

Summary reports for key Hoodia clinical studies

When the Council for Scientific and Industrial Research (CSIR) signed a cooperation agreement with Phytopharm, a United Kingdom-based pharmaceutical development and functional food company in November 2010 for the further development and commercialisation of *Hoodia gordonii*, the CSIR acquired the rights to substantial know how and IP developed when the former license agreement was in place. During this time many technical issues around the agronomy, extraction of the active ingredients, and other processing or manufacturing related challenges were resolved.

The CSIR has also acquired the reports to 14 clinical studies in which Hoodia has been assessed, using crude extracts and concentrated active ingredients formulated in a number of different ways. In many of these studies *Hoodia* was found to be generally safe and well tolerated, though in some subjects adverse events and tolerability issues were noted with the concentrated active ingredient extracts. During the period 1999 to 2003 clinical studies performed by the licensee or its partners were not published however detailed clinical reports were produced on the studies. A synopsis of the findings of the key clinical studies performed during this period is made available through the CSIR web-based research space. These studies include the following:

1. A single Phase I, double-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study in obese male subjects using a spray dried extract of Hoodia as the active substance formulated as capsules (coded P57FP). The study intended to include both and female, but only males were enrolled.
2. A Phase I, double-blind, placebo-controlled, single ascending oral dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of a spray dried extract of Hoodia formulated into capsules (coded P57FP) in male volunteers.
3. A Phase I, placebo-controlled, 14 day repeat dose study in an ascending dose parallel group design to establish the safety, tolerability and effects of a spray dried extract of Hoodia formulated into capsules (coded P57FP) in suppressing appetite in non-patient male volunteers.
4. A randomised, double-blind, placebo-controlled, 15 day repeat dose study, with a single dose escalation stage, to establish the pharmacokinetics, safety, tolerability and effects of the concentrated spray dried extract (coded PYM50027) in healthy male subjects.
5. An independent expert review of laboratory data from Hoodia studies



COUNCIL FOR SCIENTIFIC AND INDUSTRIAL RESEARCH

CLINICAL STUDY REPORT

A SYNOPSIS

A single Phase I, double-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study in obese male subjects using a spray dried extract of Hoodia as the active substance formulated as capsules (coded P57FP). The study intended to include both and female, but only males were enrolled.

**P57FP - A PHASE I, DOUBLE-BLIND, PLACEBO-CONTROLLED,
ASCENDING SINGLE ORAL DOSE, SAFETY, TOLERABILITY AND
PHARMACODYNAMIC STUDY IN OBESE MALE AND FEMALE
SUBJECTS**

Sponsor: Phytopharm plc
Corpus Christi House
9 West Street
Godmanchester
Cambridgeshire, PE18 8HG
UK

Study drug: P57FP

Drug class: Appetite suppressant

Trial phase: I

Principal Investigator: S D Oliver, BA BChir MB MA MRCP MFPM

Study centre: Covance Clinical Research Unit Ltd.
Springfield House
Hyde Street
Leeds, LS2 9NG
UK

Report authors: J Ward, BSc Dip Clin Sci
K J Bentley, BA PhD

Biostatistician: J Gorrige, BSc MSc

Covance CRU study: 1172/19

Sponsor reference: P57FP

Study start date: 8 October 1998 (first screening observation)

Study end date: 9 February 1999 (final post-study observation)

Report status: Final Report

Report date: 9 September 1999

This study was conducted in accordance with GCP and the Declaration of Helsinki (South Africa, 1996). The protocol was approved by the local Independent Ethics Committee and written informed consent was obtained prior to starting the study. All primary data, or copies thereof, and the final report will be retained in the Covance CRU archives for 15 years after submission of the final report.

SYNOPSIS

Name of Sponsor/Company: Phytopharm plc	Individual Study Table Referring to Part IV of the Dossier. Volume: Page:	<i>(For National Authority Use Only)</i>
Name of finished product: P57FP		
Name of active ingredient: P57P		
Title of study: P57FP - A Phase I, double-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacodynamic study in obese male and female subjects		
Investigator(s): S D Oliver, BA BChir MB MA MRCP MFPM		
Study centre(s): Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9NG UK		
Reference: Not applicable		
Period of study: 8 October 1998 to 9 February 1999		Phase of development: Clinical Phase I
Objectives: To determine the safety and tolerability of ascending single oral doses of P57FP in obese male and female subjects at six dose levels. To determine the effect of a single oral dose of P57FP on suppression of appetite in obese male and female subjects using a standardised battery of Visual Analogue Scales (VAS) of hunger and mood and appetite questionnaires. To collect sufficient blood and urine samples for future pharmacokinetic profiling of single oral doses of P57FP in obese male and female subjects.		
Methodology: Study design: Ascending, single oral dose study with six sequential groups Type of blinding: Double-blind Type of control: Placebo		
Number of subjects (planned and analysed): Sixty obese subjects (30 males and 30 females) were planned. Twenty obese subjects (all male) entered and completed the study and data from all subjects were analysed.		
Diagnosis and main criteria for inclusion: Healthy obese male and female subjects aged between 18 and 55 years and with a body mass index equal to or greater than 26 and less than 45. Female subjects were to be surgically sterilised or post-menopausal and have a negative serum pregnancy test.		
Test product, dose levels and batch numbers: P57FP capsules (10, 30, 100 and 300 mg); lot numbers 0211P, 0255P, 0212P and 0256P, respectively.		
Reference therapy and batch number: Placebo capsules (10, 30, 100 and 300 mg); lot numbers 0208P, 0252P, 0209P and 0253P, respectively.		
Duration and mode of administration of treatment: Single oral doses were administered. Each subject participated in one treatment period only.		
Criteria for evaluation: Safety and tolerability: Adverse events were monitored throughout the study and, at specific times, any signs were observed and any symptoms were elicited by open questioning. Vital signs, 12-lead ECG, clinical laboratory tests and physical examination were also assessed at specific times during the study.		

Date: 9 September 1999

Name of Sponsor/Company: PhytoPharm plc	Individual Study Table Referring to Part IV of the Dossier.	<i>(For National Authority Use Only)</i>
Name of finished product: P57FP	Volume:	
Name of active ingredient: P57P	Page:	
<p>Pharmacodynamics: Calorific intake and meal duration was measured for each test meal in the study. VAS of hunger and mood, post-meal palatability and end of meal questionnaires, wake questionnaires and end of day questionnaires were completed by the subjects at specific times during the study. Body weight was measured at specific times during the study.</p> <p>Pharmacokinetics: Blood samples for the analysis of the proposed two identified chemical constituents of P57P in plasma (P57AS3 and P57AS4) were taken at pre-dose and up to 72 h post-dose. Urine was collected for the analysis of the proposed two identified chemical constituents of P57P in urine at pre-dose (-2 to 0 h) and at intervals up to 24 h post-dose.</p> <p>Statistical methodology: Descriptive statistics were determined for demographic, adverse event, vital signs, 12-lead ECG, clinical laboratory, calorific intake, meal duration, body weight, VAS of hunger and mood, and the wake, end of day, post-meal palatability and end of meal questionnaire data. Statistical analysis to determine any treatment differences was performed for the following parameters: For each of the ten VAS of hunger and mood, the mean of the changes from baseline (Day -1) at all time-points from pre-breakfast to 2 h post-evening snack on Day 1 were analysed using analysis of variance (ANOVA). For the calorific content of the food eaten, the change from baseline (Day -1) on Days 1, 2, 3 and 4, for each corresponding meal were analysed using ANOVA. A post-hoc analysis using the same ANOVA model was performed to analyse the total daily calorific content of food eaten. Differences in the least squares means between each dose level and placebo and corresponding 95% CI were calculated.</p> <p>Summary: This was a Phase I, double-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacodynamic study in obese male subjects. Twenty obese male subjects entered and completed the study. Four dose levels of P57FP were studied; 10, 30, 100 and 300 mg. The planned dose levels of 600 and 1000 mg were not studied after analysis of the plasma samples from the 300 mg dose level indicated that the proposed two identified chemical constituents of P57FP in most samples were below the lower limits of quantification (LLOQ). Prior to its termination, no obese females had been included in the study.</p> <p>Safety and tolerability results: P57FP was safe and well tolerated at all dose levels studied. No serious adverse events were reported. P57FP was well tolerated in obese male subjects at dose levels of 10 to 300 mg, with very few adverse events being reported. The most frequently reported possibly drug-related adverse events were flatulence (three episodes), nausea (two episodes) and headache (two episodes). All other adverse events occurred as single episodes and were related to a variety of body systems. There were no clinically significant changes in vital signs, 12-lead ECG and clinical laboratory evaluations for the subjects. In addition there were no drug or dose-related trends in these parameters. There were no clinically significant changes noted following physical examination of the subjects.</p>		

