Synopsis

Clinical Report Synopsis for Protocol GWMD09126

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
GW Pharma Ltd	40:1 GWP42003/GWP42004	Cannabidiol/Tetrahydrocannabiverin

Title of Study:

A randomised, double-blind, placebo-controlled parallel group, pilot study of 40:1 ratio of formulated GWP42003:GWP42004 in the treatment of iatrogenic weight gain and dyslipidaemia associated with olanzapine or other antipsychotic(s) treatment in subjects with schizophrenia or other non-affective psychosis.

Investigator(s) and Study Centres:

Chief investigator: [redacted]

Publication(s) Reference:

None to date.

Study Period:	**Development Phase:**
Date of first signed informed consent: 03 January 2012 Date of Early Termination: 04 October 2012	

Objectives:

Primary: To evaluate the efficacy of a 40:1 ratio of GWP42003:GWP42004 compared with placebo on the change in bodyweight from baseline in subjects treated with olanzapine or other antipsychotic(s) for schizophrenia or other non-affective psychosis.

Secondary: To evaluate the efficacy of a 40:1 ratio of GWP42003:GWP42004 compared with placebo on: body fat parameters (adipose tissue distribution by skin fold thickness and waist:hip ratio measurements); lipid parameters; glucose control (fasting glucose); insulin control (fasting insulin); glycosylated haemoglobin A1c (HbA1c); hormonal markers including prolactin; markers of inflammation including cytokines and C-Reactive Protein (CRP); markers of adipocyte function including leptin and adiponectin; endocannabionoid plasma levels; positive symptoms of schizophrenia (assessed by the positive and negative symptom scale (PANSS) 'P'); negative symptoms of schizophrenia (assessed by the PANSS 'N'); general symptoms of schizophrenia (assessed by the PANSS 'G'); physicians global impression of illness severity (assessed by Clinicians Global Impression of Change [CGIC]); subjects quality of life (assessed by the Global Assessment of Functioning Scale [GAF]); assessment of symptoms of depression (Beck Depression Inventory [BDI]); assessment of extrapyramidal symptoms (Simpson-Angus Scale [SAS]); assessment of mood (UWIST Mood Adjective Checklist [UMACL]); assessment of appetite (0-10 Numerical Rating Scale [NRS]).

To assess the safety and tolerability of a 40:1 ratio of GWP42003:GWP42004 compared with placebo.

Methodology:

This up to 13 week (flexible baseline period of 1-6 weeks, six week treatment period and one week follow up), multicentre, randomised, double-blind, placebo-controlled, parallel group study was designed to evaluate the efficacy and safety of a 40:1 ratio of GWP42003:GWP42004 compared with placebo on body weight and various other parameters, in subjects treated with olanzapine for functional psychosis. Eligible subjects with evidence of recent weight gain attributable to antipsychotic(s) treatment (in the opinion of the investigator) entered the study and

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gave informed consent at the Screening Visit (Visit 1, Day -7 to -42) and commenced the baseline period before returning for a randomisation visit (Baseline Visit 2, Day 1). Eligible subjects who had gained at least 2% weight in the baseline period were randomised to treatment. Further visits occurred at the end of Weeks 3 (Visit 3, Day 22) and 6 (Visit 4, Day 43) to review safety and efficacy parameters with a final safety follow-up visit at the end of Week 7 (Visit 5, Day 50). In addition, olanzapine dosing and 0-10 NRS appetite data were collected daily in a diary.

Number of Subjects (planned and analysed):

No formal sample size calculation was required. There were to be a total of 60 planned subjects divided equally between the two treatment groups (active and placebo). As a result of the study being terminated early due to difficulties in recruitment, a total of 12 subjects were screened with just two being randomised both of whom completed the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion - Subjects meeting the following criteria were considered eligible for this study:

- Willing and able to give informed consent for participation in the study;
- Aged 18 years or above;
- Diagnosis (Diagnostic and statistical manual of mental disorders (DSM-IV-TR)) of schizophrenia, or other non-affective psychosis;
- Receiving at least one antipsychotic;
- Stable dose of antipsychotic(s) for at least two weeks prior to randomisation (Visit 2);
- Willing to maintain a stable dose of antipsychotic(s) for the duration of the study;
- Evidence of recent weight gain attributable to antipsychotic treatment (in the opinion of the investigator), prior to screening (Visit 1). Wherever possible, investigator must exclude other possible causes of weight gain, such as change in exercise, diet, concomitant medication or other illnesses;
- A further documented 2% weight gain attributable to antipsychotic treatment in the baseline period (between Visits 1 and 2);
- Willing to maintain a stable dose of any concomitant medications, (excluding as required [PRN] medicines at the investigator's discretion), and had been on a stable dose for a minimum of six weeks prior to screening (Visit 1) (with the exception of the antipsychotic(s));
- No changes in diet or exercise for six weeks prior to screening (Visit 1) and subject agreed to maintain stability, for the duration of the study (in the opinion of the investigator);
- Capable of complying with the study requirements and completing the study (in the opinion of the investigator);
- Willing for his or her name to be notified to the responsible authorities for participation in this study, as applicable;
- Willing to allow his or her primary care practitioner and consultant, if appropriate, to be notified of participation in the study.

