Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2008-006762-29
Study Number:	NL0804
Protocol Title:	A double-blind, randomised crossover, single dose, single centre, study examining the analgesic efficacy and tolerability of fixed-dose combinations of ibuprofen 200 mg and acetaminophen 500 mg, ibuprofen 400 mg and acetaminophen 1,000 mg and placebo in primary dysmenorrhoea.
Study Phase:	Phase II/III
Date First Subject Enrolled:	11 Feb 2009
Date Last Subject Completed:	16 July 2009
Report Date:	14 January 2010
Principal Investigator:	Professor Ronald Eccles BSc, PhD, DSc. Common Cold Centre and Healthcare Clinical Trials Unit, Cardiff School of Biosciences, Museum Avenue, Cardiff University, Cardiff, CF10 3AT. Tel +44 (0) 29 20874102, Fax +44 (0) 29 20874093. Dr Martez Jawad MB, ChB, FRCP (UK) of the same address was the qualified physician and authorised health professional responsible for all trial-site related medical decisions.
Study Conduct Statement:	This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. Documents defined by ICH GCP as "essential documents" will be archived in the RB company archive in Hull, UK

Reviewed and Agreed by:

Clinical Project Manager:

A Holbrook 26·01·10

Ms A Holbrook BSc — Date

Reckitt Benckiser Healthcare International Ltd

Statistician:

Michael A Goulder 15-JAN-10

Mr M A Goulder BSc — Date

Worldwide Clinical Trials UK Ltd

R & D Manager:

26 Jan 2010

Mr R Lewis BSc MSc — Date

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15 Jan 2010

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Insight Clinical Consulting Ltd

Reviewed and Approved by:

R&D Manager - Clinical (Healthcare):

26 Jan 10

Dr Sue Aspley BSc, PhD, MICR — Date

Reckitt Benckiser Healthcare International Ltd

Global Medical Director:

26 January 2010.

Dr P Berry MB, ChB, MPH — Date

Reckitt Benckiser Healthcare International Ltd

2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Ibuprofen 200mg and Paracetamol 500mg tablet	**Volume:**	
Name of Active Ingredient(s):	**Page:**	

Title of Trial: A double-blind, randomised crossover, single dose, single centre, study examining the analgesic efficacy and tolerability of fixed-dose combinations of ibuprofen 200 mg and acetaminophen 500 mg, ibuprofen 400 mg and acetaminophen 1,000 mg and placebo in primary dysmenorrhoea.

Investigator(s): Professor Ronald Eccles BSc, PhD, DSc. Common Cold Centre and Healthcare Clinical Trials Unit, Cardiff School of Biosciences, Museum Avenue, Cardiff University, Cardiff, CF10 3AT. Tel +44 (0) 29 20874102, Fax +44 (0) 29 20874093.

Dr Martez Jawad MB, ChB, FRCP (UK) of the same address was the qualified physician and authorised health professional responsible for all trial-site related medical decisions.

Trial Centre(s): Common Cold Centre and Healthcare Clinical Trials Unit, Cardiff School of Biosciences, Museum Avenue, Cardiff University, Cardiff, CF10 3AT. Tel +44 (0) 29 20874102, Fax +44 (0) 29 20874093.

Publication (reference): None as of the date of this Final Report

Studied Period: 6 months **Date first subject enrolled:** 11 Feb 2009 **Date last subject completed:** 16 July 2009	**Phase of Development:** Phase II/III

Objectives: The primary objective of the study was to assess the efficacy of fixed dose combination tablets of 200 mg ibuprofen plus 500 mg acetaminophen (paracetamol), administered as one or two tablets (two tablets equivalent to 400 mg ibuprofen plus 1,000 mg acetaminophen) in comparison to placebo among patients experiencing moderate to severe pain due to primary dysmenorrhoea, in terms of total analgesic effect, peak analgesic effect, onset and duration of action and the subject's overall assessment of the study medication in a home setting.

The secondary objective was to evaluate the tolerability (adverse event profile) of the fixed dose combination tablets of 200 mg ibuprofen plus 500 mg acetaminophen administered as one or two tablets (two tablets equivalent to 400 mg ibuprofen plus 1,000 mg acetaminophen) in comparison to placebo.

Methodology: Patients were recruited from the clinical centre's database of subjects and also via recommendation from enrolled patients and others and via poster advertising on the University campus. Patients attended for a screening visit at which Informed Consent was obtained before any study specific procedures were conducted. Patients underwent physical examination including recording of vital signs and provided details of their medical history and medications taken in the last month. Blood samples were taken for haematological and biochemical evaluation. Eligible patients were issued with a diary card in which to record menstrual pain intensity on a 4 point categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) before and at 0.5, 1, 1.5, 2, 4 and 6 hours after dosing. Pain relief was recorded in the diary on a 5-point scale (0 = no pain relief, 1 = a little pain relief, 2 = some pain relief, 3 = a lot of pain relief, 4 = complete pain relief) at 0.5, 1, 1.5, 2, 4 and 6 hours after dosing. A global assessment of each study medication was recorded in the patient diary by the patient 6 hours after dosing, using a 5 point categorical scale (1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = Excellent). Patients were provided with their randomised medication for the first treatment period and instructed to take it during their next menstruation when they were experiencing at least moderate menstrual pain. They were also issued with rescue medication and an alarm clock to assist in making assessments at the correct intervals. Adverse events, concomitant medications and the use of rescue medication were recorded in the diary. Patients returned to the centre within 5 days of taking study medication, for review of their diary and issue of their

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
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next allocated treatment. At their final post treatment visit, physical examination and laboratory investigations were repeated.

Number of Subjects: **Planned:** 100 to enrol to achieve 85 complete

Analysed: 103 randomised, 94 in safety set, 91 in ITT population, 88 in Per-Protocol population and 89 completers

Diagnosis and Main Criteria for Inclusion: Primary dysmenorrhoea with moderate-severe cramping pain in at least 4 of the previous 6 months, females aged ≥18.

Those with: a history of significant disease deemed by the investigator to render them unsuitable for inclusion, anaemia, any significant ongoing painful condition other than primary dysmenorrhoea, any ongoing condition that may have interfered with the absorption, distribution, metabolism, or excretion of the study medication, a history of peptic ulcer, duodenal ulcer, gastrointestinal bleeding, a history of frequent dyspepsia, heartburn or indigestion, a history of psychotic illness, attempted suicide, or neurosis, a positive history of drug or alcohol abuse within the past year, taking any concomitant medications that might have confounded assessments of pain relief, such as psychotropic drugs, antidepressants, sedative–hypnotics taken within five times of their elimination half lives, childbearing potential, who were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions, a history of inflammatory bowel disease, a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any previous history of allergy or known intolerance to any of the drugs or formulation constituents which, in the Investigator's opinion, might have precluded use of an NSAID, including aspirin sensitive asthma or a previous allergic response to a NSAID, including bronchospasm, urticaria, angioedema and rhinitis, and those who received any analgesic, anti-inflammatory, antispasmodic or other therapy for dysmenorrhoea within 6 hours of taking the study medication, were excluded from the trial.

Test Product: ibuprofen 200 mg plus acetaminophen 500 mg fixed combination, one tablet, oral administration, batch number 047074/018 Expiry date 30 April 2010.

Ibuprofen 200 mg plus acetaminophen 500 mg fixed combination, two tablets, oral administration, batch number 047074/018 Expiry date 30 April 2010.

Duration of Treatment: single-dose

Reference Therapy: Placebo, oral administration, Batch number 04074/017 Expiry date: 30 October 2010

Criteria for Evaluation:

Efficacy: The primary analgesic efficacy endpoint was the total pain relief over 6 hours post dose (TOTPAR 0-6h), i.e. the area under the pain relief by time curve between 0 and 6 hours. Secondary analgesic efficacy endpoints included:

- Total pain relief over 2 and 4 hours post-dose (TOTPAR 0-2h, TOTPAR 0-4h)
- Total analgesic effect measured as the sum of pain intensity difference (SPID) over 2, 4 and 6 hours post-dose (SPID 0-2h, SPID 0-4h, SPID 0-6h), with pain intensity difference at each post-baseline assessment being the difference in pain intensity between that assessment and baseline (pain intensity at baseline - pain intensity at time T)
- Overall effectiveness measured as the sum of pain intensity difference and pain relief score (SPRID) over 2, 4 and 6 hours post-dose (SPRID 0-2h, SPRID 0-4h, SPRID 0-6h)

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- Use of rescue medication and time of use of rescue medication.
- Subjects overall assessment of the study medication as a treatment for pain was collected at 6 hours post-dose, or just before administration of rescue medication, if sooner, using a 5 point categorical scale (1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = Excellent)

Safety: Nature, severity, duration and relationship to therapy of adverse events were recorded. Laboratory parameters and vital signs were measured before first treatment and after the last treatment. Clinically significant changes were recorded as adverse events.

Statistical Methods: Results for the primary endpoint, total pain relief (TOTPAR0-6h), were analysed by analysis of covariance (ANCOVA) using PROC MIXED in SAS with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect. Pairwise treatment comparisons between each of the fixed dose combination treatments and placebo were made based on the least squares estimates and standard errors (SEs) derived from the ANCOVA model. These were tested via a closed test procedure. If the overall effect for treatment was significant at the 5% level then firstly ibuprofen 400 mg + acetaminophen 1000 mg was formally tested against placebo at the two-sided 5% level and then if this comparison was significant, ibuprofen 200 mg + acetaminophen 500 mg was formally tested against placebo also at the two-sided 5% level. The pairwise comparison between the two combinations was reported descriptively with a two-sided 95% confidence interval for the mean difference and did not form part of the formal closed testing procedure.

Results for the secondary endpoints of pain intensity, pain relief and combined pain intensity and relief were analysed using the same ANCOVA model as the primary endpoint. Use of rescue medication (yes/no) was compared independently between each of the fixed dose combination treatments and placebo using Prescott's test. The time to first use of rescue medication was tabulated but not formally analysed. Subjects' overall assessment of the study medication as a treatment for pain collected at 6 hours post-dose (or just before administration of rescue medication, if sooner) was compared between each of the fixed dose combination treatments and placebo using independent Wilcoxon matched-pairs signed rank tests.

The incidence of adverse events was compared between treatment groups using Prescott's Test for all adverse events, adverse events classified by the Investigator as probably or possibly related to study medication and for severe adverse events.

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SUMMARY & CONCLUSIONS

EFFICACY RESULTS: For the primary endpoint (TOTPAR0-6h), the higher dose combination proved to be statistically significantly superior to placebo over the six hour assessment period, with a least squares (LS) mean for the total pain relief score of 2.35, compared to the placebo LS mean score of 1.87 ($p = 0.0001$). The lower dose combination also provided greater pain relief over six hours than placebo, with a LS mean of 2.10, but marginally failed to achieve statistical significance ($p = 0.054$). (Results quoted are for the ITT population).

The secondary analgesic endpoints confirmed the superiority of both doses of the fixed combination to placebo. Statistically significantly superior pain relief to placebo was achieved with the higher dose combination over the initial 4 hour period post dose (TOTPAR 0-4h) and at individual assessment points from 2 hours post dose onwards and with the lower dose combination at individual assessment points from 4 hours onwards. This benefit was accompanied by significant reductions in pain intensity which were statistically significantly superior for the higher dose combination compared to placebo over the initial 2, 4 and 6 hour periods post dose (SPID 0-2h, SPID 0-4h and SPID 0-6h) and at individual assessment points from 90 minutes post-dose onwards and also for the lower dose combination over the 6 hour period post dose (SPID 0-6h) and at individual assessment points from 4 hours onwards. Overall effectiveness (measured by SPRID over 6 hours) was statistically significantly superior to placebo for both the higher and lower dose combination ($p < 0.0001$ and $p = 0.03$ respectively). As with pain relief and pain intensity, SPRID separated significantly from placebo earlier with the higher dose of the combination (from 90 minutes onwards) than with the lower dose (4 hours onwards).

The analgesic benefits of increased pain relief and reduced pain intensity were reflected by significantly less use of rescue mediation with both the higher and lower dose combinations compared to placebo (2.2% and 3.3% of patients compared to 15.6% respectively, $p = 0.0009$ and $p = 0.02$ respectively). Significantly more patients rated both the higher dose combination and the lower dose combination more highly than placebo on overall assessment ($p = 0.0023$ and $p = 0.0091$ respectively).

SAFETY RESULTS: No deaths or other serious adverse events (AEs) were reported in the study. There were no withdrawals due to AEs. Both the higher and lower dose combinations were well tolerated. The incidence of events did not differ with either treatment compared to placebo. Eleven patients reported 14 events (13 mild, one moderate) after taking the lower dose combination, seven patients reported 7 events (all mild) after taking the higher dose combination and nine patients reported 13 events (seven mild, six moderate) after taking placebo. There were no clinically significant laboratory abnormalities and no changes in vital signs during the course of the study.

CONCLUSION: The fixed dose combination of ibuprofen 400 mg + acetaminophen 1000 mg and the fixed dose combination of ibuprofen 200 mg + acetaminophen 500 mg were both superior analgesics compared to placebo in patients with primary dysmenorrhoea. The higher dose combination provided greater pain relief and reduced pain intensity more than did the lower dose combination, with statistically significant differences from placebo being apparent with the higher dose combination earlier (at 90 minutes post dose) than with the lower dose combination (from four hours post dose). Adverse events occurred in only a very small proportion of patients. The events that occurred were minor, did not require medical intervention and resolved with no sequelae; the risk:benefit ratio for both the higher dose combination and lower dose combination is positive in primary dysmenorrhoea.

Date of the report: 04 December 2009

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3.1 List of Tables and Figures Contained in the Body of the Report

3.2 List of Appendices

All subjects in this study received study medication from one batch, so this appendix is not present.

16.1.7 Randomisation scheme and codes (subject identification and treatment assigned)

16.1.8 Audit certificates

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardisation methods and Quality assurance procedures if used

Multiple laboratories were not used for analyses in this study, so this appendix is not present.

16.1.11 Publications based on the study

None of the data from this study has been published, so this appendix is not present

16.1.12 Important publications referenced in the report

None of the publications referenced in the report is appended

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued Patients

16.2.2 Protocol Deviations

16.2.3 Patients Excluded from the Efficacy Analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data.

16.2.6 Individual efficacy response data.

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subject

16.2.9 Other data listings

16.3 CASE REPORT FORMS

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for adverse events.

No subjects died, experienced adverse events or withdrew because of adverse events, so no CRFs are appended

16.3.2 Other CRFs submitted – no other CRFs are appended

16.4 INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS)

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16.4.4 Patient data listing of inclusion criteria – Safety population

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4 LIST OF ABBREVIATIONS

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area under the curve
CA	Competent Authority
CFR	Code of Federal Regulations
CoAs	Certificates of Analysis
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
EC	Ethic Committee
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMSU	Investigational Material Supply Unit
IRB	Institutional Review Board
ITT	Intent to treat
LOCF	Last observation carried forward
mg	Milligram
mL	Millilitre
NA	Not applicable
PI	Pain Intensity
PID	Pain Intensity Difference
PP	Per protocol
PR	Pain Relief
RB	Reckitt Benckiser
SAE	Serious Adverse Event
SDV	Source Data Verification

Abbreviation	Abbreviation in Full
SE	Standard error
SmPC	Summary of Product Characteristics
SPID	Sum of pain intensity differences
SPRID	Sum of pain relief and pain intensity differences
SSRI	Selective serotonin reuptake inhibitor
SNRI	Selective noradrenalin reuptake inhibitor
TOTPAR	Total Pain Relief
UNK	Unknown
WCT	Worldwide Clinical Trials
WHO	World Health Organisation

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The name and full address of the single IEC consulted is provided in Appendix 16.1.3.

The study protocol and one administrative change, together with subject information and consent documents were reviewed and approved by the South East Wales Research Ethics Committee Panel B.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. It complied with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

5.3 Subject Information and Consent

Copies of a representative subject information sheet and a blank consent form are provided in Appendix 16.1.3.

Subjects who were considered by the investigator to be suitable for entry into the study were given the opportunity to read the subject information sheet and consent form, and to ask questions. If they were happy with, and understood the information, they were asked to sign the consent form. The investigator also signed the form. The subject was given a copy of the information sheet and signed consent form. No

protocol-related procedures were performed prior to the subject signing the consent form.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Appendix 16.1.4 contains a table listing the names and affiliations of the individuals whose participation materially affected the conduct of the study, together with their roles. The curriculum vita (CV) of the principal investigator is also included in the Appendix.

The study was carried out at The Common Cold Centre and Healthcare Clinical Trials Unit of Cardiff University under the guidance of the Principal Investigator, Prof. R Eccles and the medical direction of Dr M Jawad. Some study-related activities were delegated to suitably qualified centre personnel.

Analyses of clinical laboratory samples were performed by the Bioanalytical Unit at Simbec Research Ltd, Merthyr Tydfil, CF48 4DR.

The study drug supplies were packed and shipped to the Common Cold Centre by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS. Study project management tasks were conducted by Miss A Holbrook, Clinical Project Manager, RB.

Study monitoring and writing of the clinical study report was contracted to Insight Clinical Consulting Ltd, Unit 18, Heathcoat Building, Nottingham Science Park, Nottingham NG7 2QJ.

Data management and the statistical analyses were performed by Worldwide Clinical Trials UK Ltd, Isaac Newton Centre, Nottingham Science Park, Nottingham NG7 2RH.

RB was responsible for the expedited reporting of any serious adverse events occurring during the study, to the relevant Regulatory Authorities.

7 INTRODUCTION

Reckitt Benckiser Healthcare (UK) Limited (RB) has developed a fixed dose combination analgesic tablet containing ibuprofen and acetaminophen (paracetamol). The clinical and medical rationale for this combination is that pain is multifactorial, involving multiple mediators and receptor sites. Each of these drugs acts on different pathways, so the combination theoretically should be more effective than either component alone. Two dental pain studies (NL0408 and NL0604) have been conducted and the results support this theory.[1,2]

This study was conducted to satisfy the requirements of some regulatory authorities to show efficacy in more than one pain model. As the fixed combination had already been demonstrated to have superior efficacy to each of the components alone, the

design of this study compared the fixed combination at two different doses to placebo.

The primary dysmenorrhoea model was used because it is an established pain model that produces predictable moderate to severe pain. The model is widely accepted and has a proven record of assay sensitivity (i.e. separating active drugs from each other, as well as from placebo) and lends itself to a crossover design. The model is frequently used to evaluate both NSAID-type analgesics and acetaminophen. The Committee for Proprietary Medicinal Products (CPMP) guideline on medicinal products for nociceptive pain recommend that dysmenorrhoea is the subject of dedicated studies to support this indication.[3]

8 STUDY OBJECTIVES

The primary objective of the study was to assess the efficacy of fixed dose combination tablets of 200 mg ibuprofen plus 500 mg acetaminophen, administered as one or two tablets (two tablets equivalent to 400 mg ibuprofen plus 1,000 mg acetaminophen) in comparison to placebo among patients experiencing moderate to severe pain due to primary dysmenorrhoea, in terms of total analgesic effect, peak analgesic effect, onset and duration of action and the patient's overall assessment of the study medication in a home setting.

The secondary objective was to evaluate the tolerability (adverse event profile) of the fixed dose combination tablets of 200 mg ibuprofen plus 500 mg acetaminophen administered as one or two tablets (two tablets equivalent to 400 mg ibuprofen plus 1,000 mg acetaminophen) in comparison to placebo.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study protocol and Administrative Change 01 are included as Appendix 16.1.1. Unique pages from the case report form (CRF) are included as Appendix 16.1.2.

This was a double-blind, randomised crossover, single dose, single centre study.

One hundred and three female patients with primary dysmenorrhoea who met the inclusion and exclusion criteria were enrolled into the study. They were primarily recruited from the clinical centre's database of students and staff of the University of Cardiff who had previously expressed an interest in clinical studies and agreed to being contacted about possible participation.

Patients attended for a screening visit at which Informed Consent was obtained before any study specific procedures were conducted. Patients underwent physical examination including recording of vital signs and provided details of their medical history and medications taken in the last month. Blood samples were taken for haematological and biochemical evaluation. Eligible patients were issued with a diary

card in which to record menstrual pain intensity on a 4 point categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) before and at 0.5, 1, 1.5, 2, 4 and 6 hours after dosing. Pain relief was recorded in the diary on a 5-point scale (0 = no pain relief, 1 = a little pain relief, 2 = some pain relief, 3 = a lot of pain relief, 4 = complete pain relief) at 0.5, 1, 1.5, 2, 4 and 6 hours after dosing. Patients were provided with their randomised medication for the first treatment period and instructed to take it during their next menstruation when they were experiencing at least moderate menstrual pain. They were also issued with rescue medication and an alarm clock to assist in making assessments at the correct intervals. Adverse events, concomitant medications and the use of rescue medication were recorded in the diary. Patients returned to the centre within 5 days of taking study medication, for review of their diary and issue of their next allocated treatment. At their final post treatment visit, physical examination and laboratory investigations were repeated. The three treatments tested as single doses in this trial were placebo, fixed combination ibuprofen 200 mg plus acetaminophen 500 mg and fixed combination ibuprofen 400 mg plus acetaminophen 1000 mg. All treatments were given as a single-dose.

No safety data monitoring or special steering or evaluation committees were appointed and no interim analysis was planned or performed.

9.2 Discussion of Study Design, Including the Choice of Control Groups

Dysmenorrhoea is a common problem, with a prevalence reported to be as high as 90%, more often in the region of 50-70%.[4] It is recurrent and predictable, hence a crossover design is frequently used in clinical studies of this indication. The statistical power of a crossover design is superior to that of a parallel group design for a given number of subjects, so fewer subjects are generally required in crossover studies, giving advantages in terms of overall duration of a study and recruitment efforts. Issues associated with a crossover design include carryover effects and treatment period effects. Given the cyclical nature of primary dysmenorrhoea, with at least one month between single-dose treatments in this study, drug carryover is not a cause for concern. Baseline pain variability with each cycle was controlled as far as possible by requiring subjects to take medication only when they had moderate or severe pain. The CPMP Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Nociceptive Pain refers to the crossover design in trials in primary dysmenorrhoea as acceptable if precautions to control these problems are taken.[3]

This study had a placebo control arm which aids considerably in interpretation of the efficacy response seen with study drug. Whilst dysmenorrhoea is painful, placebo was considered to be acceptable as the study was single-dose, the study period was short (six hours) and rescue medication was supplied which could be taken in the event patients decided they had obtained inadequate pain relief. That in itself provides a recognized and accepted endpoint in analgesic clinical studies and at the same time addresses the ethical issues associated with provision of a placebo in a

painful condition, particularly when both study drug and rescue medication are self administered at the discretion of the participant.

9.3 Selection of Study Population

Patients were selected from the clinical centre's database of people who had previously indicated they were interested in participating in clinical studies. Additional advertising within the University Campus using posters (approved by the Ethics Committee) was also used to recruit potential participants.

9.3.1 Inclusion Criteria

Only subjects to whom all of the following conditions applied were included:

1) Age: ≥18
2) Sex: Female
3) Primary diagnosis: Primary Dysmenorrhoea, with moderate-severe cramping pain in at least 4 of the previous 6 months.
4) Status: These subjects were members of the public who responded to any study specific advertising, or indicated to staff that they wished to participate in a dysmenorrhoea trial.
5) Subjects who gave written informed consent

9.3.2 Exclusion Criteria

Subjects to whom any of the following conditions applied were excluded:

1) A history of significant disease deemed by the investigator to render the subject unsuitable for inclusion.
2) Any significant ongoing painful condition other than that associated with primary dysmenorrhoea.
3) Any ongoing condition that may interfere with the absorption, distribution, metabolism, or excretion of the study medication.
4) A history of peptic ulcer, duodenal ulcer, gastrointestinal bleeding.
5) A history of frequent dyspepsia, heartburn or indigestion.
6) A history of psychotic illness, attempted suicide, or neurosis.
7) A positive history of drug or alcohol abuse within the past year.
8) Those taking any concomitant medications that might have confounded assessments of pain relief, such as psychotropic drugs, antidepressants, sedative–hypnotics taken within five times of their elimination half lives. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenalin reuptake inhibitors (SNRIs) were permitted if the subject had been on a stable dose for at least four weeks prior to Visit 1 (screening) and remained on this dose throughout the study.

9) Women of childbearing potential, who were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions, (i.e. an oral or injectable contraceptive, an approved hormonal implant or topical patch, an intrauterine device, abstinence [should the subject have become sexually active, she must have agreed to use a double barrier method] or condoms/diaphragm and spermicide). A woman of childbearing potential was defined as any female who was less than 2 years post-menopausal or had not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
10) A history of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any previous history of allergy or known intolerance to any of the drugs or formulation constituents which, in the Investigator's opinion, precluded use of an NSAID, including aspirin sensitive asthma or a previous allergic response to a NSAID, including bronchospasm, urticaria, angioedema and rhinitis.
11) Those previously randomised into the study
12) Subjects who received any analgesic, anti-inflammatory, antispasmodic or other therapy for dysmenorrhoea within 6 hours of taking the study medication.
13) Those who participated in a clinical trial in the previous 30 days weeks as calculated from time of last dosing in the prior trial to time of anticipated dosing in this trial.
14) Those suffering with anaemia – (blood test at screening visit)
15) Those unable, in the opinion of the investigator, to comply fully with the study requirements

9.3.3 Removal of Subjects from Therapy or Assessment

The Investigator could withdraw the subject from the study at any time. Reasons for removing a subject from the study included, but were not limited to:

- adverse events that in the judgement of the Investigator may have caused severe or permanent harm (significant clinical deterioration was an adverse event)
- violation of the study protocol
- in the Investigator's judgement, it was in the subject's best interest
- subject declined further study participation

The primary reason for withdrawal was documented as one of the following: withdrawal of consent; adverse events; lack of efficacy; lost to follow-up; no further need for study medication (unless this was study end point); protocol violation; death or other. The Investigator made reasonable attempts to contact subjects who were lost to follow-up - a minimum of two documented telephone calls or a letter was considered reasonable.

9.4 Treatments

9.4.1 Treatments Administered

The following study drug treatments were administered in this trial:

- Ibuprofen 200 mg plus acetaminophen 500 mg in fixed combination, single oral dose
- Ibuprofen 400 mg plus acetaminophen 1000 mg in fixed combination, single oral dose
- Placebo, single oral dose

Each treatment was taken singly in a separate menstrual period i.e. there were three separate treatment periods.

In addition, Tramadol 100 mg, single oral dose was supplied as rescue medication for each treatment period, which could be taken if patients did not achieve adequate pain relief with study medication. Patients were encouraged to wait for 90 minutes after taking study medication before using rescue medication.

9.4.2 Identity of Investigational Product(s)

The treatments administered were:

- 1 x tablet of ibuprofen 200 mg/acetaminophen 500 mg (reference number: 047074/018, expiry date 30 April 2010) + 1 x placebo tablet matched to ibuprofen 200 mg/acetaminophen 500 mg combination tablets (reference number 04074/017, expiry date 30 October 2010)
- 2 x tablets of ibuprofen 200 mg/acetaminophen 500 mg (reference number: 047074/018, expiry date 30 April 2010)
- 2 x placebo tablets matched to ibuprofen 200 mg/acetaminophen 500 mg combination tablets (reference number 04074/017, expiry date 30 October 2010)

The overall study supplies expiry date allocated was 30 April 2010.

Each treatment (2 tablets) was administered as a single oral dose and patients were instructed to consume the tablets with approximately 300 ml of water.

Study medication was manufactured to Good Manufacturing Practice (GMP) standards by Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull HU8 7DS, UK.

Rescue medication (Tramadol 100 mg) was obtained as commercial product, Batch No. 7D011B, Expiry March 2011, from Med Pharm Ltd, Building 2000, Beach Drive, Cambridge Research Park, Waterbeach CB5 9PD.

All drug supplies were primary and secondary packed to GMP standards by the RB Investigational Material Supply Unit, Hull. The rescue medication was provided as open label product, study drug supplies were provided as double-blinded product.

9.4.3 Method of Assigning Subjects to Treatment Groups

A detailed description of the randomisation method, including how it was executed, is presented in Appendix 16.1.7.

Subjects were randomised to one of six treatment allocation schedules, allocating the three treatments to specified study periods in blocks of six using a computer-generated randomisation schedule provided by RB. On entry to the study, subjects were allocated a unique subject number in numerical sequence. Issue of the study drug in each study period as defined by the allocation schedule ensured randomisation.

9.4.4 Selection of Doses in the Study

All drugs were taken as a single-dose, orally, with approximately 300 mL of water. The doses of the fixed combination of ibuprofen and acetaminophen were chosen on the basis of previous findings in two clinical trials of the combination in post-operative dental pain.

9.4.5 Selection of Timing of Dose for Each Subject

Each study drug was taken during a separate menstrual period. Assignment was by randomisation, with patients being allocated each drug in random order according to the predetermined computer generated randomisation list. Patients self assessed the severity of their pain and took study drug when their pain was moderate or severe. It was expected that some patients would not experience moderate or severe pain in consecutive menstrual cycles, hence a period of six months for the completion of each patient was permitted in the protocol. Patients were advised not to take their allocated treatment late in the evening as assessments needed to be made for the six hours after taking study drug, but no instructions were provided in relation to food intake. Patients were instructed to take their medication with approximately 300 mL of water.

9.4.6 Blinding

The placebo exactly matched the active. Both products were white/off-white film- coated tablets embossed with the letters IP. A visual check and nominal tablet weight were documented in the Certificates of Analyses (CoAs) and the CoAs were reviewed by the Clinical Project Manager. A visual check was also performed as part

of the release procedure, to confirm that the blinding was satisfactory and the release was signed off by the GMP Qualified Person.

9.4.7 Prior and Concomitant Therapy

Concomitant therapies were defined as prescribed medications, physical therapy, and over-the-counter preparations, including herbal preparations licensed for medicinal use, other than study medication and supplementary medication that the patient received during the course of the study.

The Investigator recorded any medications given in treatment of adverse events on the concomitant medication page in the patient's case report form. Any medication taken by the patient during the course of the study was also recorded on this form. Any changes in concomitant therapy during the study were documented, including cessation of therapy, initiation of therapy and dose changes.

The use of the following treatments was not permitted:

- Anti-inflammatory, antispasmodic or other therapy for dysmenorrhoea within six hours of taking the study medication.
- SSRIs and SNRIs were permitted during the study only if patients maintained a stable dose for four weeks prior to Visit 1 and only if they remained on that stable dose throughout the study.
- Hot water bottles or other comfort measure e.g. Heat patches for specified time periods around pain measurements.

