Final study report

"Cannabidiol as an add-on therapy in treatment-refractory psychotic disorders"

Study acronym:	CBD_ADD_IN
EudraCT:	2013-000240-26
REC number:	13/EE/0304
Co-Sponsors:	King's College London & South London and Maudsley NHS Foundation Trust
IMP:	Cannabidiol (CBD) oral capsules
Indication studied:	Treatment refractory psychotic illness
Study design:	Open-label, therapeutic exploratory trial
Study initiation date:	** (first patient's first visit)
Date of early termination:	7th August 2015
Chief Investigator:	Paul Morrison

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Date of Report:

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments

SYNOPSIS

Study Title	Cannabidiol as an add-on therapy in treatment-refractory psychotic disorders
Study Centres	South London & Maudsley NHS Foundation Trust
First patient's first visit	25th September 2014
Last patient's last visit	10th July 2015
Last dose of IMP taken by a subject	26th June 2015
Date of early termination	7th August 2015
Design summary	An open-label, exploratory therapeutic trial of the molecule Cannabidiol in treatment refractory 1st episode psychosis (n=20), focusing on core psychological and metabolic outcomes. Cannabidiol will be added to an existing treatment regime (based on dopamine receptor antagonists) for 6-weeks duration. Clinical data will be collected over the duration of the trial, at 0, 2, 4 and 6 week time points.
Primary objective	In patients experiencing their first psychotic episode who have failed to recover despite treatment with at least one standard anti-psychotic drug, does the addition of the molecule cannabidiol (CBD) to an existing anti-psychotic treatment regime lead to lower scores in scales which measure the severity of core psychotic symptoms?
Secondary objectives	Is the addition of the molecule cannabidiol (CBD) to an existing anti-psychotic treatment regime associated with clinically improved metabolic indices? Can brain imaging be used to predict who will respond to CBD? Does CBD lead to changes in brain imaging markers that may shed light on the underlying mechanism of action of CBD in treating schizophrenia?
Primary endpoint	Scores on core psychotic symptoms and functioning, as measured by the following scales: - The Positive & Negative Syndrome Scale, PANSS22 (video-taped interview). - The Global Assessment of Functioning Scale, GAF - The Community Assessment of Psychotic Experiences, CAPE-4222 - The Montgomery-Asberg Depression Rating Scale, MADRS - The Clinical Global Impression scale, CGI.
Secondary endpoints	Measurement of Metabolic Indices:

	- Body weight - Body mass index - Waist-to-hip ratio - Fasting blood glucose and insulin - HbA1C ('glycosylated haemoglobin') - Fasting plasma lipids (Total cholesterol, LDL, HDL, triglycerides) - Plasma CBD concentrations MRI measures: - Anterior cingulate glutamate levels (1H-MRS) - Head of caudate nucleus glutamate levels (1H-MRS) - Blood flow (ASL) - BOLD activity (fMRI) - Brain structure (volumetric MRI)
Summary of eligibility criteria	Inclusion: 1. Patients aged 18-60, meeting DSM-IV criteria for schizophrenia 2. Previous treatment with >=1 anti-psychotic at therapeutic doses for >= 5 weeks. 3. Not currently in remission according to established criteria (Andreasen et al. 2005)[1]. 4. Patients are willing to provide written informed consent. Exclusion: 1. Pregnancy or lactation in women. 2. Participants (both men and women) of child bearing potential who are not willing to use reliable contraceptive precautions for the treatment duration and for three months after discontinuation of therapy. 3. Major physical illness. 4. Mental retardation. 5. Entry global Assessment of Functioning Scale (GAF) <20, 6. Alcohol or drug dependence. 7. A previous history indicative of suicidal/homicidal traits. 8. A previous history indicative of treatment non-compliance.
Primary efficacy parameter	The change in core psychotic symptoms as measured by the PANSS scale from baseline to under CBD treatment conditions.
IMP	Cannabidiol (GW Pharmaceuticals UK) 100mg capsules
Dosing regimen	Flexible titrated oral dosing as 100mg capsules x n/day (where n =1-8) Range: 200-800mg/day total, in 1-2 divided doses. Initial starting dose = 4 capsules/day.
Sample size	20
No. participants recruited	5

No. withdrawals	2 Subject 001: Dropped out following the 1st study visit due to concerns of intoxicating effects of IMP one day into the trial, after 400mg bd dose. Patient was very anxious and the perceived intoxicating effects of IMP may have been due to psychosomatic concerns. No other study participant reported intoxication from IMP. Subject 004: Was withdrawn following the 3rd study visit from the study due to worsening of mental state during the trial. However, it was deemed unlikely to be due to IMP as the participant had very poor compliance during the trial.
No. participants completing study	3
SAEs reported	0
IMP Dosing and recoded adverse events / important medical events	001: 400mg bd. AE: Intoxication 002: 800mg bd. No adverse events 003: 800mg bd. No adverse events 004: 800mg bd (very low compliance). AEs: Flatulence, stomach cramps, worsening of mental state. IME: Patient reviewed by community mental health team. Found to have deteriorated in mental state, potentially requiring admission to hospital. Following discussion with research team, it was decided that it would be best for the patient to be withdrawn from the trial. Change in mental state deemed unlikely to be due to IMP as adherence was very low. 005: 800mg bd. No adverse events
Protocol deviations	It was decided that the plasma cannabinoid levels would not be sent to the chosen labs (LGC labs) to be analysed as this would incur an additional cost of £2500. This was not deemed to be of value as only 3 participants had provided blood samples at all study visits.
Reason for early termination	The study suffered many delays in the start of the study mainly owing to a slow approval process. In July 2015 the IMP (which had an 18 month shelf life) expired. The IMP was sent for analysis and was found to be unstable so a shelf-life extension was not granted. Furthermore, the funding for the study would expire at the end of 2015. It was decided to prematurely terminate the study as it would not be worth applying for additional IMP and funding since the science has moved on by the time the IMP had expired.
Conclusions	No analysis of the data will be performed as there is insufficient data for a meaningful analysis.

Paul Morrison, Chief Investigator

SIGNATURE:_____

DATE: 16 May 2016

Reasons for early termination:

Protocol deviation: instead, the remaining funds will be sent back to GW Pharmaceuticals.