 5 ms, ranging from −4.1 to 5.2 ms for THC/CBD spray 8 sprays and from −5.5 to 6.2 ms for THC/CBD spray 24/36 sprays. The upper bounds of the 90% CIs for both THC/CBD spray treatment groups were below the 10 ms thresholds at all time-points, indicating no effect on cardiac repolarization.

Time-averaged analysis. Assay sensitivity was confirmed by the time-averaged analysis: placebo-corrected change from baseline in QTcI for moxifloxacin exceeded 10 ms. The time-averaged data confirmed the lack of QTc effect of THC/CBD spray. In both THC/CBD spray groups, the upper bounds of the 90% CIs for placebo-corrected change from baseline were less than 10 ms for QTcI. Small non-significant changes observed in the primary endpoint of time-matched, placebo-corrected change in QTcI from baseline were slightly greater in the therapeutic compared with the supratherapeutic THC/CBD spray dose group.

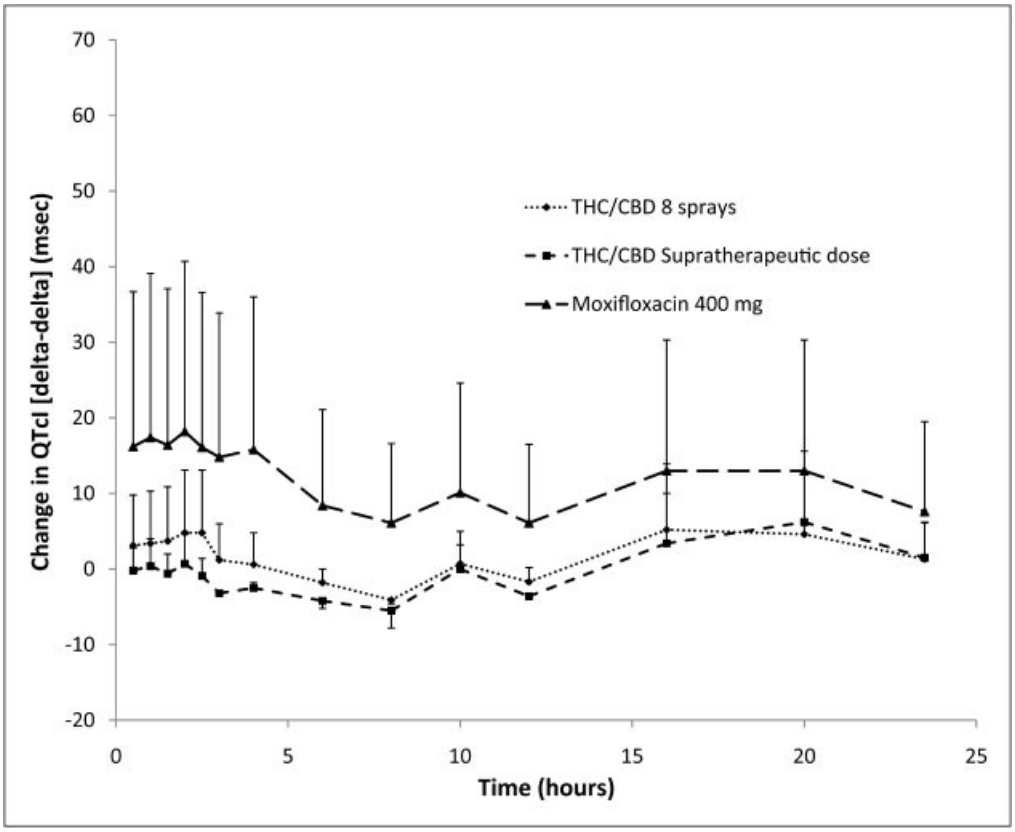

Figure 1. Placebo-corrected, change from baseline in QTcI (ms)—Estimated from mixedmodel analysis of variance (90% CI).

