# Synopsis

## Clinical Report Synopsis for Protocol GWMD1092

| **Name of Sponsor:** | **Name of Finished Product:** | **Name of Active Ingredient:** |
|---|---|---|
| GW Pharma Ltd | GWP42003<br>GWP42004 | Cannabidiol (CBD), 5/100 mg: Delta-9-tetrahydrocannabivarin (THCV), 5 mg |

**Title of Study:**

A randomised, double blind, placebo controlled, parallel group, pilot study of 1:1 and 20:1 ratio of formulated GWP42003:GWP42004 plus GWP42003 and GWP42004 alone in the treatment of dyslipidaemia in subjects with Type 2 diabetes.

**Investigator(s) and Study Centres:**

PPD Derby, PPD United Kingdom (UK). The study comprised a further four centres in the UK. PPD Manchester, PPD UK.

**Publication(s) Reference:**

None to date.

| **Study Period:** | **Development Phase:** |
|---|---|
| Date of first signed informed consent: 08 November 2010<br>Date of last study observation: 07 February 2012 | 2a |

**Objectives:**

**Primary Objective:**

To evaluate the efficacy of a 1:1 and 20:1 ratio of GWP42003:GWP42004 (hereafter referred to as 1:1and 20:1, respectively) plus GWP42003 and GWP42004 alone compared with placebo in the treatment of dyslipidaemia in subjects with Type 2 diabetes. The primary efficacy endpoint was the impact of treatment on high density lipoprotein (HDL) cholesterol (HDL-C). Secondary measures of the primary objective were the mean changes from baseline to the end of treatment in lipid parameters.

**Secondary Objectives:**

1. To evaluate the efficacy of 1:1, 20:1, GWP42003 alone and GWP42004 alone compared with placebo on:

- Lipid parameters (HDL-C by ultracentrifugation, total cholesterol, LDL cholesterol, HDL:LDL ratio, veryLDL [VLDL], serum triglycerides, serum Apo A, serum Apo B, Apo B:Apo A ratio and serum non-esterified fatty acids [NEFAs])
- Glucose control parameters (fasting plasma glucose, oral glucose tolerance test [OGTT], serum fructosamine, and glycosylated haemoglobin A1c [HbA1c] levels (measured in whole blood)
- Insulin sensitivity (fasting serum insulin, serum C-peptide and insulin resistance (assessed by traditional Homeostasis Model Assessment [HOMA] and the more recent Homeostasis Model Assessment 2 [HOMA2] calculator), insulin sensitivity and insulin beta cell function (assessed by HOMA2)
- Body weight and body mass index (BMI)
- Adipose tissue distribution (total % body fat content, waist circumference, neck

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circumference, waist-to-hip ratio, abdominal adiposity, liver triglyceride content)

- Appetite 11-point numerical rating scale (0-10 NRS)

2. To assess the safety and tolerability of 1:1, 20:1, GWP42003 alone and GWP42004 alone compared with placebo on:

- Adverse events (AE)
- Vital signs
- Beck Depression Inventory-II (BDI-II)
- Electrocardiogram (ECG)
- Laboratory findings
- Physical examination

**Tertiary Objectives:**

CCI [redacted]

**Methodology:**

This was a 15-19 week (1-5 week baseline, 13 week treatment period and one week follow-up) efficacy and safety study. Eligible subjects entered the study at a screening visit (Visit 1, Day -35 to -7) and commenced a seven to 35 day baseline period, before returning for randomisation (Visit 2, Day 1). At the discretion of the investigator (based on individual subjects), Visit 1 could be split into two separate visits (Visits 1A and B) to allow a 21-day washout period of prohibited medications prior to blood sampling for eligibility. At Visit 2 (Day 1), eligible subjects were randomised to treatment. Further outpatient study visits (for assessment purposes) took place at the study site at the end of Week 4 of treatment (Visit 3, Day 29), and at the overall end of treatment at Week 13 (Visit 5, Day 92). A telephone assessment was also performed at Day 57 (Visit 4) and at Week 14 (Visit 6, Day 99) for safety follow-up purposes.

During the 13 week randomised treatment phase, subjects received blinded, oral doses of their allocated randomised treatment twice daily. Treatment was self-administered on an outpatient basis, once in the morning and once in the evening for 13 weeks. Subjects were instructed to time study medication to 30 minutes before breakfast and evening meals.

Physical and metabolic parameters were assessed before, during and after treatment to evaluate clinical response. Diabetic and dyslipidaemic medication usage (where applicable), and appetite 0-10 NRS data were collected daily during the treatment period, using the study diary.