9.4.8 Treatment Compliance

If a patient did not comply with the dose schedule, it was deemed a protocol deviation and documented appropriately, but that patient continued in the study if considered appropriate by both the investigator and the sponsor. Used medication packs were returned to the clinical site for review, but no other assessment of compliance was made.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

Table 9.5.1 Flowchart of Study Procedures

	Screening (within 30d prior to dosing)	Randomisation	Treatment 1 (at home)	Follow-up (within 5 days)	Treatment 2 (at home)	Follow-up (within 5 days)	Treatment 3 (at home)	Follow-up and close-out (within 5 days of final treatment)
Medical history	X							
Concomitant medication	X	X	X	X	X	X	X	X
Vital signs	X	X						X
Physical examination	X							X
Pregnancy test		X		X		X		X
Blood sampling for haematology & biochemistry	X							X
Dosing			X		X		X	
Pain intensity & pain relief assessment			X		X		X	
Adverse events	X	X	X	X	X	X	X	X

The following assessments were recorded:

Demographic data (race, date of birth, height, weight, body mass index, smoking, alcohol and drugs of abuse histories and use) were recorded at baseline by the Investigator.

Vital signs (blood pressure, heart rate and oral temperature) were recorded by the Investigator at baseline and at the final visit (Visit 3) after the last study treatment had been taken or on occurrence of withdrawal.

A physical examination was conducted by the Investigator at baseline and at the final visit (Visit 3), or on occurrence of withdrawal.

A relevant medical history, including recording of primary diagnosis and date of onset of dysmenorrhoea was taken by the Investigator at baseline.

Current medication usage and therapy taken in the previous 30 days was recorded at baseline by the Investigator. Changes to concomitant medication were recorded by both the patient (in their diary, during treatment periods 1, 2 and 3) and the Investigator (in the CRF at visits 1, 2 and 3).

Urine pregnancy testing was conducted by the Investigator at each visit when study medication was to be issued (Baseline, Visit 1, Visit 2).

Blood samples were taken by the Investigator for haematology and biochemistry at baseline and at the close-out visit.

Menstrual pain intensity on a 4 point categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) before and at 0.5, 1, 1.5, 2, 4 and 6 hours after dosing with each study treatment was recorded in a paper diary by each patient. Pain relief was recorded in the diary on a 5-point scale (0 = no pain relief, 1 = a little pain relief, 2 = some pain relief, 3 = a lot of pain relief, 4 = complete pain relief) at 0.5, 1, 1.5, 2, 4 and 6 hours after dosing. A global assessment of each study medication was recorded in the patient diary by the patient 6 hours after dosing, using a 5 point categorical scale (1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, 5 = Excellent).

Concomitant medications, the use of rescue medication and details of any adverse events were recorded by each patient in their diary.

The diaries were reviewed by the Investigator at each visit, and any adverse events recorded by the patients were transferred into the CRF with additional details supplied by the patient on questioning by the Investigator. The Investigator also queried whether the patient had experienced any other adverse events.

The severity and relationship to treatment ratings that the Investigator used are described in table 9.5.2.

Table 9.5.2 Rating Systems used to Determine Adverse Event Severity and Relationship to Study Medication

Variable	Category	Definition
Severity		Severity was determined by the Investigator. For symptomatic AEs the following definitions were applied but medical experience and judgement was also used in the assessment of severity.
	Mild	The AE did not limit usual activities; the subject may experience slight discomfort.
	Moderate	The AE resulted in some limitation of usual activities; the subject may experience significant discomfort.
	Severe	The AE resulted in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain.
Relationship to study medication	Definite	An AE that followed an anticipated response to the study medication; and that was confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge)
	Probable	An AE that followed a reasonable temporal sequence from administration of the study medication, that is an anticipated response to the study medication; and that could not have been reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy
	Possible	An AE that followed a reasonable temporal sequence from administration of the study medicines; that might have been an anticipated response to the study medication; but that could have been produced by the subject's clinical state or concomitant therapy.
	Unlikely	An AE that did not follow an anticipated response to the study medication; which may have been attributable to other than the study medication, and that was more likely to have been produced by the subject's clinical state or concomitant therapy.
	None	An AE that was known beyond all reasonable doubt to be caused by the subject's state or concomitant therapy.

9.5.2 Appropriateness of Measurements

All assessments of efficacy and safety parameters were made using standard, widely used, published and reliable methodologies.

9.5.3 Primary Efficacy Variable(s)

The primary analgesic efficacy endpoint was the total pain relief over 6 hours post dose (TOTPAR 0-6h), i.e. the area under the pain relief by time curve between 0 and

6 hours, with pain relief (PR) rated on a 5-point scale of 0 = no pain relief, 1 = a little pain relief, 2 = some pain relief, 3 = a lot of pain relief, 4 = complete pain relief.

9.5.4 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

The protocol and CRFs were subject to Quality Control checks and several reviews during their development, by the Sponsor and Investigator and other study staff, including the data management staff.

An initial study meeting was held with the clinical site, during which the protocol and CRFs were reviewed and the study staff informed and reminded of key aspects of the study, including record keeping, obtaining informed consent, SAE reporting requirements and the need to conduct the study to GCP.

The study was monitored throughout by appropriately educated, trained and experienced Clinical Research Associates who reviewed the CRFs and conducted Source Data Verification (SDV) for each patient.

A single laboratory conducted the haematology and biochemical analyses according to their Standard Operating Procedures (SOPs).

All data were entered onto the WCT NODES computer database by a member of the Data Management Section and then verified by repeat data entry by a further Section member. SAS Version 9.1 edit checks were used for consistency checks.

Before database lock, a database audit was performed which had three components.

Audit component 1: Consistency checking and query generation

Five cases were selected at random to undergo full consistency checking where an error was failure to issue a query when current procedure calls for a data enquiry to be raised, or failure to appropriately respond to a consistency check. A total of one query was missed.

Audit component 2: Transcription and annotation procedures

The five cases selected for component 1 were also selected for full audit where errors were either transcription or other failures with respect to standard procedures for annotating working copies etc. No errors were found.

Audit component 3: Critical data fields

The critical fields were checked for 100% of cases. Any errors found were corrected. The fields were determined by the Study Statistician and Clinical Project Leader and were:

- Randomisation number
- Date and time of study medication
- Time of assessments for all observations recorded in the patient diary
- All pain relief data recorded within the subject diary
- All Adverse Event data

The findings of the audit indicated that data entry procedures had been followed carefully. No remedial actions were considered necessary.

The following aspects of this study were subject to a GCP compliance audit, conducted by appropriately trained and experienced personnel at Quorn Consultancy (Clinical site audit) and at Worldwide Clinical Trials Ltd (all other aspects):

- Conduct of the study at the clinical site
- Study database
- Statistical analyses

The audit certificate for the biostatistical aspects of the study is included in Appendix 16.1.8. The audit certificate for the clinical site audit was not available at the time this clinical study report was compiled.

The second draft of this study report was subject to QC conducted by ICC and the form recording this is available in the Trial Master File.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

A copy of the final statistical analysis plan is presented as Appendix 16.1.9.

All statistical tests performed were 2-tailed with significance determined by reference to the 5% significance level, unless otherwise stated. The null hypothesis unless otherwise specified was the equality of the treatments being compared. All comparisons between the treatments were reported with 95% confidence intervals for the difference. For each statistical test, an observed significance level was quoted. Where this value was less than 0.05, 0.01 or 0.001, attention was drawn to the fact using the conventional "*", "**" or "***" annotation, respectively.

Normality assumptions were tested by an examination of the residual plots and the Shapiro-Wilk test of normality. Depending on the degree of departure from these assumptions, an alternate nonparametric approach could have been used instead.

As treatment doses were at least a month apart, carryover effects were not allowed for in any of the formal statistical models.

All scheduled diary assessments completed after the subject had taken rescue medication were considered missing. For pain relief (PR) and Pain Intensity Difference (PID), missing values between two available assessments were linearly interpolated. Missing readings that could not be interpolated were replaced with the baseline pain intensity (PI) or no relief.

Computation of area under the curve (AUC) based assessments (TOTPAR, SPID and SPRID) were based on the assumption that the baseline assessment took place at time zero. Computations also used actual assessment times rather than the nominal assessment times. If the actual time was not recorded the scheduled time was used instead. All AUC (0-x hours) values were calculated using the trapezoidal rule and were divided by the actual time of the assessment at time x for ease of interpretation.

All calculations and figures were produced using SAS Version 9.1 or S-PLUS 6.2.

For continuous variables, the mean, median, standard deviation, standard error of the mean, minimum, maximum and lower and upper 95% confidence limits for the mean for the population and for the individual treatments were given.

Categorical data were presented in contingency tables with cell frequencies and percentages for the patient population and for the individual treatments.

The comparability of treatment sequences with respect to patient demographics and baseline characteristics was assessed in a descriptive manner, but no formal statistical testing was performed.

Concomitant medications ongoing at time of first dose of study medication were coded using the ATC level 2 categories from the WHO dictionary.

Primary Endpoint

The primary analgesic efficacy endpoint was the total pain relief over 6 hours post dose (TOTPAR 0-6h), i.e. the area under the pain relief by time curve between 0 and 6 hours, with pain relief (PR) rated on a 5-point scale: 0 = no pain relief, 1 = a little pain relief, 2 = some pain relief, 3 = a lot of pain relief, 4 = complete pain relief.

Results for the primary endpoint were summarised by treatment using number of observations (treatment periods), number of treatment periods completed without rescue medication, mean, standard deviation, median, minimum and maximum values. The results were analysed by analysis of covariance (ANCOVA) using

PROC MIXED in SAS with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect. Pairwise treatment comparisons between each of the fixed dose combination treatments and placebo were made based on the least squares estimates and standard errors (SEs) derived from the ANCOVA model. These were tested via a closed test procedure, if the overall effect for treatment was significant at the 5% level then firstly ibuprofen 400 mg + acetaminophen 1000 mg were formally tested against placebo at the two-sided 5% level and then if this comparison was significant, ibuprofen 200 mg + acetaminophen 500 mg was formally tested against placebo also at the two-sided 5% level. The pairwise comparison between the two combinations was reported descriptively with a two-sided 95% confidence interval for the mean difference and did not form part of the formal closed testing procedure.

The primary efficacy analysis endpoint was analysed using both the ITT and the PP analysis populations. The ITT analysis was considered to be the primary analysis.

Sensitivity analyses were also presented, these included using last observation carried forward (LOCF) for observations that could not be interpolated and replacing all missing values with the worst possible score for the active treatments and the best possible score for placebo.

Secondary endpoints

All secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analysed without any procedures to account for multiple comparisons.

Results for the AUC-based secondary endpoints (TOTPAR, SPID and SPRID) were summarised by treatment using number of observations (treatment periods), number of treatment periods completed without rescue medication, mean, standard deviation, median, minimum and maximum values. The results were analysed using the same ANCOVA model as used for the primary efficacy endpoint.

Pain intensity (PI), Pain intensity difference (PID), Pain relief (PR) and the sum of pain intensity difference and pain relief (SPRID) were summarised by assessment and treatment using number of treatment periods, number of missing values, mean, standard deviation, median, minimum and maximum values. The data from each follow-up assessment for SPRID, PID and PR was formally analysed using the same ANCOVA model as described above.

Mean profiles for PR, PI, PID and SPRID were presented by treatment.

Use of rescue medication (yes/no) was summarised by treatment and compared independently between each of the fixed dose combination treatments and placebo using Prescott's test. Tramadol (100 mg) was provided as rescue medication, but for the purpose of this analysis, a rescue medication was defined as any medication,

other than study medication, taken to control period pain. The time to first use of rescue medication was tabulated.

Patients overall assessment of the study medication as a treatment for pain collected at six hours post-dose (or just before administration of rescue medication, if sooner) was summarised by treatment using a frequency distribution and mean, standard deviation and median values. Pairwise treatment comparisons between each of the fixed dose combination treatments and placebo were made using independent Wilcoxon matched-pairs signed rank tests.

Exploratory Analysis

Analyses of the primary efficacy endpoint were performed by key baseline characteristics. For each subgroup, the main effect and treatment-by-subgroup interaction terms were added to the standard model used in the primary endpoint analysis. Key variables of interest were age (≤ median, > median), length of time since diagnosis (≤ median, > median) and BMI at screening (≤ median, > median). These models were used to estimate treatment comparisons within the subgroups that correspond with the sub-grouping factor.

Extent of exposure

Extent of exposure was described by whether the patient took each of the respective treatments.

Adverse events

All adverse events were listed and tabulated by treatment, severity, relationship to therapy and Primary System Organ Class according to MedDRA Version 12.1. In counting the number of events reported, a continuous event, i.e. an event reported more than once and which did not cease, was counted only once; non-continuous adverse events reported several times by the same patient were counted as multiple events. Events present immediately prior to the study medication dose that did not worsen in severity were not included. Events that first occur or worsen in severity during the washout phase were assigned to the washout if they occurred more than 24 hours after study medication dosing. Events that occurred more than 24 hours after the last study medication dose were assigned to the post-treatment phase.

The incidence of adverse events (number and percent of subjects reporting the adverse event at least once during the study) were summarised for all adverse events, by investigator attribution of relationship to study medication and by severity. The incidence of adverse events was compared between treatment groups using Prescott's Test for all adverse events, for those adverse events classified by the Investigator as definitely, probably or possibly related to study medication and for severe adverse events.

Laboratory data

The change from screening to post-study follow-up for each haematology and biochemistry variable was assessed via a paired t-test. In addition, each reading was classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables for the baseline and follow-up measurements were presented.

Vital Signs

Summary statistics for absolute and change from baseline vital sign values were presented using n, mean, standard deviation, median, minimum, maximum and lower and upper 95% confidence limits for the mean.

If appropriate the incidence of clinically meaningful changes, as designated by the investigator, in blood pressure, heart rate and temperature were to be summarised.

Any clinically significant changes in vital signs during the study were presented and recorded as AEs.

Physical examination

Changes from screening to follow-up visit in the physical examination were tabulated.

Withdrawals

The number of patients who withdrew from the study was presented. The period and reasons for withdrawal were summarised by treatment sequence.

Concomitant medications

Concomitant medications commencing after randomisation were coded using the ATC level 2 categories from the WHO dictionary.

9.7.2 Determination of Sample Size

In a study of the efficacy of ibuprofen 400 mg in primary dysmenorrhoea reported by Marchini,[5] the mean (SD) scores for total pain relief over 6 hours (TOTPAR 0-6h adjusted for time) for ibuprofen 400 mg and placebo were 2.97 (0.83) and 2.45 (1.32) respectively. The within subject standard deviation was not reported but was assumed to be of the order of 0.8 - 0.9. It was also assumed that the underlying effects for ibuprofen 400 mg + acetaminophen 1,000 mg and ibuprofen 200 mg + acetaminophen 500 mg relative to placebo would be of the order of 120% and 60% of the effect of ibuprofen 400 mg, with values of approximately 3.10 and 2.75 respectively for TOTPAR 0-6h and a within subject standard deviation of 0.85. Given these assumptions, it was calculated that a cross-over study with 85 completed subjects would have at least 90% power to demonstrate that both fixed dose

combination treatments provided statistically significantly greater pain relief (as assessed by TOTPAR 0-6h) than placebo, using a two-sided paired t-test at the two-sided 5% significance level.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

One non-substantial protocol amendment (Protocol Amendment 01, dated 16 January 2009) was issued before the start of the study. This related to the presentation form of the rescue medication (Tramadol 100 mg) which was stated in the protocol to be a tablet formulation, but was provided as a capsule formulation.

This change was initiated by RB and was not considered to have any implications for the analysis and interpretation of the study.

It was noted during preparation of the study report that the combined patient information sheet and consent form referred to the provision of capsules of study medication. However, the study medication was supplied in a tablet formulation. It was not considered appropriate to issue an amendment retrospectively and a note to this effect explaining the observation was placed in the trial master file and in the site file.

9.8.2 Changes in the Planned Statistical Analysis of the Study

The requirement for inclusion within the per-protocol set was amended from having to have efficacy data for all three treatment periods to having valid efficacy data for at least two treatment periods.

While the protocol and analysis plan described the ITT population as "all patients who were recruited to the study and received at least one dose of study medication and had efficacy data for at least two treatment periods", in practice this meant that the ITT population consisted of "all patients who were recruited to the study and received at least ***two doses*** of study medication and had efficacy data for at least two treatment periods"

Due to the small of number of subjects using rescue medication, the time to rescue medication was tabulated but not formally analysed.

10 STUDY SUBJECTS

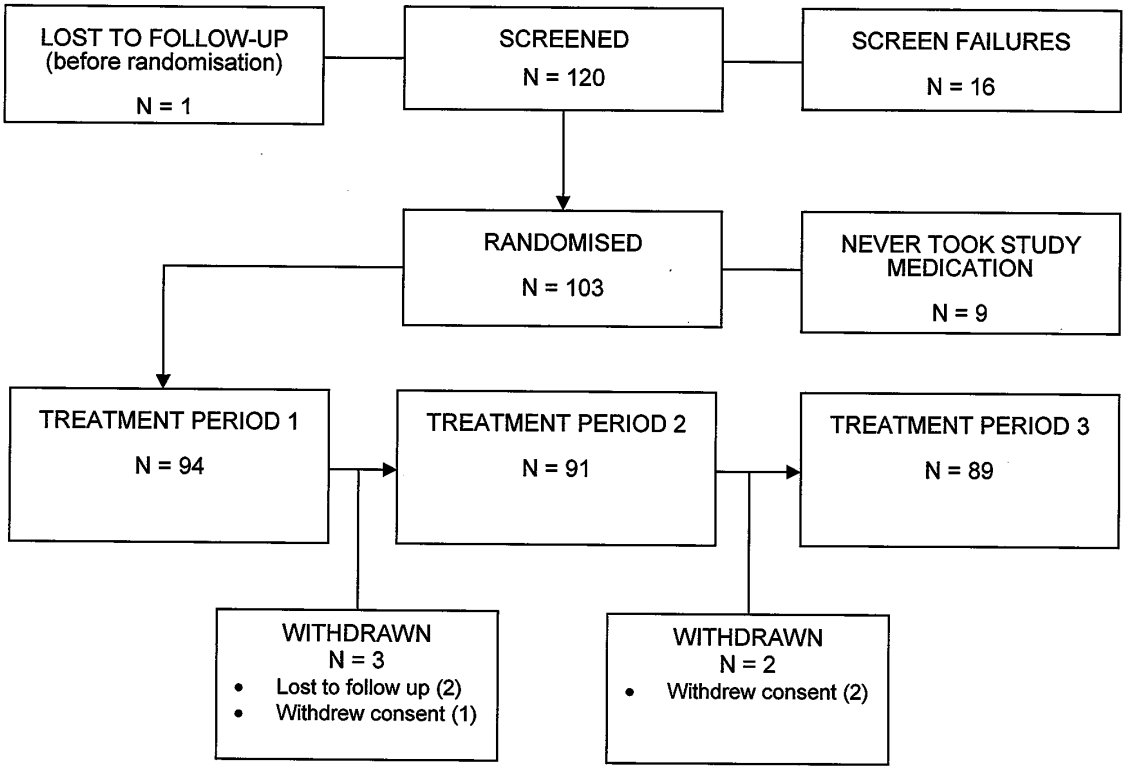
10.1 Disposition of Subjects

A total of 103 patients were enrolled into the study between 11th February 2009 and 5th March 2009. Nine patients did not take any study medication, so 94 were included in the safety population. Five patients withdrew during the study; a total of 89 patients completed the study. Three withdrew from the study after the first period

of treatment. Two of these were lost to follow-up and one withdrew consent. Two had received ibuprofen 400 mg + acetaminophen 1000 mg and the other had received ibuprofen 200 mg + acetaminophen 500 mg. Two patients withdrew after treatment period 2. One had received ibuprofen 400 mg + acetaminophen 1000 mg but was "unable to complete the study". The other had received placebo and stated they did not want to continue the study. No other reason was given for their discontinuation. Withdrawal information is provided in Table 14.1.1.

A listing of all patients discontinued from the study after enrolment is provided in Appendix 16.2.1. A flow chart summarising the disposition is given in Figure 10.1.1.

Figure 10.1.1: Disposition of Subjects



10.2 Protocol Deviations

A listing of individual subjects who deviated from the protocol is presented in Appendix 16.2.2.

There were a total of 20 deviations involving 16 patients. There were 17 instances of inadmissible timing of assessments (11 during the ibuprofen 400 mg + acetaminophen 1000 mg phase, four during the ibuprofen 200 mg + acetaminophen 500 mg phase and two during the placebo phase). The other three deviations reported occurred during treatment with placebo; two subjects only took one capsule

of study medication and another took inadmissible concomitant medication (acetaminophen) at an unspecified time during the six-hour study treatment period.

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Appendix 16.2.3 contains a tabular listing of all subjects, visits and observations excluded from the efficacy analysis. The reasons for exclusion are presented for the whole treatment group over time.

The strategy for the inclusion/exclusion criteria for each of the data sets analysed was included in the statistical analysis plan for the study and finalised following discussions of evaluability which were performed immediately prior to database lock.

Three analysis sets were used in the analysis. These populations were defined as follows:

The **safety population** contained all patients who were recruited to the study and received at least one dose of study medication. This population contained ninety-four patients and was used for analyses of demography and safety.

Five patients within the safety population withdrew from the study (numbers 003, 045, 047, 059 and 103) including three (numbers 003, 047 and 103) who only provided data from the first treatment period.

The **Intention to Treat (ITT) population** included all patients who were recruited to the study and received at least two doses of study medication and had efficacy data for at least two treatment periods. Three patients (numbers 003, 047 and 103) withdrew from the study after treatment period 1 so this population contained ninety-one patients. This population was used for the efficacy analyses.

The **Per Protocol (PP) population** consisted of all patients recruited to the study who satisfied all of the inclusion/exclusion criteria, received the correct study medication (as randomised) and had valid efficacy data for at least two treatment periods with no major protocol violations. This analysis population was used only for the analysis of the primary efficacy endpoint, total pain relief over six hours post-dose (TOTPAR 0-6h), in support of the ITT analysis. Major protocol violations included:

- Non-compliance with study medication.
- Taking inadmissible concomitant medication
- Inadmissible timing of the follow-up assessments within the first 2 hours post-dosing as follows:
    - 30 and 60 minute assessments not performed within +/- 5 minutes of the scheduled times.

- 90, 120, 240 and 360 minute assessments not performed within +/- 15 minutes of the scheduled times.

Four patients who satisfied the criteria for inclusion in the ITT population did not provide valid data for at least two periods (numbers 010, 034, 038 and 041); therefore eight-seven patients were included in the per-protocol population. Eleven patients had partial exclusion of data from this set.

11.2 Demographic and Other Baseline Characteristics

A full summary of demographic information is presented in Tables 14.1.2 to 14.1.9. Summary statistics and frequency distributions are presented both overall and by treatment sequence. In general, the treatment sequences were well balanced for the demographic variables.

Overall, patient age ranged from 18 to 46 years, with a mean of 22.1 years. The majority of patients, 87/94, (93%) were Caucasian. A further 5/94 (5%) were Asian, one (1%) was Afro-Caribbean and one (1%) was Chinese. Height ranged from 145 to 180 cm, with mean 163.2 cm. Mean weight was 63.1 kg, range 42.8 kg to 111.7 kg. Body Mass Index (BMI) ranged from 16.9 kg/m^2 to 39.4 kg/m^2 with a mean of 23.7 kg/m^2. A total of 89 patients (95%) drank alcohol, one (1%) was a current smoker and three (3%) were former smokers. No patients reported taking drugs of abuse. Table 11.2.1 provides an abbreviated summary of key demographic variables

Table 11.2.1 Demographics – Safety Population

Variable	
Number of subjects	94
Age (yr) (Mean ± sd)	22.1±5.7
Race (% Caucasian)	92.6%
Height (cm) (Mean ± sd)	163.2±6.4
Weight (kg) (Mean ± sd)	63.1±11.5
BMI (kg/m^2) (Mean ± sd)	23.7±4.2
Alcohol drinker (%)	94.7%
Current smoker (%)	1.1%
Former smoker (%)	3.2%

Source: Table 14.1.2

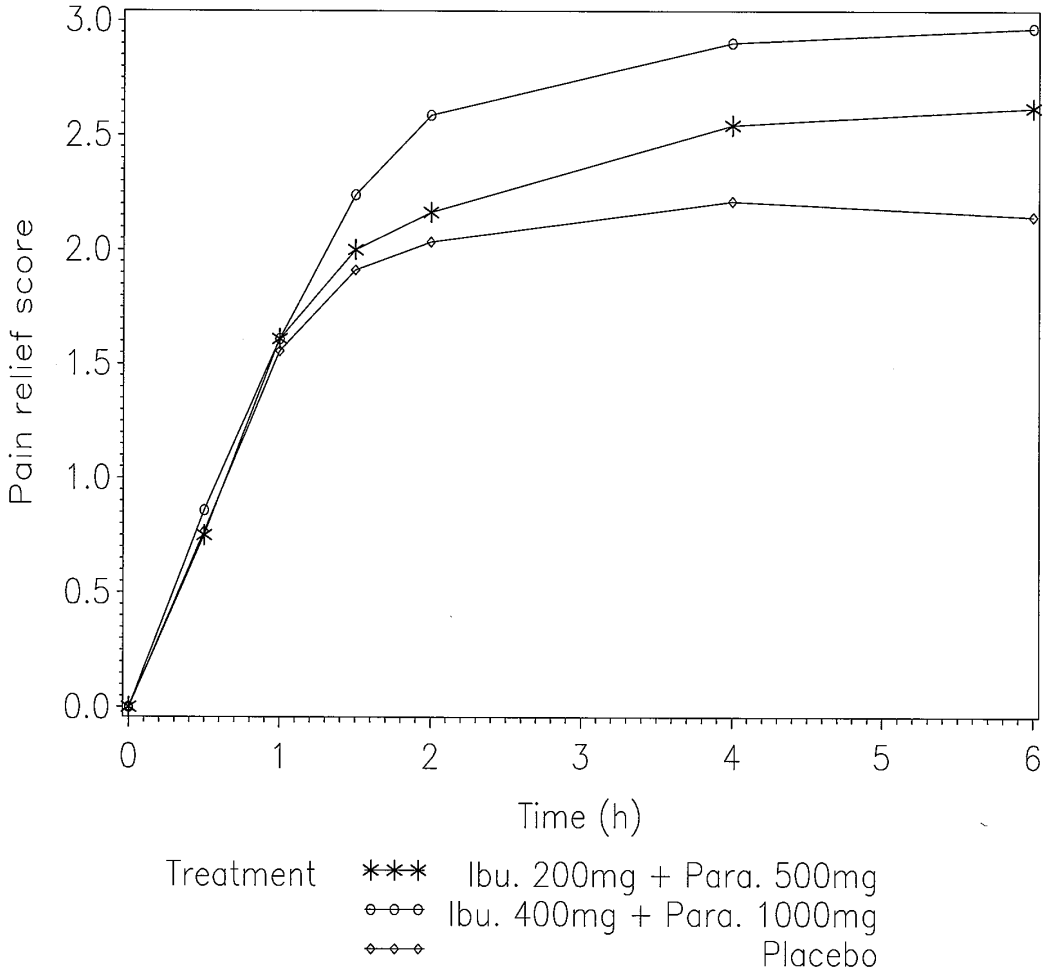
The duration of dysmenorrhoea ranged from one to 34 years with median of 8.0 years. Seven patients (7%) had suffered from dysmenorrhoea for over 20 years (Table 14.1.3).

Three patients (3%) reported previous relevant medical histories and nine patients (10%) had concomitant disease, including five (5%) with allergies/drug sensitivities (Table 14.1.4).

Pain Relief Scores at Individual Timepoints

The mean pain relief scores at each assessment are presented graphically in Figure 11.4.1 and summarised in Table 11.4.4 below. Full details are provided in Table 14.2.4.

Figure 11.4.1 Mean pain relief - ITT population



Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

Maximum mean pain relief was reported at six hours post-dose for both the active treatments. Divergences in the mean pain relief scores for the different treatments are apparent beyond the one hour assessment.

Table 14.1.5 presents full summary statistics of vital signs at screening and randomisation. Table 11.2.2 provides an abbreviated summary of key values at baseline (randomisation).

Table 11.2.2 Vital Signs at baseline (randomisation) – Safety Population

Variable	
Number of subjects	94
Systolic blood pressure (mmHg) (Mean ± sd)	125.0±12.1
Diastolic blood pressure (mmHg) (Mean ± sd)	72.0±11.1
Heart rate (bpm) (Mean ± sd)	75.8±11.7
Temperature (degrees C) (Mean ± sd)	36.1±0.6

Source: Table 14.1.5

No abnormalities were reported on physical examination at screening (Table 14.1.6).

Details of haematology and biochemistry at screening are presented in Tables 14.1.7 and 14.1.8.

Fifty-nine (63%) patients reported ongoing concomitant medication at the time of first dose of medication including 56 (60%) who were using contraceptive medication.

11.3 Measurements of Treatment Compliance

In this single-dose, three treatment period study, compliance was assessed by diary review and review of returned medication and packaging.

Ninety-four patients took at least one study medication and were included in the safety set. Ninety-two (98%) patients received ibuprofen 200 mg + acetaminophen 500 mg, ninety-two (98%) received ibuprofen 400 mg + acetaminophen 1000 mg and ninety (96%) received placebo. Two patients (numbers 011 and 041) only took one capsule of study medication during treatment period 1. Both had been allocated to receive placebo in this treatment period.

11.4 Efficacy Results

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint

The primary endpoint was the total pain relief over six hours (TOTPAR 0-6h). Results of the analyses of the primary endpoint are summarised for both the ITT dataset and the PP dataset in Table 11.4.1.

Table 11.4.1 Primary Efficacy Endpoint: Total pain relief over six hours post-dose (TOTPAR 0-6h)

	Ibuprofen 200mg + Paracetamol 500mg	Ibuprofen 400mg + Paracetamol 1000mg	Placebo
INTENT-TO-TREAT POPULATION			
N	91	90	90
Mean±sd	2.11±1.07	2.37±0.99	1.87±1.17
LS mean[a]	2.10	2.35	1.85
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.51	0.25,0.76	0.0001 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.25	-0.00,0.51	0.054
PER-PROTOCOL POPULATION			
N	85	79	84
Mean±sd	2.15±1.07	2.39±0.98	1.86±1.18
LS mean[a]	2.13	2.32	1.84
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.49	0.22,0.75	0.0005 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.30	0.04,0.56	0.03 *

a Estimated from ANCOVA model with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect
b A positive difference favours the active treatment
* Comparison statistically significant at 5% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.1.1 and 14.2.1.2
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

In the ANCOVA model for the intent-to-treat dataset, the overall effect of treatment was statistically significant (p=0.0007), whereas the effects of baseline pain intensity (p=0.71), period (p=0.42) and sequence (p=0.09) were not statistically significant. The LS means were 2.35 (ibuprofen 400 mg + paracetamol 1000 mg), 2.10 (ibuprofen 200mg + paracetamol 500mg) and 1.85 (placebo). The comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo was statistically significant (p=0.0001), whereas the comparison between the lower dose combination and placebo marginally failed to achieve statistical significance (p=0.054; Table 14.2.1.1).

Four patients were completely excluded from the per-protocol set and a further 11 had partial exclusion of data from this set. For this analysis, both pairwise comparisons against placebo were statistically significant (p=0.0005 for the higher dose combination and p=0.03 for the lower dose combination). The LS means (Table 14.2.1.2) were 2.32 (ibuprofen 400 mg + paracetamol 1000 mg), 2.13 (ibuprofen 200 mg + paracetamol 500 mg) and 1.84 (placebo).