Name of Sponsor/Company: Phytopharm plc	Individual Study Table Referring to Part IV of the Dossier. Volume: Page:	<i>(For National Authority Use Only)</i>
Name of finished product: P57FP		
Name of active ingredient: P57P		
Pharmacodynamic results:		
<p>Visual examination showed that there were no apparent drug or dose-related trends in the VAS data for hunger and mood during the study. Statistical analysis showed that for the ten VAS of hunger and mood, there were no statistically significant differences between any of the dose levels and placebo.</p> <p>Visual examination of the calorific content of food eaten and the duration of the test meals showed there were no apparent drug or dose-related trends in these parameters during the study. Overall the placebo and 30 mg P57FP treatment groups consumed more calories than the 10, 100 and 300 mg P57FP groups. The only notable difference across the study days was the higher calorie consumption at the evening meal on Day 1 for all groups, compared to the other days, with mean values ranging from 1391 to 1689 kcal, compared to 704 to 1053 kcal for all other days.</p> <p>Statistical analysis of the changes from baseline (Day -1) in the calorific content of food eaten, showed that there were differences between the placebo and 100 mg P57FP dose levels on Day 2 (breakfast and evening snack) and Day 3 (breakfast), and between the placebo and 300 mg P57FP dose levels on Day 2 (evening snack). In general, the placebo treatment showed an increase from baseline in the calorific content of food eaten and the P57FP treatment group showed a decrease. These changes were not apparent on other days or for other dose levels. The post-hoc statistical analysis of the total daily calorie intake showed decreases from placebo in total calorie intake for all dose levels of P57FP on Day 2 and for the three higher dose levels (30, 100 and 300 mg P57FP) on Day 3. Overall, for calorific intake, the analysis of each meal individually showed no consistent differences, however, the analysis of total daily intake showed decreases for the P57FP doses compared to placebo on Days 2 and 3. These trends were not present on Day 1.</p> <p>There were no apparent drug or dose-related trends in body weight data during the study. The body weights of the individual subjects generally remained constant throughout the study with changes from Day -2 to Day 4 ranging from -1.1 to 1.9 kg. For two subjects at the 30 mg P57FP dose level (Subjects 11 and 12), however, greater increases in body weight of 3.8 and 3.0 kg, respectively, were considered to have resulted from excessive eating.</p> <p>There were no apparent drug or dose-related trends in the data for the wake, end of day, post-meal palatability and end of meal questionnaires during the study.</p>		
Pharmacokinetic results:		
Plasma samples for all subjects in Groups C and D (100 and 300 mg P57FP or placebo) only were analysed.		
At the 100 mg P57FP dose level, plasma concentrations of P57AS3 and P57AS4 were below the LLOQ at all time-points.		
At the 300 mg P57FP dose level, plasma concentrations of P57AS3 and P57AS4 were quantifiable in three of the four subjects at one or two time-points (0.5 and 1 h post-dose) only, ranging from levels of 0.20 to 0.96 ng/mL. For the fourth subject, all plasma concentrations of P57AS3 and P57AS4 were below the LLOQ. These results showed that little or none of the drug was systemically available, possibly due to poor absorption or pre-systemic metabolism.		
Conclusions:		
<ul style="list-style-type: none"> • P57FP administered as single oral doses at dose levels of 10, 30, 100 and 300 mg were safe and well tolerated by healthy obese male subjects. • There was some evidence of a pharmacological effect of P57FP in obese subjects. Although there was no suppression of appetite indicated by the subjective assessments during the conduct of the study, the calorific content of food eaten decreased for all dose levels of P57FP compared to placebo on Day 2 and for the three higher dose levels of P57FP on Day 3. These trends were not present on Day 1. • The plasma concentrations of the proposed two identified chemical constituents (P57AS3 and P57AS4) were below quantifiable limits, possibly indicating negligible absorption of P57P. 		

Name of Sponsor/Company: Phytopharm plc	Individual Study Table Referring to Part IV of the Dossier. Volume: Page:	<i>(For National Authority Use Only)</i>
Name of finished product: P57FP		
Name of active ingredient: P57P		
Date of report: 9 September 1999		

Date: 9 September 1999



CLINICAL STUDY REPORT

A SYNOPSIS

A Phase I, double-blind, placebo-controlled, single ascending oral dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of a spray dried extract of Hoodia formulated into capsules (coded P57FP) in male volunteers.

CLINICAL STUDY REPORT

A phase I, double-blind, placebo-controlled, single ascending oral dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of P57FP in male volunteers

Protocol Number: P57/06CR/99/02

PPD Development Study Number: 170-5-056

Developmental Phase: I

Study Design: Double-blind, placebo-controlled, randomised, single ascending dose study

Name of Investigational Product: P57FP

Indication: Obesity

Principal Investigator: Dr Salvatore Febbraro
PPD Development Clinic*
72 Hospital Close
Evington
Leicester LE5 4WW
United Kingdom
Tel: +44 (0) 116 273 3553
Fax: +44 (0) 116 249 8201

Sponsor: Phytopharm plc
Corpus Christi House
9 West Street
Godmanchester PE18 8HG
United Kingdom
Tel: +44 (0) 1480 437 697
Fax: +44 (0) 1480 417 090

Sponsor's Signatory: Dr Rob Grover
Medical Director
Phytopharm plc

Date of first enrollment: 05 May 1999
Date of last visit: 02 June 1999

Status/Date: Final: 21 July 2000

*At the time the study protocol was written the contract research organisation (CRO) was known as PPD Pharmaco Leicester Clinical Research Centre; it is now known as PPD Development Clinic

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (1996).

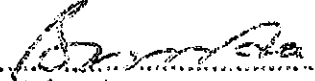
APPROVAL SIGNATURES

A phase I, double-blind, placebo-controlled, single ascending oral dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of P57FP in male volunteers

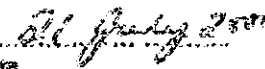
Protocol Number: P57/06CR/99/02

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

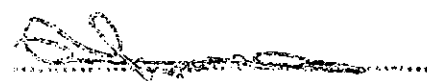
Principal Investigator:



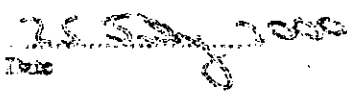
Dr Boyd Mudge*
Associate Medical Director
PPD Development Clinic
72 Hospital Close
Evington
Leicester, LE5 4WW
United Kingdom


Date

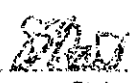
Sponsor:



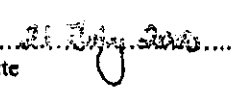
Dr Bob Green
Medical Director
Phytepharm plc
Corpus Christi House
5 West Street
Geddes Green, PE12 8BQ
United Kingdom


Date

Medical Writer:



Dr Suzanne Stait
Medical Writer
PPD Development Clinic
72 Hospital Close
Evington
Leicester, LE5 4WW
United Kingdom


Date

* The Principal Investigator, Dr S Febbraro, left the PPD Development Clinic on 24 September 1999. Dr B Mudge (a, who was previously a Co-Investigator, replaced Dr Febbraro as Principal Investigator on 16 September 1999.