Secondary Objective Results

When the additional corrected QTc values of QTcF and QTcB were calculated according to their appropriate formulae, they showed similar results to the primary endpoint of QTcI; there was no signal of a THC/CBD spray effect on cardiac repolarization based on QTcF (data not shown) and only a very small effect when based on the less accurate QTcB (data not shown). Time-averaged analysis for QTcF and QTcB mirrored the finding for QTcI, further supporting the fact that THC/CBD spray had no effect on cardiac repolarization (data not shown).

Analysis of the remaining secondary endpoints of heart rate, PR interval, QRS interval, and uncorrected QT interval all showed little of note between treatment groups.

Treatment emergent abnormalities in ECG morphological patterns observed on Day 5 included inverted T wave abnormalities in four (7%) of subjects receiving THC/CBD spray in the 8 spray group, three (5%) receiving moxifloxacin, and three (5%) placebo subjects. Other events included ST segment depression in two (4%) of subjects in the 24/36 spray THC/CBD spray group, two (3%) in the moxifloxacin group, and one (2%) in the placebo group. None of the new morphological changes observed was considered clinically significant.

Safety variables. AEs were analyzed separately for Days 1–5 pre-dose and Day 5 post-dose onwards, because the subjects in the moxifloxacin group received placebo sprays from Day 1 to Day 4 and did not receive moxifloxacin until Day 5. A summary of treatment-emergent AEs which occurred in at least 10% of subjects in any given treatment group is presented in Table 1.

Overall, the therapeutic dose of THC/CBD spray (eight sprays) was well-tolerated, while the supratherapeutic doses (24 and 36 sprays) were not well-tolerated with numerous central nervous system (CNS) and psychiatric AEs reported. The most common AEs in the study were somnolence, dizziness, euphoric mood, headache, nausea, and dry mouth, and the most commonly affected body systems were the nervous system and gastrointestinal system, followed by psychiatric disorders and general disorders and administration site conditions.

There were no deaths in this study. Four subjects (9.8%) in the THC/CBD spray 36 sprays group experienced SAEs, all of which were psychiatric in nature. Most events had resolved within an hour following treatment although one delusional disorder took 3 days to resolve completely.

There were few apparent treatment- or dose-related changes in laboratory parameters, although five subjects

Table 1. Treatment-Emergent Adverse Events (Preferred Term) Reported in at Least 10% of Subjects in Any Treatment Group

Preferred Term	Placebo		THC/CBD spray						Moxifloxacin	
			8 Sprays		24 Sprays		36 Sprays			
	Number of subjects (%)									
Day[a]	1–5 (n = 60)	5+ (n = 59)	1–5 (n = 60)	5+ (n = 60)	1–5 (n = 35)	5+ (n = 29)	1–5 (n = 41)	5+ (n = 22)	1–5[b] (n = 61)	5+ (n = 60)
Somnolence	7 (11.7)	6 (10.2)	16 (26.7)	6 (10.0)	12 (34.3)	6 (20.7)	20 (48.8)	4 (18.2)	12 (19.7)	1 (1.7)
Dizziness	3 (5.0)	0	18 (30.0)	4 (6.7)	19 (54.3)	2 (6.9)	17 (41.5)	2 (9.1)	4 (6.6)	3 (5.0)
Euphoric mood	4 (6.7)	0	10 (16.7)	2 (3.3)	15 (42.9)	1 (3.4)	16 (39.0)	0	0	1 (1.7)
Headache	10 (16.7)	4 (6.8)	6 (10.0)	3 (5.0)	5 (14.3)	3 (10.3)	7 (17.1)	0	3 (4.9)	4 (6.7)
Nausea	2 (3.3)	1 (1.7)	3 (5.0)	0	10 (28.6)	0	9 (22.0)	1 (4.5)	4 (6.6)	5 (8.3)
Dry mouth	0	0	6 (10.0)	0	12 (34.3)	2 (6.9)	3 (7.3)	0	1 (1.6)	0
Vomiting	1 (1.7)	0	1 (1.7)	0	5 (14.3)	0	10 (24.4)	1 (4.5)	2 (3.3)	2 (3.3)
Constipation	3 (5.0)	0	8 (13.3)	1 (1.7)	2 (5.7)	0	2 (4.9)	1 (4.5)	2 (3.3)	0
Fatigue	2 (3.3)	0	7 (11.7)	0	2 (5.7)	0	5 (12.2)	0	0	1 (1.7)
Pallor	0	0	1 (1.7)	1 (1.7)	4 (11.4)	0	5 (12.2)	0	0	0
Decreased appetite	0	0	0	0	2 (5.7)	0	5 (12.2)	1 (4.5)	1 (1.6)	1 (1.7)
Tachycardia	0	0	0	0	4 (11.4)	0	5 (12.2)	0	0	0
Feeling hot	0	0	0	1 (1.7)	1 (2.9)	0	5 (12.2)	1 (4.5)	0	0
Feeling of relaxation	0	0	2 (3.3)	0	4 (11.4)	0	2 (4.9)	0	2 (3.3)	0
Inappropriate affect	0	0	2 (3.3)	0	4 (11.4)	0	2 (4.9)	0	0	0
Disorientation	0	0	0	1 (1.7)	0	0	6 (14.6)	0	0	0