Exclusion - The subject was not eligible for the study if ANY of the following applied:

- Subject had Axis I (DSM-IV-TR) diagnosis of schizoaffective disorder;
- Subject had drug induced or toxic psychosis (in the opinion of the investigator);
- Subject presented with a clinical picture and/ or history that was consistent with:

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- Delirium, dementia, amnesia or other cognitive disorder
- Bipolar disorder or major depression;

- Subject had a significant history of anxiety, suicidal ideation or self-harm based on history or routine psychiatric status examination (in the opinion of the investigator);
- Subject had an unstable thyroid pathology (including hypo or hyperthyroidism), within the past six months (in the opinion of the investigator);
- Subject had a history of neuroleptic malignant syndrome;
- Subject required or had electroconvulsive therapy (ECT) treatment in the two-month period prior to randomisation (Visit 2);
- Subject had a clinical diagnosis of diabetes;
- Subject was taking insulin (i.e.: was insulin dependent) or had had insulin within six months prior to Screening (Visit 1);
- Currently using or had used recreational cannabis, medicinal cannabis, cannabinoid medications (including Sativex®), or synthetic cannabinoid based medications within one month prior to screening (Visit 1) and unwilling to abstain for the duration of the study;
- Any known or suspected history of (in the opinion of the investigator):
  - Alcohol or substance abuse
  - Epilepsy or recurrent seizures;
- Any known or suspected history of depression sufficient to require treatment or disrupt ordinary life (excluding episodes of reactive depression - in the opinion of the investigator);
- BDI Score ≥ 19 (at Visit 1 or 2);
- Clinically significant cardiac, renal or hepatic impairment in the opinion of the investigator;
- Genetic dyslipidaemic condition in the opinion of the investigator;
- Female subject who was pregnant, lactating or planning pregnancy during the course of the study and for three months from the date of last dose;
- Female subjects of child bearing potential, unless willing to use two forms of contraception, one of which was to be a barrier contraception (e.g. female condom or occlusive cap [diaphragm or cervical vault/caps] with spermicide) during the study and for three months from the date of last dose (however a male condom was not be used in conjunction with the female condom);
- Male subject whose partner was of child bearing potential, unless willing to use an appropriate barrier method of contraception (condom and spermicide) in addition to having their female partner use another form of barrier contraception (e.g. occlusive cap [diaphragm or cervical vault/caps] with spermicide) during the study and for three months from date of last dose (however a male condom was not be used in conjunction with a female condom);
- Travel outside the country of residence planned during the study treatment period;
- Received an investigational medicinal product (IMP) within the 90 days before the

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screening visit (Visit 1);

- In the opinion of the investigator, was not considered to be suitable for the study;
- Poor compliance as observed during screening period;
- Any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP(s);
- Any other significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, may influence the result of the study, or the subject's ability to participate in the study;
- Any abnormalities identified during the physical examination at Visit 1 that in the opinion of the investigator would prevent the subject from safe participation in the study;
- Unwilling to abstain from donation of blood during the study;
- Previously randomised into this study.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number:

400 mg GWP42003 presented as four hard gelatin capsules containing 100 mg cannabidiol (CBD) each in Cremophor EL and Labrafil M1944CS excipients + 10 mg GWP42004 presented as two hard gelatin capsules containing 5 mg tetrahydrocannabiverin (THCV) in Cremophor EL and Labrafil M1944CS excipients.

Dosed once daily each evening 30 minutes before the evening meal.

Batch numbers: K11005B and K11006B.

Duration of Treatment:

Six weeks

Reference Therapy, Dose and Mode of Administration, Batch Number:

Matching placebo containing excipients only: Cremophor EL and Labrafil M1944CS.

Subjects received placebo as hard gelatin capsules once daily each evening 30 minutes before the evening meal.

Batch number: K11004A.

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint:

Efficacy of a 40:1 ratio of GWP42003:GWP42004 compared with placebo in the change from baseline in body weight after 42 days (6 weeks) in subjects treated with olanzapine or other antipsychotic(s) for schizophrenia or other non-affective psychosis.