2. SYNOPSIS

Sponsor: Phytopharm plc	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: P57FP	Volume:	
Name of Active Ingredient: P57P	Page:	
Title of Study: A phase I, double-blind, placebo-controlled, single ascending oral dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of P57FP in male volunteers		
Investigators: Dr Salvatore Febbraro MD* (Principal Investigator); Dr Boyd Mudenda BSc MB ChB MSc MD FRCSEd, Dr Fabio Magrini MD, Dr Brion Benninger BSc MB ChB MSc (Co-investigators)		
Study centre(s): PPD Development Clinic [†] , 72 Hospital Close, Evington, Leicester, LE5 4WW, UK		
Publication (reference): None		
Studied period (years): Date of first enrolment: 05 May 1999 Date of last completed: 02 June 1999		Phase of development: I
Objectives: Primary: To investigate the safety and tolerability of ascending single doses of P57FP following oral administration in healthy male non-obese volunteers receiving a hypocaloric diet. Secondary: To determine the effect of a single dose of P57FP on suppression of appetite in healthy volunteers receiving a hypocaloric diet; to determine the effect of a single dose of P57FP on satiety, satiation and mood in healthy volunteers receiving a hypocaloric diet; to collect sufficient blood and urine samples for pharmacokinetic profiling of a single dose of P57FP following oral administration to healthy volunteers receiving a hypocaloric diet		
Methodology: This was a double-blind, placebo-controlled, single ascending oral dose study in 32 healthy male non-obese subjects. Each group of eight subjects participated in one treatment period only		
Number of subjects (planned and analysed): Thirty-two subjects (four groups of eight subjects) were planned and analysed. Each group was randomly assigned to receive either P57FP (n=6) or placebo (n=2)		
Diagnosis and main criteria for inclusion: Healthy male subjects aged 18 years to 55 years (inclusive), with a body mass index (BMI) between 21 kg/m ² and 28 kg/m ² who gave written informed consent and who fulfilled all of the inclusion criteria and none of the exclusion criteria		
Test product, dose, mode of administration and batch number: P57FP 500, 1000, 2000 or 4000 mg administered orally as 500 mg white opaque capsules; lot number 0115R		
Duration of study: Approximately 3 weeks for each subject, including the 2 week pre-study screening interval and post-study follow-up (7-10 days post-dose)		
Reference therapy, dose, mode of administration and batch number: Placebo capsules were identical in appearance to the P57FP capsules. Placebo capsules contained 400 mg excipients only and were administered orally; lot number 0116R		
Criteria for evaluation:		
Safety/tolerability: Adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs) and routine laboratory assessments (haematology, biochemistry and urinalysis)		
Efficacy/pharmacodynamics: Questionnaires using visual analogue scales were designed to assess satiety and mood		
Pharmacokinetics: Analysis of plasma concentrations of P57AS3 and P57AS4 (known active constituents of P57FP)		
Statistical methods: Summary and descriptive statistics (mean, standard deviation, median, minimum, maximum) were provided for the clinical and safety data recorded in this study		

Sponsor: Phytopharm plc	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: P57FP		
Name of Active Ingredient: P57P		
Summary - Conclusions		
Safety/tolerability results:		
<p>There were no serious AEs or severe AEs reported during the study. A total of 25 AEs were reported during the study by 17 subjects. Three AEs were reported by one subject in the 500 mg P57FP group; five AEs were reported by four subjects in the 1000 mg P57FP group; seven AEs were reported by five subjects in the 2000 mg P57FP group; and five AEs were reported by four subjects in the 4000 mg P57FP group. A total of five AEs were reported by three subjects in the placebo group. Eleven AEs were considered by the Principal Investigator to be not related to study drug (three in the placebo group and two in each of the four active treatment groups). Nine AEs were considered to be possibly related to study drug (two in the placebo group; one in the 500 mg group; three in the 1000 mg group; and three in the 2000 mg group). Five AEs (all inappetence; preferred term anorexia), were considered to be probably related to study drug. None of the AEs were considered to be definitely related to study drug. Two AEs were considered to be moderate in severity: increased alanine transaminase (ALT) and aspartate transaminase (AST) (preferred term: enzyme abnormality) in the 1000 mg group, and abrasion right knee (preferred term: abrasion) in the 2000 mg group. All other AEs were considered to be mild in severity. The most common AEs were inappetence (anorexia) (five AEs reported by five subjects: two in the 2000 mg group and three in the 4000 mg group), headache (five AEs reported by five subjects: one in the 500 mg group, one in the 1000 mg group, two in the 2000 mg group, and one in the 4000 mg group). All other AEs were reported only once, or were reported in only one subject. A total of 23 out of 25 AEs resolved without treatment; two subjects were lost to follow-up. One subject in the 1000 mg P57FP group had clinically significant ALT and AST results, which was recorded as an AE. There were no clinically significant changes from baseline within any group for any of the laboratory safety parameters, ECG, vital sign parameters or the physical examination</p>		
Efficacy/pharmacodynamic results:		
<p>Because of the nature of visual analogue scales, and the amount of summary data generated from the questionnaires in this study, it was difficult to interpret the data reliably. The results, however, suggest that subjects receiving the highest P57FP dose, 4000 mg, were more full, less hungry, and found their hunger more satisfied on Day 1 compared to Day -1. There were no notable differences in anxiety, alertness, contentment, or irritability between groups</p>		
Pharmacokinetic results:		
<p>The pharmacokinetic results are presented in a separate report in Appendix 16.4</p>		
Conclusions:		
<p>The results of this study show that oral administration of single 500 mg, 1000 mg, 2000 mg, and 4000 mg doses of P57FP appears to be safe and well tolerated by healthy male subjects. The questionnaire data showed no clear affect on hunger, satiety or mood at any dose. Two out of four subjects in the 2000 mg group and three out of four subjects in the 4000 mg group experienced inappetence 2 to 3 days after dosing, suggesting that the higher doses may have had a delayed effect on appetite. In conclusion, the results of the study suggest that P57FP is suitable for further evaluation as an appetite suppressant</p>		
Date of report: 21 July 2000		

* The Principal Investigator, Dr S Febraro, left the PPD Development Clinic on 24 September 1999 after the clinical phase of the study had been completed. Dr B Mudenda, who was previously the Co-Investigator, replaced Dr Febraro as Principal Investigator on 16 September 1999

† At the time the study protocol was written the Contract Research Organisation was known as PPD Pharmaco Leicester Clinical Research Centre (LCRC); it is now known as the PPD Development Clinic



CLINICAL STUDY REPORT

A SYNOPSIS

A Phase I, placebo-controlled, 14 day repeat dose study in an ascending dose parallel group design to establish the safety, tolerability and effects of a spray dried extract of Hoodia formulated into capsules (coded P57FP) in suppressing appetite in non-patient male volunteers.

CLINICAL STUDY REPORT

A Phase I, placebo-controlled, 14-day repeat dose study in an ascending dose parallel group design to establish the safety, tolerability and effects of P57FP in suppressing appetite in non-patient volunteers

Protocol Number: P57/06CR/99/03

PPD Development Study Number: 170-5-061

Developmental Phase: I

Study Design: Double blind, parallel group, randomised, placebo-controlled, ascending dose study

Name of Investigational Product: P57FP

Indication: Obesity

Principal Investigator: Dr Salvatore Febraro
PPD Development Clinic
72 Hospital Close
Evington
Leicester LE5 4WW
United Kingdom
Tel: +44 (0) 116 273 3553
Fax: +44 (0) 116 273 3411

Sponsor: Phytopharm plc
Corpus Christi House
9 West Street
Godmanchester PE18 8HG
United Kingdom
Tel: +44 (0) 1480 437 697
Fax: +44 (0) 1480 417 090

Sponsor's Signatory: Dr Rob Grover
Medical Director
Phytopharm plc

Date of first enrollment: 20 August 1999
Date of last visit: 01 October 1999

Status/Date: Final: 26 November 1999

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (1996).