**Number of Subjects (planned and analysed):**

As this was an exploratory pilot study, there was no formal sample size calculated for this study. In total there were five treatment groups: 1:1, 20:1, GWP42003 alone, GWP42004 alone and placebo. It was planned that each treatment group would include at least 10

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subjects, giving a total of 50 subjects planned overall.

In practice, 62 subjects were randomised and analysed. The 1:1, 20:1, GWP42003 alone, GWP42004 alone and placebo treatment groups contained 11, 12, 13, 12 and 14 subjects, respectively.

**Diagnosis and Main Criteria for Inclusion:**

In order to be eligible for enrolment, subjects were aged 18 years or over and had been clinically diagnosed with Type 2 diabetes, with residual islet cell function. Subject's Type 2 diabetes had to be diet controlled, or be receiving oral metformin (or other biguanides) and/or sulphonylurea as anti-diabetic treatment, a stable dose of which had to be maintained for at least three months prior to enrolment. Subjects had HDL-C ≤ 1.3 mmol/L (females) or ≤ 1.2 mmol/L (males), HbA1c level of ≤ 10% and triglycerides ≤ 10 mmol/L. Subjects had to be willing to maintain a stable dose of oral anti-diabetic and/or lipid-lowering medications that had the potential to affect plasma/serum glucose, insulin or lipid parameters for the study duration, had no changes in diet or exercise for four weeks prior to the study (and agree to keep these stable for the duration of the study). Additionally, subjects had to be capable of complying with the study requirements and completing the study. Finally, subjects had to be willing and able to give informed consent, and be willing for his or her name to be notified to the responsible authorities and primary care consultant or practitioner for participation in this study.

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

The treatment groups were:

1. 5 mg GWP42003 and 5 mg GWP42004 twice daily (1:1)
2. 100 mg GWP42003 and 5 mg GWP42004 twice daily (20:1)
3. 100 mg GWP42003 twice daily (GWP42003 alone)
4. 5 mg GWP42004 twice daily (GWP42004 alone)

The IMP consisted of three types of medications:

1. Hard gelatin capsules containing 5 mg GWP42004 (Delta-9-tetrahydrocannabivarin)
2. Hard gelatin capsules containing 5 mg GWP42003 (Cannabidiol)
3. Hard gelatin capsules containing 100 mg GWP42003

Each subject received the appropriate combination and number of capsules in order to maintain blinding throughout the study. IMP was taken twice daily, each morning 30 min before breakfast (fasted), and each evening 30 min before the evening meal, typically 12 hours apart.

Batch Numbers (BN) of IMP: K10005, K10006, K10007, K10020, K10022, K10027, K11005A, K11006A, K11014A, K11015B and K11017B.

**Duration of Treatment:**

13 week treatment period.

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

Placebo: contained the excipients CCI [redacted] and CCI [redacted].

Subjects received placebo as hard gelatin capsules twice daily (each morning 30 min before breakfast (fasted) and each evening 30 min before the evening meal, typically 12 hours apart). BNs: K10004, K11004B and K11013B.

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**Criteria for Evaluation:**

**Efficacy:**

Primary efficacy endpoint: the change from baseline in serum HDL-C concentration after 91 days (13 weeks) of treatment.

Secondary efficacy endpoints: to evaluate the efficacy of 1:1, 20:1, GWP42003 alone and GWP42004 alone compared with placebo on lipid parameters, glycaemic parameters, insulin sensitivity, body weight and fat loss parameters and appetite 0-10 NRS.

Lipid parameters included the mean change from baseline to the end of treatment in serum and ultracentrifugation levels of total cholesterol, LDL cholesterol, HDL:LDL cholesterol ratio, triglycerides and apolipoprotein markers (Apo A and Apo B and the Apo B:Apo A ratio). HDL-C levels were also determined by ultracentrifugation. Other lipid parameters included the mean change from baseline to the end of treatment in NEFA levels, levels of veryLDL (VLDL) calculated by ultracentrifugation, and an analysis of the proportion of subjects with a HDL response (defined as an ≥ 10% increase in mean HDL-C from baseline to the end of treatment).

Glucose control measurements included the mean change from baseline in the following parameters: fasting plasma glucose, glucose tolerance measured by OGTT, serum fructosamine and HbA1c (whole blood) levels to the end of treatment.

Insulin sensitivity measurements included the mean change from baseline to the end of treatment in fasting serum insulin levels, insulin resistance (calculated by HOMA and HOMA2), insulin sensitivity (calculated by HOMA2), insulin beta cell function (calculated by HOMA2) and insulin response to an OGTT. Also investigated were mean changes from baseline in islet cell function (serum C-peptide levels) to the end of treatment.