Sensitivity analyses were also performed using: (1) last observation carried forward (LOCF) for observations that could not be interpolated and (2) replacing all missing values with the worst possible score for the active treatments and the best possible score for placebo. These analyses are summarised in Table 11.4.2. In the latter analysis, the overall treatment effect marginally failed to achieve statistical significance and neither pairwise comparison was statistically significant. For the LOCF analysis, the overall treatment effect was statistically significant (p=0.0027) and the ibuprofen 400 mg + paracetamol 1000 mg comparison against placebo was highly statistically significant (p=0.0006), whereas the comparison of the low-dose combination against placebo was not statistically significant (p=0.15). Further details are given in Table 14.2.1.3.

Table 11.4.2 Primary Efficacy Endpoint: Total pain relief over six hours post-dose (TOTPAR 0-6h) - Sensitivity Analyses

	Ibuprofen 200mg + Paracetamol 500mg (N=91)	Ibuprofen 400mg + Paracetamol 1000mg (N=90)	Placebo (N=90)
REPLACING ALL MISSING VALUES WITH THE WORST POSSIBLE SCORE FOR THE ACTIVE TREATMENTS AND THE BEST POSSIBLE SCORE FOR PLACEBO			
Mean±sd	2.11±1.07	2.37±0.99	2.16±1.04
LS mean[a]	2.10	2.36	2.14
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.22	-0.00,0.45	0.054
Ibuprofen 200mg + Paracetamol 500mg - Placebo	-0.04	-0.26,0.19	0.73
USING LAST OBSERVATION CARRIED FORWARD FOR OBSERVATIONS THAT CANNOT BE INTERPOLATED			
Mean±sd	2.11±1.06	2.37±0.99	1.96±1.10
LS mean[a]	2.10	2.35	1.93
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.42	0.18,0.66	0.0006 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.17	-0.06,0.41	0.15

a Estimated from ANCOVA model with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect
b A positive difference favours the active treatment
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.1.3
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

11.4.1.2 Secondary Endpoints

TOTPAR 0-2h, TOTPAR 0-4h

For the total pain relief over the first two hours post-dose (TOTPAR 0-2h) none of the effects included in the ANCOVA model achieved statistical significance. The LS

means were 1.48 (ibuprofen 400 mg + paracetamol 1000 mg), 1.36 (ibuprofen 200 mg + paracetamol 500 mg) and 1.30 (placebo: Table 14.2.2).

The results for total pain relief over the first four hours post-dose (TOTPAR 0-4h) mirrored those for the primary efficacy endpoint. In the ANCOVA model for the intent-to-treat population, the overall effect of treatment was statistically significant (p=0.008), whereas the effects of baseline pain intensity (p=0.99), period (p=0.35) and sequence (p=0.14) were not statistically significant. The LS means were 2.08 (ibuprofen 400 mg + paracetamol 1000 mg), 1.85 (ibuprofen 200mg + paracetamol 500 mg) and 1.69 (placebo). The comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo was statistically significant (p=0.002), whereas the comparison between the low-dose combination and placebo was not significant (p=0.20; Table 14.2.3).

A summary of these results is presented in Table 11.4.3.

Table 11.4.3 Total pain relief over two and four hours post-dose - ITT population

	Ibuprofen 200mg + Paracetamol 500mg (N=91)	Ibuprofen 400mg + Paracetamol 1000mg (N=90)	Placebo (N=90)
TOTPAR 0-2h			
Mean±sd	1.36±0.91	1.48±0.86	1.31±0.90
LS mean[a]	1.36	1.48	1.30
Parameter estimates	LS mean[b]	95% CI	P
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.18	-0.03,0.39	0.10
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.06	-0.15,0.27	0.57
TOTPAR 0-4h			
Mean±sd	1.86±1.02	2.09±0.97	1.72±1.08
LS mean[a]	1.85	2.08	1.69
Parameter estimates	LS mean[b]	95% CI	P
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.39	0.14,0.63	0.002 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.16	-0.08,0.40	0.20

a Estimated from ANCOVA model with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect

b A positive difference favours the active treatment

*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.2 and 14.2.3

Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

Table 11.4.4 Mean ± sd (n) for pain relief at 30, 60, 90, 120, 240 and 360 minutes post-dose - ITT population

Minutes post-dose	Ibuprofen 200mg + Paracetamol 500mg (n=91)	Ibuprofen 400mg + Paracetamol 1000mg (n=90)	Placebo (n=90)	Ibuprofen 400mg + Paracetamol 1000mg versus Placebo	Ibuprofen 200mg + Paracetamol 500mg versus Placebo
30	0.75±1.04	0.81±0.98	0.77±0.92	ns	ns
60	1.60±1.18	1.58±1.14	1.56±1.18	ns	ns
90	2.00±1.23	2.20±1.25	1.91±1.30	ns	ns
120	2.19±1.30	2.56±1.26	2.03±1.37	**	ns
240	2.57±1.36	2.88±1.27	2.21±1.50	***	*
360	2.65±1.40	2.94±1.23	2.14±1.57	***	**

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.4
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

The comparisons between ibuprofen 400 mg + paracetamol 1000 mg and placebo were statistically significant from two hours post-dose onwards ($p<0.01$) and the comparisons for ibuprofen 200 mg + paracetamol 500 mg versus placebo were statistically significant at four and six hours post-dosing ($p<0.05$ and $p < 0.01$ respectively).

Sum of Pain Intensity Differences (SPID)

Details of total analgesic effect over two, four and six hours post-dose as measured by SPID are summarised in Table 11.4.5 below and presented in more details in Tables 14.2.5 to 14.2.7.

For SPID 0-2h, the covariate in the ANCOVA model for baseline pain intensity was statistically significant ($p<0.0001$) while the effects of treatment ($p=0.09$), period ($p=0.44$) and sequence ($p=0.39$) were not statistically significant. The LS means were 0.81 (ibuprofen 400 mg + paracetamol 1000 mg), 0.72 (ibuprofen 200 mg + paracetamol 500 mg) and 0.67 (placebo). Although the overall treatment effect was not statistically significant, the LS mean difference of 0.14 for ibuprofen 400 mg + paracetamol 1000 mg versus placebo was statistically significant ($p=0.03$).

For SPID 0-4h, the effects of baseline pain intensity ($p<0.0001$) and treatment ($p=0.004$) were statistically significant in the ANCOVA model. The comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo was statistically significant ($p=0.0009$) whereas the comparison between ibuprofen 200mg + paracetamol 500 mg and placebo was not statistically significant ($p=0.09$). The LS means were 1.17 (ibuprofen 400 mg + paracetamol 1000 mg), 1.05 (ibuprofen 200mg + paracetamol 500 mg) and 0.92 (placebo).

For SPID 0-6h, the effects of baseline pain intensity (p<0.0001) and treatment (p=0.0004) were statistically significant in the ANCOVA model and both comparisons between the active treatments and placebo were statistically significant (p<0.0001 for the higher-dose combination and p=0.02 for the lower-dose combination). The LS means were 1.33 (ibuprofen 400 mg + paracetamol 1000 mg), 1.21 (ibuprofen 200 mg + paracetamol 500 mg) and 1.02 (placebo).

Table 11.4.5 Total analgesic effect over two, four and six hours post-dose - ITT population

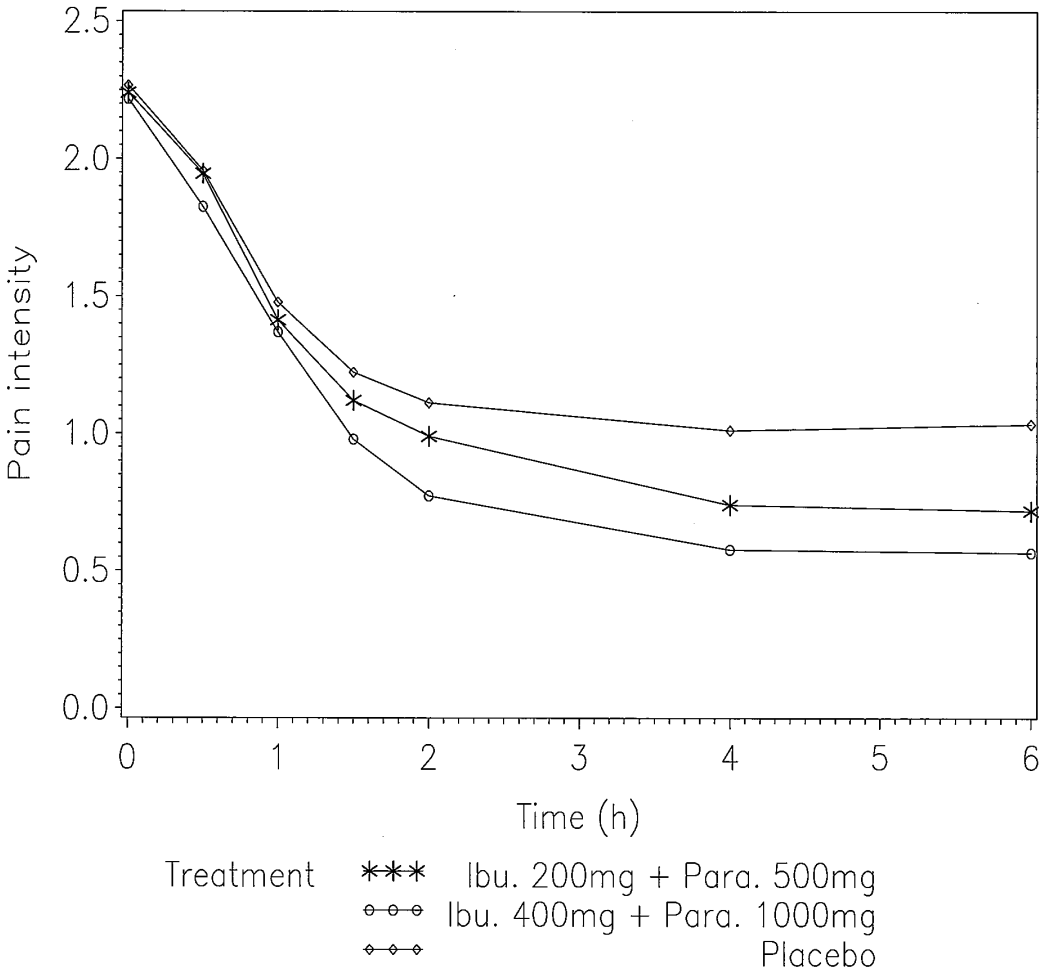
	Ibuprofen 200mg + Paracetamol 500mg (N=91)	Ibuprofen 400mg + Paracetamol 1000mg (N=90)	Placebo (N=90)
SPID 0-2h			
Mean±sd	0.72±0.61	0.80±0.57	0.68±0.53
LS mean[a]	0.72	0.81	0.67
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.14	0.01,0.27	0.03 *
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.05	-0.08,0.18	0.43
SPID 0-4h			
Mean±sd	1.05±0.66	1.17±0.64	0.94±0.66
LS mean[a]	1.05	1.17	0.92
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.25	0.10,0.40	0.0009 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.13	-0.02,0.27	0.09
SPID 0-6h			
Mean±sd	1.21±0.69	1.32±0.65	1.04±0.72
LS mean[a]	1.21	1.33	1.02
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.31	0.16,0.46	<0.0001 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.18	0.03,0.34	0.02 *

a Estimated from ANCOVA model with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect
b A positive difference favours the active treatment
* Comparison statistically significant at 5% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.5 to 14.2.7
Pain intensity measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

Pain Intensity Scores at Individual Timepoints

The mean pain intensity scores at each timepoint are presented graphically in Figure 11.4.2.

Figure 11.4.2 Mean pain intensity - ITT population

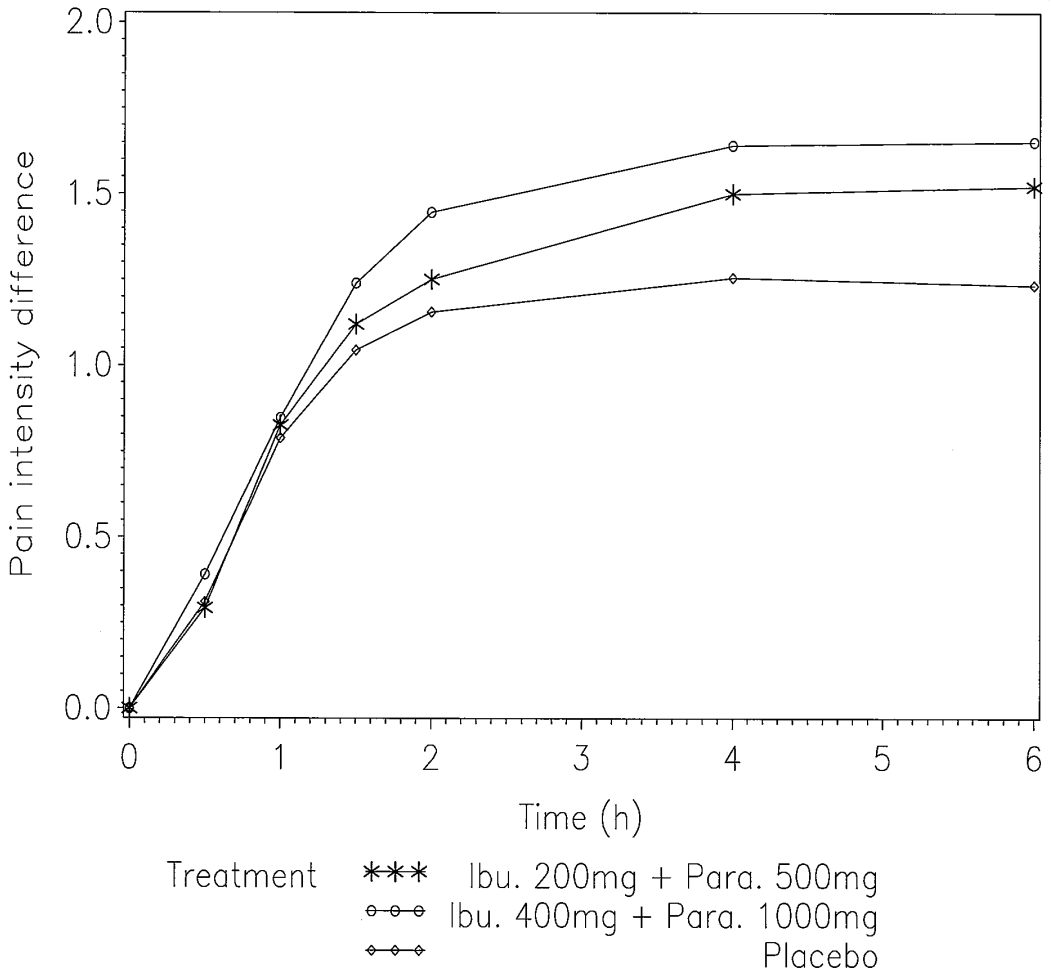


Pain intensity measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

Mean pain intensity decreased rapidly and markedly over the first two hours in all treatment groups, but more extensively with both the higher and lower dose fixed combinations than with placebo. Thereafter, the placebo group mean score stabilised, while further, but smaller decreases were seen with the active treatment groups.

Figure 11.4.3 illustrates graphically the mean pain intensity differences from baseline (PID) and Table 11.4.6 summarises the mean pain intensity differences at each timepoint.

Figure 11.4.3 Mean pain intensity difference - ITT population



Maximum mean pain intensity differences were reported at six hours post-dose for both active treatments. The curves separate from 60 minutes onwards with statistical differences compared to placebo being apparent from 90 minutes onwards for the higher dose combination and at four and six hours for the lower dose combination as shown in Table 11.4.6.

Table 11.4.6 Mean pain intensity differences at 30, 60, 90, 120, 240 and 360 minutes post-dose - ITT population

Minutes post-dose	Ibuprofen 200mg + Paracetamol 500mg (n=91)	Ibuprofen 400mg + Paracetamol 1000mg (n=90)	Placebo (n=90)	Ibuprofen 400mg + Paracetamol 1000mg versus Placebo	Ibuprofen 200mg + Paracetamol 500mg versus Placebo
Baseline pain	2.24±0.43[a]	2.22±0.42	2.27±0.44		
30	0.30±0.62	0.38±0.59	0.31±0.49	ns	ns
60	0.82±0.82	0.84±0.82	0.79±0.76	ns	ns
90	1.12±0.88	1.22±0.83	1.04±0.82	*	ns
120	1.26±0.84	1.43±0.85	1.16±0.89	**	ns
240	1.52±0.91	1.63±0.81	1.26±0.97	***	*
360	1.54±0.93	1.64±0.84	1.23±1.05	***	**

a Mean ± standard deviation
ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.8
Pain intensity measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

Sum of Pain Relief and Pain Intensity Differences (SPRID)

Details of the overall effectiveness over two, four and six hours post-dose as measured by SPRID are summarised in Table 11.4.7 below and presented in more details in Tables 14.2.9 to 14.2.11.

For SPRID 0-2h, none of the effects included in the ANCOVA model achieved statistical significance. The LS means were 2.29 (ibuprofen 400 mg + paracetamol 1000 mg), 2.08 (ibuprofen 200 mg + paracetamol 500 mg) and 1.96 (placebo).

For SPRID 0-4h, the effects of baseline pain intensity (p=0.02) and treatment (p=0.005) were statistically significant in the ANCOVA model. The comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo was statistically significant (p=0.0011) whereas the comparison between ibuprofen 200 mg + paracetamol 500 mg and placebo was not statistically significant (p=0.13). The LS means were 3.25 (ibuprofen 400 mg + paracetamol 1000 mg), 2.91 (ibuprofen 200 mg + paracetamol 500 mg) and 2.62 (placebo).

For SPRID 0-6h, the effects of baseline pain intensity (p=0.003) and treatment (p=0.0004) were statistically significant in the ANCOVA model and both comparisons between the active treatments and placebo were statistically significant (p<0.0001 for the higher dose combination and p=0.03 for the lower dose combination). The LS means were 3.68 (ibuprofen 400 mg + paracetamol 1000 mg), 3.30 (ibuprofen 200 mg + paracetamol 500 mg) and 2.87 (placebo).

Table 11.4.7 Overall effectiveness as measured by SPRID over two, four and six hours post-dose - ITT population

	Ibuprofen 200mg + Paracetamol 500mg (N=91)	Ibuprofen 400mg + Paracetamol 1000mg (N=90)	Placebo (N=90)
SPRID 0-2h			
Mean±sd	2.08±1.45	2.28±1.36	1.99±1.37
LS mean[a]	2.08	2.29	1.96
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.32	-0.01,0.65	0.054
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.11	-0.21,0.44	0.49
SPRID 0-4h			
Mean±sd	2.91±1.58	3.26±1.53	2.66±1.66
LS mean[a]	2.91	3.25	2.62
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.64	0.26,1.01	0.0011 **
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.29	-0.09,0.66	0.13
SPRID 0-6h			
Mean±sd	3.31±1.64	3.69±1.55	2.91±1.82
LS mean[a]	3.30	3.68	2.87
Parameter estimates	LS mean[b]	95% CI	p
Ibuprofen 400mg + Paracetamol 1000mg - Placebo	0.82	0.42,1.21	<0.0001 ***
Ibuprofen 200mg + Paracetamol 500mg - Placebo	0.44	0.04,0.83	0.03 *

a Estimated from ANCOVA model with a covariate for baseline pain intensity (for the relevant period), fixed effect terms for treatment, sequence and period and with subject within sequence included as a random effect
b A positive difference favours the active treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

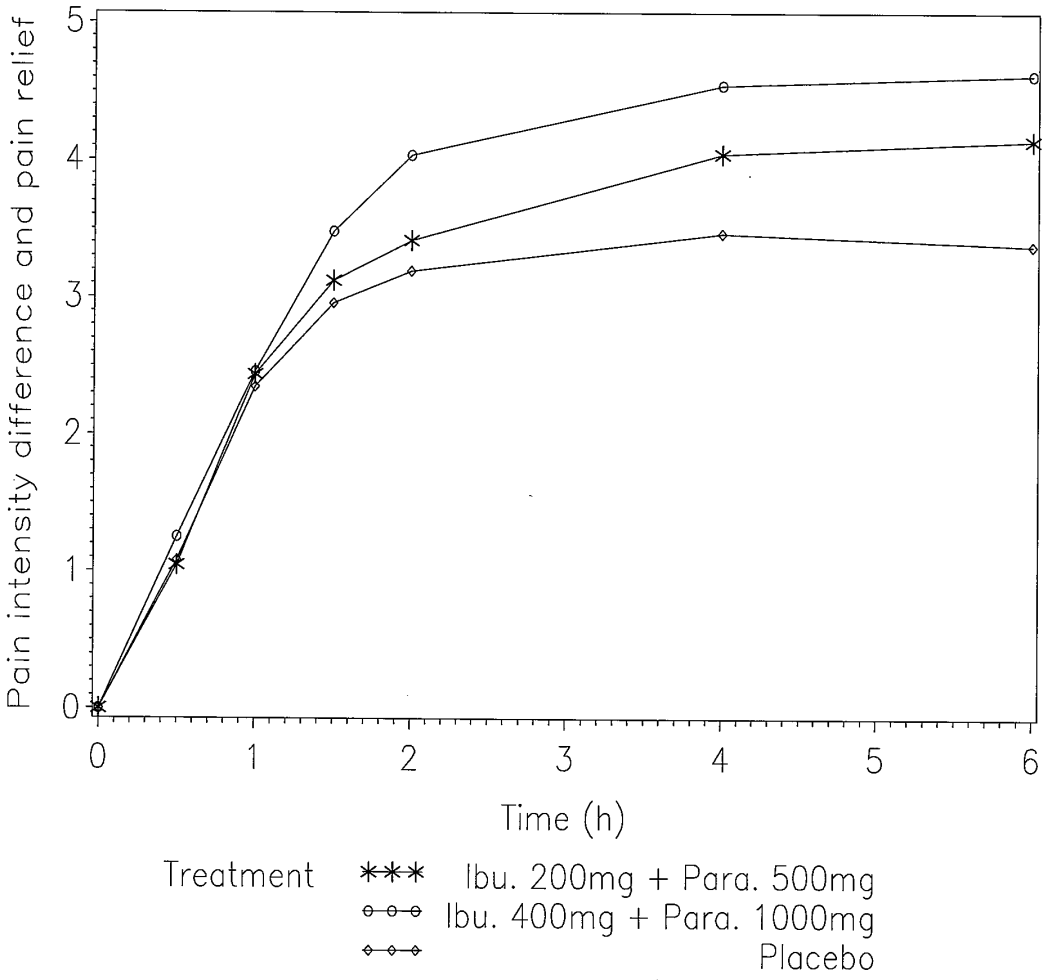
Source: Tables 14.2.9 to 14.2.11

Pain measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

The sum of the change from baseline for the pain intensity difference and pain relief scores at each follow-up assessment are illustrated graphically in Figure 11.4.4, summarised in Table 11.4.8 below and presented in more detail in Table 14.2.12.

Figure 11.4.4 Mean SPRID - ITT population



Maximum mean SPRID was achieved at six hours post-dose for both the active treatments.

As shown in Table 11.4.8, the comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo was statistically significant from 90 minutes onwards ($p<0.05$) and the comparison between ibuprofen 200 mg + paracetamol 500 mg and placebo comparison was statistically significant from four hours post-dosing ($p<0.05$).

Table 11.4.8 Mean change from baseline for SPRID at 30, 60, 90, 120, 240 and 360 minutes post-dose - ITT population

Minutes post-dose	Ibuprofen 200mg + Paracetamol 500mg (n=91)	Ibuprofen 400mg + Paracetamol 1000mg (n=90)	Placebo (n=90)	Ibuprofen 400mg + Paracetamol 1000mg versus Placebo	Ibuprofen 200mg + Paracetamol 500mg versus Placebo
30	1.04±1.60[a]	1.19±1.50	1.08±1.33	ns	ns
60	2.43±1.91	2.42±1.85	2.34±1.85	ns	ns
90	3.12±1.98	3.42±1.98	2.96±2.01	*	ns
120	3.45±1.97	3.99±1.97	3.19±2.14	**	ns
240	4.09±2.10	4.51±1.98	3.47±2.37	***	*
360	4.19±2.16	4.59±1.93	3.38±2.50	***	**

a Mean ± standard deviation
ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.12
Pain intensity measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

Use of Rescue Medication

Statistically significantly more patients used rescue medication after receiving placebo compared to each of the active combination treatments (p=0.0009 for the higher dose combination and p=0.02 for the lower dose combination). The numbers of patients who used rescue medication are shown in Table 11.4.9.

Table 11.4.9 Use of rescue medication - ITT population

	Ibuprofen 200mg + Paracetamol 500mg (n=91)	Ibuprofen 400mg + Paracetamol 1000mg (n=90)	Placebo (n=90)	Ibuprofen 400mg + Paracetamol 1000mg versus Placebo	Ibuprofen 200mg + Paracetamol 500mg versus Placebo
Used rescue	3 (3.3%)	2 (2.2%)	14 (15.6%)	0.0009 ***	0.0154 *

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.13
Pain measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

Overall Patient Assessment of Study Medication

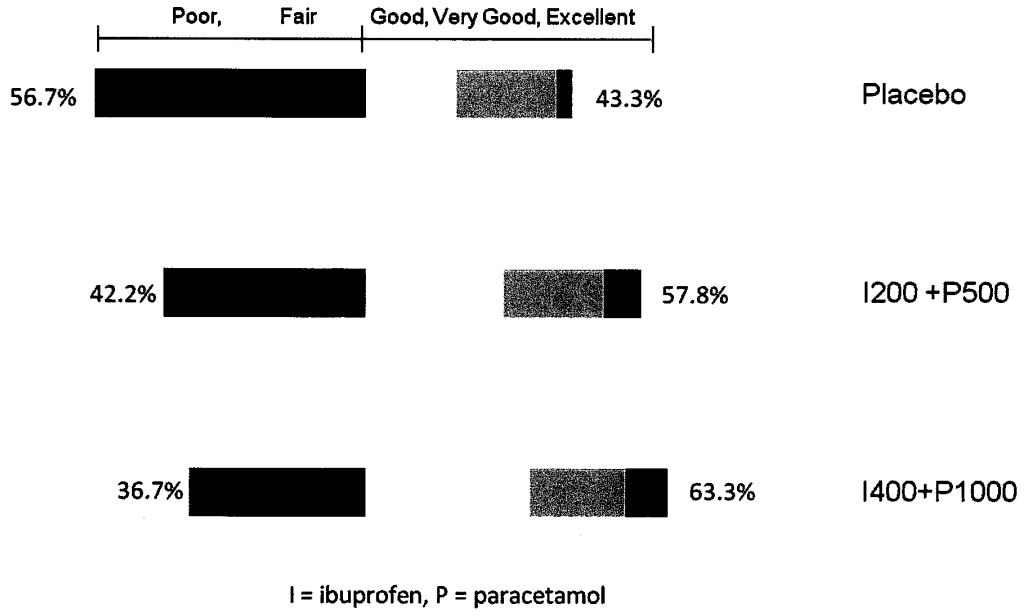
At six hours post-dose the patients were asked to provide their overall assessment of the study medication on a 5-point scale of 1 = poor, 2 = fair, 3 = good, 4 = very good and 5 = excellent. Table 11.4.10 summarises the results, which are presented in Figure 11.4.5

Table 11.4.10 Patients overall assessment of study medication - ITT population

	Ibuprofen 200mg + Paracetamol 500mg (n=91)	Ibuprofen 400mg + Paracetamol 1000mg (n=90)	Placebo (n=90)
1 Poor	14 (15.4%)	11 (12.2%)	28 (31.1%)
2 Fair	24 (26.4%)	22 (24.4%)	23 (25.6%)
3 Good	26 (28.6%)	31 (34.4%)	17 (18.9%)
4 Very good	19 (20.9%)	18 (20.0%)	19 (21.1%)
5 Excellent	7 (7.7%)	8 (8.9%)	3 (3.3%)
Not recorded	1 (1.1%)	0 (0.0%)	0 (0.0%)
p-value versus placebo[a]	0.0091 **	0.0023 **	

a From Wilcoxon matched-pairs signed rank test
** Comparison statistically significant at 1% level
Source: Table 14.2.14

Figure 11.4.5 Patients overall assessment of study medication - ITT population



Twenty eight patients (31%) rated placebo as 'poor' compared to 14 (15%) who rated ibuprofen 200 mg + paracetamol 500 mg group as 'poor' and 11 (12%) who rated ibuprofen 400 mg + paracetamol 1000 mg group as 'poor'.

The proportions of patients who rated their study medication as "good", "very good" or "excellent" were 57% (52/91) for the lower dose combination, 63% (57/90) for the higher dose combination and 43% (39/90) for placebo.

The overall pairwise comparisons of the scores were tested via Wilcoxon matched-pairs signed rank tests. Both comparisons between the active treatments and placebo were statistically significant (p=0.0023 for ibuprofen 400 mg + paracetamol 1000 mg and p=0.0091 for ibuprofen 200 mg + paracetamol 500 mg).

11.4.2 Analytical Issues

Detailed documentation of statistical methods, as the final Statistical Analysis Plan, is presented in Appendix 16.1.9.

11.4.2.1 Adjustments for Covariates

A covariate for baseline pain intensity was included in each statistical analysis (ANCOVA) model together with factors for period and sequence. The period and sequence effects did not achieve statistical significance in any of the analyses. Baseline pain intensity was statistically significant in the majority of the ANCOVA models fitted.

11.4.2.2 Handling of Dropouts or Missing Data

All incomplete dates were entered on the database as they were recorded in the CRF. Thereafter, incomplete dates were completed using pre-defined rules. If a day or month was recorded as unknown (UNK) or not available (NA) it was replaced by the first day of the month or January respectively, provided this did not contradict any other recorded dates. For missing adverse event and medication dates during the trial, the worst-case date was used (e.g. the end of the month for a stop date, the randomisation date for start of AE).

All scheduled diary assessments completed after the subject had taken rescue medication were considered to be missing. For pain relief and pain intensity difference, missing values between two available assessments were linearly interpolated. Missing readings that could not be interpolated were replaced with the baseline pain intensity or no relief (i.e. not reported). The number of values missing at random was very small; a single pain intensity value and three pain relief values. The proportion of patients taking rescue medication in each treatment period was relatively small; 16% during placebo treatment, 3% during treatment with ibuprofen 200 mg + paracetamol 500 mg and 2% during treatment with ibuprofen 400 mg + paracetamol 1000 mg, so the study results were relatively robust.

Two sensitivity analyses were performed on the primary endpoint. Further details are provided in Tables 11.4.2 and 14.2.1.3.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed and there was no interim data monitoring, therefore this section is not applicable.

11.4.2.4 Multi-centre Studies

This was a single centre study, therefore this section is not applicable.

11.4.2.5 Multiple Comparison/Multiplicity

For the primary efficacy endpoint, pairwise treatment comparisons between each of the fixed dose combination treatments and placebo were made via a closed test procedure. As the overall effect for treatment was significant at the 5% significance level then firstly ibuprofen 400 mg + acetaminophen 1000 mg was formally tested against placebo at the two-sided 5% significance level. As this comparison was significant, the comparison of ibuprofen 200 mg + acetaminophen 500 mg was formally tested against placebo also at the two-sided 5% significance level.

All secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analysed without any formal procedures to account for multiple comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

The use of the PP population (defined in Section 11.1) was restricted to the primary efficacy endpoint, the total pain relief over six hours post-dose. Four patients were completely excluded from the PP dataset and a further 11 patients had partial exclusion of data from this set. For the ITT analysis of the primary endpoint, the comparison between ibuprofen 400 mg + paracetamol 1000 mg and placebo was statistically significant (p=0.0001), whereas the comparison between the low-dose combination and placebo just missed reaching significance (p=0.054). For the equivalent analysis based on the per-protocol set, both pairwise comparisons were statistically significant (p=0.0005 for the high-dose combination and p=0.03 for the low-dose combination).

11.4.2.7 Active-Control Studies Intended to Show Equivalence

This study was not designed to test equivalence, therefore this section is not applicable.

11.4.2.8 Examination of Subgroups

Exploratory subgroup analyses of the primary efficacy endpoint were performed for several key baseline characteristics. For each characteristic, the main effect and

treatment-by-subgroup interaction terms were added to the model used in the primary endpoint analysis. Key variables of interest were age (≤ median, > median: Table 14.2.15.1), length of time since diagnosis (≤ median, > median: Table 14.2.15.2) and BMI at screening (≤ median, > median: Table 14.2.15.3).

None of the exploratory subgroup analyses of the primary efficacy endpoint revealed treatment-by-subgroup interactions that were statistically significant at the 10% level.

11.4.3 Tabulation of Individual Response Data

In addition to tables giving group data for efficacy variables, relevant individual subject data are presented in by-subject tabular listings in Appendix 16.2.

No individual response data are presented in the body of the report.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

This was not a dose response study and fixed doses of study medication were used, therefore this section is not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Drug/drug or drug/disease interactions were not examined in this study and so this section is not applicable.

11.4.6 By-subject Displays

Group mean data represent the principal analysis in this study and so this section is not applicable.

11.4.7 Efficacy Conclusions

Both the higher dose combination and the lower dose combination provided more effective analgesia in primary dysmenorrhoea than placebo. Both products delivered substantially more pain relief than placebo over the six hour assessment period. This benefit was accompanied by reduced pain intensity, reduced use of additional analgesic (rescue) medication and resulted in higher proportions of patients who rated the combination products as good, very good or excellent compared to placebo. Although this was not a dose-response study, and no formal comparisons between the two active treatments were made, the higher dose combination was superior to the lower dose combination for all the key analgesic endpoints, and separated earlier from placebo than the lower dose combination, suggesting faster onset of action.

12 SAFETY EVALUATION

All patients who received at least one dose of study medication are included in the safety analysis.

12.1 Extent of Exposure

Ninety-four patients took at least one dose of study medication and were included in the safety population. Ninety-two patients (98%) received a single dose of fixed combination ibuprofen 200 mg + paracetamol 500 mg, ninety-two patients (98%) received a single dose of fixed combination ibuprofen 400 mg + paracetamol 1000 mg and ninety patients (96%) received a single dose of placebo, in a crossover design. Two patients (numbers 011 and 041) only took one capsule of study medication during treatment period 1. Both patients had been allocated to placebo for that treatment period.

12.2 Adverse Events (AEs)

All treatment emergent adverse events for each patient, including the same event on several occasions, are listed in Listing 16.2.7.1 in Appendix 16.2.7, giving both the preferred term according to MedDRA Version 12.1 and the original term used by the investigator. A treatment emergent event was defined as any event that occurred within 24 hours of dosing with study medication. Events which occurred prior to first dose of study medication are given in Listing 16.2.7.2 and events during the mid-trial washout periods are presented in Listing 16.2.7.3, in Appendix 16.2.7.

The tables that follow describe adverse events occurring after the initiation of treatment with study medication. Where appropriate, abbreviated tables are included here, with full tables included in Section 14.3.

12.2.1 Brief Summary of Events

A total of 34 treatment-emergent adverse events were reported during the study. Table 12.2.1 summarises the number of patients reporting treatment-emergent AEs. Overall, eleven patients (12%) reported 14 events after dosing with ibuprofen 200 mg + paracetamol 500 mg, compared to nine patients (10%) who reported 13 events whilst on placebo and seven patients (8%) who reported 7 events after dosing with ibuprofen 400 mg + paracetamol 1000 mg. The pairwise treatment comparisons of incidence of adverse event reporting (proportion of patients), both for all events and treatment-related events, were not statistically significant.

Table 12.2.1 Number of patients reporting treatment emergent adverse events - safety population

	Ibuprofen 200mg + Paracetamol 500mg (n=92)	Ibuprofen 400mg + Paracetamol 1000mg (n=92)	Placebo (n=90)	Ibuprofen 400mg + Paracetamol 1000mg versus Placebo	Ibuprofen 200mg + Paracetamol 500mg versus Placebo
All events[(a)]	11 (12.0%)	7 (7.6%)	9 (10.0%)	ns	ns
Treatment-related events	3 (3.3%)	2 (2.2%)	2 (2.2%)	ns	ns
Mild	11 (12.0%)	7 (7.6%)	6 (6.7%)		
Moderate	1 (1.0%)	0 (0.0%)	4 (4.4%)		
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)		

ns Comparison not statistically significant via Prescott's test
Source: Tables 14.3.2
(a) Patients could report more than 1 event, but were counted only once for the total

For treatment-related events (i.e. those with a definite, probable or possible relationship to study drug), three patients (3%) reported 4 events following dosing with ibuprofen 200 mg + paracetamol 500 mg, two patients (2%) reported 2 events following treatment with ibuprofen 400 mg + paracetamol 1000 mg and two patients (2%) reported 3 events following placebo.

The majority of AEs (27 events) were categorised as mild. No event was categorised as severe and there were no deaths or other serious AEs in the study. No patient withdrew from the study due to an AE. All events resolved fully with no long-term sequelae.

12.2.2 Display of Adverse Events

Table 12.2.2 summarises the severity and relationship to treatment of the AEs reported within 24 hours of taking study drug.

Table 12.2.2 Severity and relationship of treatment emergent adverse events to therapy (safety population) in study NL0804

	Ibuprofen 200mg + Paracetamol 500mg (n=92)		Ibuprofen 400mg + Paracetamol 1000mg (n=92)		Placebo (n=90)	
	Number of subjects reporting	Number of reports (% of total)	Number of subjects reporting	Number of reports (% of total)	Number of subjects reporting	Number of reports (% of total)
Total[(a)]	11 (12%)	14	7 (8%)	7	9 (10%)	13
Severity:						
Mild	11 (12%)	13 (93%)	7 (8%)	7 (100%)	6 (7%)	7 (54%)
Moderate	1 (1%)	1 (7%)	-	-	4 (4%)	6 (46%)
Severe	-	-	-	-	-	-
Relationship:						
Definite	-	-	-	-	-	-
Probable	-	-	1 (1%)	1 (14%)	-	-
Possible	3 (3%)	4 (29%)	1 (1%)	1 (14%)	2 (2%)	3 (23%)
Unlikely	3 (3%)	4 (29%)	1 (1%)	1 (14%)	6 (7%)	7 (54%)
None	5 (5%)	6 (43%)	4 (4%)	4 (57%)	2 (2%)	3 (23%)

Source: Appendix 16.2. Listing 16.2.7.1
(a) Patients could report more than 1 event, but were counted only once for the total

Table 14.3.3 presents a summary of treatment emergent adverse events by primary system organ class (SOC). The most common SOC was nervous system disorders with seventeen reports (seven after placebo dosing, five after dosing with the higher dose combination and five after dosing with the lower dose combination). The next most commonly affected SOC was gastrointestinal disorders with thirteen reports (eight in the lower dose combination group, four in the placebo group and one in the higher dose combination group).

Table 14.3.4 shows the number of patients reporting each preferred term. The most common treatment emergent AEs reported were headache and nausea, with nine reports of each. There were four reports of headache after dosing with ibuprofen 400mg + paracetamol 1000mg, four reports of headache after placebo and one report after dosing with ibuprofen 200 mg + paracetamol 500 mg.

There were six reports of nausea after dosing with ibuprofen 200 mg + paracetamol 500 mg and three reports following dosing with placebo.

Table 14.3.5 presents a summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication. No adverse events were categorised as severe or as being definitely related to the study medication. One event had a probable relationship to therapy; patient number 030 reported mild dyspepsia 1.75 hours after receiving ibuprofen 400 mg + paracetamol 1000 mg. The event resolved completely three hours later.

12.2.3 Analysis of Adverse Events

There was no statistically significant pairwise treatment difference between either of the two active treatment groups and placebo in the proportion of subjects reporting treatment emergent adverse events or treatment-related adverse events.

12.3 Other Serious Adverse Events (SAEs) and other Significant Adverse Events

There were no deaths, other serious or significant adverse events in this study.

12.3.1 Listing of Deaths, other Serious Adverse Events, and other Significant Adverse Events

12.3.1.1 Deaths

There were no deaths in this study.

12.3.1.2 Other Serious Adverse Events

There were no other serious adverse events in this study.

12.3.1.3 Other Significant Adverse Events

There were no other significant adverse events in this study.

12.3.2 Narratives of Deaths, other Serious Adverse Events and certain other Significant Adverse Events

There were no deaths, other serious or significant adverse events in this study.

12.3.3 Analysis and Discussion of Deaths, other Serious Adverse Events and other Significant Adverse Events

This section is not applicable.

12.4 Clinical Laboratory Evaluation

Clinical biochemistry and haematology were evaluated before enrolment into the study and at the final evaluation visit.

12.4.1 Listing of Individual Laboratory Measurements by Subject and each Clinically Significant Abnormal Laboratory Value

No clinically significant abnormal laboratory values were reported. Listings of individual laboratory measurements by subject are given in Appendix 16.2.8.

12.4.2 Evaluation of Each Laboratory Parameter

The active moieties of the study medications used in this study have been licensed for use in man for many years. Their safety profile is very well established. No clinically significant abnormal laboratory values were reported. Therefore no "in-text" tables are presented in this section.

Summary statistics for the change from baseline to post-study follow-up in the haematology variables are presented in Table 14.3.6. There was a statistically significant increase in red blood cells over the course of the study and statistically significant decreases in white blood cells, neutrophils, lymphocytes, monocytes and eosinophils. None of the mean changes were considered to be clinically significant.

Summary statistics for the change from baseline to post-study follow-up in the biochemistry variables are presented in Table 14.3.7. There was a statistically significant decrease in potassium over the course of the study and statistically significant increases in creatinine, calcium, inorganic phosphorous, total protein, albumin, cholesterol and triglycerides. None of the mean changes were considered to be clinically significant.

12.4.2.1 Laboratory Values over Time

Details of the movement from baseline to post-study follow-up in haematology and biochemistry variables in relation to the normal range are presented in Tables 14.3.8 and 14.3.9.

12.4.2.2 Individual Subject Changes

Shifts from baseline to end of study in the haematology and biochemistry parameters are summarised in Tables 12.4.1 and 12.4.2 below. None of the shifts was regarded as clinically significant and no changes in laboratory parameters were recorded or reported as adverse events.

Table 12.4.1 Shifts From Baseline in Haematology Data (n=91)

Variable	----Decrease @----			---No Change @----			----Increase @-----		
	HL	NL	HN	LL	NN	HH	LN	NH	LH
Haemoglobin (g/L)	0	6	1	0	82	0	0	2	0
Red blood cells (10^12/L)	0	0	2	0	81	1	1	6	0
Haematocrit (ratio L/L)	0	2	4	0	76	2	0	7	0
Mean cell volume (fL)	0	0	1	0	87	0	0	3	0
Mean cell haemoglobin (pg)	0	0	0	3	87	0	0	1	0
Mean cell haemoglobin concentration (g/L)	0	21	0	24	31	0	15	0	0
White blood cells (10^9/L)	0	0	1	0	89	0	0	1	0
Platelets (10^9/L)	0	0	4	0	62	9	2	14	0
Neutrophils (10^9/L)	0	0	3	0	87	0	1	0	0
Lymphocytes (10^9/L)	0	1	1	0	88	0	0	1	0
Monocytes (10^9/L)	0	0	1	0	88	1	0	1	0
Basophils (10^9/L)	0	0	0	0	90	0	0	1	0
Eosinophils (10^9/L)	0	0	6	0	78	4	0	3	0
PT (secs)	0	0	5	0	76	3	0	6	1
APTT (secs)	0	1	2	0	81	7	0	0	0

Source: Section 14.3, Table 14.3.8

@ 1st letter denotes baseline pre-study assessment, 2nd letter denotes post-study assessment

L = Low, N = Normal, H = High

Table 12.4.2 Shifts From Baseline in Biochemistry Data (n=91)

	-----Decrease @----			---No Change @----			-----Increase @------		
Variable	HL	NL	HN	LL	NN	HH	LN	NH	LH
Sodium ($mmol.L^{-1}$)	0	0	11	0	70	5	0	5	0
Potassium ($mmol.L^{-1}$)	0	6	0	0	79	0	6	0	0
Urea ($mmol.L^{-1}$)	0	1	1	0	89	0	0	0	0
Creatinine ($\mu mol.L^{-1}$)	0	6	0	5	73	0	7	0	0
Uric Acid ($mmol.L^{-1}$)	0	0	2	1	87	0	1	0	0
Glucose ($mmol.L^{-1}$)	0	5	11	0	62	1	3	9	0
Calcium ($mmol.L^{-1}$)	0	0	0	2	85	0	4	0	0
Phosphorus ($mmol.L^{-1}$)	0	0	1	0	80	1	5	4	0
Total Bilirubin ($\mu mol.L^{-1}$)	0	6	1	3	74	0	6	1	0
ALP ($IU.L^{-1}$)	0	0	1	0	89	0	0	1	0
ALT ($IU.L^{-1}$)	0	0	3	0	84	0	1	3	0
AST ($IU.L^{-1}$)	0	0	0	1	90	0	0	0	0
GGT ($IU.L^{-1}$)	0	2	1	6	73	1	8	0	0
HBD ($IU.L^{-1}$)	0	0	1	1	85	0	0	4	0
Creatine Kinase ($IU.L^{-1}$)	0	0	5	0	80	1	0	5	0
Total Protein ($g.L^{-1}$)	0	0	2	0	82	2	0	5	0
Albumin ($g.L^{-1}$)	0	0	10	0	64	3	0	14	0
Cholesterol ($mmol.L^{-1}$)	0	0	4	0	67	7	0	13	0
Triglycerides ($mmol.L^{-1}$)	0	0	0	0	83	2	0	6	0

Source: Section 14.3, Table 14.3.9

@ 1st letter denotes baseline pre-study assessment, 2nd letter denotes post-study assessment

L = Low, N = Normal, H = High

12.4.2.3 Individual Clinically Significant Abnormalities

Based on the clinical judgement of the investigator no individual clinically significant abnormalities or changes in laboratory parameters were reported in this study.

12.5 Vital Signs, Physical Findings and other Observations Related to Safety

Changes in vital signs between the baseline visit and the post-study follow-up visit are presented in Table 14.3.10. Changes were unremarkable and clinically insignificant. No changes in vital signs were considered by the investigator to be adverse events.

No abnormalities were reported in the physical examination conducted at the follow-up assessment (Table 14.3.11).

Table 14.3.12 details concomitant medications taken after the first dose of study medication. Thirty-one (33%) patients reported the use of concomitant medication, including twenty (21%) subjects who used additional analgesics. Only one patient took inadmissible concomitant medication during a six-hour study period; patient 034 took paracetamol at an unspecified time. All other analgesics taken were either rescue medication or other analgesic medication taken after the six hour treatment period.

12.6 Safety Conclusions

Both the higher dose combination and the lower dose combination were well tolerated in this single dose study, the incidence and profile of events being indistinguishable from placebo. The incidence of events and the nature of events reported were consistent with the extensive clinical experience gained over decades of use of paracetamol and ibuprofen as single active drugs.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The objectives of this study were to determine the analgesic benefits associated with each of the higher dose combination and lower dose combination compared to placebo and to assess the tolerability of these in patients with primary dysmenorrhoea. Patients were recruited from a University environment and student population, so they are likely to be representative of the wider patient population who suffer from this disorder. The population studied in this trial was young (mean age of 22 years, ranging from 18 to 46 years, Table 14.1.2) and time since first diagnosis of primary dysmenorrhoea was a few years (mean of 8.9, ranging from 1 to 34 years, Table 14.1.3). This is in keeping with published prevalence figures for primary dysmenorrhoea, which is highest in the 20-24 year old age group and decreases progressively after this.[6] It is also consistent with the disease aetiology; initial onset of primary dysmenorrhoea occurs within 6-12 months of menarche.[7] The majority of participants in this study were Caucasian (92.6%), with 5.3% being Asian, 1.1% Afro-Caribbean and 1.1% Chinese. Other published studies of drugs used in the treatment of primary dysmenorrhoea enrolled similar populations to this trial.[8-10] The demographics of the population studied here do not differ markedly from the

published literature that supports the efficacy and safety of standard treatments for this indication.

The study design was optimised for determining analgesic efficacy by requiring patients to have at least moderate pain before dosing. Such a design is commonly used when treating painful conditions. An alternative approach occasionally used in primary dysmenorrhoea is to administer drug before the onset of abdominal pain. However, prevention of pain is more difficult to assess than pain intensity and pain relief, since it is not possible to be certain that the patient would have experienced pain. Indeed, a number of patients in this study did not take their allocated medication in three consecutive menstrual cycles because they did not experience sufficient pain in one or more cycles. The "in-home" setting reflects "real-life" usage of medication but has the drawback in clinical trial terms of loss of control over exactly when the patient takes their allocated medication and the subsequent timing of the assessments. To try and assist patients with the timing they were provided with an alarm clock to set for each timed assessment. This was moderately successful as there were relatively few protocol deviations based on assessments being conducted outside the prespecified "window" for each time.

The results of this study show that both the higher and lower dose fixed combinations were more effective analgesics than placebo. Increased pain relief was accompanied by reduced pain intensity, reduced incidence of usage of rescue analgesia and resulted in increased overall patient ratings when compared to placebo. There was a discernible dose response in the findings, with the higher dose providing numerically greater analgesic benefits than the lower dose combination, although the two were not formally compared. The lower dose combination, whilst clearly numerically superior to placebo for the primary endpoint of TOTPAR 0-6h, marginally failed to achieve statistical significance for this endpoint for the ITT population, although statistical significance was achieved using the PP set. This was not due to reduced power because of having too few patients – the study recruited the required number as per the power calculation completed for the protocol. The pain intensity and pain relief curves show that there was a substantial placebo response in this trial. This may have been a consequence of the home setting. Other similar trials conducted using diary cards have also observed a high placebo response in this indication.[5,19] Analgesic studies, especially single-dose studies in other indications such as dental pain or sore throat, are frequently conducted "in-clinic" where the assessments can be strictly administered and controlled. Patients have few distractions in such a setting and focus on their pain and how they are feeling. In the home setting, patients are more likely to feel comfortable, at ease and have numerous distractions from their pain such as music and television. They are likely to interact more with other people e.g. friends or partners. Distraction is known to affect pain ratings[11] and so the high placebo response seen in this trial may be explained on this basis. Since many of the secondary endpoints for the lower dose combination did achieve statistical significance, the overall picture is one of analgesic benefit that is less than that provided by the higher dose combination but still superior to placebo.

A number of published studies have shown that ibuprofen is an effective analgesic in primary dysmenorrhoea. In 1980, Morrison *et al* showed in a randomised, crossover, blinded study comparing ibuprofen 400 mg, propoxyphene hydrochloride 64 mg and placebo that ibuprofen 400 mg was superior to both other treatments for pain relief, use of additional analgesia and patient preference.[12] However, treatments were taken every four hours as needed, up to a maximum of five times per day, which is more than the current recommended maximum daily dose of ibuprofen for this indication. Milsom and Andersch compared 400 mg ibuprofen three times daily with naproxen sodium 250 mg twice daily in a randomised, double blind crossover study.[13] Both drugs reduced pain severity, provided pain relief and reduced absenteeism from school or work. There was no statistically significant difference between treatments. A placebo group was considered but not instigated due to the severity of dysmenorrhoea required for study entry. Marchini *et al* enrolled patients with less severe disease, in a randomised, double-blind study comparing diclofenac 50 mg with ibuprofen 400 mg and placebo.[5] They did not separate ibuprofen 400 mg from placebo for TOTAR 0-6h. However, for SPID 0-6h ibuprofen 400 mg was statistically superior to placebo ($p = 0.01$) whilst diclofenac was not superior to placebo. In their study, pairwise comparisons of pain intensity differences from baseline were significant for ibuprofen from three hours onwards, compared to the two hours onwards seen for the higher dose combination in this study, perhaps suggesting the combination of ibuprofen and paracetamol may provide earlier pain relief than ibuprofen alone. In a formal systematic review of randomised controlled trials in dysmenorrhoea, ibuprofen was clearly superior to placebo, not only for pain relief, but also for consumption of rescue analgesics and reported restriction of daily life (70% less likely with ibuprofen than placebo).[14] Ibuprofen has also been shown to be effective in this indication using the objective methodology of measuring intrauterine pressure, at doses of 800 mg and 400 mg.[15,16]

Evidence for efficacy of paracetamol in primary dysmenorrhoea is somewhat less robust than that for ibuprofen, but fewer studies have been conducted.[17] Akin *et al* compared the use of a topical heat wrap with 1000 mg acetaminophen four times daily for one day, in a randomised, single (investigator) blind, parallel-group study.[18] Pain relief was similar for the first two hours, but thereafter, the benefit of acetaminophen was less than that of the heat wrap. In their systematic review of minor analgesics in primary dysmenorrhoea, Zhang and Li Wan Po found three randomised controlled trials of paracetamol that met their inclusion and exclusion criteria.[14] Only one of these made a comparison to placebo, which was not statistically significant. More recently, a paracetamol plus caffeine fixed combination was compared to paracetamol alone, caffeine alone and placebo in a randomised, double-blind, crossover, single-dose study.[19] For the primary endpoint of TOTPAR 0-2h, the combination proved statistically superior to either component alone and to placebo. Interestingly, paracetamol alone just failed to achieve a statistically significant difference compared to placebo for TOTPAR 0-2h, with $p = 0.058$. Pain relief benefits with paracetamol that were superior to placebo only became apparent for TOTPAR 0-3h, TOTPAR 0-4h and TOTPAR 0-6h.

The adverse events reported were minor and consistent with those reported in other studies of ibuprofen or paracetamol in primary dysmenorrhoea. All treatments were well tolerated, since there were no discontinuations due to AEs. In a review of trials of prostaglandin synthetase inhibitors in primary dysmenorrhoea, Owen reported that in eight trials covering 25 menstrual cycles, only five women dropped out because of side effects.[20] Similarly, as in this study, Ozogli found no severe events in a study of 50 women taking 400 mg ibuprofen four times a day for three days during their menstrual cycle.[8]

As both ibuprofen and paracetamol have been shown to be effective in primary dysmenorrhoea, (the former more so than the latter), the efficacy and safety results from this study of two fixed dose combinations of ibuprofen and paracetamol are consistent with expectations. They support the use of the combination in this indication.

13.2 Conclusion

The fixed dose combination of ibuprofen 400 mg + acetaminophen 1000 mg and the fixed dose combination of ibuprofen 200 mg + acetaminophen 500 mg were both superior analgesics compared to placebo in patients with primary dysmenorrhoea. The higher dose combination provided greater pain relief and reduced pain intensity more than did the lower dose combination, with statistically significant differences from placebo being apparent with the higher dose combination earlier (at 90 minutes post dose) than with the lower dose combination (from four hours post dose). Adverse events occurred in only a very small proportion of patients. The events that occurred were minor, did not require medical intervention and resolved with no sequelae; the risk:benefit ratio for both the higher dose combination and lower dose combination is positive in primary dysmenorrhoea.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Due to the number of tables, and figures, the following are provided in a separate section after section 15 of this study report.

14.1 Demographic data

Table number	Table Title
14.1.1	Reasons for withdrawal - Safety set
14.1.2	Demography – Safety set
14.1.3	Primary diagnosis: Length of time diagnosed with dysmenorrhoea (years) – Safety set
14.1.4	Medical history – Safety set
14.1.5	Vital Signs at screening and randomisation – Safety set
14.1.6	Physical Examination – Safety set
14.1.7	Haematology – Safety set
14.1.8	Biochemistry – Safety set
14.1.9	Concomitant medications ongoing at time of first dose of study medication – Safety set

14.2 Efficacy data

Table number	Table Title
14.2.1.1	Primary efficacy endpoint – Total pain relief over six hours post-dose (TOTPAR 0-6h) - Intention-to-treat population
14.2.1.2	Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR 0-6h) – Per-protocol population
14.2.1.3	Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR 0-6h) – Sensitivity analyses
14.2.2	Total pain relief over two hours post-dose (TOTPAR 0-2h) - Intention-to-treat population
14.2.3	Total pain relief over four hours post-dose (TOTPAR 0-4h) - Intention-to-treat population
14.2.4	Pain relief at each follow-up assessment - Intention-to-treat population
14.2.5	Total analgesic effect over two hours post-dose (SPID 0-2h) - Intention-to-treat population
14.2.6	Total analgesic effect over four hours post-dose (SPID 0-4h) - Intention-to-treat population
14.2.7	Total analgesic effect over six hours post-dose (SPID 0-6h) - Intention-to-treat population
14.2.8	Pain intensity difference (PID) at each follow-up assessment - Intention-to-treat population
14.2.9	Overall effectiveness over two hours post-dose (SPRID 0-2h) - Intention-to-treat population
14.2.10	Overall effectiveness over two hours post-dose (SPRID 0-4h) - Intention-to-treat population
14.2.11	Overall effectiveness over two hours post-dose (SPRID 0-6h) - Intention-to-treat population
14.2.12	SPRID at each follow-up assessment - Intention-to-treat population
14.2.13	Use of rescue medication - Intention-to-treat population
14.2.14	Subjects overall assessment of the study medication as a treatment for pain at six hours post-dose - Intention-to-treat population
14.2.15.1	Primary efficacy endpoint – Total pain relief over six hours post-dose (TOTPAR 0-6h) by age - Intention-to-treat population
14.2.15.2	Primary efficacy endpoint – Total pain relief over six hours post-dose (TOTPAR 0-6h) by length of time since diagnosis - Intention-to-treat population
14.2.15.3	Primary efficacy endpoint – Total pain relief over six hours post-dose (TOTPAR 0-6h) by BMI at screening - Intention-to-treat population

14.3 Safety Data

Table number	Table Title
14.3.1	Extent of exposure to study medication - Safety set
14.3.2	Summary of treatment emergent adverse event reporting – Safety set
14.3.3	MedDRA Summary of treatment emergent adverse events by primary system organ class – Safety set
14.3.4	MedDRA Summary of treatment emergent adverse events by primary system organ class and preferred term – Safety set
14.3.5	MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication – Safety set
14.3.6	Change from baseline for haematology variables at post-study follow-up – Safety set
14.3.7	Change from baseline for biochemistry variables at post-study follow-up – Safety set
14.3.8	Movement from baseline to post-study follow-up in haematology variables in relation to the normal range – Safety set
14.3.9	Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range – Safety set
14.3.10	Change from baseline for vital signs recorded at post-study follow-up visit – Safety set
14.3.11	Physical examination at post-study follow-up visit – Safety set
14.3.12	Concomitant medication commencing after the first dose of study medication – Safety set

FIGURES

Figure number	Figure Title
14.2.1	Mean pain relief at each assessment- Intention-to-treat population
14.2.2	Mean pain intensity at each assessment- Intention-to-treat population
14.2.3	Mean pain intensity difference at each assessment- Intention-to-treat population
14.2.4	Mean pain intensity difference and pain relief (PRID) at each assessment- Intention-to-treat population

15 REFERENCE LIST

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Table 14.1.1
Reasons for withdrawal
Safety set

(a) WHETHER SUBJECT WITHDREW PREMATURELY FROM THE STUDY

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Yes	1 (6.3%)	2 (13.3%)	1 (7.1%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	5 (5.3%)
No	15 (93.8%)	13 (86.7%)	13 (92.9%)	17 (94.4%)	15 (100.0%)	16 (100.0%)	89 (94.7%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(b) REASON FOR WITHDRAWAL

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Withdrew consent	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
Lost to follow up	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
Other reason	1 (100.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)

Table 14.1.1
Reasons for withdrawal
Safety set

(c) PERIOD OF WITHDRAWAL

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
1	0 (0.0%)	1 (50.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)
2	1 (100.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
Total	1 (100.0%)	2 (100.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)

Table 14.1.2
Demography
Safety set

(a) AGE (years)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	22.1	5.7	18.0	46.0	20.0	0.6	20.9	23.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	21.9	4.9	18.0	39.0	20.0	1.2	19.3	24.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	24.1	7.9	18.0	46.0	21.0	2.0	19.8	28.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	21.8	6.8	18.0	45.0	20.0	1.8	17.9	25.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	21.1	3.5	18.0	34.0	20.0	0.8	19.3	22.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	21.2	4.8	18.0	38.0	20.0	1.2	18.6	23.8
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	22.5	6.0	19.0	44.0	21.0	1.5	19.3	25.7

Table 14.1.2
Demography
Safety set

(b) RACE

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Caucasian	15 (93.8%)	15 (100.0%)	14 (100.0%)	15 (83.3%)	15 (100.0%)	13 (81.3%)	87 (92.6%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	0 (0.0%)	2 (12.5%)	5 (5.3%)
Afro-Caribbean	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
Other (Chinese)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.2
Demography
Safety set

(c) HEIGHT (cm)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	163.2	6.4	145.0	180.0	163.5	0.7	161.9	164.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	164.1	4.3	158.0	173.0	163.5	1.1	161.8	166.4
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	163.9	5.8	156.0	172.0	161.0	1.5	160.7	167.1
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	164.9	8.0	152.0	180.0	165.0	2.1	160.3	169.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	161.2	8.1	145.0	176.0	164.0	1.9	157.2	165.2
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	162.9	5.5	154.0	173.0	163.0	1.4	159.9	166.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	162.9	5.9	151.0	171.0	164.0	1.5	159.8	166.1

Table 14.1.2
Demography
Safety set

(d) WEIGHT (kg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	63.1	11.5	42.8	111.7	60.7	1.2	60.8	65.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	67.4	14.6	48.8	109.9	64.1	3.6	59.7	75.2
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	65.4	11.9	50.1	88.8	63.5	3.1	58.9	72.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	63.5	7.8	53.5	80.2	61.9	2.1	59.0	68.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	59.0	7.2	44.9	77.5	58.0	1.7	55.4	62.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	63.8	15.3	46.7	111.7	60.0	4.0	55.3	72.3
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	60.4	9.3	42.8	82.4	58.6	2.3	55.5	65.3

Table 14.1.2
Demography
Safety set

(e) BMI (kg/m^2)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	23.7	4.2	16.9	39.4	22.6	0.4	22.9	24.6
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	25.1	5.5	18.1	39.4	22.8	1.4	22.2	28.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	24.4	4.4	17.5	33.6	22.5	1.1	22.0	26.8
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	23.5	3.8	17.3	33.0	22.8	1.0	21.3	25.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	22.7	2.3	18.7	27.7	22.7	0.5	21.5	23.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	23.9	4.7	16.9	38.2	23.4	1.2	21.3	26.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	22.8	3.9	18.8	33.9	22.2	1.0	20.7	24.9

Table 14.1.2
Demography
Safety set

(f) DOES THE PATIENT DRINK ALCOHOL?