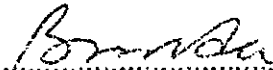
APPROVAL SIGNATURES

A Phase I, placebo-controlled, 14-day repeat dose study in an ascending dose parallel group design to establish the safety, tolerability and effects of PST22 in suppressing sporadic in non-patient volunteers

Protocol Number: PST/96CB/92/03

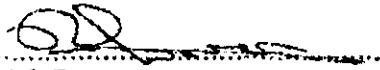
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Principal Investigator:


.....
Dr Boyd Mulenda*
Associate Medical Director
FPD Development Clinic
72 Hospital Close
Evington
Leicester, LE5 4WW
United Kingdom


26 Nov 99
.....
Date

Sponsor:


.....
Dr Rob Grover
Medical Director
PhytoPharm plc
Corpus Christi House
9 West Street
Oldmanchester, PS16 8HG
United Kingdom

30/11/99
.....
Date

Report author:


.....
Dr Shona Hunt
Medical Writer
FPD Development Clinic
72 Hospital Close
Evington
Leicester, LE5 4WW
United Kingdom

26 Nov 99
.....
Date

* The Principal Investigator, Dr S Febbraro, left the FPD Development Clinic on 24 September 1999. Dr B Mulenda, who was previously a Co-Investigator, replaced Dr Febbraro as Principal Investigator on 16 September 1999.

2. SYNOPSIS

Sponsor: Phytopharm plc	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: P57FP		
Name of Active Ingredient: P57P		
Title of Study: A Phase I, placebo-controlled, 14-day repeat dose study in an ascending dose parallel group design to establish the safety, tolerability and effects of P57FP in suppressing appetite in non-patient volunteers		
Investigators: Dr Salvatore Febraro MD* (Principal Investigator); Dr Boyd Mudenda BSc MB ChB MSc MD FRCSEd, Dr Fabio Magrini MD, Dr Paul Wharton MBChB (Co-Investigators)		
Study centre: PPD Development Clinic, 72 Hospital Close, Evington, Leicester, LE5 4WW, UK		
Publication (reference): None		
Studied period (years): Date of first enrolment: 20 August 1999 Date of last completed: 01 October 1999	Phase of development: I	
Objectives: Primary: To investigate the tolerability, safety and effects on appetite and food intake of P57FP in male non-patient volunteers over 14 days with repeated dosing. Secondary: To establish a preliminary safety profile for 14 days' repeated dosing with P57FP; to evaluate the effect of 14 days' dosing with P57FP on the suppression of appetite in male non-patient subjects as measured by self-report questionnaires; to evaluate the effect of P57FP on the inhibition of food intake in male non-patient subjects during 14 days' dosing with P57FP; to obtain sufficient blood samples for pharmacokinetic profiling during 14 days' dosing with P57FP; to investigate the time course of return of appetite		
Methodology: This was a single-centre, double-blind, randomised, placebo-controlled, ascending dose, parallel group study in healthy male volunteers. Subjects received either P57FP or placebo for 14 days. Subjects were discharged on Day 15 and returned to the PPD Development Clinic on Day 22 for a follow-up visit		
Number of subjects (planned and analysed): A total of 16 subjects were planned and analysed. Eight subjects received P57FP and eight subjects received placebo		
Diagnosis and main criteria for inclusion: Healthy male non-patient subjects aged 18 to 50 years (inclusive) with a body mass index (BMI) between 21 kg/m ² and 30 kg/m ² who gave written informed consent and who fulfilled all of the inclusion criteria and none of the exclusion criteria		
Test product, dose, mode of administration and batch number: P57FP administered orally as 500 mg hard gelatin capsules. The batch number for the P57FP capsules was 0188R		
Duration of treatment: From Day 1 to Day 7, subjects received four capsules (2 g P57FP) 1 hour before breakfast. From Day 8 to Day 14, subjects received 2 g P57FP 1 hour before breakfast and 2g P57FP 12 hours after the morning dose		
Reference therapy dose, mode of administration and batch number: Placebo capsules identical in appearance to the P57FP capsules. Placebo capsules contained 400 mg excipients only and were administered orally. The batch number for the placebo capsules was 0189R		
Criteria for evaluation: Effects of P57FP: The following variables were compared between treatment groups (subjects who received P57FP and subjects who received placebo):		
<ul style="list-style-type: none"> • <i>Ad libitum</i> calorie intake on Day -1, Day 7 and Day 14; • Standardised diet calorie intake on Day -2, Day 2, Day 5 and Day 12; • Change in body weight over 14 days of dosing; • BMI on Day -1 and Day 15; • Subjects' pre-meal and post-meal assessment of hunger, satiety and mood using questionnaire on Day -1, Day 2, Day 5, Day 7, Day 12 and Day 14; • Wake questionnaires on Day -1, Day 2, Day 5, Day 7, Day 12 and Day 14; • End of day questionnaires on Day -1, Day 2, Day 5, Day 7, Day 12, Day 14 and Day 15 to Day 21; • Return of appetite post-discharge using the end of day questionnaire 		

Sponsor: Phytopharm plc	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: P57FP		
Name of Active Ingredient: P57P		
Pharmacokinetic: Analysis of plasma concentrations of AS3 and AS4 (active constituents of P57FP) over time		
Safety and Tolerability: Clinical laboratory investigations (haematology, clinical chemistry and urinalysis), measurement of vital signs [supine systolic and diastolic blood pressure and pulse rate (body temperature was measured at screening only)], adverse events (AEs), 12-lead electrocardiogram (ECG), physical examination		
Statistical methods: This was an exploratory study. A formal statistical analysis was not planned or conducted. Summary statistics [mean, median, range and standard deviation (SD)] were produced for all safety and tolerability data and for data on the effects of P57FP on appetite, body weight and calorie intake		
Summary - Conclusions		
<p>Effects of P57FP compared to placebo: There were no notable differences between treatment groups in any of the outcome variables. Mean calorie intake on the <i>ad libitum</i> food days was slightly lower in the P57FP group compared to the placebo group [3502 ± 875 kcal (P57FP group on Day 7) and 3935 ± 1110 kcal (placebo group on Day 7); 3741 ± 880 kcal (P57FP group on Day 14) and 3979 ± 1177 kcal (placebo group on Day 14)]. The mean calorie intake on Day 7 and Day 14 in both groups was similar to the pre-dose <i>ad libitum</i> day (Day -1). Mean body weight decreased slightly in the P57FP group (82.8 ± 12.3 kg on Day -1 and 82.4 ± 12.1 kg on Day 15), and increased slightly in the placebo group (73.5 ± 6.7 kg on Day -1 and 73.9 ± 7.1 kg on Day 15). The mean BMI decreased slightly in the P57FP group (25.0 ± 3.3 kg/m² on Day -1 and 24.9 ± 3.2 kg/m² on Day 15) and increased slightly in the placebo group (23.8 ± 2.5 kg/m² on Day -1 and 23.9 ± 2.5 kg/m² on Day 15). There were no notable differences in the questionnaire results between subjects taking P57FP and subjects taking placebo on Day 2, Day 5 or Day 12 or on the <i>ad libitum</i> days (Day 7 and Day 14). The mean calorie intake on the hypocaloric diet days was slightly higher in the P57FP group compared to the placebo group [2047 ± 123 kcal (P57FP group on Day 2) and 2002 ± 138 kcal (placebo group on Day 2); 1996 ± 160 kcal (P57FP group on Day 12) and 1971 ± 127 kcal (placebo group on Day 12)]</p>		
Pharmacokinetic results: The pharmacokinetic (PK) results are presented in a separate report in Appendix 16.4		
Safety and tolerability results: There were no serious adverse events (SAEs) reported during the study. A total of 22 AEs were reported during the study by eight subjects. Six out of eight subjects (75%) in the placebo group reported 20 AEs. In the opinion of the Principal Investigator, 16 out of these 20 AEs (80.0%) were not related to study medication and four out of 20 AEs (20.0%) were possibly related to study medication. The AEs that were considered to be possibly related to study medication were taste perversion (four AEs reported by two subjects). Two AEs were reported by two subjects in the P57FP group. Both AEs were considered not to be related to study medication by the Principal Investigator. All AEs reported during the study were mild in severity. The most common AEs were headache (five AEs reported by four subjects in the placebo group) and taste perversion (four AEs reported by two subjects in the placebo group). There were no clinically significant changes from baseline within either group for any of the laboratory safety parameters, vital sign parameters or the physical examination		
Conclusion: The results of this study show that oral administration of P57FP 2 g once daily for 7 days followed by 2 g twice daily for a further 7 days is associated with a good emergent safety profile and is well tolerated by healthy male subjects. No substantial differences were observed over time between the treatment groups for either appetite, calorie intake or body weight during the study. The apparent lack of effect of P57FP may have been partly because of a sub-therapeutic dosing regimen and the relatively small sample size of this exploratory study		
Date of report 26 November 1999		