Body weight and fat loss were measured as mean changes from baseline to the end of treatment in body weight parameters (BMI, waist-to-hip ratio, neck circumference, skin fold thickness, body weight, waist circumference, abdominal adiposity), as well as the proportion of subjects showing a response (defined as a loss ≥ 5% or ≥ 10% in body weight from baseline to the end of treatment). Finally, the mean change from baseline to the end of treatment in adipose tissue distribution (liver triglycerides, body fat and abdominal adiposity was measured by Magnetic Resonance Imaging [MRI] scan), was also used as a measure of body weight and fat loss.

Appetite was assessed as the mean change from baseline in appetite 0-10 NRS score to end of treatment.

Tertiary efficacy endpoints: CCI [redacted]

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CCI [redacted]

**Safety:**

Assessments of the safety and tolerability of the IMPs was by volunteered AEs, laboratory and physical examination parameters, vital signs, BDI-II score and ECG.

**Statistical Methods:**

The primary analyses of all efficacy endpoints used data from subjects in the intention-to-treat (ITT) analysis set, which comprised all randomised subjects who received at least one dose of study medication and had on-treatment efficacy data. The primary analysis variable was the mean change from baseline to end of treatment (Visit 5) in serum HDL-C levels. This was analysed by analysis of covariance (ANCOVA) with baseline HDL-C levels as covariate and treatment and gender as factors. Analyses of the primary endpoint were also performed for the per protocol population, which comprised all of the same subjects in the ITT analysis set, with the further exclusion of subjects with major protocol violations.

The majority of secondary and tertiary efficacy were also analysed using an ANCOVA model analogous to the primary endpoint. The fitted ANCOVA models included the baseline parameter scores as covariate, with treatment group and gender as factors. The proportion of responders was also analysed for HDL-C response and reduction in overall body weight using the difference in proportions and the odds ratio comparing the treatment groups along with their respective 90% confidence intervals.

The subject global impression of change (SGIC) and clinician global impression of change (CGIC) were analysed with ordinal logistic regression using the cumulative proportional odds model.

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

The safety variables for analysis were the incidence, type and severity of all AEs, vital signs, BDI-II score, ECG, laboratory and physical examination parameters. All safety data was collected, listed and summarised appropriately.

**Summary - Conclusions:**

**Efficacy Results:**

A total of 62 subjects were randomised in this study. The demographics between the treatment groups were similar, with the exception of the distribution of males and females, which varied a little between treatment groups, with a slightly greater proportion of male to female subjects overall in this study. The mean duration since diagnosis of Type 2 diabetes was 4.2 years, and the mean duration since most recent diagnosis of dyslipidaemia was 2.9 years.

The results of the primary efficacy analysis of the mean change from baseline in serum HDL-C concentration after 91 days (13 weeks) of treatment revealed no significant differences compared with placebo for any active treatment (estimated treatment differences: 1:1 = -0.01 mmol/L [$P$ = 0.766]; 20:1 = 0.03 mmol/L [$P$ = 0.424]; GWP42003 alone = -0.03 mmol/L [$P$ = 0.412]; GWP42004 alone = 0.02 mmol/L [$P$ = 0.668]). However, since 82% of subjects

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were concomitantly taking lipid-lowering agents (statins), this may have limited the potential to observe a significant effect in this efficacy outcome.

A number of secondary and tertiary efficacy measures were also not significantly improved by active treatments. However, GWP42004 alone was superior to placebo in increasing mean Apo A levels ($P$ = 0.019), and subsequently decreasing the mean Apo B:Apo A ratio ($P$ = 0.075), decreasing mean fasting glucose levels ($P$ = 0.040), and increasing beta cell function as measured by HOMA2 ($P$ = 0.007). Further treatment effects with GWP42004 included significantly increasing mean levels of adiponectin ($P$ = 0.002), reducing mean IL-6 levels ($P$ = 0.076) and reducing mean systolic blood pressure ($P$ = 0.100), all effects in favour of active treatment. There were also significant treatment effectS between GWP42004 alone and placebo on mean RBP-4 ($P$ = 0.046) and PEA ($P$ = 0.077) levels that were not in favour of a benefit with GWP42004 alone treatment.