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Yes	15 (93.8%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	12 (75.0%)	89 (94.7%)
No	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (25.0%)	5 (5.3%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.2
Demography
Safety set

(g) IF YES, NUMBER OF UNITS PER WEEK

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	89	0	8.2	5.0	1.0	21.0	8.0	0.5	7.1	9.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	9.2	4.9	3.0	18.0	8.0	1.3	6.5	11.9
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	8.3	5.1	2.0	20.0	8.0	1.3	5.4	11.1
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	9.1	7.3	2.0	21.0	6.5	2.0	4.9	13.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	5.8	3.6	1.0	12.0	6.0	0.8	4.0	7.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	9.0	4.2	3.0	20.0	10.0	1.1	6.7	11.3
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	12	0	8.1	4.0	4.0	15.0	7.0	1.1	5.6	10.6

Table 14.1.2
Demography
Safety set

(h) DOES THE PATIENT SMOKE?

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Never	16 (100.0%)	14 (93.3%)	13 (92.9%)	17 (94.4%)	14 (93.3%)	16 (100.0%)	90 (95.7%)
Former	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (5.6%)	1 (6.7%)	0 (0.0%)	3 (3.2%)
Current	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.2
Demography
Safety set

(i) IF FORMER OR CURRENT SMOKER, AVERAGE NUMBER OF CIGARETTES PER DAY

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	4	0	7.5	2.9	5.0	10.0	7.5	1.4	2.9	12.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	1	0	10.0		10.0	10.0	10.0			
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	1	0	5.0		5.0	5.0	5.0			
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	1	0	5.0		5.0	5.0	5.0			
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	1	0	10.0		10.0	10.0	10.0			

Table 14.1.2
Demography
Safety set

(j) HAS THE PATIENT USED DRUGS OF ABUSE?

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Never	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.3
Primary diagnosis: Length of time diagnosed with dysmenorrhoea (years)
Safety set

(a) Frequency distribution

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
1 to 5	1 (6.3%)	5 (33.3%)	4 (28.6%)	1 (5.6%)	4 (26.7%)	4 (25.0%)	19 (20.2%)
6 to 10	11 (68.8%)	7 (46.7%)	8 (57.1%)	15 (83.3%)	10 (66.7%)	10 (62.5%)	61 (64.9%)
11 to 20	3 (18.8%)	1 (6.7%)	1 (7.1%)	1 (5.6%)	0 (0.0%)	1 (6.3%)	7 (7.4%)
>20	1 (6.3%)	2 (13.3%)	1 (7.1%)	1 (5.6%)	1 (6.7%)	1 (6.3%)	7 (7.4%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.3
Primary diagnosis: Length of time diagnosed with dysmenorrhoea (years)
Safety set

(b) Summary statistics

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	8.9	6.1	1.0	34.0	8.0	0.6	7.6	10.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	9.1	5.5	1.0	27.0	8.0	1.4	6.2	12.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	10.1	8.1	5.0	32.0	7.0	2.1	5.7	14.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	8.4	7.5	2.0	33.0	7.0	2.0	4.0	12.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	8.8	3.7	5.0	22.0	8.0	0.9	7.0	10.7
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	8.0	4.2	3.0	21.0	7.0	1.1	5.7	10.3
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	8.9	7.3	2.0	34.0	8.0	1.8	5.0	12.8

Table 14.1.4
Relevant medical history
Safety set

(a) Previous medical history

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Yes	0 (0.0%)	0 (0.0%)	1 (7.1%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
No	16 (100.0%)	15 (100.0%)	13 (92.9%)	16 (88.9%)	15 (100.0%)	16 (100.0%)	91 (96.8%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(b) Number reporting previous medical history by category

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Musculoskeletal	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	2 (2.1%)

Table 14.1.4
Relevant medical history
Safety set

(c) Ongoing medical history

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Yes	1 (6.3%)	2 (13.3%)	0 (0.0%)	1 (5.6%)	3 (20.0%)	2 (12.5%)	9 (9.6%)
No	15 (93.8%)	13 (86.7%)	14 (100.0%)	17 (94.4%)	12 (80.0%)	14 (87.5%)	85 (90.4%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(d) Number reporting ongoing medical history by category

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Respiratory	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (2.1%)
Endocrine/metabolic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Dermatological	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Allergies/Drug sensitivity	1 (6.3%)	2 (13.3%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (6.3%)	5 (5.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(a) Systolic blood pressure at screening (mmHg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	121.3	12.8	93.0	148.0	121.0	1.3	118.6	123.9
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	120.8	13.7	93.0	146.0	121.0	3.4	113.4	128.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	121.5	14.0	100.0	144.0	120.0	3.6	113.7	129.2
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	118.4	11.5	95.0	137.0	117.0	3.1	111.8	125.1
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	122.3	14.7	101.0	147.0	122.0	3.5	115.0	129.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	124.0	13.4	100.0	148.0	124.0	3.5	116.6	131.4
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	120.3	9.7	105.0	136.0	120.5	2.4	115.1	125.5

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(b) Diastolic blood pressure at screening (mmHg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	72.5	8.4	50.0	96.0	72.0	0.9	70.8	74.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	73.1	11.6	60.0	96.0	71.5	2.9	66.9	79.2
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	74.2	10.2	59.0	91.0	73.0	2.6	68.6	79.8
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	70.4	5.5	61.0	81.0	71.5	1.5	67.3	73.6
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	72.4	8.4	58.0	85.0	72.5	2.0	68.3	76.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	71.5	7.7	50.0	81.0	74.0	2.0	67.2	75.7
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	73.3	5.7	66.0	88.0	72.0	1.4	70.2	76.3

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(c) Heart rate at screening (mmHg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	73.0	10.0	51.0	96.0	73.0	1.0	70.9	75.0
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	70.8	7.4	58.0	84.0	69.5	1.9	66.9	74.8
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	72.5	9.5	55.0	86.0	70.0	2.4	67.2	77.7
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	71.9	11.0	54.0	96.0	73.5	2.9	65.6	78.3
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	73.5	10.0	51.0	92.0	74.0	2.4	68.5	78.5
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	77.6	9.8	59.0	96.0	78.0	2.5	72.2	83.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	71.5	11.7	54.0	93.0	73.5	2.9	65.3	77.7

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(d) Temperature at screening (degrees C)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	36.6	0.5	35.1	37.6	36.7	0.1	36.5	36.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	36.3	0.5	35.1	37.1	36.3	0.1	36.0	36.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	36.8	0.3	36.3	37.2	36.8	0.1	36.7	36.9
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	36.5	0.7	35.2	37.6	36.5	0.2	36.1	36.9
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	36.6	0.5	35.5	37.0	36.7	0.1	36.3	36.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	36.5	0.4	35.3	37.1	36.6	0.1	36.3	36.8
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	36.7	0.4	35.6	37.1	36.7	0.1	36.4	36.9

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(e) Systolic blood pressure at randomisation (mmHg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	125.0	12.1	96.0	158.0	124.5	1.2	122.5	127.4
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	125.9	11.8	107.0	158.0	125.0	2.9	119.6	132.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	126.1	10.6	109.0	141.0	127.0	2.7	120.3	132.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	129.4	12.0	106.0	149.0	131.5	3.2	122.5	136.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	123.9	14.3	96.0	146.0	124.0	3.4	116.8	131.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	126.9	12.6	110.0	153.0	127.0	3.3	119.9	133.9
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	118.3	9.2	102.0	136.0	120.0	2.3	113.4	123.2

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(f) Diastolic blood pressure at randomisation (mmHg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	72.0	11.1	51.0	141.0	71.0	1.1	69.7	74.3
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	76.4	19.4	51.0	141.0	72.5	4.9	66.0	86.7
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	71.1	6.2	63.0	83.0	71.0	1.6	67.7	74.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	74.4	14.6	59.0	121.0	72.5	3.9	65.9	82.8
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	70.5	7.3	61.0	87.0	70.0	1.7	66.9	74.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	70.1	4.4	63.0	76.0	72.0	1.1	67.6	72.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	69.8	7.5	59.0	93.0	71.0	1.9	65.8	73.8

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(g) Heart rate at randomisation (mmHg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	75.8	11.7	54.0	128.0	75.0	1.2	73.4	78.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	78.6	15.9	55.0	128.0	75.0	4.0	70.1	87.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	78.1	10.5	62.0	92.0	78.0	2.7	72.3	83.9
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	77.6	11.1	59.0	100.0	79.0	3.0	71.1	84.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	72.4	9.4	54.0	91.0	73.5	2.2	67.8	77.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	75.7	12.2	57.0	104.0	72.0	3.1	68.9	82.4
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	72.9	10.6	54.0	92.0	73.0	2.7	67.3	78.6

Table 14.1.5
Vital Signs at screening and randomisation
Safety set

(h) Temperature at randomisation (degrees C)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	36.1	0.6	34.1	37.5	36.2	0.1	36.0	36.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	36.0	0.5	34.8	36.7	36.1	0.1	35.8	36.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	36.1	0.7	34.2	37.0	36.3	0.2	35.8	36.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	36.2	0.4	35.6	36.8	36.3	0.1	36.0	36.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	36.2	0.6	34.5	37.5	36.2	0.1	35.9	36.4
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	36.2	0.5	34.7	36.8	36.3	0.1	35.9	36.4
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	35.9	0.7	34.1	36.5	36.0	0.2	35.5	36.3

Table 14.1.6
Physical Examination
Safety set

(a) ANY ABNORMALITIES

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
No	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(b) SKIN

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.6
Physical Examination
Safety set

(c) EYES

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(d) EARS

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.6
Physical Examination
Safety set

(e) NOSE

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(f) CHEST AND LUNGS

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.6
Physical Examination
Safety set

(g) LYMPH NODES

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

(h) MOUTH AND THROAT

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.6
Physical Examination
Safety set

(i) OTHER

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)
Total	16 (100.0%)	15 (100.0%)	14 (100.0%)	18 (100.0%)	15 (100.0%)	16 (100.0%)	94 (100.0%)

Table 14.1.7
Haematology
Safety set

(a) Haemoglobin (g/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	132.7	7.2	120.0	153.0	132.0	0.7	131.2	134.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	134.3	8.4	120.0	153.0	133.5	2.1	129.8	138.8
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	129.8	6.2	120.0	141.0	130.0	1.6	126.3	133.3
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	131.6	5.1	122.0	142.0	132.5	1.4	128.7	134.6
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	134.7	8.6	123.0	148.0	134.0	2.0	130.4	139.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	134.3	6.2	122.0	145.0	134.0	1.6	130.8	137.7
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	130.9	6.9	121.0	147.0	130.0	1.7	127.2	134.6

Table 14.1.7
Haematology
Safety set

(b) Red blood cells (10^12/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	4.54	0.30	3.94	5.39	4.52	0.03	4.48	4.60
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	4.50	0.31	4.05	5.26	4.54	0.08	4.34	4.66
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	4.48	0.32	4.12	5.39	4.42	0.08	4.30	4.66
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.47	0.23	4.09	4.85	4.53	0.06	4.34	4.60
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	4.69	0.31	4.12	5.14	4.67	0.07	4.54	4.84
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.53	0.26	4.13	5.10	4.52	0.07	4.39	4.68
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.53	0.33	3.94	5.15	4.50	0.08	4.35	4.70

Table 14.1.7
Haematology
Safety set

(c) Haematocrit (ratio L/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	0.41	0.02	0.37	0.47	0.41	0.00	0.41	0.42
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	0.42	0.03	0.37	0.47	0.42	0.01	0.41	0.43
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	0.41	0.02	0.37	0.44	0.41	0.01	0.39	0.42
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.41	0.02	0.38	0.45	0.41	0.00	0.40	0.42
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	0.42	0.03	0.38	0.46	0.41	0.01	0.40	0.43
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.41	0.02	0.38	0.45	0.41	0.01	0.40	0.42
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.41	0.02	0.37	0.46	0.40	0.01	0.39	0.42

Table 14.1.7
Haematology
Safety set

(d) Mean cell volume (fL)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	91.1	4.2	80.9	101.5	91.7	0.4	90.3	92.0
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	93.3	4.2	85.2	99.7	93.6	1.0	91.1	95.5
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	91.1	4.1	80.9	98.6	91.7	1.1	88.9	93.4
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	92.0	4.2	85.5	101.5	92.1	1.1	89.6	94.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	89.1	3.7	83.5	95.9	89.7	0.9	87.3	91.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	91.5	4.6	81.8	99.0	91.4	1.2	89.0	94.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	90.1	3.5	84.2	96.5	90.2	0.9	88.2	92.0

Table 14.1.7
Haematology
Safety set

(e) Mean cell haemoglobin (pg)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	29.3	1.5	24.4	32.6	29.3	0.2	29.0	29.6
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	29.9	1.6	26.5	32.0	30.0	0.4	29.0	30.7
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	29.0	1.7	24.4	30.9	29.5	0.4	28.1	30.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	29.5	1.6	26.8	32.4	29.5	0.4	28.6	30.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	28.8	1.3	26.2	31.2	28.9	0.3	28.1	29.4
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	29.7	1.6	25.8	32.6	29.6	0.4	28.8	30.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	29.0	1.4	26.8	31.2	28.5	0.3	28.2	29.7

Table 14.1.7
Haematology
Safety set

(f) Mean cell haemoglobin concentration (g/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	321.4	8.8	295.0	339.0	322.0	0.9	319.6	323.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	320.0	7.4	308.0	334.0	319.5	1.9	316.1	323.9
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	318.7	9.8	301.0	333.0	322.0	2.5	313.3	324.2
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	321.0	12.4	295.0	339.0	319.5	3.3	313.8	328.2
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	322.6	7.3	308.0	336.0	322.5	1.7	318.9	326.2
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	324.3	6.8	313.0	338.0	325.0	1.8	320.5	328.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	321.6	8.9	304.0	336.0	322.0	2.2	316.8	326.3

Table 14.1.7
Haematology
Safety set

(g) White blood cells (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	7.48	1.89	4.30	13.10	7.15	0.19	7.10	7.87
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	8.09	1.91	4.60	13.10	8.40	0.48	7.07	9.11
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	8.14	2.61	4.40	12.70	7.50	0.67	6.69	9.59
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	6.94	0.96	4.80	8.30	6.80	0.26	6.38	7.49
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	7.66	1.75	4.80	11.50	7.55	0.41	6.78	8.53
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	7.05	1.48	4.40	9.70	6.50	0.38	6.24	7.87
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	6.95	2.04	4.30	11.00	6.85	0.51	5.86	8.04

Table 14.1.7
Haematology
Safety set

(h) Platelets (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	300.0	63.5	147.0	541.0	298.0	6.6	287.0	313.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	337.9	70.7	252.0	541.0	325.0	17.7	300.2	375.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	285.5	64.2	147.0	396.0	287.0	16.6	250.0	321.1
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	291.2	65.8	158.0	378.0	309.0	17.6	253.2	329.2
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	316.8	68.9	195.0	438.0	302.5	16.2	282.5	351.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	278.7	51.5	183.0	386.0	286.0	13.3	250.2	307.2
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	284.7	41.3	217.0	375.0	281.0	10.3	262.7	306.7

Table 14.1.7
Haematology
Safety set

(i) Neutrophils (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	4.60	1.63	1.80	10.30	4.25	0.17	4.27	4.93
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	4.97	1.68	2.40	9.10	5.15	0.42	4.07	5.87
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	5.32	2.33	2.40	10.30	4.50	0.60	4.03	6.61
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.35	0.74	2.70	5.60	4.30	0.20	3.92	4.78
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	4.58	1.66	1.80	7.70	4.25	0.39	3.76	5.41
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.25	1.27	2.70	6.60	3.60	0.33	3.55	4.95
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.12	1.56	2.10	7.50	4.10	0.39	3.29	4.95

Table 14.1.7
Haematology
Safety set

(j) Lymphocytes (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	2.07	0.50	1.10	3.60	2.00	0.05	1.97	2.17
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	2.18	0.39	1.50	3.00	2.15	0.10	1.98	2.39
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	2.03	0.67	1.10	3.50	1.90	0.17	1.66	2.40
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.84	0.40	1.30	2.60	1.90	0.11	1.61	2.07
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	2.26	0.52	1.60	3.60	2.30	0.12	2.00	2.52
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.99	0.43	1.20	2.70	1.90	0.11	1.76	2.23
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	2.08	0.50	1.20	2.60	2.20	0.12	1.81	2.34

Table 14.1.7
Haematology
Safety set

(k) Monocytes (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	0.41	0.14	0.20	0.90	0.40	0.01	0.38	0.43
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	0.48	0.21	0.20	0.90	0.40	0.05	0.37	0.59
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	0.40	0.14	0.20	0.60	0.40	0.04	0.32	0.48
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.40	0.11	0.30	0.70	0.40	0.03	0.34	0.46
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	0.39	0.11	0.20	0.60	0.40	0.03	0.33	0.45
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.39	0.10	0.20	0.50	0.40	0.02	0.34	0.45
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.37	0.13	0.20	0.60	0.40	0.03	0.30	0.44

Table 14.1.7
Haematology
Safety set

(l) Basophils (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	0.07	0.05	0.00	0.10	0.10	0.00	0.06	0.08
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	0.08	0.04	0.00	0.10	0.10	0.01	0.06	0.10
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	0.06	0.05	0.00	0.10	0.10	0.01	0.03	0.09
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.06	0.05	0.00	0.10	0.10	0.01	0.03	0.09
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	0.09	0.02	0.00	0.10	0.10	0.01	0.08	0.11
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.05	0.05	0.00	0.10	0.10	0.01	0.02	0.08
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.05	0.05	0.00	0.10	0.05	0.01	0.02	0.08

Table 14.1.7
Haematology
Safety set

(m) Eosinophils (10^9/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	0.21	0.17	0.00	1.10	0.20	0.02	0.17	0.24
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	0.24	0.22	0.00	0.80	0.15	0.05	0.12	0.35
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	0.20	0.14	0.10	0.60	0.20	0.04	0.12	0.28
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.18	0.07	0.10	0.30	0.20	0.02	0.14	0.22
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	0.19	0.12	0.10	0.50	0.15	0.03	0.13	0.25
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.24	0.26	0.10	1.10	0.20	0.07	0.10	0.38
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.20	0.13	0.00	0.50	0.20	0.03	0.13	0.27

Table 14.1.7
Haematology
Safety set

(n) PT (secs)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	93	1	14.1	0.9	11.7	18.1	14.1	0.1	13.9	14.3
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	14.1	0.6	13.0	15.3	14.3	0.2	13.8	14.5
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	13.7	0.9	12.3	15.3	13.8	0.2	13.2	14.1
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	14.0	0.8	12.8	15.1	14.0	0.2	13.5	14.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	1	14.4	0.8	12.8	15.9	14.5	0.2	13.9	14.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	14.1	0.9	11.7	15.3	14.3	0.2	13.5	14.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	14.2	1.2	12.9	18.1	14.0	0.3	13.6	14.9

Table 14.1.7
Haematology
Safety set

(o) APTT (secs)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	93	1	31.1	3.5	24.9	43.0	30.8	0.4	30.4	31.9
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	31.5	3.0	28.0	37.6	30.4	0.7	29.9	33.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	31.0	3.6	24.9	40.2	30.9	0.9	29.0	33.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	32.4	3.7	26.5	41.8	32.2	1.0	30.2	34.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	1	31.3	3.7	24.9	39.9	31.6	0.9	29.4	33.2
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	31.2	4.6	26.8	43.0	29.3	1.2	28.7	33.8
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	29.4	2.2	24.9	31.6	30.4	0.6	28.3	30.6

Table 14.1.8
Biochemistry
Safety set

(a) Sodium (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	141.2	1.6	138.2	145.1	141.1	0.2	140.8	141.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	141.2	1.8	138.2	144.2	141.0	0.5	140.2	142.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	140.5	1.3	138.2	143.1	140.5	0.3	139.8	141.1
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	141.2	1.3	139.5	143.5	141.0	0.3	140.5	142.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	141.3	1.7	138.2	145.1	141.2	0.4	140.5	142.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	141.5	1.7	138.4	144.2	141.1	0.4	140.6	142.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	141.3	1.6	138.3	144.8	141.3	0.4	140.4	142.1

Table 14.1.8
Biochemistry
Safety set

(b) Potassium (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	4.18	0.24	3.63	4.83	4.17	0.02	4.13	4.23
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	4.19	0.33	3.63	4.83	4.17	0.08	4.01	4.37
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	4.16	0.18	3.85	4.52	4.12	0.05	4.07	4.26
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.17	0.22	3.72	4.53	4.16	0.06	4.04	4.29
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	4.23	0.21	3.90	4.66	4.24	0.05	4.12	4.33
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.09	0.20	3.69	4.48	4.12	0.05	3.98	4.20
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.24	0.26	3.87	4.69	4.19	0.07	4.10	4.38

Table 14.1.8
Biochemistry
Safety set

(c) Urea (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	4.18	1.04	2.30	7.90	3.90	0.11	3.96	4.39
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	3.83	0.57	2.90	4.80	3.75	0.14	3.52	4.13
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	4.18	1.27	2.60	6.40	3.70	0.33	3.47	4.89
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.57	1.04	3.20	6.20	4.60	0.28	3.97	5.17
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	4.16	1.24	2.30	7.90	4.05	0.29	3.55	4.78
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.19	1.08	2.40	5.90	3.80	0.28	3.59	4.78
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.20	0.95	2.80	5.50	3.95	0.24	3.69	4.71

Table 14.1.8
Biochemistry
Safety set

(d) Creatinine (umol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	63.9	8.1	41.9	81.1	63.0	0.8	62.2	65.6
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	64.0	5.6	54.3	75.3	62.8	1.4	61.0	67.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	61.6	9.8	41.9	74.5	63.1	2.5	56.2	67.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	65.9	8.7	53.3	81.1	62.5	2.3	60.9	70.9
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	65.3	7.5	46.9	76.3	65.2	1.8	61.5	69.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	63.9	9.7	46.0	78.2	63.4	2.5	58.6	69.3
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	62.6	7.8	50.2	78.6	61.2	1.9	58.4	66.7

Table 14.1.8
Biochemistry
Safety set

(e) Uric acid (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	0.25	0.05	0.13	0.41	0.25	0.01	0.24	0.26
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	0.24	0.04	0.13	0.30	0.24	0.01	0.21	0.26
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	0.24	0.05	0.14	0.34	0.25	0.01	0.21	0.27
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.26	0.03	0.21	0.32	0.27	0.01	0.24	0.27
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	0.26	0.05	0.17	0.41	0.26	0.01	0.24	0.29
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.27	0.06	0.19	0.39	0.26	0.01	0.24	0.31
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.23	0.04	0.15	0.30	0.24	0.01	0.21	0.25

Table 14.1.8
Biochemistry
Safety set

(f) Glucose (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	4.87	0.72	2.60	6.90	4.85	0.07	4.72	5.02
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	4.72	0.42	3.90	5.30	4.65	0.11	4.49	4.94
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	5.18	0.78	3.50	6.60	5.30	0.20	4.75	5.61
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.82	0.69	4.10	6.30	4.55	0.18	4.42	5.22
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	4.65	0.84	2.60	6.20	4.55	0.20	4.23	5.07
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	5.00	0.73	3.90	6.40	4.90	0.19	4.59	5.41
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.91	0.77	4.00	6.90	4.75	0.19	4.50	5.32

Table 14.1.8
Biochemistry
Safety set

(g) Calcium (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	2.34	0.07	2.14	2.49	2.35	0.01	2.33	2.36
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	2.35	0.08	2.24	2.47	2.35	0.02	2.31	2.39
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	2.34	0.09	2.18	2.47	2.36	0.02	2.30	2.39
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	2.33	0.04	2.26	2.42	2.34	0.01	2.31	2.36
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	2.33	0.06	2.22	2.44	2.33	0.01	2.30	2.36
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	2.36	0.08	2.23	2.47	2.37	0.02	2.32	2.41
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	2.35	0.09	2.14	2.49	2.36	0.02	2.31	2.40

Table 14.1.8
Biochemistry
Safety set

(h) Inorganic phosphorous (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	1.12	0.15	0.68	1.49	1.13	0.02	1.09	1.15
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	1.15	0.14	0.90	1.46	1.13	0.03	1.08	1.22
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	1.02	0.14	0.80	1.32	1.04	0.04	0.94	1.10
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.12	0.17	0.68	1.31	1.17	0.05	1.02	1.22
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	1.17	0.13	0.96	1.49	1.15	0.03	1.10	1.23
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.13	0.16	0.78	1.42	1.09	0.04	1.04	1.22
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.13	0.16	0.87	1.44	1.17	0.04	1.05	1.22

Table 14.1.8
Biochemistry
Safety set

(i) Total bilirubin (umol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	7.6	4.4	2.3	23.3	6.3	0.5	6.7	8.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	6.4	2.4	2.4	11.5	6.0	0.6	5.1	7.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	7.7	4.1	4.4	19.8	6.2	1.0	5.5	10.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	7.7	5.0	2.6	18.2	6.2	1.3	4.9	10.6
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	8.7	6.0	2.5	23.3	6.8	1.4	5.7	11.7
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	8.0	3.8	2.6	17.3	8.3	1.0	5.9	10.1
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	6.9	4.7	2.3	21.2	5.1	1.2	4.4	9.5

Table 14.1.8
Biochemistry
Safety set

(j) Alkaline phosphatase (IU/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	151.9	36.9	89.9	295.3	143.7	3.8	144.4	159.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	168.2	35.2	106.1	226.0	175.2	8.8	149.5	187.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	163.8	55.1	109.2	295.3	153.0	14.2	133.3	194.3
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	146.1	15.0	123.5	170.2	147.1	4.0	137.5	154.8
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	141.4	32.1	89.9	192.5	138.4	7.6	125.4	157.4
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	160.8	34.3	110.1	227.2	162.5	8.9	141.8	179.8
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	133.1	29.3	98.8	207.5	127.6	7.3	117.5	148.7

Table 14.1.8
Biochemistry
Safety set

(k) Alanine transaminase (IU/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	17.7	8.0	8.8	58.5	15.3	0.8	16.1	19.4
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	20.5	11.0	11.3	52.8	15.8	2.7	14.6	26.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	17.2	6.6	11.0	38.5	15.1	1.7	13.6	20.8
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	15.9	3.5	11.2	23.8	15.4	0.9	13.9	17.9
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	17.4	5.1	9.6	26.7	17.1	1.2	14.9	19.9
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	16.9	6.2	8.8	30.1	14.6	1.6	13.5	20.3
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	18.1	12.2	10.3	58.5	14.4	3.0	11.6	24.6

Table 14.1.8
Biochemistry
Safety set

(I) Aspartate transaminase (IU/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	20.4	4.8	6.4	35.9	20.0	0.5	19.4	21.4
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	21.5	4.9	15.0	32.5	20.9	1.2	18.9	24.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	19.6	5.0	12.3	29.8	18.6	1.3	16.9	22.4
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	20.0	3.6	14.1	28.4	19.7	1.0	17.8	22.1
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	21.0	4.0	12.4	28.5	21.3	0.9	19.0	22.9
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	19.8	3.4	15.1	26.3	19.2	0.9	17.9	21.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	20.4	7.3	6.4	35.9	18.3	1.8	16.5	24.3

Table 14.1.8
Biochemistry
Safety set

(m) Gamma glutamyl transferase (IU/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	14.1	9.7	3.4	80.7	12.2	1.0	12.1	16.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	15.0	9.8	5.5	49.1	12.6	2.5	9.7	20.2
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	17.3	18.5	6.9	80.7	11.7	4.8	7.1	27.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	12.4	5.3	6.3	23.4	12.0	1.4	9.4	15.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	14.1	8.1	3.4	36.9	13.4	1.9	10.1	18.2
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	14.3	5.0	6.3	27.7	12.3	1.3	11.5	17.1
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	11.5	5.3	5.2	27.5	9.7	1.3	8.6	14.3

Table 14.1.8
Biochemistry
Safety set

(n) Alpha-hydroxybutyrate dehydrogenase (IU/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	122.74	24.79	51.10	256.40	120.30	2.56	117.66	127.81
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	124.41	17.02	101.60	166.00	124.15	4.26	115.34	133.48
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	114.57	23.44	57.50	149.50	117.20	6.05	101.59	127.55
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	130.94	40.98	96.20	256.40	119.80	10.95	107.28	154.60
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	121.22	17.22	100.70	169.30	119.30	4.06	112.66	129.78
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	122.95	27.91	51.10	171.00	125.90	7.21	107.50	138.41
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	123.04	18.77	100.90	165.70	116.95	4.69	113.04	133.04

Table 14.1.8
Biochemistry
Safety set

(o) Creatinine kinase (IU/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	114.4	72.9	36.0	517.5	92.9	7.5	99.4	129.3
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	109.8	68.4	62.8	355.3	92.8	17.1	73.4	146.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	101.2	40.3	53.4	203.4	85.3	10.4	78.9	123.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	112.0	71.5	50.4	282.5	86.1	19.1	70.7	153.3
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	110.2	47.0	36.0	217.3	93.2	11.1	86.8	133.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	95.6	47.0	40.5	212.0	78.3	12.1	69.6	121.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	155.6	124.0	45.6	517.5	107.0	31.0	89.5	221.7

Table 14.1.8
Biochemistry
Safety set

(p) Total protein (g/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	75.5	3.4	68.2	84.2	75.5	0.4	74.8	76.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	76.7	3.3	69.9	84.0	76.8	0.8	75.0	78.4
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	75.3	3.7	70.4	81.9	75.6	0.9	73.3	77.3
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	74.6	2.4	69.5	78.3	74.7	0.6	73.2	76.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	76.0	3.6	68.2	82.3	76.8	0.8	74.2	77.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	75.8	3.9	71.1	84.2	74.5	1.0	73.6	78.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	74.7	3.6	68.2	81.4	74.7	0.9	72.8	76.6

Table 14.1.8
Biochemistry
Safety set

(q) Albumin (g/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	45.7	2.5	39.9	51.5	45.3	0.3	45.2	46.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	45.5	2.5	40.9	49.5	44.9	0.6	44.2	46.8
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	44.9	2.0	41.7	48.5	44.5	0.5	43.8	46.0
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	46.5	2.3	42.8	49.8	46.6	0.6	45.2	47.8
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	45.6	2.1	42.4	50.2	45.7	0.5	44.5	46.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	46.4	3.0	41.2	51.5	46.5	0.8	44.7	48.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	45.3	3.0	39.9	51.2	44.7	0.8	43.7	46.9