* The Principal Investigator, Dr S Febbraro, left the PPD Development Clinic on 24 September 1999. Dr B Mudenda, who was previously a Co-Investigator, replaced Dr Febbraro as Principal Investigator on 16 September 1999.



CLINICAL STUDY REPORT

A SYNOPSIS

A randomised, double-blind, placebo-controlled, 15 day repeat dose study, with a single dose escalation stage, to establish the pharmacokinetics, safety, tolerability and effects of the concentrated spray dried extract (coded PYM50027) in healthy male subjects.

CLINICAL STUDY REPORT

A Randomised, Double-Blind, Placebo-Controlled, Repeat Dose Study, with a Single Dose Escalation Stage, to Establish the Pharmacokinetics, Safety, Tolerability and Effects of PYM50027 in Healthy Male Subjects

Study code: P57/09ME/00/01

PPD Development Clinic study number: 1700079

Developmental phase: I

Name of investigational product: PYM50027

Principal Investigators: Dr B Mudenda, BSc, MB ChB, MSc, MD, FRCS
Dr G Pohl, BSc, MB BS, FRCP
Dr J Richards, FRCA
PPD Development Clinic
72 Hospital Close
Evington
Leicester, LE5 4WW
United Kingdom.

Tel: +44 (0) 116 273 3553
Fax: +44 (0) 116 249 8201

Sponsor's signatory: Dr R Grover, BSc, MB BS, FRCA
Medical Director
Phytopharm plc
Corpus Christi House
9 West Street
Godmanchester
Cambridgeshire, PE29 2HY
United Kingdom

Tel: +44 (0)1480 437697
Fax: +44 (0)1480 417090

Study initiation date: 16 February 2001

Study completion date: 24 October 2001

Status/date: Final: 22 January 2003

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (1996).

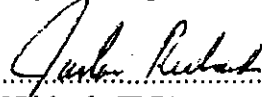
APPROVAL SIGNATURES

A Randomised, Double-Blind, Placebo-Controlled, Repeat Dose Study, with a Single Dose Escalation Stage, to Establish the Pharmacokinetics, Safety, Tolerability and Effects of PYM50027 in Healthy Male Subjects

PPD Development Clinic study number: 1700079

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

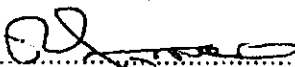
Principal Investigator:


.....
Dr J Richards, FRCA
Executive Director
PPD Development Clinic
72 Hospital Close
Evington
Leicester, LE5 4WW
United Kingdom

28th January 2003
.....
Date

Dr George Pohl was responsible for the clinical conduct of the study. The responsibility for approval of the clinical study report was assumed by Dr Justin Richards.

Sponsor:


.....
Dr R Grover, BSc, MB BS, FRCA
Medical Director
Phytopharm plc
Corpus Christi House
9 West Street
Godmanchester
Cambridgeshire, PE29 2HY
United Kingdom

30 January 2003
.....
Date

2 SYNOPSIS

Sponsor: Phytopharm plc	Individual study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: PYM50027 200 mg capsule	Volume:	
Name of Active Ingredient: PYM50027	Page:	
Title of Study: A randomised, double-blind, placebo-controlled, repeat dose study, with a single dose escalation stage, to establish the pharmacokinetics, safety, tolerability and effects of PYM50027 in healthy male subjects		
Investigators: Principal Investigators: Dr B Mudenda, Dr G Pohl, Dr J Richards Sub-investigators: Dr M Mahi, Dr K Hughes and Dr A Tse		
Study centre: PPD Development Clinic, 72 Hospital Close, Evington, Leicester, LE5 4WW, UK		
Publication (reference): None		
Date of first enrolment: 16 February 2001	Phase of development: I	
Date of last completed: 24 October 2001		
Objectives: To evaluate the pharmacokinetics, safety and tolerability of single doses of PYM50027 in healthy male subjects with a body mass index (BMI) of 21-28 kg/m ² and body fat content (BFC) less than 25%. To evaluate the pharmacokinetics, safety and tolerability of repeat doses of PYM50027 in healthy male subjects with a BMI of 28-36 kg/m ² and BFC more than 25%. To evaluate the effects of 15 days repeat dosing of PYM50027 on calorie intake in healthy male subjects with a BMI of 28-36 kg/m ² and BFC more than 25%.		
Methodology: This was a phase I, randomised, single-centre, double-blind, placebo-controlled, repeat dose study, with a single dose escalation stage, to include up to 62 healthy male subjects. The study was conducted in three stages: a single dose escalation stage in up to 24 healthy male subjects (BMI 21-28 kg/m ² and BFC < 25%), a 5 day repeat dose escalation stage in up to 18 healthy male subjects (BMI 28-36 kg/m ² and BFC > 25%), and a 15 day repeat dose stage in 20 healthy male subjects (BMI 28-36 kg/m ² and BFC > 25%). Body fat content was estimated using bioimpedance. Subjects attended a screening visit within 21 days of their first dosing day. Single dose stage: Subjects were admitted to the Clinic on the evening before dosing (Day -1) and were fasted overnight. Subjects were randomly allocated to receive a single dose of either PYM50027 (n=4) or placebo (n=2). Subjects remained fasted until 1 hour post-dose, but were allowed to drink water. They were provided with standard meals when resident in the Clinic. Subjects were discharged from the Clinic on the morning of Day 2 after the 24 hour post-dose pharmacokinetic (PK) blood sample had been obtained. They returned for further PK samples on the evening of Day 2 and the morning of Day 3 (follow-up visit). Four dose groups were studied (200, 600, 1200 and 2400 mg PYM50027; groups 1A to 1D). Each subject was recruited to only one dose group. Dose escalation occurred after review of the safety, tolerability and PK data from the previous dose group. 5 Day repeat dose stage: Following review of the safety and PK data from the single dose stage, this repeat dose stage was initiated. Subjects were dosed as three groups of six subjects, and were resident in the Clinic from the evening of Day -2 until the morning of Day 7. Group 2A was eliminated by protocol amendment and the study proceeded immediately to group 2B. Subjects in groups 2B and 2C were randomly allocated to receive either PYM50027 (n=4) or placebo (n=2) twice daily (b.d.) for 5 days. Subjects in group 2D were randomly allocated to receive either PYM50027 (n=4) or		