In the secondary efficacy measure of serum total cholesterol, there was a reduction in mean serum total cholesterol with 1:1 treatment ($P$ = 0.088), an effect that was not reproduced in the ultracentrifugation analysis ($P$ = 0.829). In the secondary efficacy measure of chest/pectoral skin fold thickness, there was a treatment difference of 4.96 mm ($P$ = 0.032) between 20:1 and placebo treatments,, but only a small mean increase from baseline overall in chest/pectoral thickness in the 20:1 active treatment group. In the 1:1 treatment group, there was a statistically significant estimated treatment difference of 4.37 mm ($P$ = 0.097) between 1:1 and placebo treatment in the mean abdominal skin fold thickness measurement, due to a small mean increase from baseline in abdomen thickness in the 1:1 treatment group, and a small mean decrease from baseline in the placebo treatment group. No other skin fold measurements were significantly affected by any other active treatment. Significant changes for all active treatments compared with placebo were seen in the MRI parameters of subcutaneous non-abdominal fat, total non-abdominal fat, total subcutaneous fat, and total fat. However, there was a large treatment effect in the placebo treatment group, and small sample sizes for these analyses.

In the analysis of SGIC and CGIC, there was a statistically significant treatment improvement on 1:1 treatment compared with placebo, with respective odds ratios of 4.51 ($P$ = 0.089) and 9.53 ($P$ = 0.018).

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[redacted]

**Safety Results:**

The majority of AEs in the study were reported as mild in severity, and treatment compliance was similar across the five different treatment cohorts. Seven of the 11 AEs leading to discontinuation of study medication were considered to be treatment-related. The incidence of AEs leading to discontinuation of study medication in the 20:1 and GWP42004 alone treatment groups was higher than that of placebo (both 16.7% vs. 0%), with the incidence in

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the 1:1 and GWP42003 alone treatment groups being the same as placebo (0%).

No deaths occurred during the course of the study, and there were four serious adverse events (SAEs) reported, three of which were considered unrelated to the study treatment. One subject (1.6%) receiving 20:1 treatment experienced a SAE of myocardial infarction that was considered to be moderate in severity, and the subject recovered during the study. One subject (1.6%) receiving placebo treatment experienced a SAE of myocardial ischaemia, which occurred on study Day 92 and was on-going at the end of the study, but was considered to be mild in severity. Two subjects (3.2%) experienced psychiatric SAEs; both events were requested by the Sponsor to be reported as SAEs following Sponsor review of the Beck Depression Inventory-II (BDI-II) findings. One subject (1.6%) receiving 20:1 treatment (the same subject who had an earlier myocardial infarction) experienced moderate suicidal ideation, which recovered and was considered as related to study treatment. One subject (1.6%) receiving 1:1 treatment experienced mild 'self-injurious ideation', which was considered as not related to study treatment (the latter two SAEs were taken from the GW pharmacovigilance database, see section 13 for further SAE narrative details).

There were no clinically significant abnormalities observed in the laboratory results, and no subjects were withdrawn from the study due to AEs related to laboratory results. There were individual clinically significant increases and decreases in some systolic and diastolic BP and heart rate in comparison to baseline levels across all of the treatment cohorts, which did not correlate with any specific treatment allocation. The overall reporting rate of ECG abnormalities that were AEs in subjects randomised to active treatments was comparable or less than those AEs on placebo.

In the BDI-II, subjects randomised to 20:1 treatment showed the most notable mean increase in BDI-II scale score from screening to the end of treatment (a statistically significant change from screening of 4.91 points [2.75 at screening to 7.91 at the end of treatment], but which was still within the 'minimal depression' [best outcome] range (score of 0-13) [$P = 0.006$]). This was mainly due to one subject's score in this group increasing from one to 24 (Subject 399002; recorded as an AE). Subjects randomised to placebo showed a slight decrease in score of 0.08 points, from a screening score of 3.50 to an end of treatment score of 3.54. Mean changes from screening to the end of treatment in BDI-II scores for the 1:1, GWP42003 alone and GWP42004 alone treatment groups were 0.27, 0.85, and 0.58, respectively, which were not statistically significant from placebo, and remained within the 'minimal depression' range for all treatments.

**Conclusion:**

The majority of efficacy measures were not met in this exploratory study; however, GWP42004 alone seemed to have the most potential, eliciting positive treatment effects on a number of key parameters such as glycaemic control (fasting glucose), increased beta cell function, inflammation (IL-6), and increased adiponectin levels and reduced systolic blood pressure, with the potential to benefit certain symptoms of Type 2 diabetes. In view of this, GWP42004 warrants further investigation in this subject population, and future dose-ranging studies should be considered. While there were some statistically significant treatment effects with the other active treatments, these were often equivocal, and as such it is difficult to draw any conclusions from these findings.

The incidence of AEs in this study was similar between treatment groups, and there was no apparent correlation between the different treatment groups and the incidence of AEs or by reported preferred term. There were no deaths in the study; only one of the four SAEs was considered to be related to the study medication. Furthermore, the majority of the AEs were

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| reported as mild in severity. | | |
| **Date of the Report:** 24 September 2013 | | |