Table 14.1.8
Biochemistry
Safety set

(r) Cholesterol (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	4.37	0.81	2.46	6.99	4.25	0.08	4.20	4.54
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	4.41	0.83	3.00	6.00	4.47	0.21	3.97	4.85
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	4.48	0.94	3.18	6.99	4.26	0.24	3.96	5.00
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	3.99	0.68	2.89	5.52	3.85	0.18	3.60	4.38
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	4.38	0.86	2.46	5.96	4.18	0.20	3.95	4.81
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.63	0.95	3.21	6.45	4.56	0.25	4.10	5.15
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.31	0.52	3.36	5.09	4.28	0.13	4.03	4.59

Table 14.1.8
Biochemistry
Safety set

(s) Triglycerides (mmol/L)

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	94	0	1.06	0.42	0.40	3.00	1.00	0.04	0.98	1.15
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	16	0	1.03	0.29	0.60	1.60	1.00	0.07	0.87	1.18
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	15	0	1.11	0.41	0.60	1.70	1.10	0.10	0.88	1.33
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.93	0.26	0.60	1.30	0.90	0.07	0.78	1.08
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	18	0	1.13	0.45	0.60	2.60	1.10	0.11	0.91	1.36
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.16	0.65	0.40	3.00	1.00	0.17	0.80	1.52
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.02	0.34	0.60	1.80	0.90	0.09	0.84	1.20

Table 14.1.9
Concomitant medications ongoing at time of first dose of study medication
Safety set

ATC level 2 category	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo (n=16)	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg (n=15)	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo (n=14)	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg (n=18)	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg (n=15)	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg (n=16)	Total (n=94)
ANY	10 (62.5%)	10 (66.7%)	8 (57.1%)	12 (66.7%)	9 (60.0%)	10 (62.5%)	59 (62.8%)
ANTIANEMIC PREPARATIONS	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
ANTIBACTERIALS FOR SYSTEMIC USE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (2.1%)
MINERAL SUPPLEMENTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	10 (62.5%)	9 (60.0%)	8 (57.1%)	12 (66.7%)	7 (46.7%)	10 (62.5%)	56 (59.6%)
THYROID THERAPY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
VITAMINS	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)

Table 14.2.1.1
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR 0-6h)
Intention-to-treat population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.11	1.07	0.00	3.83	2.29	0.11	1.88	2.33
Ibu. 400mg + Para. 1000mg	90	0	2.37	0.99	0.00	3.83	2.54	0.10	2.16	2.57
Placebo	90	0	1.87	1.17	0.00	3.75	1.92	0.12	1.62	2.12

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.7098	
Treatment	2	175	0.0007	***
Period	2	175	0.4163	
Sequence	5	85	0.0915	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.51	0.13	0.25,0.76	0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.25	0.13	-0.00,0.51	0.0537	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.25	0.13	-0.51,0.00		

	LS Mean
Ibu. 200mg + Para. 500mg	2.10
Ibu. 400mg + Para. 1000mg	2.35
Placebo	1.85

Created by Michael Goulder on 01OCT2009 10:49
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.1.1 TOTPAR6 ITT.sas

Table 14.2.1.2
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR 0-6h)
Per-protocol population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	85	0	2.15	1.07	0.00	3.83	2.36	0.12	1.92	2.38
Ibu. 400mg + Para. 1000mg	79	0	2.39	0.98	0.00	3.83	2.58	0.11	2.17	2.61
Placebo	84	0	1.86	1.18	0.00	3.75	1.92	0.13	1.60	2.12

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	156	0.9009	
Treatment	2	156	0.0020	**
Period	2	156	0.5999	
Sequence	5	81	0.2406	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.49	0.14	0.22,0.75	0.0005	***
Ibu. 200mg + Para. 500mg - Placebo	0.30	0.13	0.04,0.56	0.0264	*
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.19	0.14	-0.46,0.08		

	LS Mean
Ibu. 200mg + Para. 500mg	2.13
Ibu. 400mg + Para. 1000mg	2.32
Placebo	1.84

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Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.1.2 TOTPAR6 PP.sas

Table 14.2.1.3
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR 0-6h)
Sensitivity analyses
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(i) Replacing all missing values with the worst possible score for the active treatments and the best possible score for placebo

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.11	1.07	0.00	3.83	2.29	0.11	1.88	2.33
Ibu. 400mg + Para. 1000mg	90	0	2.37	0.99	0.00	3.83	2.54	0.10	2.16	2.57
Placebo	90	0	2.16	1.04	0.00	3.75	2.29	0.11	1.95	2.38

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.3344
Treatment	2	175	0.0511
Period	2	175	0.1066
Sequence	5	85	0.1242

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.22	0.11	-0.00,0.45	0.0543
Ibu. 200mg + Para. 500mg - Placebo	-0.04	0.11	-0.26,0.19	0.7348
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.26	0.11	-0.48,-0.04	

	LS Mean
Ibu. 200mg + Para. 500mg	2.10
Ibu. 400mg + Para. 1000mg	2.36
Placebo	2.14

Table 14.2.1.3
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR 0-6h)
Sensitivity analyses
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(ii) Using last observation carried forward for observations that cannot be interpolated

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.11	1.06	0.00	3.83	2.29	0.11	1.89	2.33
Ibu. 400mg + Para. 1000mg	90	0	2.37	0.99	0.00	3.83	2.54	0.10	2.16	2.57
Placebo	90	0	1.96	1.10	0.00	3.75	1.92	0.12	1.73	2.19

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.5490	
Treatment	2	175	0.0027	**
Period	2	175	0.2632	
Sequence	5	85	0.0993	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.42	0.12	0.18,0.66	0.0006	***
Ibu. 200mg + Para. 500mg - Placebo	0.17	0.12	-0.06,0.41	0.1522	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.25	0.12	-0.49,-0.01		

	LS Mean
Ibu. 200mg + Para. 500mg	2.10
Ibu. 400mg + Para. 1000mg	2.35
Placebo	1.93

Table 14.2.2
Total pain relief over two hours post-dose (TOTPAR 0-2h)
Intention-to-treat population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.36	0.91	0.00	3.50	1.25	0.09	1.17	1.55
Ibu. 400mg + Para. 1000mg	90	0	1.48	0.86	0.00	3.50	1.26	0.09	1.30	1.66
Placebo	90	0	1.31	0.90	0.00	3.27	1.37	0.10	1.12	1.50

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.9188
Treatment	2	175	0.2431
Period	2	175	0.4612
Sequence	5	85	0.3100

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.18	0.11	-0.03,0.39	0.0985
Ibu. 200mg + Para. 500mg - Placebo	0.06	0.11	-0.15,0.27	0.5691
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.12	0.11	-0.33,0.09	

	LS Mean
Ibu. 200mg + Para. 500mg	1.36
Ibu. 400mg + Para. 1000mg	1.48
Placebo	1.30

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Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.2 TOTPAR2.sas

Table 14.2.3
Total pain relief over four hours post-dose (TOTPAR 0-4h)
Intention-to-treat population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.86	1.02	0.00	3.75	1.86	0.11	1.65	2.07
Ibu. 400mg + Para. 1000mg	90	0	2.09	0.97	0.00	3.75	2.00	0.10	1.89	2.30
Placebo	90	0	1.72	1.08	0.00	3.63	1.63	0.11	1.49	1.94

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.9887	
Treatment	2	175	0.0083	**
Period	2	175	0.3487	
Sequence	5	85	0.1441	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.39	0.12	0.14,0.63	0.0021	**
Ibu. 200mg + Para. 500mg - Placebo	0.16	0.12	-0.08,0.40	0.1956	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.23	0.12	-0.47,0.02		

	LS Mean
Ibu. 200mg + Para. 500mg	1.85
Ibu. 400mg + Para. 1000mg	2.08
Placebo	1.69

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Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.3 TOTPAR4.sas

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(a) 30 minute assessment

(i) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 No pain relief	50 (54.9%)	44 (48.9%)	45 (50.0%)
1 A little pain relief	24 (26.4%)	26 (28.9%)	27 (30.0%)
2 Some pain relief	10 (11.0%)	15 (16.7%)	12 (13.3%)
3 A lot of pain relief	4 (4.4%)	3 (3.3%)	6 (6.7%)
4 Complete pain relief	3 (3.3%)	2 (2.2%)	0 (0.0%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.75	1.04	0.00	4.00	0.00	0.11	0.53	0.96
Ibu. 400mg + Para. 1000mg	90	0	0.81	0.98	0.00	4.00	1.00	0.10	0.61	1.02
Placebo	90	0	0.77	0.92	0.00	3.00	0.50	0.10	0.57	0.96

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(a) 30 minute assessment (Cont.)

(iii) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.7305
Treatment	2	175	0.7988
Period	2	175	0.5858
Sequence	5	85	0.5910

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.06	0.12	-0.18,0.31	0.6063
Ibu. 200mg + Para. 500mg - Placebo	-0.01	0.12	-0.25,0.23	0.9115
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.08	0.12	-0.32,0.16	

	LS Mean
Ibu. 200mg + Para. 500mg	0.74
Ibu. 400mg + Para. 1000mg	0.82
Placebo	0.76

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(b) 1 hour assessment

(i) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 No pain relief	15 (16.5%)	14 (15.6%)	19 (21.1%)
1 A little pain relief	33 (36.3%)	36 (40.0%)	28 (31.1%)
2 Some pain relief	26 (28.6%)	21 (23.3%)	23 (25.6%)
3 A lot of pain relief	7 (7.7%)	12 (13.3%)	14 (15.6%)
4 Complete pain relief	10 (11.0%)	7 (7.8%)	6 (6.7%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.60	1.18	0.00	4.00	1.00	0.12	1.36	1.85
Ibu. 400mg + Para. 1000mg	90	0	1.58	1.14	0.00	4.00	1.00	0.12	1.34	1.82
Placebo	90	0	1.56	1.18	0.00	4.00	1.00	0.12	1.31	1.80

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(b) 1 hour assessment (Cont.)

(iii) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.7992
Treatment	2	175	0.9317
Period	2	175	0.8973
Sequence	5	85	0.5057

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.03	0.15	-0.26,0.33	0.8323
Ibu. 200mg + Para. 500mg - Placebo	0.06	0.15	-0.24,0.35	0.7080
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	0.02	0.15	-0.27,0.32	

	LS Mean
Ibu. 200mg + Para. 500mg	1.60
Ibu. 400mg + Para. 1000mg	1.57
Placebo	1.54

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(c) 90 minute assessment

(i) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 No pain relief	8 (8.8%)	8 (8.9%)	14 (15.6%)
1 A little pain relief	27 (29.7%)	18 (20.0%)	23 (25.6%)
2 Some pain relief	30 (33.0%)	32 (35.6%)	24 (26.7%)
3 A lot of pain relief	9 (9.9%)	12 (13.3%)	15 (16.7%)
4 Complete pain relief	17 (18.7%)	20 (22.2%)	14 (15.6%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.00	1.23	0.00	4.00	2.00	0.13	1.74	2.26
Ibu. 400mg + Para. 1000mg	90	0	2.20	1.25	0.00	4.00	2.00	0.13	1.94	2.46
Placebo	90	0	1.91	1.30	0.00	4.00	2.00	0.14	1.64	2.18

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(c) 90 minute assessment (Cont.)

(iii) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.9899
Treatment	2	175	0.1506
Period	2	175	0.2642
Sequence	5	85	0.2980

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.30	0.16	-0.01,0.61	0.0552
Ibu. 200mg + Para. 500mg - Placebo	0.11	0.15	-0.20,0.41	0.4904
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.19	0.15	-0.50,0.11	

	LS Mean
Ibu. 200mg + Para. 500mg	2.00
Ibu. 400mg + Para. 1000mg	2.19
Placebo	1.89

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(d) 2 hour assessment

(i) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 No pain relief	10 (11.0%)	7 (7.8%)	13 (14.4%)
1 A little pain relief	19 (20.9%)	10 (11.1%)	24 (26.7%)
2 Some pain relief	26 (28.6%)	28 (31.1%)	19 (21.1%)
3 A lot of pain relief	16 (17.6%)	16 (17.8%)	15 (16.7%)
4 Complete pain relief	20 (22.0%)	29 (32.2%)	19 (21.1%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.19	1.30	0.00	4.00	2.00	0.14	1.92	2.46
Ibu. 400mg + Para. 1000mg	90	0	2.56	1.26	0.00	4.00	2.50	0.13	2.29	2.82
Placebo	90	0	2.03	1.37	0.00	4.00	2.00	0.14	1.75	2.32

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(d) 2 hour assessment (Cont.)

(iii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.8145	
Treatment	2	175	0.0049	**
Period	2	175	0.1680	
Sequence	5	85	0.2012	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.53	0.16	0.21,0.85	0.0014	**
Ibu. 200mg + Para. 500mg - Placebo	0.17	0.16	-0.15,0.49	0.2859	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.35	0.16	-0.67,-0.04		

	LS Mean
Ibu. 200mg + Para. 500mg	2.18
Ibu. 400mg + Para. 1000mg	2.53
Placebo	2.01

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(e) 4 hour assessment

(i) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 No pain relief	9 (9.9%)	7 (7.8%)	16 (17.8%)
1 A little pain relief	14 (15.4%)	7 (7.8%)	19 (21.1%)
2 Some pain relief	15 (16.5%)	15 (16.7%)	11 (12.2%)
3 A lot of pain relief	22 (24.2%)	22 (24.4%)	18 (20.0%)
4 Complete pain relief	31 (34.1%)	39 (43.3%)	26 (28.9%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.57	1.36	0.00	4.00	3.00	0.14	2.29	2.85
Ibu. 400mg + Para. 1000mg	90	0	2.88	1.27	0.00	4.00	3.00	0.13	2.61	3.14
Placebo	90	0	2.21	1.50	0.00	4.00	2.00	0.16	1.90	2.53

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(e) 4 hour assessment (Cont.)

(iii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.7037	
Treatment	2	175	0.0010	***
Period	2	175	0.6178	
Sequence	5	85	0.0824	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.67	0.18	0.32,1.02	0.0002	***
Ibu. 200mg + Para. 500mg - Placebo	0.37	0.18	0.02,0.71	0.0376	*
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.30	0.18	-0.65,0.05		

	LS Mean
Ibu. 200mg + Para. 500mg	2.56
Ibu. 400mg + Para. 1000mg	2.85
Placebo	2.19

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(f) 6 hour assessment

(i) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 No pain relief	12 (13.2%)	5 (5.6%)	20 (22.2%)
1 A little pain relief	8 (8.8%)	7 (7.8%)	16 (17.8%)
2 Some pain relief	14 (15.4%)	19 (21.1%)	13 (14.4%)
3 A lot of pain relief	23 (25.3%)	16 (17.8%)	13 (14.4%)
4 Complete pain relief	34 (37.4%)	43 (47.8%)	28 (31.1%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.65	1.40	0.00	4.00	3.00	0.15	2.36	2.94
Ibu. 400mg + Para. 1000mg	90	0	2.94	1.23	0.00	4.00	3.00	0.13	2.69	3.20
Placebo	90	0	2.14	1.57	0.00	4.00	2.00	0.17	1.82	2.47

Table 14.2.4
Pain relief at each follow-up assessment
Intention-to-treat population

(f) 6 hour assessment (Cont.)

(iii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.1629	
Treatment	2	175	<0.0001	***
Period	2	175	0.6022	
Sequence	5	85	0.0714	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.82	0.17	0.48,1.16	<0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.53	0.17	0.19,0.87	0.0025	**
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.29	0.17	-0.63,0.05		

	LS Mean
Ibu. 200mg + Para. 500mg	2.64
Ibu. 400mg + Para. 1000mg	2.93
Placebo	2.11

Table 14.2.5
Total analgesic effect over two hours post-dose (SPID 0-2h)
Intention-to-treat population
Pain measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.72	0.61	-0.75	2.38	0.63	0.06	0.59	0.84
Ibu. 400mg + Para. 1000mg	90	0	0.80	0.57	-0.38	2.38	0.75	0.06	0.68	0.92
Placebo	90	0	0.68	0.53	-0.63	1.88	0.63	0.06	0.57	0.79

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.0890	
Period	2	175	0.4415	
Sequence	5	85	0.3911	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.14	0.07	0.01,0.27	0.0300	*
Ibu. 200mg + Para. 500mg - Placebo	0.05	0.07	-0.08,0.18	0.4251	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.09	0.07	-0.22,0.04		

	LS Mean
Ibu. 200mg + Para. 500mg	0.72
Ibu. 400mg + Para. 1000mg	0.81
Placebo	0.67

Created by Michael Goulder on 01OCT2009 13:56
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.5 SPID2.sas

Table 14.2.7
Total analgesic effect over six hours post-dose (SPID 0-6h)
Intention-to-treat population
Pain measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.21	0.69	-0.25	2.71	1.21	0.07	1.06	1.35
Ibu. 400mg + Para. 1000mg	90	0	1.32	0.65	-0.29	2.79	1.38	0.07	1.19	1.46
Placebo	90	0	1.04	0.72	-0.38	2.63	1.10	0.08	0.89	1.19

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.0004	***
Period	2	175	0.5304	
Sequence	5	85	0.2928	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.31	0.08	0.16,0.46	<0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.18	0.08	0.03,0.34	0.0177	*
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.13	0.08	-0.28,0.03		

	LS Mean
Ibu. 200mg + Para. 500mg	1.21
Ibu. 400mg + Para. 1000mg	1.33
Placebo	1.02

Created by Michael Goulder on 05OCT2009 9:40
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.7 SPID6.sas

Table 14.2.6
Total analgesic effect over four hours post-dose (SPID 0-4h)
Intention-to-treat population
Pain measured on a 4-point scale where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.05	0.66	-0.38	2.69	0.94	0.07	0.91	1.19
Ibu. 400mg + Para. 1000mg	90	0	1.17	0.64	-0.44	2.69	1.13	0.07	1.03	1.30
Placebo	90	0	0.94	0.66	-0.56	2.44	0.94	0.07	0.80	1.08

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.0039	**
Period	2	175	0.5014	
Sequence	5	85	0.3522	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.25	0.07	0.10,0.40	0.0009	***
Ibu. 200mg + Para. 500mg - Placebo	0.13	0.07	-0.02,0.27	0.0866	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.12	0.07	-0.27,0.02		

	LS Mean
Ibu. 200mg + Para. 500mg	1.05
Ibu. 400mg + Para. 1000mg	1.17
Placebo	0.92

Created by Michael Goulder on 01OCT2009 14:00
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.6 SPID4.sas

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(a) Baseline assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
2 Moderate	69 (75.8%)	70 (77.8%)	66 (73.3%)
3 Severe	22 (24.2%)	20 (22.2%)	24 (26.7%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.24	0.43	2.00	3.00	2.00	0.05	2.15	2.33
Ibu. 400mg + Para. 1000mg	90	0	2.22	0.42	2.00	3.00	2.00	0.04	2.13	2.31
Placebo	90	0	2.27	0.44	2.00	3.00	2.00	0.05	2.17	2.36

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(b) 30 minute assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 None	3 (3.3%)	2 (2.2%)	1 (1.1%)
1 Mild	14 (15.4%)	21 (23.3%)	19 (21.1%)
2 Moderate	59 (64.8%)	56 (62.2%)	53 (58.9%)
3 Severe	15 (16.5%)	11 (12.2%)	17 (18.9%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.95	0.67	0.00	3.00	2.00	0.07	1.80	2.09
Ibu. 400mg + Para. 1000mg	90	0	1.84	0.65	0.00	3.00	2.00	0.07	1.71	1.98
Placebo	90	0	1.96	0.67	0.00	3.00	2.00	0.07	1.82	2.10

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(b) 30 minute assessment (Cont.)

(iii) Frequency distribution for PID

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
-1	2 (2.2%)	1 (1.1%)	0 (0.0%)
0	66 (72.5%)	58 (64.4%)	63 (70.0%)
1	17 (18.7%)	27 (30.0%)	26 (28.9%)
2	6 (6.6%)	4 (4.4%)	1 (1.1%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(iv) Summary statistics for PID

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.30	0.62	-1.00	2.00	0.00	0.07	0.17	0.43
Ibu. 400mg + Para. 1000mg	90	0	0.38	0.59	-1.00	2.00	0.00	0.06	0.25	0.50
Placebo	90	0	0.31	0.49	0.00	2.00	0.00	0.05	0.21	0.41

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(b) 30 minute assessment (Cont.)

(v) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0244	*
Treatment	2	175	0.3594	
Period	2	175	0.9755	
Sequence	5	85	0.5975	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.08	0.07	-0.06,0.22	0.2432
Ibu. 200mg + Para. 500mg - Placebo	-0.01	0.07	-0.15,0.13	0.8966
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.09	0.07	-0.23,0.05	

	LS Mean
Ibu. 200mg + Para. 500mg	0.30
Ibu. 400mg + Para. 1000mg	0.39
Placebo	0.31

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(c) 1 hour assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 None	13 (14.3%)	13 (14.4%)	10 (11.1%)
1 Mild	33 (36.3%)	37 (41.1%)	38 (42.2%)
2 Moderate	39 (42.9%)	33 (36.7%)	31 (34.4%)
3 Severe	6 (6.6%)	7 (7.8%)	11 (12.2%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.42	0.82	0.00	3.00	1.00	0.09	1.25	1.59
Ibu. 400mg + Para. 1000mg	90	0	1.38	0.83	0.00	3.00	1.00	0.09	1.20	1.55
Placebo	90	0	1.48	0.85	0.00	3.00	1.00	0.09	1.30	1.66

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(c) 1 hour assessment (Cont.)

(iii) Frequency distribution for PID

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
-1	1 (1.1%)	1 (1.1%)	2 (2.2%)
0	34 (37.4%)	31 (34.4%)	31 (34.4%)
1	39 (42.9%)	43 (47.8%)	41 (45.6%)
2	14 (15.4%)	11 (12.2%)	16 (17.8%)
3	3 (3.3%)	4 (4.4%)	0 (0.0%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(iv) Summary statistics for PID

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.82	0.82	-1.00	3.00	1.00	0.09	0.65	1.00
Ibu. 400mg + Para. 1000mg	90	0	0.84	0.82	-1.00	3.00	1.00	0.09	0.67	1.02
Placebo	90	0	0.79	0.76	-1.00	2.00	1.00	0.08	0.63	0.95

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(c) 1 hour assessment (Cont.)

(v) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0011	**
Treatment	2	175	0.7302	
Period	2	175	0.3265	
Sequence	5	85	0.2544	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.08	0.10	-0.12,0.27	0.4384
Ibu. 200mg + Para. 500mg - Placebo	0.05	0.10	-0.14,0.24	0.5961
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.02	0.10	-0.22,0.17	

	LS Mean
Ibu. 200mg + Para. 500mg	0.82
Ibu. 400mg + Para. 1000mg	0.85
Placebo	0.77

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(d) 90 minute assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 None	20 (22.0%)	27 (30.0%)	19 (21.1%)
1 Mild	44 (48.4%)	38 (42.2%)	36 (40.0%)
2 Moderate	23 (25.3%)	23 (25.6%)	31 (34.4%)
3 Severe	4 (4.4%)	2 (2.2%)	4 (4.4%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.12	0.80	0.00	3.00	1.00	0.08	0.95	1.29
Ibu. 400mg + Para. 1000mg	90	0	1.00	0.81	0.00	3.00	1.00	0.09	0.83	1.17
Placebo	90	0	1.22	0.83	0.00	3.00	1.00	0.09	1.05	1.40

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(d) 90 minute assessment (Cont.)

(iii) Frequency distribution for PID

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
-1	1 (1.1%)	1 (1.1%)	2 (2.2%)
0	21 (23.1%)	14 (15.6%)	19 (21.1%)
1	41 (45.1%)	45 (50.0%)	45 (50.0%)
2	22 (24.2%)	24 (26.7%)	21 (23.3%)
3	6 (6.6%)	6 (6.7%)	3 (3.3%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(iv) Summary statistics for PID

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.12	0.88	-1.00	3.00	1.00	0.09	0.94	1.30
Ibu. 400mg + Para. 1000mg	90	0	1.22	0.83	-1.00	3.00	1.00	0.09	1.05	1.40
Placebo	90	0	1.04	0.82	-1.00	3.00	1.00	0.09	0.87	1.22

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(d) 90 minute assessment (Cont.)

(v) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.1334	
Period	2	175	0.3468	
Sequence	5	85	0.4940	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.21	0.10	0.00,0.41	0.0451	*
Ibu. 200mg + Para. 500mg - Placebo	0.10	0.10	-0.10,0.30	0.3311	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.11	0.10	-0.31,0.10		

	LS Mean
Ibu. 200mg + Para. 500mg	1.13
Ibu. 400mg + Para. 1000mg	1.24
Placebo	1.03

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(e) 2 hour assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 None	25 (27.5%)	38 (42.2%)	27 (30.0%)
1 Mild	46 (50.5%)	34 (37.8%)	32 (35.6%)
2 Moderate	17 (18.7%)	17 (18.9%)	25 (27.8%)
3 Severe	3 (3.3%)	1 (1.1%)	6 (6.7%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.98	0.77	0.00	3.00	1.00	0.08	0.82	1.14
Ibu. 400mg + Para. 1000mg	90	0	0.79	0.79	0.00	3.00	1.00	0.08	0.62	0.95
Placebo	90	0	1.11	0.92	0.00	3.00	1.00	0.10	0.92	1.30

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(e) 2 hour assessment (Cont.)

(iii) Frequency distribution for PID

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
-1	0 (0.0%)	1 (1.1%)	1 (1.1%)
0	16 (17.6%)	11 (12.2%)	22 (24.4%)
1	42 (46.2%)	33 (36.7%)	33 (36.7%)
2	26 (28.6%)	38 (42.2%)	30 (33.3%)
3	7 (7.7%)	7 (7.8%)	4 (4.4%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(iv) Summary statistics for PID

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.26	0.84	0.00	3.00	1.00	0.09	1.09	1.44
Ibu. 400mg + Para. 1000mg	90	0	1.43	0.85	-1.00	3.00	1.50	0.09	1.26	1.61
Placebo	90	0	1.16	0.89	-1.00	3.00	1.00	0.09	0.97	1.34

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(e) 2 hour assessment (Cont.)

(v) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.0116	*
Period	2	175	0.6594	
Sequence	5	85	0.6721	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.31	0.10	0.11,0.51	0.0030	**
Ibu. 200mg + Para. 500mg - Placebo	0.13	0.10	-0.07,0.33	0.1981	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.18	0.10	-0.38,0.02		

	LS Mean
Ibu. 200mg + Para. 500mg	1.27
Ibu. 400mg + Para. 1000mg	1.44
Placebo	1.13

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(f) 4 hour assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 None	44 (48.4%)	48 (53.3%)	34 (37.8%)
1 Mild	32 (35.2%)	32 (35.6%)	26 (28.9%)
2 Moderate	11 (12.1%)	9 (10.0%)	25 (27.8%)
3 Severe	4 (4.4%)	1 (1.1%)	5 (5.6%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.73	0.84	0.00	3.00	1.00	0.09	0.55	0.90
Ibu. 400mg + Para. 1000mg	90	0	0.59	0.72	0.00	3.00	0.00	0.08	0.44	0.74
Placebo	90	0	1.01	0.94	0.00	3.00	1.00	0.10	0.81	1.21

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(f) 4 hour assessment (Cont.)

(iii) Frequency distribution for PID

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0	15 (16.5%)	8 (8.9%)	26 (28.9%)
1	25 (27.5%)	28 (31.1%)	22 (24.4%)
2	40 (44.0%)	43 (47.8%)	35 (38.9%)
3	11 (12.1%)	11 (12.2%)	7 (7.8%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(iv) Summary statistics for PID

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.52	0.91	0.00	3.00	2.00	0.10	1.33	1.71
Ibu. 400mg + Para. 1000mg	90	0	1.63	0.81	0.00	3.00	2.00	0.09	1.46	1.80
Placebo	90	0	1.26	0.97	0.00	3.00	1.00	0.10	1.05	1.46

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(f) 4 hour assessment (Cont.)

(v) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.0009	***
Period	2	175	0.5972	
Sequence	5	85	0.3162	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.41	0.11	0.19,0.63	0.0003	***
Ibu. 200mg + Para. 500mg - Placebo	0.28	0.11	0.07,0.50	0.0101	*
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.13	0.11	-0.34,0.09		

	LS Mean
Ibu. 200mg + Para. 500mg	1.52
Ibu. 400mg + Para. 1000mg	1.64
Placebo	1.23

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(g) 6 hour assessment

(i) Frequency distribution for pain

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0 None	49 (53.8%)	50 (55.6%)	35 (38.9%)
1 Mild	24 (26.4%)	29 (32.2%)	27 (30.0%)
2 Moderate	14 (15.4%)	10 (11.1%)	18 (20.0%)
3 Severe	4 (4.4%)	1 (1.1%)	10 (11.1%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(ii) Summary statistics for pain

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	0.70	0.89	0.00	3.00	0.00	0.09	0.52	0.89
Ibu. 400mg + Para. 1000mg	90	0	0.58	0.73	0.00	3.00	0.00	0.08	0.42	0.73
Placebo	90	0	1.03	1.02	0.00	3.00	1.00	0.11	0.82	1.25

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(g) 6 hour assessment (Cont.)

(iii) Frequency distribution for PID

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
-1	1 (1.1%)	0 (0.0%)	4 (4.4%)
0	15 (16.5%)	10 (11.1%)	21 (23.3%)
1	19 (20.9%)	23 (25.6%)	23 (25.6%)
2	46 (50.5%)	46 (51.1%)	34 (37.8%)
3	10 (11.0%)	11 (12.2%)	8 (8.9%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(iv) Summary statistics for PID

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.54	0.93	-1.00	3.00	2.00	0.10	1.34	1.73
Ibu. 400mg + Para. 1000mg	90	0	1.64	0.84	0.00	3.00	2.00	0.09	1.47	1.82
Placebo	90	0	1.23	1.05	-1.00	3.00	1.00	0.11	1.01	1.45

Table 14.2.8
Pain intensity difference (PID) at each follow-up assessment
Intention-to-treat population

(g) 6 hour assessment (Cont.)