Sponsor: Phytopharm plc	Individual study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: PYM50027 200 mg capsule	Volume:	
Name of Active Ingredient: PYM50027	Page:	
<p>placebo (n=2) three times daily (t.d.s.) for 5 days. The test products were administered at 07:00 h and 17:00 h (groups 2B and 2C) or at 07:00 h, 12:00 h (before lunch) and 17:00 h (group 2D). The doses studied were 1200 mg b.d., 2400 mg b.d. and 1600 mg t.d.s. in groups 2B, 2C and 2D, respectively.</p> <p>Breakfast was provided 1 hour after the morning dose and the evening meal was provided 1 hour after the evening dose. Subjects consumed the standard meals and drinks provided <i>ad libitum</i> during the specified meal time periods. Calorie intake was recorded for every meal on Day -1 and Day 5. Calorie intake was also recorded for every meal on Day 3 for subjects in group 2D. Subjects were discharged from the Clinic on the morning of Day 7 and returned for a final visit on the evening of Day 7.</p> <p>15 Day repeat dose stage:</p> <p>After review of the safety and PK data from the single and 5 day repeat dose stages, the 15 day repeat dose stage was conducted. Subjects were dosed in a single group of 20, and were resident from the morning of Day -4 until Day 18. Day -4 was used to familiarise subjects with the Clinic environment and the mealtime routine. Subjects were randomly allocated to receive either PYM50027 or placebo on Day -3. All subjects received placebo b.d. on Day -3 to Day -1. Subjects then received either 1800 mg PYM50027 b.d. (n=10) or placebo b.d. (n=10) for 15 days according to the randomisation schedule. The test products were administered at 07:00 h and 17:00 h. Breakfast was provided 1 hour after the morning dose, and the evening meal was provided 1 hour after the evening dose. Subjects consumed standardised meals and drinks <i>ad libitum</i> during the specified mealtime periods. Calorie intake was recorded for every meal from breakfast on Day -3 until Day 17 and appetite data were recorded on selected days. Subjects were allowed to leave the Clinic on Day 18, three days after completion of dosing. Additional follow-up visits were conducted on Day 29 ± 2 and Day 43 ± 2 for measurement of body weight, BMI and BFC.</p>		
<p>Number of subjects (planned and actual):</p> <p>Planned:</p> <p>Up to a total of 62 healthy male subjects.</p> <p>Single dose escalation stage: up to 24 subjects (BMI 21-28 kg/m², BFC < 25%).</p> <p>5 day repeat dose stage: up to 18 healthy male subjects (BMI 28-36 kg/m², BFC > 25%).</p> <p>15 day repeat dose stage: up to 20 healthy male subjects (BMI 28-36 kg/m², BFC > 25%).</p> <p>Actual:</p> <p>Single dose escalation stage: 23 subjects</p> <p>5 day repeat dose stage: 18 subjects</p> <p>15 day repeat dose stage: 19 subjects</p>		
<p>Diagnosis and main criteria for inclusion:</p> <p>Healthy males aged 18 to 45 years (inclusive), with BMI 21-28 kg/m² and BFC < 25%, or BMI 28-36 kg/m² and BFC > 25%, who fulfilled the entry criteria and gave written informed consent.</p>		
<p>Test product, dose and mode of administration, batch number:</p> <p>PYM50027 200 mg capsules, administered orally, batch number: 0069T (single dose stage and 5 day repeat dose stage), 0295T (15 day repeat dose stage)</p> <p>Single dose stage: 200 mg (Group 1A), 600 mg (Group 1B), 1200 mg (Group 1C) or 2400 mg (Group 1D) single dose</p> <p>5 day repeat dose stage: 1200 mg b.d. (Group 2B), 2400 mg b.d. (Group 2C) or 1600 mg t.d.s. (Group 2D) for 5 days</p>		

Sponsor: Phytopharm plc	Individual study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: PYM50027 200 mg capsule	Volume:	
Name of Active Ingredient: PYM50027	Page:	
15 day repeat dose stage: 1800 mg b.d. (Group 3) for 15 days		
Reference therapy dose and mode of administration, batch number: Placebo capsules, administered orally, batch number: 0077T		
Single dose stage: 1 capsule (Group 1A), 3 capsules (Group 1B), 6 capsules (Group 1C), 12 capsules (Group 1D) as single dose		
5 day repeat dose stage: 6 capsules b.d. (Group 2B), 12 capsules b.d. (Group 2C) or 8 capsules t.d.s. (Group 2D) for 5 days		
15 day repeat dose stage: 9 capsules b.d. for 3 days (all subjects), 9 capsules b.d. for 15 days (randomised subjects)		
Duration of treatment: Approximately 4 weeks for single dose stage, 4.5 weeks for 5 day repeat dose stage, and 9.5 to 10 weeks for the final repeat dose stage, including the 21 day pre-study screening interval and follow-up visits.		
Criteria for evaluation: The outcome variables for the single dose and the 5 day repeat dose stages were PK, safety and tolerability. The primary outcome variable for the 15 day repeat dose stage was the effect of PYM50027 on caloric intake. All other measures, including body weight, BMI and BFC, were analysed as secondary outcome variables.		
Effects of PYM50027: Caloric intake from Day -3 until 2 days after completion of dosing in the 15 day repeat dose stage. Body weight, BMI and BFC (assessed by bioimpedance) measured at screening, daily before the morning dose from Days 1 to 7 in the 5 day repeat dose stage, and daily before each morning dose from Day -3 until the third morning after completion of dosing in the 15 day repeat dose stage. On each occasion the subjects were weighed whilst barefoot, in a dressing gown and after voiding. Appetite data were collected during the 15 day repeat dose stage on Days -3, -1, 5, 10, 15, 16 and 17 within 30 minutes before and after they finished breakfast, lunch and dinner and at the scheduled start time of the evening snack mealtime period.		
Pharmacokinetics: Blood samples for analysis of plasma concentrations of PYM50057 (P57AS3) and PYM50087 (P57AS4) (known active constituents of PYM50027) were collected at the following times: Single dose stage: pre-dose, 0.5, 1, 2, 4, 8, 12, 16, 24, 36 and 48 hours post-dose. 5 Day repeat dose stage (Group 2B): relative to Day 1, Day 3 and Day 5 morning doses: pre-dose, 1, 4, 10 (before 17:00 h dose), 11, 14 and 24 hours post-dose, with additional samples at 34, 48 and 58 hours after the last morning dose on Day 5. 5 Day repeat dose stage (Groups 2C and 2D): relative to Day 1, Day 3 and Day 5 morning doses: pre-dose, 1, 2, 4, 5, 7, 10 (before 17:00 h dose), 11, 12, 14 and 24 hours post-dose, with additional samples at 34, 48 and 58 hours after the last morning dose on Day 5. 15 Day repeat dose stage: relative to Day 1 morning dose: pre-dose, 1, 4, 10 (before 17:00 h dose), 11, 14 and 24 hours post-dose. relative to Days 3, 5, 7 and 10 morning dose: pre-dose, 1 and 10 hours (before 17:00 h dose) post-dose. relative to Day 15 morning dose: pre-dose, 1, 4, 10 (before 17:00 h dose), 11, 14, 24, 34, 48, 58 and 72 hours post-dose.		