[a]Days 1–5 = Day 1 post-dose to Day 5 pre-dose; Day 5+ = Day 5 post-dose to end of study.
[b]Moxifloxacin group received placebo on Day 1 to Day 5 pre-dose.

had clinically significant abnormal liver function tests that were recorded as AEs at follow-up. One subject in the eight sprays THC/CBD spray group had a mild AE of liver function tests abnormal (ALT; Alanine aminotransferase) at follow-up on study Day 15. Two subjects in the 24 sprays THC/CBD spray group had clinically significant elevations in aspartate aminotransferase (AST) and ALT values at follow-up, which were recorded as AEs of hepatic enzyme increased. One subject in the 36 sprays THC/CBD spray group had a high ALT value that was recorded as an AE at follow-up. One subject in the moxifloxacin group also had elevated AST and ALT at follow-up.

Slight increases in blood pressure and pulse rate were observed in subjects in the supratherapeutic THC/CBD spray dose group, particularly on Day 1. This was mirrored in the safety ECG results which demonstrated an increase in ventricular rate and a decrease in QT interval for the same group over the same time scale. In addition, nine subjects in this group had AEs of tachycardia and two subjects were discontinued due to intolerable AEs which included ECG QT prolonged. There were no apparent effects on respiratory rate and oral temperature.

Pharmacokinetic variables. Mean plasma concentrations of THC and CBD peaked between approximately 1–3 hours post-dose at mean concentrations of 3.1 and 1.5 ng/mL, respectively, for the 8 sprays group and 9.2 and 4.8 ng/mL for the 24/36 sprays group. In the THC/CBD spray 24/36 sprays group, the initial peak was followed by a second rise at approximately 6 hours post-dose. Mean plasma levels of 11-OH-THC peaked later at approximately 2–3 hours post-dose. The PK parameters for THC, CBD, and 11-OH-THC are summarized in Table 2 and mean plasma concentration versus time curves for each analyte are presented in Figure 2. There was a relatively high degree of inter-subject variability in PK parameters.

Pharmacokinetic-pharmacodynamic analysis. The slopes for placebo-corrected change in QTcI from baseline versus THC, 11–OH–THC, and CBD plasma concentrations were flat to negative. The upper bounds of the 95% CIs for predicted change in QTcI at average THC, 11–OH–THC, and CBD C_{max} (at all THC/CBD spray doses) were less than 10 ms ($\leq$5.821 ms). In contrast, the corresponding upper bound for moxifloxacin was 15.61 ms. These PK-pharmacodynamic data further support the lack of effect of THC/CBD spray (THC, 11–OH–THC, and CBD) on cardiac repolarization.