(v) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	<0.0001	***
Treatment	2	175	0.0002	***
Period	2	175	0.7032	
Sequence	5	85	0.4309	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.45	0.11	0.24,0.67	<0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.33	0.11	0.12,0.55	0.0025	**
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.12	0.11	-0.33,0.10		

	LS Mean
Ibu. 200mg + Para. 500mg	1.54
Ibu. 400mg + Para. 1000mg	1.66
Placebo	1.21

Table 14.2.9
Overall effectiveness over two hours post-dose (SPRID 0-2h)
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.08	1.45	-0.38	5.63	1.88	0.15	1.78	2.38
Ibu. 400mg + Para. 1000mg	90	0	2.28	1.36	0.00	5.63	2.05	0.14	2.00	2.57
Placebo	90	0	1.99	1.37	-0.63	4.78	1.94	0.14	1.71	2.28

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.0619
Treatment	2	175	0.1478
Period	2	175	0.4561
Sequence	5	85	0.3530

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.32	0.17	-0.01,0.65	0.0542
Ibu. 200mg + Para. 500mg - Placebo	0.11	0.17	-0.21,0.44	0.4945
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.21	0.17	-0.54,0.12	

	LS Mean
Ibu. 200mg + Para. 500mg	2.08
Ibu. 400mg + Para. 1000mg	2.29
Placebo	1.96

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Table 14.2.10
Overall effectiveness over four hours post-dose (SPRID 0-4h)
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.91	1.58	0.00	6.31	2.82	0.17	2.58	3.24
Ibu. 400mg + Para. 1000mg	90	0	3.26	1.53	-0.19	6.31	3.30	0.16	2.94	3.58
Placebo	90	0	2.66	1.66	-0.56	5.81	2.53	0.17	2.31	3.00

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0155	*
Treatment	2	175	0.0046	**
Period	2	175	0.3965	
Sequence	5	85	0.2153	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.64	0.19	0.26,1.01	0.0011	**
Ibu. 200mg + Para. 500mg - Placebo	0.29	0.19	-0.09,0.66	0.1336	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.35	0.19	-0.73,0.03		

	LS Mean
Ibu. 200mg + Para. 500mg	2.91
Ibu. 400mg + Para. 1000mg	3.25
Placebo	2.62

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Table 14.2.11
Overall effectiveness over six hours post-dose (SPRID 0-6h)
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(a) Summary

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	3.31	1.64	0.00	6.29	3.58	0.17	2.97	3.65
Ibu. 400mg + Para. 1000mg	90	0	3.69	1.55	-0.13	6.54	3.97	0.16	3.36	4.02
Placebo	90	0	2.91	1.82	-0.38	6.21	2.90	0.19	2.53	3.29

(b) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0032	**
Treatment	2	175	0.0004	***
Period	2	175	0.4471	
Sequence	5	85	0.1472	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.82	0.20	0.42,1.21	<0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.44	0.20	0.04,0.83	0.0306	*
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.38	0.20	-0.77,0.01		

	LS Mean
Ibu. 200mg + Para. 500mg	3.30
Ibu. 400mg + Para. 1000mg	3.68
Placebo	2.87

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Table 14.2.12
SPRID at each follow-up assessment
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(a) 30 minute assessment

(i) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	1.04	1.60	-1.00	6.00	0.00	0.17	0.71	1.38
Ibu. 400mg + Para. 1000mg	90	0	1.19	1.50	-1.00	6.00	1.00	0.16	0.88	1.50
Placebo	90	0	1.08	1.33	0.00	5.00	1.00	0.14	0.80	1.36

(ii) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.2718
Treatment	2	175	0.5938
Period	2	175	0.8063
Sequence	5	85	0.6128

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.15	0.18	-0.21,0.50	0.4157
Ibu. 200mg + Para. 500mg - Placebo	-0.02	0.18	-0.38,0.33	0.9014
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.17	0.18	-0.52,0.19	

	LS Mean
Ibu. 200mg + Para. 500mg	1.04
Ibu. 400mg + Para. 1000mg	1.21
Placebo	1.06

Table 14.2.12
SPRID at each follow-up assessment
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(b) 1 hour assessment

(i) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	2.43	1.91	-1.00	7.00	2.00	0.20	2.03	2.83
Ibu. 400mg + Para. 1000mg	90	0	2.42	1.85	-1.00	7.00	2.00	0.19	2.04	2.81
Placebo	90	0	2.34	1.85	-1.00	6.00	2.00	0.19	1.96	2.73

(ii) Analysis of Covariance

Source	d.f.	Error d.f.	p
Baseline pain	1	175	0.2264
Treatment	2	175	0.8666
Period	2	175	0.6659
Sequence	5	85	0.3841

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p
Ibu. 400mg + Para. 1000mg - Placebo	0.11	0.23	-0.35,0.57	0.6436
Ibu. 200mg + Para. 500mg - Placebo	0.11	0.23	-0.35,0.57	0.6432
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.00	0.23	-0.46,0.46	

	LS Mean
Ibu. 200mg + Para. 500mg	2.42
Ibu. 400mg + Para. 1000mg	2.42
Placebo	2.31

Table 14.2.12
SPRID at each follow-up assessment
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(c) 90 minute assessment

(i) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	3.12	1.98	0.00	7.00	3.00	0.21	2.71	3.53
Ibu. 400mg + Para. 1000mg	90	0	3.42	1.98	-1.00	7.00	3.00	0.21	3.01	3.84
Placebo	90	0	2.96	2.01	-1.00	7.00	3.00	0.21	2.54	3.38

(ii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0223	*
Treatment	2	175	0.1177	
Period	2	175	0.2692	
Sequence	5	85	0.3943	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.51	0.25	0.02,0.99	0.0400	*
Ibu. 200mg + Para. 500mg - Placebo	0.21	0.25	-0.28,0.69	0.3978	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.30	0.25	-0.79,0.18		

	LS Mean
Ibu. 200mg + Para. 500mg	3.12
Ibu. 400mg + Para. 1000mg	3.43
Placebo	2.92

Table 14.2.12
SPRID at each follow-up assessment
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(d) 2 hour assessment

(i) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	3.45	1.97	0.00	7.00	3.00	0.21	3.04	3.86
Ibu. 400mg + Para. 1000mg	90	0	3.99	1.97	-1.00	7.00	4.00	0.21	3.58	4.40
Placebo	90	0	3.19	2.14	-1.00	7.00	3.00	0.23	2.74	3.64

(ii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0406	*
Treatment	2	175	0.0039	**
Period	2	175	0.2932	
Sequence	5	85	0.3743	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	0.84	0.25	0.34,1.33	0.0010	**
Ibu. 200mg + Para. 500mg - Placebo	0.31	0.25	-0.19,0.80	0.2221	
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.53	0.25	-1.02,-0.04		

	LS Mean
Ibu. 200mg + Para. 500mg	3.44
Ibu. 400mg + Para. 1000mg	3.98
Placebo	3.14

Table 14.2.12
SPRID at each follow-up assessment
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(e) 4 hour assessment

(i) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	4.09	2.10	0.00	7.00	4.00	0.22	3.65	4.53
Ibu. 400mg + Para. 1000mg	90	0	4.51	1.98	0.00	7.00	5.00	0.21	4.10	4.93
Placebo	90	0	3.47	2.37	0.00	7.00	4.00	0.25	2.97	3.96

(ii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0056	**
Treatment	2	175	0.0006	***
Period	2	175	0.5949	
Sequence	5	85	0.1413	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	1.08	0.28	0.53,1.62	0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.65	0.28	0.11,1.19	0.0188	*
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.42	0.28	-0.97,0.12		

	LS Mean
Ibu. 200mg + Para. 500mg	4.07
Ibu. 400mg + Para. 1000mg	4.50
Placebo	3.42

Table 14.2.12
SPRID at each follow-up assessment
Intention-to-treat population
SPRID = Sum of the change from baseline for the pain intensity and relief scores
Pain measured on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe)
Pain relief measured on a 5-point scale (0=None, 1=A little, 2=Some, 3=A lot, 4=Complete)

(f) 6 hour assessment

(i) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	91	0	4.19	2.16	-1.00	7.00	5.00	0.23	3.74	4.64
Ibu. 400mg + Para. 1000mg	90	0	4.59	1.93	0.00	7.00	5.00	0.20	4.18	4.99
Placebo	90	0	3.38	2.50	-1.00	7.00	4.00	0.26	2.85	3.90

(ii) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	175	0.0003	***
Treatment	2	175	<0.0001	***
Period	2	175	0.6146	
Sequence	5	85	0.1471	

Pairwise Comparisons: parameter estimates	estimate	s.e.	95% CI	p	
Ibu. 400mg + Para. 1000mg - Placebo	1.27	0.27	0.74,1.80	<0.0001	***
Ibu. 200mg + Para. 500mg - Placebo	0.86	0.27	0.33,1.39	0.0015	**
Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	-0.41	0.27	-0.94,0.12		

	LS Mean
Ibu. 200mg + Para. 500mg	4.18
Ibu. 400mg + Para. 1000mg	4.59
Placebo	3.32

Table 14.2.13
Use of rescue medication
Intention-to-treat population

(a) Did the subject use rescue medication

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
Yes	3 (3.3%)	2 (2.2%)	14 (15.6%)
No	88 (96.7%)	88 (97.8%)	76 (84.4%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(b) Pairwise comparisons

Prescott's test	p-value	
Comparison between Ibu. 400mg + Para. 1000mg versus Placebo	0.0009	***

Prescott's test	p-value	
Comparison between Ibu. 200mg + Para. 500mg versus Placebo	0.0154	*

Table 14.2.13
Use of rescue medication
Intention-to-treat population

(c) Frequency distribution of time to use of rescue medication for those subjects reporting

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
90	2 (66.7%)	0 (0.0%)	2 (14.3%)
93	0 (0.0%)	0 (0.0%)	1 (7.1%)
94	0 (0.0%)	0 (0.0%)	1 (7.1%)
95	1 (33.3%)	0 (0.0%)	0 (0.0%)
120	0 (0.0%)	0 (0.0%)	2 (14.3%)
123	0 (0.0%)	1 (50.0%)	1 (7.1%)
125	0 (0.0%)	1 (50.0%)	0 (0.0%)
135	0 (0.0%)	0 (0.0%)	1 (7.1%)
190	0 (0.0%)	0 (0.0%)	1 (7.1%)
200	0 (0.0%)	0 (0.0%)	1 (7.1%)
224	0 (0.0%)	0 (0.0%)	1 (7.1%)
238	0 (0.0%)	0 (0.0%)	1 (7.1%)
255	0 (0.0%)	0 (0.0%)	1 (7.1%)
380	0 (0.0%)	0 (0.0%)	1 (7.1%)
Total	3 (100.0%)	2 (100.0%)	14 (100.0%)

Table 14.2.14
Subjects overall assessment of the study medication as a treatment for pain at six hours post-dose
Intention-to-treat population

(a) Frequency distribution

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
1 Poor	14 (15.4%)	11 (12.2%)	28 (31.1%)
2 Fair	24 (26.4%)	22 (24.4%)	23 (25.6%)
3 Good	26 (28.6%)	31 (34.4%)	17 (18.9%)
4 Very good	19 (20.9%)	18 (20.0%)	19 (21.1%)
5 Excellent	7 (7.7%)	8 (8.9%)	3 (3.3%)
Not recorded	1 (1.1%)	0 (0.0%)	0 (0.0%)
Total	91 (100.0%)	90 (100.0%)	90 (100.0%)

(b) Summary statistics

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	90	1	2.79	1.18	1.00	5.00	3.00	0.12	2.54	3.04
Ibu. 400mg + Para. 1000mg	90	0	2.89	1.14	1.00	5.00	3.00	0.12	2.65	3.13
Placebo	90	0	2.40	1.23	1.00	5.00	2.00	0.13	2.14	2.66

Table 14.2.14
Subjects overall assessment of the study medication as a treatment for pain at six hours post-dose
Intention-to-treat population

(c) Comparison between treatments (frequency distribution)

	Ibu. 200mg + Para. 500mg - Ibu. 400mg + Para. 1000mg	Ibu. 200mg + Para. 500mg - Placebo	Ibu. 400mg + Para. 1000mg - Placebo
-4	4 (4.5%)	1 (1.1%)	0 (0.0%)
-3	4 (4.5%)	2 (2.2%)	0 (0.0%)
-2	2 (2.2%)	5 (5.6%)	5 (5.6%)
-1	19 (21.3%)	13 (14.6%)	21 (23.6%)
0	34 (38.2%)	25 (28.1%)	20 (22.5%)
1	18 (20.2%)	25 (28.1%)	22 (24.7%)
2	5 (5.6%)	11 (12.4%)	13 (14.6%)
3	2 (2.2%)	6 (6.7%)	5 (5.6%)
4	1 (1.1%)	1 (1.1%)	3 (3.4%)
Total	89 (100.0%)	89 (100.0%)	89 (100.0%)

Table 14.2.14
Subjects overall assessment of the study medication as a treatment for pain at six hours post-dose
Intention-to-treat population

(d) Comparison between treatments (summary statistics)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	89	0	-0.15	1.50	-4.00	4.00	0.00	0.16	-0.46	0.17
Ibu. 400mg + Para. 1000mg	89	0	0.40	1.47	-4.00	4.00	0.00	0.16	0.09	0.72
Placebo	89	0	0.49	1.45	-2.00	4.00	0.00	0.15	0.19	0.80

Wilcoxon matched-pairs signed rank test	p-value	
Ibu. 400mg + Para. 1000mg versus Placebo	0.0023	**

Wilcoxon matched-pairs signed rank test	p-value	
Ibu. 200mg + Para. 500mg versus Placebo	0.0091	**

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Table 14.2.15.1
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR0-6h) by age
Intention-to-treat population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary statistics (Age <=20 years)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	47	0	2.17	1.06	0.08	3.83	2.46	0.16	1.86	2.48
Ibu. 400mg + Para. 1000mg	46	0	2.39	0.99	0.00	3.67	2.66	0.15	2.10	2.69
Placebo	46	0	1.92	1.25	0.00	3.75	1.96	0.18	1.55	2.29

(b) Summary statistics (Age >20 years)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	44	0	2.04	1.08	0.00	3.58	2.19	0.16	1.71	2.37
Ibu. 400mg + Para. 1000mg	44	0	2.34	1.00	0.33	3.83	2.35	0.15	2.03	2.64
Placebo	44	0	1.81	1.10	0.00	3.75	1.91	0.17	1.48	2.15

(c) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	173	0.7299	
Treatment	2	173	0.0007	***
Period	2	173	0.4193	
Sequence	5	84	0.0945	
Age	1	173	0.5908	
Treatment-by-Age interaction	2	173	0.9589	

Created by Michael Goulder on 01OCT2009 10:58
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.15.1 TOTPAR6 by age.sas

Table 14.2.15.2
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR0-6h) by length of time since diagnosis
Intention-to-treat population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary statistics (Length of time <=8 years)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	59	0	2.05	1.13	0.00	3.83	2.10	0.15	1.75	2.34
Ibu. 400mg + Para. 1000mg	58	0	2.37	1.00	0.00	3.83	2.56	0.13	2.11	2.64
Placebo	58	0	1.96	1.18	0.00	3.75	1.96	0.15	1.65	2.27

(b) Summary statistics (Length of time >8 years)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	32	0	2.22	0.94	0.46	3.58	2.35	0.17	1.88	2.56
Ibu. 400mg + Para. 1000mg	32	0	2.35	0.99	0.58	3.59	2.52	0.18	1.99	2.71
Placebo	32	0	1.70	1.17	0.00	3.58	1.77	0.21	1.28	2.12

(c) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	173	0.6985	
Treatment	2	173	0.0004	***
Period	2	173	0.3415	
Sequence	5	84	0.0922	
Time since diagnosis	1	173	0.7549	
Treatment-by-Time since diagnosis interaction	2	173	0.2305	

Created by Michael Goulder on 01OCT2009 10:58
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.15.2 TOTPAR6 by duration of dysmenorrhoea.sas

Table 14.2.15.3
Primary efficacy endpoint - Total pain relief over six hours post-dose (TOTPAR0-6h) by BMI at screening
Intention-to-treat population
Pain relief measured on a 5-point scale where 0 = No pain relief, 1 = A little pain relief, 2 = Some pain relief, 3 = A lot of pain relief, 4 = Complete pain relief

(a) Summary statistics (BMI <=22.6 kg/m^2)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	48	0	2.08	1.00	0.17	3.83	2.19	0.14	1.79	2.37
Ibu. 400mg + Para. 1000mg	47	0	2.15	1.01	0.00	3.67	2.33	0.15	1.86	2.45
Placebo	48	0	1.72	1.10	0.00	3.75	1.54	0.16	1.40	2.04

(b) Summary statistics (BMI >22.6 kg/m^2)

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Ibu. 200mg + Para. 500mg	43	0	2.14	1.15	0.00	3.58	2.33	0.18	1.79	2.50
Ibu. 400mg + Para. 1000mg	43	0	2.60	0.93	0.33	3.83	2.88	0.14	2.31	2.88
Placebo	42	0	2.04	1.25	0.00	3.75	2.19	0.19	1.65	2.43

(c) Analysis of Covariance

Source	d.f.	Error d.f.	p	
Baseline pain	1	173	0.5975	
Treatment	2	173	0.0007	***
Period	2	173	0.3428	
Sequence	5	84	0.1214	
BMI	1	173	0.2049	
Treatment-by-BMI interaction	2	173	0.2588	

Created by Michael Goulder on 01OCT2009 10:58
Source: J:\trials\NL0804\Analysis\table programs\Table 14.2.15.3 TOTPAR6 by BMI at screening.sas

Table 14.3.1
Extent of exposure to study medication
Safety set

(i) Whether took study medication

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
Yes	92 (97.9%)	92 (97.9%)	90 (95.7%)
No	2 (2.1%)	2 (2.1%)	4 (4.3%)
Total	94 (100.0%)	94 (100.0%)	94 (100.0%)

(ii) Number of capsules taken

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
0	2 (2.1%)	2 (2.1%)	4 (4.3%)
1	0 (0.0%)	0 (0.0%)	2 (2.1%)
2	92 (97.9%)	92 (97.9%)	88 (93.6%)
Total	94 (100.0%)	94 (100.0%)	94 (100.0%)

Table 14.3.2
Summary of treatment emergent adverse event reporting
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

(a) Did the subject report a treatment emergent adverse event following each of the respective treatments?

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
Yes	11 (12.0%)	7 (7.6%)	9 (10.0%)
No	81 (88.0%)	85 (92.4%)	81 (90.0%)
Total	92 (100.0%)	92 (100.0%)	90 (100.0%)

(b) Pairwise comparisons

Prescott's test	p-value
Comparison between Ibu. 400mg + Para. 1000mg versus Placebo	0.2848

Prescott's test	p-value
Comparison between Ibu. 200mg + Para. 500mg versus Placebo	0.8909

Table 14.3.2
Summary of treatment emergent adverse event reporting
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

(c) Did the subject report a treatment-related adverse event following each of the respective treatments?

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
Yes	3 (3.3%)	2 (2.2%)	2 (2.2%)
No	89 (96.7%)	90 (97.8%)	88 (97.8%)
Total	92 (100.0%)	92 (100.0%)	90 (100.0%)

(d) Pairwise comparisons

Prescott's test	p-value
Comparison between Ibu. 400mg + Para. 1000mg versus Placebo	1.0000

Prescott's test	p-value
Comparison between Ibu. 200mg + Para. 500mg versus Placebo	1.0000

Table 14.3.2
Summary of treatment emergent adverse event reporting
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

(e) Did the subject report a severe adverse event following each of the respective treatments?

	Ibu. 200mg + Para. 500mg	Ibu. 400mg + Para. 1000mg	Placebo
No	92 (100.0%)	92 (100.0%)	90 (100.0%)
Total	92 (100.0%)	92 (100.0%)	90 (100.0%)

Table 14.3.3
MedDRA Summary of treatment emergent adverse events by primary system organ class
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
MedDRA Primary System Organ Class	Number of subjects reporting	Number of reports	Number of subjects reporting	Number of reports	Number of subjects reporting	Number of reports
Any	11 (12.0)	14	7 (7.6)	7	9 (10.0)	13
Gastrointestinal disorders	8 (8.7)	8 (57.1)	1 (1.1)	1 (14.3)	3 (3.3)	4 (30.8)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (7.7)
Immune system disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (14.3)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.1)	1 (7.1)	0 (0.0)	0 (0.0)	1 (1.1)	1 (7.7)
Nervous system disorders	5 (5.4)	5 (35.7)	5 (5.4)	5 (71.4)	7 (7.8)	7 (53.8)

Table 14.3.4
MedDRA Summary of treatment emergent adverse events by primary system organ class and preferred term
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
n	92		92		90	
ANY	11(12.0)	14	7(7.6)	7	9(10.0)	13
GASTROINTESTINAL DISORDERS	8(8.7)	8	1(1.1)	1	3(3.3)	4
Diarrhoea	1(1.1)	1	0(0.0)	0	0(0.0)	0
Dyspepsia	0(0.0)	0	1(1.1)	1	0(0.0)	0
Nausea	6(6.5)	6	0(0.0)	0	3(3.3)	3
Vomiting	1(1.1)	1	0(0.0)	0	1(1.1)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0(0.0)	0	0(0.0)	0	1(1.1)	1
Asthenia	0(0.0)	0	0(0.0)	0	1(1.1)	1
IMMUNE SYSTEM DISORDERS	0(0.0)	0	1(1.1)	1	0(0.0)	0
Seasonal allergy	0(0.0)	0	1(1.1)	1	0(0.0)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1(1.1)	1	0(0.0)	0	1(1.1)	1
Back pain	1(1.1)	1	0(0.0)	0	1(1.1)	1
NERVOUS SYSTEM DISORDERS	5(5.4)	5	5(5.4)	5	7(7.8)	7
Dizziness	3(3.3)	3	0(0.0)	0	3(3.3)	3
Head discomfort	1(1.1)	1	0(0.0)	0	0(0.0)	0

Table 14.3.4
MedDRA Summary of treatment emergent adverse events by primary system organ class and preferred term
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
Headache	1(1.1)	1	4(4.3)	4	4(4.4)	4
Somnolence	0(0.0)	0	1(1.1)	1	0(0.0)	0

Table 14.3.5
MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
Severity Relationship	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
n	92		92		90	
Severity:						
Mild	11(12.0)	13	7(7.6)	7	6(6.7)	7
Moderate	1(1.1)	1	0(0.0)	0	4(4.4)	6
Relationship:						
Probable	0(0.0)	0	1(1.1)	1	0(0.0)	0
Possible	3(3.3)	4	1(1.1)	1	2(2.2)	3
Unlikely	3(3.3)	4	1(1.1)	1	6(6.7)	7
None	5(5.4)	6	4(4.3)	4	2(2.2)	3
GASTROINTESTINAL DISORDERS						
Diarrhoea						

Table 14.3.5
MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
Severity Relationship	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
Severity:						
Mild	1(1.1)	1	0(0.0)	0	0(0.0)	0
Relationship:						
Unlikely	1(1.1)	1	0(0.0)	0	0(0.0)	0
Dyspepsia						
Severity:						
Mild	0(0.0)	0	1(1.1)	1	0(0.0)	0
Relationship:						
Probable	0(0.0)	0	1(1.1)	1	0(0.0)	0
Nausea						
Severity:						
Mild	5(5.4)	5	0(0.0)	0	1(1.1)	1
Moderate	1(1.1)	1	0(0.0)	0	2(2.2)	2
Relationship:						
Possible	3(3.3)	3	0(0.0)	0	1(1.1)	1

Table 14.3.5
MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
Severity Relationship	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
Unlikely	2(2.2)	2	0(0.0)	0	1(1.1)	1
None	1(1.1)	1	0(0.0)	0	1(1.1)	1
Vomiting						
Severity:						
Mild	1(1.1)	1	0(0.0)	0	0(0.0)	0
Moderate	0(0.0)	0	0(0.0)	0	1(1.1)	1
Relationship:						
Possible	0(0.0)	0	0(0.0)	0	1(1.1)	1
None	1(1.1)	1	0(0.0)	0	0(0.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Asthenia						
Severity:						
Moderate	0(0.0)	0	0(0.0)	0	1(1.1)	1
Relationship:						
Unlikely	0(0.0)	0	0(0.0)	0	1(1.1)	1

Table 14.3.5
MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
Severity Relationship	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
IMMUNE SYSTEM DISORDERS						
Seasonal allergy						
Severity:						
Mild	0(0.0)	0	1(1.1)	1	0(0.0)	0
Relationship:						
None	0(0.0)	0	1(1.1)	1	0(0.0)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Back pain						
Severity:						
Mild	1(1.1)	1	0(0.0)	0	1(1.1)	1
Relationship:						
None	1(1.1)	1	0(0.0)	0	1(1.1)	1

Table 14.3.5
MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
Severity Relationship	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
NERVOUS SYSTEM DISORDERS						
Dizziness						
Severity:						
Mild	3(3.3)	3	0(0.0)	0	2(2.2)	2
Moderate	0(0.0)	0	0(0.0)	0	1(1.1)	1
Relationship:						
Possible	1(1.1)	1	0(0.0)	0	1(1.1)	1
Unlikely	1(1.1)	1	0(0.0)	0	2(2.2)	2
None	1(1.1)	1	0(0.0)	0	0(0.0)	0
Head discomfort						
Severity:						
Mild	1(1.1)	1	0(0.0)	0	0(0.0)	0
Relationship:						
None	1(1.1)	1	0(0.0)	0	0(0.0)	0
Headache						

Table 14.3.5
MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication
Safety set
A treatment emergent adverse event is any event commencing within 24 hours of the dose of study medication

MedDRA Primary System Organ Class Preferred Term	Ibu. 200mg + Para. 500mg (N=92)		Ibu. 400mg + Para. 1000mg (N=92)		Placebo (N=90)	
Severity Relationship	No. of Patients	No. of Reports	No. of Patients	No. of Reports	No. of Patients	No. of Reports
Severity:						
Mild	1(1.1)	1	4(4.3)	4	3(3.3)	3
Moderate	0(0.0)	0	0(0.0)	0	1(1.1)	1
Relationship:						
Unlikely	0(0.0)	0	1(1.1)	1	3(3.3)	3
None	1(1.1)	1	3(3.3)	3	1(1.1)	1
Somnolence						
Severity:						
Mild	0(0.0)	0	1(1.1)	1	0(0.0)	0
Relationship:						
Possible	0(0.0)	0	1(1.1)	1	0(0.0)	0

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(a) Haemoglobin (g/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	133.9	8.7	113.0	156.0	134.0	0.9	132.1	135.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	136.4	9.3	118.0	150.0	139.0	2.4	131.3	141.5
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	133.9	8.3	118.0	147.0	133.5	2.2	129.1	138.7
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	133.5	9.1	116.0	145.0	136.5	2.4	128.2	138.8
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	134.4	12.2	113.0	156.0	134.0	3.0	128.1	140.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	132.4	6.3	124.0	143.0	131.0	1.6	128.9	135.9
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	132.8	5.8	123.0	143.0	133.0	1.4	129.7	135.8

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(a) Haemoglobin (g/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	1.1	7.2	-20.0	17.0	2.0	0.8	-0.4	2.6	0.1386	
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	1.4	7.4	-14.0	14.0	1.0	1.9	-2.7	5.5	0.4783	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	3.5	5.5	-4.0	16.0	3.5	1.5	0.3	6.7	0.0340	*
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.9	8.7	-12.0	15.0	3.0	2.3	-3.1	6.9	0.4365	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.2	7.8	-20.0	17.0	1.0	1.9	-3.8	4.3	0.9030	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-1.9	8.0	-17.0	11.0	0.0	2.1	-6.3	2.6	0.3824	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.9	4.7	-7.0	12.0	1.0	1.2	-0.6	4.4	0.1327	

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(b) Red blood cells (10^12/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	4.59	0.32	4.08	5.50	4.58	0.03	4.52	4.66
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	4.59	0.34	4.15	5.21	4.64	0.09	4.40	4.78
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	4.64	0.42	4.08	5.50	4.57	0.11	4.39	4.88
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.56	0.24	4.13	4.99	4.57	0.06	4.42	4.70
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	4.66	0.36	4.21	5.43	4.58	0.09	4.48	4.85
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.49	0.29	4.13	5.21	4.47	0.07	4.33	4.65
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.58	0.24	4.09	4.94	4.60	0.06	4.46	4.71

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(b) Red blood cells (10^12/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.06	0.25	-0.65	0.74	0.09	0.03	0.01	0.11	0.0311	*
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.11	0.29	-0.58	0.56	0.11	0.07	-0.05	0.26	0.1748	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.14	0.22	-0.17	0.74	0.10	0.06	0.01	0.27	0.0321	*
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.09	0.27	-0.37	0.41	0.17	0.07	-0.06	0.24	0.2259	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.00	0.28	-0.65	0.53	0.06	0.07	-0.14	0.14	0.9655	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.04	0.26	-0.50	0.35	-0.01	0.07	-0.19	0.10	0.5569	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.06	0.14	-0.21	0.34	0.07	0.03	-0.02	0.13	0.1180	

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(c) Haematocrit (ratio L/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.42	0.03	0.36	0.50	0.42	0.00	0.41	0.42
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.43	0.03	0.38	0.48	0.43	0.01	0.41	0.44
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.42	0.03	0.36	0.47	0.42	0.01	0.40	0.44
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.42	0.03	0.37	0.45	0.43	0.01	0.40	0.43
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.42	0.04	0.36	0.50	0.41	0.01	0.40	0.44
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.41	0.02	0.39	0.45	0.41	0.00	0.40	0.42
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.41	0.01	0.39	0.44	0.41	0.00	0.40	0.42

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(c) Haematocrit (ratio L/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.00	0.02	-0.05	0.05	0.01	0.00	-0.00	0.01	0.0733	
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.01	0.02	-0.04	0.05	0.00	0.01	-0.01	0.02	0.2877	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.01	0.02	-0.02	0.04	0.01	0.01	0.00	0.03	0.0491	*
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.01	0.03	-0.04	0.04	0.02	0.01	-0.01	0.02	0.2712	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.00	0.03	-0.05	0.05	0.00	0.01	-0.01	0.02	0.7598	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.00	0.03	-0.05	0.04	-0.00	0.01	-0.02	0.01	0.4937	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.00	0.02	-0.04	0.03	0.01	0.00	-0.01	0.01	0.4554	

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(d) Mean cell volume (fL)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	91.1	4.2	79.4	104.8	90.9	0.4	90.2	92.0
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	93.0	3.7	86.6	102.4	92.3	1.0	91.0	95.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	91.3	4.1	85.0	100.6	91.4	1.1	88.9	93.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	91.8	3.3	84.8	96.2	91.7	0.9	89.9	93.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	89.5	3.4	82.1	95.0	90.0	0.8	87.8	91.3
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	91.4	5.6	79.4	104.8	90.6	1.5	88.2	94.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	89.8	4.3	83.3	98.5	88.5	1.1	87.5	92.1

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(d) Mean cell volume (fL) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	-0.2	3.1	-8.2	11.6	-0.3	0.3	-0.8	0.5	0.6171
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.8	3.0	-8.2	2.7	0.1	0.8	-2.5	0.8	0.3115
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.2	3.7	-6.4	7.0	0.6	1.0	-1.9	2.3	0.8436
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.2	3.0	-7.2	5.2	-0.1	0.8	-1.9	1.6	0.8366
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.2	3.1	-4.9	6.8	-0.2	0.7	-1.3	1.8	0.7612
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.1	3.6	-3.2	11.6	-1.1	0.9	-2.1	1.9	0.8990
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.3	2.3	-4.9	3.3	-0.1	0.6	-1.5	0.9	0.5980

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(e) Mean cell haemoglobin (pg)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	29.2	1.4	25.3	33.4	29.2	0.2	28.9	29.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	29.7	1.5	27.7	33.4	29.8	0.4	28.9	30.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	29.0	1.3	25.9	30.7	29.0	0.4	28.2	29.7
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	29.3	1.3	26.6	31.6	29.3	0.4	28.5	30.1
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	28.8	1.3	25.6	30.8	28.8	0.3	28.1	29.4
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	29.6	1.6	25.3	32.7	29.6	0.4	28.7	30.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	29.0	1.5	26.7	32.6	28.8	0.4	28.2	29.8