Sponsor: Phytopharm plc	Individual study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: PYM50027 200 mg capsule	Volume:	
Name of Active Ingredient: PYM50027	Page:	
Safety: Adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations, routine laboratory assessments.		
Statistical methods: This was an exploratory study. Descriptive statistics were used to summarise the data. The association of measures such as vital signs, laboratory results, AEs, calorie intake and weight with study drug dose or PK parameters could be explored statistically. If appropriate, statistical modelling could be performed.		
Effects of PYM50027: All data were listed. Descriptive summary statistics (mean, median, minimum, maximum and standard deviation) or frequency counts and percentages were presented, as appropriate. The summaries for the 5 day stage were presented by treatment group, or treatment group and time-point, as appropriate. The following data obtained from the 15 day repeat dose stage were analysed: calorie intake, weight, BMI, BFC and appetite questionnaire data. The primary variable was the total caloric intake during treatment (mean of Days 13-15). The two treatment groups were compared using analysis of covariance with the baseline calorie intake (mean of Days -3 to -1) as covariate. Secondary variables included the calorie intake during treatment for each meal. All tests were two-tailed, at a significance level of 5%.		
Pharmacokinetics: The following non-compartmental PK parameters were estimated from the plasma concentration-time profiles for each subject: maximum plasma concentration over the entire sampling phase (C _{max}); area under the plasma concentration-time curve for 24 hours from time of dosing (AUC _(0-24h)); area under the plasma concentration-time curve from time of dosing to time of last quantifiable concentration (AUC _{last}); area under the plasma concentration-time curve from time of dosing to infinity (AUC _{inf}); time to C _{max} (T _{max}); first order rate constant (λ _z); terminal elimination half-life (t _{1/2}).		
Safety: All data were listed. Descriptive summary statistics (mean, median, minimum, maximum and standard deviation) were presented for continuous data. The summaries were presented by treatment group, or treatment group and time-point, as appropriate. Categorical data were presented as frequency counts and percentages by treatment group, or treatment group and time-point, as appropriate. All subjects were included in the analyses.		
Summary of results: Effects of PYM50027: In the 5 day repeat dose stage, the 2400 mg b.d. and 1600 mg t.d.s. groups had statistically significantly less total calorie intake than placebo and the 1200 mg b.d. group. A similar pattern was seen for each of the meals individually although a statistically significant effect was detected only for breakfast and the evening snack. Body weight was statistically significantly reduced in the 1600 mg t.d.s. group compared to each of the other three groups. There were, however, no statistically significant changes in body fat content. In the 15 day repeat dose stage, mean calorie intake at all meals was lower for the PYM50027 group compared to the placebo group. The difference was statistically significant for dinner calorie intake and for total daily calorie intake (p=0.032 and 0.036, respectively). There was no		

Sponsor: Phytopharm plc	Individual study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: PYM50027 200 mg capsule	Volume:	
Name of Active Ingredient: PYM50027	Page:	

statistically significant difference in body weight or BMI between groups on Day 16. There was a statistically significant difference for the change from baseline in body fat content between dose groups ($p=0.035$) with the PYM50027 group having the lower body fat content on Day 16. There was no statistically significant difference in body fat mass between groups.

In the appetite questionnaires, there was an increased feeling of nausea on Day 15 compared to Day -1, which was statistically significantly greater in the PYM50027 group compared to the placebo group ($p=0.038$, median test). Inspection of the data revealed that this was largely due to two subjects who reported feeling nauseous both before and after the meals. There were no statistically significant differences between groups in the pre-meal parameters termed "feeling tired", "feeling hungry", "feeling anxious" or "feeling full". The two groups had similar post-meal scores on Day -1 and there was a small statistically significant decrease in the "feeling full" parameter for the PYM50027 group on Day 15 compared to placebo ($p=0.015$). There was no statistically significant difference between the two groups for either fasting glucose or cholesterol. There was a statistically significant difference between the groups for the change in triglycerides, with a lower mean value in the PYM50027 group compared with the placebo group on Day 15 ($p=0.021$).

Pharmacokinetics:

From the single dose pharmacokinetic data, there appeared to be a linear relationship between both C_{max} and exposure (AUC) for PYM50057 and PYM50087 across the dose range, although there did not appear to be dose proportionality. C_{max} increased by 20 to 30-fold over the 12-fold dose range and the AUC increased by nearly 100-fold for the 12-fold increase in dose. These data may suggest that the clearance of both PYM50057 and PYM50087 had approached saturation. However, AUC may have been under-estimated for the 200 and 600 mg doses because of a lack of plasma concentration data.

Considerable variability was observed between subjects and within subjects on different days during the 5-day repeat dose stage. The data indicated an increase in the parameters C_{max} , C_{last} and AUC(0-24h) from Day 1 to Day 5 for all three groups, suggesting a degree of accumulation of both PYM50057 and PYM50087 with repeat oral dose administration. This may be explained by the terminal half-lives calculated for Day 5 where values approached the dosing interval, suggesting that the drug was not fully cleared from the systemic circulation before the next dose and hence a degree of accumulation was inevitable.

The plasma concentration-time profiles obtained for the 15-day repeat dose stage showed a clear increase in the C_{max} observed for both PYM50057 and PYM50087 following repeat dosing, with the biggest differential between Days 10 and 15. A comparison of AUC(0-24h) and C_{max} for PYM50057 and PYM50087 showed that for the majority of the subjects there was an obvious increase in both C_{max} and AUC values. The maximum increase in the AUC observed for PYM50057 was greater than 12-fold and the C_{max} was increased by a factor of 19. Some individuals showed little increase in the C_{max} , but still experienced a notable increase in exposure (AUC).

Safety:

There were no serious AEs reported during the study. There were 255 treatment-emergent AEs reported by 32 (53.3%) of the 60 subjects recruited. Twenty-six subjects had at least one AE that was considered to be treatment-related (possibly, probably or definitely related to study medication). The most commonly reported AEs were headache (49 reported by 23 subjects).

Sponsor: Phytopharm plc	Individual study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: PYM50027 200 mg capsule	Volume:	
Name of Active Ingredient: PYM50027	Page:	
<p>paraesthesia (42 reported by 14 subjects), dizziness (19 reported by 12 subjects), nausea (18 reported by 11 subjects), myalgia (12 reported by 10 subjects), abdominal pain (16 reported by 9 subjects), somnolence (9 reported by 8 subjects) and polyuria (8 reported by 8 subjects). All other AEs were reported by less than six subjects. The majority of AEs were reported as mild (247 AEs, 96.9%). The remaining eight AEs were of moderate severity and there were no severe AEs. One subject withdrew during the 15 day repeat dose stage because of an AE (maculopapular rash). The majority of treatment-emergent AEs (194/255; 76%) were reported during the 15 day repeat dose stage, which had the largest number of subjects and the longest period of dosing.</p> <p>During the single dose stage, one subject in the placebo group reported a single AE and two subjects in the PYM50027 groups reported three AEs.</p> <p>During the 5 day repeat dose stage, four subjects in the placebo group reported eight AEs, two subjects in group 2B (1200 mg b.d.) reported eight AEs, three subjects in group 2C (2400 mg b.d.) reported 13 AEs and four subjects in group 2D (1600 mg t.d.s.) reported 28 AEs. A twice daily regimen of the same total daily dose (4800 mg) appeared to be better tolerated than a thrice daily dosing regimen.</p> <p>During the 15 day repeat dose stage, six subjects in the placebo group reported 65 AEs and ten subjects in the PYM50027 group (1800 mg b.d.) reported 129 AEs (including 25 AEs in nine subjects that were reported on Days -3 to -1 when subjects were taking placebo). The AEs most commonly reported by subjects in the 15 day repeat dose stage of the PYM50027 group compared to the placebo group were paraesthesia, headache, taste perversion, vasodilation and somnolence.</p> <p>During the 15 day repeat dose stage, an isolated hyperbilirubinaemia was detected in eight out of the ten subjects that received PYM50027 (1800 mg b.d.). Further laboratory investigation confirmed a mixed conjugated/unconjugated hyperbilirubinaemia, in the absence of any apparent effect on bile acids or other liver function tests (including gamma-glutamyl transferase). The hyperbilirubinaemia was reversible, with serum bilirubin levels restored to normal during the follow-up period.</p> <p>There were no other clinically significant changes from baseline detected either between or within the treatment groups for any other laboratory safety parameters. There were no abnormal ECG, vital signs or physical examination findings during the study.</p> <p>Conclusion:</p> <p>Short-term oral dosing with PYM50027 demonstrated a clear anorectic effect. Dosing for 15 days (1800 mg b.d.) caused a substantial reduction in caloric intake, however it was associated with mild side effects (including paraesthesia, taste perversion and isolated reversible hyperbilirubinaemia). Although this dosing regimen is not suitable for further clinical investigation, the exaggerated effect on caloric intake strongly suggests that either lower dose levels and/or related products should be evaluated.</p> <p>Date of report: 22 January 2003</p>		



EXPERT REPORT

**An independent expert review of laboratory data
from Hoodia studies**

EXPERT REPORT

Submitted on 10th February 2002 by:

Dr Phillip M. Harrison BSc MBBS PhD MD FRCP

Who has been a Senior Lecturer/Consultant Hepatologist since January 1994 at:

The Institute of Liver Studies,
King's College Hospital,
Denmark Hill,
London,
SE1 9PJ.