Secondary efficacy endpoints:

Efficacy of a 40:1 ratio of GWP42003:GWP42004 compared with placebo on:

Body Fat Parameters:

Change from baseline to end of treatment in skin fold measurements

Change from baseline to end of treatment in waist:hip ratio

Lipid Parameters:

Change from baseline to end of treatment in serum total cholesterol

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Change from baseline to end of treatment in serum low density lipoprotein (LDL) cholesterol

Change from baseline to end of treatment in serum high density lipoprotein (HDL) cholesterol

Change from baseline to end of treatment in HDL:LDL cholesterol ratio

Change from baseline to end of treatment in serum triglycerides

Change from baseline to end of treatment in serum apolipoprotein markers (ApoA and ApoB)

Change from baseline to end of treatment in serum ApoA:ApoB ratio

Change from baseline to end of treatment in serum non-esterified ('free') fatty acids

Glucose Control:

Change from baseline to end of treatment in glucose control parameters (fasting plasma glucose)

Change from baseline to end of treatment in HbA1c (whole blood)

Insulin Control:

Change from baseline to end of treatment in insulin control parameters (fasting serum insulin)

Hormonal Marker:

Change from baseline to end of treatment in serum prolactin concentration

Markers of Inflammation:

Change from baseline to end of treatment in serum CRP and cytokines (including tumour necrosis factor (TNF-α), interleukin (IL)-6 and IL-2)

Markers of Adipocyte Function:

Change from baseline to end of treatment in serum leptin and serum adiponectin concentrations

Endocannabinoid Levels (where facilities allow):

Change from baseline to end of treatment in endocannabinoid plasma levels

Psychiatric/Clinical Assessments:

Change from baseline to end of treatment in the following assessments: PANSS 'P', PANSS 'N', PANSS 'G', GAF, BDI, UMACL, SAS, end of treatment assessment of CGIC

Appetite Assessments:

Change from baseline in mean appetite 0-10 NRS score (taken from the last seven days of baseline period [Days -7 to 0]) to the end of treatment (taken from the last seven days of treatment period)

Safety:

To assess the safety and tolerability of a 40:1 ratio of GWP42003:GWP42004 compared with placebo on adverse events (AEs), vital signs, electrocardiogram (ECG), laboratory findings and physical examination.

Statistical Methods:

Two analysis sets were planned. An intention to treat (ITT) analysis set for all efficacy endpoints and a safety set (all subjects who were randomised and received at least one dose of IMP) for all safety analyses.

A per-protocol analysis set may also have been required, should there had been sufficient protocol deviations/violations during the study, which could have affected result interpretation.

All statistical tests were to be two-sided at the 10% significance level.

All data were to be listed and summarised as appropriate. In addition, the primary and secondary endpoints were to be analysed using analysis of covariance (ANCOVA) of the changes from baseline to the end of treatment in the associated parameter. The parameter's baseline value was

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to be included as a covariate. The efficacy endpoints were to be the parameter values at the end of treatment and so use of 'last observation carried forward' imputation was implicit in their definition.

All safety data including clinical laboratory data and vital signs were to be listed and summarised appropriately. AEs were to be coded according to the MedDRA dictionary. Descriptive presentations of treatment emergent AEs were to be given by preferred term (PT) and System Organ Class (SOC) by treatment group.

In fact, following the early termination of the study with only two subjects randomised, the planned statistical analyses were no longer relevant. There were inadequate data to enable any efficacy or safety analysis evaluation and so it was decided that information for these two subjects should be presented in the format of individual subject narratives.

Summary - Conclusions:

Efficacy Results:

Due to the early termination of the study as a consequence of low recruitment, only two subjects were randomised. One subject was randomised to receive 40:1 GWP42003:GWP42004, and the other to placebo.

Both subjects' body weight increased gradually throughout the study period and alongside this, the majority of the body fat parameters (skin fold measurements and waist, hip and neck circumference) also increased. Neither subject recorded any significant changes in their appetite 0-10 NRS score between the beginning and end of the study.

The secondary efficacy data for lipid parameters, glucose and insulin control and the psychiatric scales remained largely unchanged, whilst many of the remaining secondary efficacy parameters showed more variation across the study period. However, with data from only two subjects, this information is of little value and no efficacy conclusions can be drawn.

Safety Results:

There were no major safety concerns identified. Only one treatment-related AE was reported for the subject randomised to active study medication. This was a case of mild diarrhoea that was on going throughout the study period and resolved two days after the last dose of study medication was taken.

No clinically significant changes were identified on physical examination, ECG or vital signs for either subject, and the only laboratory results of note were elevations in total cholesterol and LDL-cholesterol that were considered to be AEs by the investigator (but were present prior to the treatment period).

Conclusion:

The efficacy data from only two subjects is of minimal use and no efficacy conclusions can be drawn.

There were no new concerns with regard to safety.

Date of the Report: 13 Aug 2013