Discussion

This thorough QTc study at a range of doses including supratherapeutic doses of THC/CBD spray demonstrated

Table 2. Summary of Pharmacokinetic Parameters for THC, CBD and 11–OH–THC

	THC				CBD				11-OH-THC			
Parameter	Cmax (ng/mL)	Tmax (hour)	AUC_{0-t} (h × ng/mL)	AUC_{0-inf} (h × ng/mL)	Cmax (ng/mL)	Tmax (hour)	AUC_{0-t} (h × ng/mL)	AUC_{0-inf} (h × ng/mL)	Cmax (ng/mL)	Tmax (hour)	AUC_{0-t} (h × ng/mL)	AUC_{0-inf} (h × ng/mL)
Statistic	Mean (SD)	Median (min–max)	Mean (SD)	Mean (SD)	Mean (SD)	Median (min–max)	Mean (SD)	Mean (SD)	Mean (SD)	Median (min-max)	Mean (SD)	Mean (SD)
THC/CBD 8 sprays (n = 60)	3.1 (1.64)	1.9 (0.87–23.95)	14.4 (11.29)	20.3 (11.64)	1.5 (0.78)	1.4 (0–8.45)	6.1 (5.76)	14.8 (7.87)	3.9 (2.23)	1.9 (0.87–6.48)	28.6 (23.37)	38.2 (26.90)
THC/CBD 24/36 sprays (n = 51)	9.2 (6.29)	2.4 (0–23.95)	63.2 (55.55)	79.3 (57.63)	4.8 (3.40)	1.5 (0–6.45)	38.9 (33.75)	60.3 (37.71)	10.0 (6.86)	2.5 (0–6.45)	90.6 (72.16)	109.4 (80.57)

AUC_{0-inf}, area under the curve from time = 0 to infinity; AUC_{0-t}, area under the curve from time = 0 to last concentration; C_{max}, peak plasma concentration; SD, standard deviation; T_{max}, time to peak plasma concentration.

no significant effects on cardiac repolarization for any of the correction methods applied. Furthermore, THC/CBD spray had no significant effects on heart rate, PR, or QRS interval duration or cardiac morphology. Therefore, the results of this study reliably demonstrate that THC/CBD spray does not significantly affect ECG parameters. The study was valid and sensitive: moxifloxacin demonstrated the expected increase in QTcI duration at all of the pre-specified time points. In addition, placebo group data demonstrated a control of background QTc variability. The sample size used in the study was also large compared with other similar QT/QTc studies, thus providing a considerable amount of information regarding both the cardiovascular effects of THC/CBD spray as well as more general safety data.

The endocannabinoid system is thought to play a key role in the control of heart rate and blood pressure, but also contributes to pathological conditions by affecting the heart and arterial performance through alteration of cardiometabolic risk factors.[17] The use of cannabis on a whole has been associated with tachycardia and transient changes in blood pressure,[7–11] and due to its effects on blood pressure and heart frequency, its use is thought to increase the risk of heart attacks.[18] The current investigation demonstrates that THC/CBD spray does not usually significantly affect