Tel: 44 20 7346 3169
Fax: 44 20 7346 3899
phillip.harrison@kcl.ac.uk

Report Requested by:

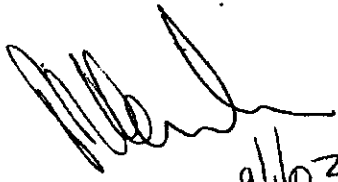
Dr Robert Grover BSc MBBS FRCA,
Medical Director,
Phytopharm plc,
Corpus Christi House,
9 West Street,
Godmanchester,
Cambridge,
PE29 2HY.

Purpose of Instruction:

I was asked to perform an independent review of laboratory data in the phase I multiple dose studies with PYM50027 giving specific reference to the relevance of the observed changes in serum bilirubin levels.

For the purpose of writing this report I had at my disposal:

1. The laboratory safety data from a blinded 15 day repeat dose study of PYM50027 (1800 mg bd, n=10) versus placebo (n=9) in healthy overweight male volunteers.
2. The laboratory safety data from a 5 day repeat multi-dose study of PYM50027 (1200 mg bd, n=4; 2400 mg bd, n=4; 1600 mg tds, n=4) versus placebo (n=6) in healthy male volunteers.



9/10/02

EVALUATION OF DATA

In the 15 day repeat dose study of PYM50027 at 1800 mg BD

A rise in plasma bilirubin above the upper limit of normal was observed in 6 of 10 subjects by day 5 and in 8 of 10 subjects by day 15 of active drug dosing. The highest level recorded was 72 $\mu\text{mol/L}$. The split bilirubin was measured in 3 subjects, and at day 15 was 40%, 37% and 31% conjugated. All bilirubin levels returned to baseline values post dosing. There were no significant changes in bilirubin in those subjects receiving placebo.

The haemoglobin levels were unchanged with drug dosing but no specific tests were performed to exclude haemolysis.

The other liver tests demonstrated no significant changes from baseline -- specifically no significant rises in γGT or transaminases.

No subject reported itching and the plasma bile salts were unchanged during drug dosing, in those subjects where they were measured.

In the 5 day repeat dose study of PYM50027 at 1200 mg bd, 2400 mg bd, 1600 mg tds

There were no significant biochemical changes recorded.

CONCLUSIONS

The data from the 15 day repeat dose study suggests that PYM50027 interferes with bilirubin metabolism, causing a mixed conjugated/unconjugated hyperbilirubinaemia, in the absence of any apparent effect on bile salt secretion and without causing a rise in γGT or other liver tests.

The phenotype produced by PYM50027 is similar to that seen in individuals with Dubin-Johnson syndrome, who have a defect in the ATP-dependent canalicular multispecific organic anion transporter, MRP2, which is responsible for the export of bilirubin glucuronides. This observation suggests that PYM50027 might inhibit MRP2 or compete with bilirubin glucuronides for export by this transporter.

Inhibition of bilirubin metabolism by PYM50027 at multiple levels can not be excluded by the data and, specifically, inhibition of glucuronidation, hepatic uptake and other canalicular transporters also needs to be investigated.

RECOMMENDATIONS FOR INVESTIGATION OF THE MECHANISM OF INCREASED BILIRUBIN FOLLOWING ADMINISTRATION OF PYM50027

A. Unconjugated bilirubin will accumulate in the plasma if there is a marked increase in the rate of formation of bilirubin (i.e. haemolysis). In order to look for evidence of haemolysis:

1. In vitro red cell fragility studies could be performed with PYM50027.
2. Stored samples from the 15 day repeat dose study of PYM50027 could be assayed for haptoglobin, which falls during haemolysis.
3. Future human studies should include measurements of reticulocyte count to look for increased red cell turn-over.

B. Unconjugated bilirubin will also accumulate in the plasma if there is a defect in any of the processes underlying the hepatic clearance of the unconjugated pigment (i.e. hepatic uptake, intracellular binding, conjugation). In order to investigate these processes:

1. In vitro studies should be performed to examine the effect of PYM50027 on organic anion transporting proteins (OATPs), which are involved in the uptake of organic anions into hepatocytes.
2. Bilirubin uptake is a carrier-mediated, saturable process that is shared, at least in part, by a variety of other organic anions (e.g., sulfobromophthalein [BSP] and indocyanine green [ICG]) but not by bile acids. In vivo rat studies, reduced plasma clearance of both ICG and BSP would suggest a defect in hepatic uptake.
3. Bilirubin uridine-diphosphate (UDP) glucuronosyltransferase (UGT) is responsible for the conjugation of bilirubin to mono- and diglucuronides. Other UGT isoforms, generated from the same gene, conjugate other specific substrates. Multiple unique exon 1s, which confer substrate specificity, are differentially spliced to the four common exons (exons 2 through 5), which encode the catalytic site. Conjugation of bilirubin (and all other substrates) is dependent on a co-factor UDP-GA and enzyme activity is reduced upon a fall in hepatic UDP-GA concentration. Moreover, glucuronidation of high concentrations of substances such as paracetamol may deplete hepatic UDP-GA levels. Conjugation of the high steroid load in subjects given PYM50027 might deplete hepatic UDP-GA levels reducing activity of bilirubin-UGT. Alternatively, induction of the UGT isoforms that conjugate PYM50027 might have a reciprocal effect on transcription of the bilirubin-UGT. The effect of PYM50027 on hepatic UDP-GA levels and bilirubin-UGT activity could be measured in rats or in human hepatocytes in microspheres. In addition, the effect of PYM50027 on hepatic levels of specific exons of isoforms of UGT mRNA could be examined.

C. Impaired hepatic clearance of conjugated bilirubin (from decreased biliary excretion or bile flow at either the canalicular or ductular level) will cause efflux of conjugated bilirubin into the plasma.

1. The effect of PYM50027 on the bile salt export pump (BSEP), canalicular organic anion transporter MRP2, and the multidrug resistance 3 P-glycoprotein (MDR3) should be investigated in vitro. These assays can be performed by:

Prof. Dr. Peter J Meier-Abt
Division of Clinical Pharmacology
Department of Medicine
University Hospital
Racmistrasse 100
CH-8091 Zuerich
Switzerland
Tel. + 41 1 255 3652
Fax. + 41 1 255 4411
email: meierabt@kpt.unizh.ch

2. If PYM50027 is inhibiting MRP2 in vivo, then a number of secondary effects can be predicted and investigated:
 - I. Hepatic uptake of BSP will be normal or only mildly impaired but the biliary excretion of conjugated BSP will be markedly impaired. Following injection of BSP, there will be efflux of conjugated BSP back into the circulation, producing a secondary rise in plasma concentration 60 to 90 later.
 - II. The pattern of bilirubin conjugates in plasma will show BDG > BMG, which is dissimilar to that observed in acquired hepatobiliary disease.
 - III. Total urinary coproporphyrin excretion will be normal but the coproporphyrin I isomer will be over-represented (80% rather than the normal 25%).