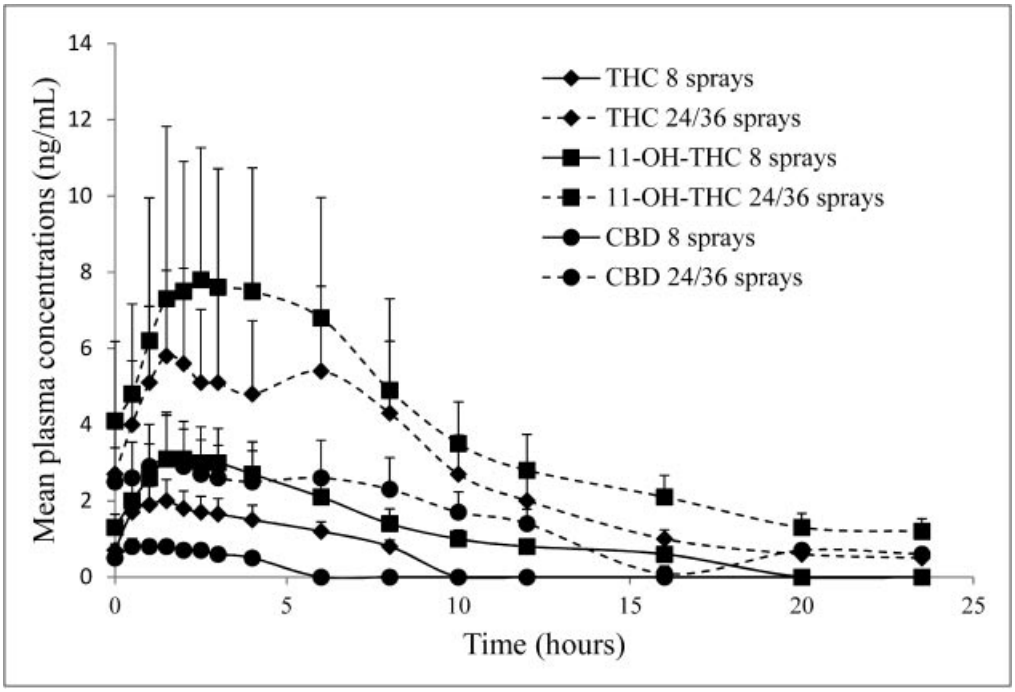

Figure 2. Mean (SEM) plasma concentration versus time curves for THC, 11-OH-THC and CBD following 8 and 24/36 sprays of THC/CBD spray. Values below the limit of quantification are entered as zero.

ECG parameters, even at supratherapeutic doses. However, plasma levels of THC and CBD in this study were much lower than those seen with smoked cannabis, even at the supratherapeutic dose.

There was a relatively high degree of variability in PK parameters for all analytes following THC/CBD spray administration, but all data were consistent with the results seen in previous studies[19,20] and suggest that there is little if any accumulation of cannabinoids in plasma during chronic dosing, at least over a 5 day dosing period.

Overall, the therapeutic dose of THC/CBD spray was well tolerated, while supratherapeutic doses were not. Psychiatric SAEs were reported by four subjects, all of whom were taking 36 sprays/day. All subjects who experienced a SAE ceased treatment and withdrew from the study. This study was carried out in accordance with ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs guidance, which suggests testing at substantial multiples of the anticipated maximum therapeutic exposure.[1] The dose selected for this study was expected to be close to the maximum tolerated dose in healthy volunteers. As such, the SAE findings are not surprising. Interestingly, the number of events of toxic psychoses in this study suggests that THC/CBD spray was better tolerated in this respect than the synthetic cannabinoid, dronabinol. Numerous instances of toxic psychoses were encountered during clinical trials of oral dronabinol on doses as low as 16.5–20 mg THC in two of eight cannabis-experienced subjects,[21] and at even lower doses when administered intravenously.[22] Recent publications have strongly supported the ability of CBD[23–25] and other phytocannabinoid and terpenoid components[2] to improve the therapeutic index of THC, particularly with respect to its psychoactive sequelae. CBD is present in THC/CBD spray at levels similar to those of THC, and it is reasonable to conclude that its presence may have attenuated the psychoactivity of THC at the high doses used in this study. Subjects taking the therapeutic dose of eight sprays a day did not differ substantially from subjects in the placebo group. This confirms that the current recommended dosing schedule within the normal clinical setting is unlikely to carry the risk of the significant psychiatric AEs seen in this study.

Conclusions

In conclusion, this thorough QT/QTc study demonstrates that THC/CBD spray does not significantly affect ECG parameters, even at the maximum tolerated dose. It is not possible to exclude an effect on the QT interval at doses above this. This is a reassuring finding considering the cardiovascular concerns associated with cannabis use. In addition, THC/CBD spray is well tolerated at therapeutic doses reflective of those administered in a clinical setting, with a similar AE profile to those seen in previous clinical studies of the drug.

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Conflict of Interest Disclosure and Funding Declaration

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