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(e) Mean cell haemoglobin (pg) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	-0.1	0.7	-2.0	2.2	-0.2	0.1	-0.3	0.0	0.0847
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.3	0.8	-2.0	1.4	-0.4	0.2	-0.8	0.1	0.1220
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.1	0.7	-1.0	1.5	-0.1	0.2	-0.5	0.3	0.5337
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.2	0.7	-1.2	1.3	-0.3	0.2	-0.6	0.2	0.2490
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.0	0.5	-0.7	1.1	-0.1	0.1	-0.3	0.2	0.8235
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.1	0.7	-1.5	0.9	0.0	0.2	-0.5	0.3	0.4992
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.0	0.7	-1.0	2.2	-0.1	0.2	-0.3	0.4	0.7871

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(f) Mean cell haemoglobin concentration (g/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	320.9	10.7	293.0	344.0	320.0	1.1	318.7	323.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	319.8	10.8	305.0	340.0	320.0	2.8	313.8	325.8
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	317.3	7.3	304.0	327.0	319.0	1.9	313.1	321.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	318.9	8.2	310.0	340.0	317.0	2.2	314.2	323.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	321.5	12.4	299.0	343.0	323.0	3.0	315.1	327.9
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	323.8	12.0	293.0	342.0	322.0	3.1	317.2	330.4
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	323.4	11.7	306.0	344.0	320.5	2.9	317.2	329.7

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(f) Mean cell haemoglobin concentration (g/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	-0.6	11.4	-45.0	25.0	0.0	1.2	-3.0	1.7	0.5883
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.8	9.2	-14.0	24.0	-1.0	2.4	-5.9	4.3	0.7416
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-2.0	11.0	-22.0	19.0	-0.5	2.9	-8.4	4.4	0.5084
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-2.1	11.6	-21.0	16.0	0.5	3.1	-8.7	4.6	0.5140
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.8	12.2	-25.0	25.0	-2.0	2.9	-7.0	5.5	0.7986
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.5	14.3	-45.0	15.0	4.0	3.7	-8.4	7.5	0.9013
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.9	10.9	-16.0	21.0	2.5	2.7	-3.9	7.7	0.5021

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(g) White blood cells (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	6.91	1.95	4.20	14.50	6.40	0.20	6.50	7.31
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	6.95	1.54	4.80	9.50	6.50	0.40	6.10	7.81
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	7.38	2.90	4.50	14.50	6.40	0.77	5.70	9.05
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	6.86	1.52	5.30	10.10	6.20	0.41	5.99	7.74
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	6.97	2.00	4.60	12.30	6.80	0.49	5.94	8.00
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	6.84	1.74	4.20	10.70	6.70	0.45	5.88	7.80
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	6.49	1.93	4.30	11.10	6.00	0.48	5.46	7.52

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(g) White blood cells (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	-0.60	1.89	-6.30	4.40	-0.70	0.20	-0.99	-0.20	0.0034	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-1.20	1.42	-3.60	1.50	-1.40	0.37	-1.99	-0.41	0.0055	**
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.84	2.58	-6.30	3.90	-0.55	0.69	-2.33	0.65	0.2428	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.07	1.25	-1.80	2.00	0.15	0.33	-0.79	0.65	0.8336	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.76	2.17	-5.20	3.10	-0.70	0.53	-1.87	0.36	0.1680	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.21	1.94	-4.60	2.80	-0.40	0.50	-1.29	0.86	0.6767	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.46	1.76	-3.40	4.40	-0.80	0.44	-1.40	0.47	0.3096	

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(h) Platelets (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	305.3	64.2	198.0	507.0	298.0	6.7	291.9	318.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	310.7	66.1	211.0	432.0	299.0	17.1	274.1	347.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	309.6	69.6	203.0	406.0	326.0	18.6	269.4	349.8
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	309.5	64.9	198.0	409.0	324.0	17.3	272.0	347.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	340.6	75.8	227.0	507.0	315.0	18.4	301.6	379.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	274.8	48.6	210.0	366.0	276.0	12.5	247.9	301.7
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	283.9	39.8	229.0	365.0	278.0	10.0	262.7	305.2

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(h) Platelets (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	4.9	48.5	-142.0	196.0	5.0	5.1	-5.2	15.0	0.3420
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-27.5	54.4	-142.0	39.0	-20.0	14.0	-57.6	2.6	0.0707
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	20.9	39.2	-19.0	119.0	8.5	10.5	-1.8	43.5	0.0680
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	18.3	37.2	-44.0	108.0	18.0	9.9	-3.2	39.8	0.0889
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	22.1	62.6	-103.0	196.0	19.0	15.2	-10.1	54.3	0.1644
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-3.9	43.7	-87.0	80.0	-8.0	11.3	-28.1	20.4	0.7371
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.8	31.0	-52.0	43.0	2.0	7.8	-17.3	15.8	0.9242

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(i) Neutrophils (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	4.17	1.57	2.00	8.70	3.60	0.16	3.84	4.49
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	4.16	1.44	2.00	7.00	3.90	0.37	3.36	4.96
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	4.39	2.07	2.40	8.70	3.65	0.55	3.20	5.59
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.41	1.36	2.60	6.90	4.15	0.36	3.62	5.19
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	3.89	1.44	2.30	7.80	3.40	0.35	3.16	4.63
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.25	1.60	2.00	7.70	3.70	0.41	3.36	5.13
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	3.98	1.64	2.20	8.20	3.40	0.41	3.11	4.86

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(i) Neutrophils (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	-0.45	1.65	-6.20	3.60	-0.40	0.17	-0.79	-0.10	0.0116	*
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.83	1.25	-2.60	1.50	-1.20	0.32	-1.53	-0.14	0.0217	*
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-1.02	2.26	-6.20	2.70	-0.65	0.60	-2.32	0.28	0.1141	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.06	1.07	-1.40	1.80	0.00	0.29	-0.56	0.68	0.8454	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.72	1.87	-4.80	2.30	-0.50	0.45	-1.69	0.24	0.1311	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.01	1.72	-4.20	2.70	-0.10	0.44	-0.96	0.94	0.9882	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.14	1.39	-2.80	3.60	-0.35	0.35	-0.88	0.60	0.6979	

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(j) Lymphocytes (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	1.98	0.56	1.00	4.30	1.90	0.06	1.87	2.10
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	2.01	0.50	1.50	3.30	1.90	0.13	1.73	2.28
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	2.21	0.85	1.40	4.30	2.00	0.23	1.72	2.70
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.77	0.39	1.10	2.30	1.65	0.10	1.55	2.00
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	2.22	0.64	1.00	3.40	2.20	0.16	1.89	2.55
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.85	0.44	1.20	2.60	1.70	0.11	1.61	2.10
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.83	0.31	1.30	2.30	1.80	0.08	1.66	1.99

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(j) Lymphocytes (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	-0.09	0.40	-0.90	0.80	-0.10	0.04	-0.17	-0.01	0.0287	*
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.19	0.47	-0.90	0.80	-0.20	0.12	-0.45	0.07	0.1309	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.19	0.39	-0.60	0.80	0.20	0.10	-0.03	0.42	0.0880	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.07	0.33	-0.60	0.50	-0.10	0.09	-0.26	0.12	0.4282	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.06	0.41	-0.60	0.60	-0.20	0.10	-0.28	0.15	0.5267	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.14	0.35	-0.80	0.50	-0.10	0.09	-0.33	0.05	0.1416	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.25	0.32	-0.90	0.30	-0.25	0.08	-0.42	-0.08	0.0070	**

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(k) Monocytes (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.36	0.15	0.20	1.10	0.30	0.02	0.33	0.39
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.41	0.23	0.20	1.10	0.40	0.06	0.28	0.54
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.37	0.16	0.20	0.80	0.30	0.04	0.28	0.47
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.35	0.12	0.20	0.60	0.30	0.03	0.28	0.42
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.37	0.14	0.20	0.60	0.30	0.03	0.30	0.44
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.36	0.12	0.20	0.60	0.40	0.03	0.29	0.43
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.31	0.11	0.20	0.60	0.30	0.03	0.25	0.37

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(k) Monocytes (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	-0.05	0.13	-0.40	0.20	0.00	0.01	-0.07	-0.02	0.0009	***
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.07	0.17	-0.40	0.20	0.00	0.04	-0.17	0.02	0.1189	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.03	0.13	-0.30	0.20	0.00	0.04	-0.11	0.05	0.4346	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.05	0.12	-0.30	0.20	-0.05	0.03	-0.12	0.02	0.1506	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.03	0.13	-0.20	0.20	0.00	0.03	-0.09	0.04	0.3513	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.03	0.10	-0.20	0.10	-0.10	0.03	-0.09	0.02	0.2377	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.06	0.11	-0.30	0.20	-0.10	0.03	-0.12	-0.00	0.0457	*

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(I) Basophils (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.07	0.05	0.00	0.20	0.10	0.01	0.06	0.08
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.07	0.05	0.00	0.10	0.10	0.01	0.04	0.09
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.05	0.05	0.00	0.10	0.05	0.01	0.02	0.08
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.08	0.04	0.00	0.10	0.10	0.01	0.05	0.10
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.09	0.04	0.00	0.20	0.10	0.01	0.07	0.12
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.07	0.05	0.00	0.10	0.10	0.01	0.04	0.09
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.07	0.05	0.00	0.10	0.10	0.01	0.04	0.09

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(l) Basophils (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	0.00	0.05	-0.10	0.10	0.00	0.01	-0.01	0.01	0.5346
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.01	0.06	-0.10	0.10	0.00	0.02	-0.05	0.02	0.4332
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.01	0.04	-0.10	0.00	0.00	0.01	-0.04	0.01	0.1648
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.02	0.04	0.00	0.10	0.00	0.01	-0.00	0.05	0.0823
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.01	0.04	-0.10	0.10	0.00	0.01	-0.03	0.02	0.5795
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.01	0.04	0.00	0.10	0.00	0.01	-0.01	0.03	0.1643
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.02	0.07	-0.10	0.10	0.00	0.02	-0.02	0.05	0.2702

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(m) Eosinophils (10^9/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.17	0.13	0.00	0.70	0.10	0.01	0.14	0.20
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.17	0.12	0.10	0.50	0.10	0.03	0.11	0.24
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.19	0.14	0.10	0.60	0.15	0.04	0.11	0.27
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.13	0.07	0.00	0.30	0.10	0.02	0.09	0.17
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.20	0.17	0.10	0.70	0.10	0.04	0.11	0.29
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.15	0.10	0.00	0.30	0.10	0.03	0.10	0.21
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.17	0.13	0.00	0.50	0.10	0.03	0.10	0.24

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(m) Eosinophils (10^9/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	-0.04	0.14	-0.80	0.40	0.00	0.02	-0.07	-0.01	0.0185	*
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.07	0.15	-0.40	0.10	0.00	0.04	-0.16	0.01	0.0853	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.00	0.15	-0.30	0.40	0.00	0.04	-0.08	0.08	1.0000	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.05	0.07	-0.20	0.00	0.00	0.02	-0.09	-0.01	0.0130	*
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.02	0.12	-0.20	0.40	0.00	0.03	-0.05	0.08	0.5645	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.09	0.22	-0.80	0.10	0.00	0.06	-0.21	0.04	0.1493	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.03	0.10	-0.20	0.20	0.00	0.03	-0.09	0.02	0.2369	

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(n) PT (secs)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	14.1	0.8	11.8	16.6	14.1	0.1	13.9	14.3
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	13.9	0.7	12.6	15.0	14.1	0.2	13.5	14.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	13.7	0.9	12.1	15.3	13.9	0.2	13.2	14.2
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	14.0	0.9	11.8	15.3	14.1	0.2	13.5	14.6
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	14.4	0.8	13.2	15.9	14.3	0.2	14.0	14.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	14.1	1.0	12.9	16.6	13.9	0.2	13.6	14.7
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	14.3	0.6	13.5	15.8	14.4	0.1	14.0	14.6

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(n) PT (secs) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	90	1	0.0	0.8	-3.7	2.1	0.1	0.1	-0.1	0.2	0.7683
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.2	0.5	-0.9	0.6	-0.4	0.1	-0.5	0.1	0.1286
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.1	0.7	-0.9	1.5	0.1	0.2	-0.3	0.5	0.6571
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.1	0.8	-1.8	0.9	0.2	0.2	-0.4	0.5	0.8114
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	16	1	0.0	0.8	-1.2	1.7	0.0	0.2	-0.4	0.4	0.8987
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.1	0.9	-1.3	2.1	0.0	0.2	-0.4	0.6	0.7241
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.1	1.2	-3.7	1.4	0.3	0.3	-0.5	0.7	0.7209

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(o) APTT (secs)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	30.9	3.6	17.5	42.6	30.8	0.4	30.1	31.6
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	29.3	4.6	17.5	35.5	29.5	1.2	26.8	31.9
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	31.1	3.1	27.0	38.7	30.9	0.8	29.3	32.9
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	31.5	3.5	24.8	39.1	32.2	0.9	29.5	33.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	32.1	3.2	25.0	37.9	33.0	0.8	30.5	33.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	31.4	4.0	26.8	42.6	30.4	1.0	29.2	33.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	29.7	2.4	25.3	33.1	30.1	0.6	28.4	30.9

Table 14.3.6
Change from baseline for haematology variables at post-study follow-up
Safety set

(o) APTT (secs) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	90	1	-0.2	2.9	-17.3	5.2	0.5	0.3	-0.8	0.4	0.4802
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-1.8	5.0	-17.3	3.1	-0.5	1.3	-4.5	1.0	0.1927
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.0	1.8	-3.6	2.7	-0.5	0.5	-1.1	1.0	0.9655
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.9	2.1	-4.1	1.8	-0.3	0.6	-2.1	0.3	0.1474
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	16	1	0.8	2.1	-4.1	4.7	0.7	0.5	-0.3	1.9	0.1440
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.2	2.6	-7.9	3.6	0.6	0.7	-1.3	1.6	0.8088
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.2	2.4	-3.5	5.2	0.5	0.6	-1.0	1.5	0.7093

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(a) Sodium (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	141.0	1.7	135.4	146.9	141.0	0.2	140.6	141.3
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	140.9	1.2	138.9	142.4	141.0	0.3	140.3	141.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	140.3	1.7	135.4	142.5	140.8	0.5	139.3	141.3
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	141.3	1.9	138.1	144.8	141.5	0.5	140.2	142.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	140.9	1.3	137.8	142.8	140.9	0.3	140.2	141.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	142.0	2.1	136.8	146.9	141.8	0.5	140.8	143.1
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	140.6	1.6	137.8	145.0	140.9	0.4	139.7	141.4

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(a) Sodium (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	-0.2	1.9	-5.9	4.3	0.0	0.2	-0.6	0.2	0.4197
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.2	1.7	-3.2	2.8	-0.2	0.4	-1.2	0.7	0.6140
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.1	1.7	-2.8	2.2	-0.0	0.5	-1.1	0.9	0.7758
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.0	2.0	-4.3	2.4	0.6	0.5	-1.1	1.2	0.9383
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.3	2.1	-5.9	2.4	-0.2	0.5	-1.4	0.7	0.5021
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.4	2.2	-4.3	4.3	0.2	0.6	-0.8	1.7	0.4491
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.7	1.8	-5.2	1.3	-0.6	0.5	-1.7	0.3	0.1543

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(b) Potassium (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	4.12	0.21	3.62	4.75	4.13	0.02	4.07	4.16
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	4.17	0.23	3.78	4.61	4.15	0.06	4.04	4.30
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	4.10	0.21	3.81	4.47	4.03	0.06	3.98	4.22
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.07	0.27	3.62	4.75	4.09	0.07	3.92	4.23
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	4.17	0.21	3.69	4.51	4.19	0.05	4.06	4.27
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.12	0.24	3.83	4.64	4.10	0.06	3.98	4.25
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.08	0.14	3.85	4.27	4.08	0.03	4.01	4.15

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(b) Potassium (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	-0.06	0.29	-0.66	0.61	-0.06	0.03	-0.12	-0.01	0.0337	*
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.03	0.41	-0.58	0.51	-0.01	0.11	-0.25	0.20	0.8087	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.08	0.17	-0.30	0.23	-0.07	0.04	-0.17	0.02	0.1049	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.10	0.30	-0.65	0.41	-0.10	0.08	-0.27	0.07	0.2407	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.05	0.29	-0.64	0.61	-0.04	0.07	-0.20	0.10	0.4725	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.03	0.24	-0.28	0.52	-0.04	0.06	-0.10	0.16	0.6523	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.17	0.27	-0.66	0.30	-0.19	0.07	-0.31	-0.02	0.0298	*

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(c) Urea (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	4.22	1.01	1.90	6.20	4.10	0.11	4.01	4.43
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	4.01	0.76	3.00	5.60	4.00	0.20	3.59	4.43
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	4.26	1.10	2.50	6.20	4.00	0.29	3.62	4.89
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.48	0.98	2.70	5.70	4.65	0.26	3.91	5.04
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	4.44	1.19	1.90	6.20	4.50	0.29	3.83	5.06
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.24	1.05	2.50	5.80	4.10	0.27	3.66	4.82
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	3.90	0.95	2.70	6.20	3.75	0.24	3.39	4.41

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(c) Urea (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	0.03	0.98	-2.90	2.90	0.00	0.10	-0.17	0.24	0.7563
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.13	0.90	-1.20	2.20	0.00	0.23	-0.37	0.63	0.5960
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.16	1.13	-1.80	2.90	0.25	0.30	-0.49	0.82	0.5958
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.09	0.83	-1.50	1.00	-0.10	0.22	-0.57	0.39	0.6829
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.24	1.24	-2.90	1.80	0.20	0.30	-0.40	0.87	0.4443
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.05	0.93	-1.10	1.90	-0.20	0.24	-0.46	0.57	0.8281
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.30	0.78	-1.70	0.80	0.00	0.19	-0.71	0.11	0.1426

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(d) Creatinine (umol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	66.2	8.8	42.8	90.4	65.5	0.9	64.4	68.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	66.1	6.6	55.9	76.7	66.1	1.7	62.5	69.7
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	65.9	12.7	53.7	90.4	60.9	3.4	58.6	73.2
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	68.8	8.2	55.7	83.0	67.7	2.2	64.1	73.6
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	67.6	9.9	42.8	84.8	67.4	2.4	62.5	72.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	64.5	9.0	43.7	78.0	63.3	2.3	59.5	69.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	64.5	6.0	58.7	80.8	62.7	1.5	61.3	67.7

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(d) Creatinine (umol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	2.4	6.8	-9.5	21.0	0.0	0.7	1.0	3.8	0.0010	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	2.1	6.0	-7.5	11.1	-0.3	1.5	-1.2	5.4	0.1995	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	5.1	9.2	-6.2	21.0	3.8	2.5	-0.2	10.4	0.0583	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	2.9	6.4	-5.9	12.2	3.1	1.7	-0.8	6.6	0.1140	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	2.1	7.8	-9.5	16.0	0.0	1.9	-1.9	6.1	0.2753	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.6	4.7	-5.4	10.8	-1.3	1.2	-2.0	3.2	0.6367	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.9	5.9	-5.1	13.1	-0.5	1.5	-1.2	5.0	0.2148	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(e) Uric acid (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.26	0.04	0.09	0.34	0.26	0.00	0.25	0.26
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.24	0.05	0.09	0.31	0.25	0.01	0.21	0.27
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.25	0.04	0.16	0.34	0.26	0.01	0.22	0.28
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.28	0.04	0.21	0.34	0.28	0.01	0.26	0.30
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.26	0.03	0.22	0.31	0.26	0.01	0.25	0.28
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.27	0.04	0.20	0.34	0.28	0.01	0.24	0.29
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.24	0.05	0.15	0.32	0.25	0.01	0.21	0.27

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(e) Uric acid (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.01	0.04	-0.09	0.09	0.01	0.00	-0.00	0.02	0.0519	
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.00	0.04	-0.04	0.09	0.00	0.01	-0.02	0.02	0.8430	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.02	0.04	-0.05	0.08	0.02	0.01	-0.01	0.04	0.1565	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.02	0.03	-0.03	0.07	0.03	0.01	0.00	0.04	0.0318	*
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.01	0.02	-0.03	0.05	0.01	0.01	-0.00	0.02	0.2156	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.01	0.05	-0.09	0.09	-0.01	0.01	-0.03	0.02	0.5613	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.01	0.04	-0.05	0.08	0.00	0.01	-0.01	0.03	0.4137	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(f) Glucose (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	4.85	0.70	3.20	7.70	4.80	0.07	4.70	4.99
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	4.69	0.67	3.20	5.90	4.80	0.17	4.32	5.06
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	5.21	0.87	4.10	7.70	5.10	0.23	4.71	5.72
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.70	0.65	3.40	5.80	4.70	0.17	4.33	5.07
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	4.84	0.66	3.60	6.40	4.80	0.16	4.50	5.18
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	5.01	0.72	3.90	6.20	4.90	0.18	4.62	5.41
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.64	0.59	3.60	6.30	4.60	0.15	4.32	4.95

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(f) Glucose (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	-0.02	0.92	-1.80	2.80	0.00	0.10	-0.21	0.18	0.8647
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.04	0.65	-1.20	1.00	-0.10	0.17	-0.40	0.32	0.8139
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.14	1.23	-1.70	2.80	-0.20	0.33	-0.58	0.85	0.6874
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.12	0.97	-1.30	1.50	-0.00	0.26	-0.68	0.44	0.6477
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.18	0.91	-1.50	2.30	0.10	0.22	-0.29	0.65	0.4225
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.01	0.86	-1.50	1.30	0.30	0.22	-0.46	0.49	0.9530
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.28	0.91	-1.80	2.00	-0.20	0.23	-0.76	0.21	0.2445

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(g) Calcium (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	2.36	0.07	2.16	2.50	2.37	0.01	2.35	2.38
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	2.38	0.06	2.31	2.50	2.38	0.01	2.35	2.41
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	2.36	0.06	2.28	2.49	2.34	0.02	2.32	2.40
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	2.35	0.07	2.26	2.48	2.35	0.02	2.32	2.39
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	2.34	0.06	2.23	2.42	2.36	0.01	2.31	2.37
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	2.35	0.07	2.26	2.49	2.33	0.02	2.31	2.39
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	2.40	0.07	2.16	2.48	2.41	0.02	2.36	2.43

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(g) Calcium (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.02	0.07	-0.21	0.17	0.03	0.01	0.01	0.04	0.0096	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.03	0.08	-0.09	0.17	0.03	0.02	-0.01	0.07	0.1849	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.02	0.08	-0.11	0.13	0.04	0.02	-0.02	0.07	0.3265	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.02	0.05	-0.07	0.13	0.03	0.01	-0.01	0.05	0.1461	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.02	0.05	-0.07	0.14	0.02	0.01	-0.01	0.05	0.1357	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.01	0.09	-0.21	0.11	-0.01	0.02	-0.06	0.04	0.5925	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.04	0.08	-0.10	0.17	0.03	0.02	-0.00	0.08	0.0539	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(h) Inorganic phosphorous (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	1.18	0.16	0.89	1.63	1.15	0.02	1.15	1.21
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	1.21	0.21	0.94	1.63	1.13	0.06	1.09	1.33
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	1.11	0.12	0.89	1.32	1.07	0.03	1.04	1.18
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.24	0.13	1.08	1.42	1.23	0.03	1.16	1.32
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	1.22	0.16	0.94	1.49	1.28	0.04	1.14	1.30
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.13	0.16	0.89	1.41	1.09	0.04	1.04	1.22
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.17	0.14	0.92	1.48	1.15	0.04	1.09	1.24

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(h) Inorganic phosphorous (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.06	0.20	-0.44	0.74	0.06	0.02	0.02	0.10	0.0058	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.06	0.21	-0.23	0.39	0.07	0.06	-0.06	0.18	0.2900	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.10	0.16	-0.25	0.29	0.09	0.04	0.01	0.19	0.0375	*
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.12	0.24	-0.22	0.74	0.09	0.07	-0.02	0.26	0.0965	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.05	0.21	-0.36	0.38	0.04	0.05	-0.06	0.15	0.3493	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.00	0.20	-0.44	0.26	-0.01	0.05	-0.11	0.12	0.9604	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.03	0.16	-0.33	0.31	0.02	0.04	-0.05	0.12	0.4132	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(i) Total bilirubin (umol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	7.8	4.1	2.6	22.5	7.2	0.4	6.9	8.6
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	6.8	2.0	3.7	9.7	6.9	0.5	5.7	7.9
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	6.3	2.2	2.7	11.2	6.6	0.6	5.1	7.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	9.7	6.2	3.3	22.5	7.3	1.7	6.1	13.3
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	8.7	4.6	2.6	19.2	8.2	1.1	6.3	11.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	6.6	3.5	2.9	13.9	6.4	0.9	4.7	8.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	8.4	4.2	3.6	18.2	7.6	1.0	6.2	10.6

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(i) Total bilirubin (umol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.3	3.3	-10.4	7.8	-0.1	0.3	-0.4	1.0	0.3918	
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.2	3.1	-4.7	6.2	-0.7	0.8	-1.5	1.9	0.8062	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.5	3.2	-5.7	6.8	-0.8	0.8	-2.4	1.3	0.5313	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	2.0	2.2	-0.8	6.2	2.1	0.6	0.7	3.2	0.0054	**
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.1	3.8	-10.4	5.7	1.1	0.9	-1.8	2.0	0.9240	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-1.4	3.3	-5.6	7.3	-2.1	0.9	-3.2	0.5	0.1352	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.5	3.2	-4.3	7.8	1.6	0.8	-0.3	3.2	0.0895	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(j) Alkaline phosphatase (IU/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	152.0	36.3	90.4	263.6	147.9	3.8	144.4	159.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	159.6	38.7	103.4	241.3	166.8	10.0	138.1	181.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	166.1	44.0	102.9	243.5	158.9	11.8	140.7	191.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	156.9	31.0	90.4	216.4	156.6	8.3	139.0	174.8
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	143.4	30.5	97.6	193.2	151.7	7.4	127.7	159.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	156.6	43.4	105.5	263.6	139.8	11.2	132.5	180.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	133.0	22.4	98.0	175.5	133.0	5.6	121.0	144.9

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(j) Alkaline phosphatase (IU/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	2.0	24.2	-51.8	52.9	2.7	2.5	-3.0	7.1	0.4269
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-4.8	24.1	-44.7	50.8	-9.2	6.2	-18.2	8.5	0.4515
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	8.2	27.9	-51.8	52.9	15.1	7.4	-7.9	24.3	0.2903
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	10.7	23.8	-43.2	46.2	12.5	6.4	-3.0	24.5	0.1160
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	3.3	18.7	-35.4	32.0	1.3	4.5	-6.3	13.0	0.4718
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-4.2	30.1	-49.8	48.1	-12.7	7.8	-20.9	12.4	0.5958
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.1	19.8	-32.0	34.1	3.2	4.9	-10.7	10.4	0.9792

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(k) Alanine transaminase (IU/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	18.1	6.5	8.9	46.7	16.8	0.7	16.8	19.5
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	18.3	6.0	10.1	30.3	16.1	1.6	15.0	21.6
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	19.0	9.3	8.9	46.7	17.2	2.5	13.6	24.4
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	17.4	4.4	10.6	26.3	17.1	1.2	14.9	20.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	19.2	6.2	11.3	34.5	18.1	1.5	16.0	22.3
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	17.3	6.8	9.1	34.3	16.0	1.8	13.5	21.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	17.5	6.5	10.2	32.5	15.5	1.6	14.0	21.0

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(k) Alanine transaminase (IU/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	0.3	8.2	-40.3	23.6	1.1	0.9	-1.4	2.0	0.7272
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-2.7	11.0	-36.7	9.4	0.1	2.8	-8.8	3.4	0.3573
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	1.9	8.9	-15.4	23.6	1.3	2.4	-3.2	7.0	0.4363
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.5	3.6	-5.4	6.3	2.6	1.0	-0.6	3.6	0.1445
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	1.5	6.9	-15.4	15.0	1.1	1.7	-2.1	5.0	0.3917
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.4	4.3	-9.1	10.5	0.4	1.1	-2.0	2.7	0.7507
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-0.6	11.3	-40.3	14.4	1.0	2.8	-6.7	5.4	0.8282

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(l) Aspartate transaminase (IU/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	21.5	5.1	6.1	41.7	21.3	0.5	20.4	22.6
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	22.3	7.0	15.0	41.7	21.0	1.8	18.5	26.2
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	23.6	5.8	14.7	39.6	22.2	1.6	20.2	26.9
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	22.1	4.5	15.7	29.4	21.4	1.2	19.6	24.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	20.9	3.7	13.2	29.1	21.5	0.9	19.0	22.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	21.1	4.7	14.4	31.2	21.5	1.2	18.5	23.7
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	19.3	4.4	6.1	25.9	20.5	1.1	16.9	21.7

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(l) Aspartate transaminase (IU/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	1.1	5.8	-13.5	27.0	1.3	0.6	-0.1	2.3	0.0742
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.4	6.2	-12.6	17.4	0.3	1.6	-3.0	3.9	0.7898
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	4.3	8.4	-7.2	27.0	2.9	2.2	-0.5	9.2	0.0748
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	2.2	4.5	-9.4	9.5	2.2	1.2	-0.4	4.8	0.0917
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-0.0	3.5	-7.2	7.0	0.8	0.8	-1.8	1.8	0.9619
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.4	4.6	-5.2	8.9	1.4	1.2	-1.2	3.9	0.2711
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-1.1	6.0	-13.5	8.7	-0.3	1.5	-4.3	2.1	0.4673

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(m) Gamma glutamyl transferase (IU/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	14.3	6.8	5.1	47.6	13.0	0.7	12.9	15.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	14.3	4.4	8.5	22.3	13.5	1.1	11.8	16.7
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	16.8	11.7	7.3	47.6	12.9	3.1	10.0	23.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	13.9	5.3	6.4	24.3	13.0	1.4	10.9	17.0
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	14.3	7.0	5.5	29.1	13.0	1.7	10.7	17.9
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	14.0	4.8	5.1	22.3	13.7	1.2	11.4	16.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	12.9	5.7	6.2	30.7	11.1	1.4	9.9	16.0

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(m) Gamma glutamyl transferase (IU/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.2	6.5	-33.1	15.5	0.4	0.7	-1.1	1.6	0.7202	
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.9	9.2	-32.7	6.3	-0.1	2.4	-6.0	4.2	0.7183	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	-0.8	10.0	-33.1	8.9	0.7	2.7	-6.6	4.9	0.7665	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.5	2.6	-3.3	7.6	1.2	0.7	0.1	3.0	0.0425	*
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.4	6.6	-13.0	15.5	0.1	1.6	-3.0	3.7	0.8160	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.3	4.9	-9.3	10.3	-1.1	1.3	-3.0	2.4	0.8067	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.5	3.1	-1.5	10.7	0.5	0.8	-0.2	3.1	0.0786	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(n) Alpha-hydroxybutyrate dehydrogenase (IU/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	126.8	23.5	62.5	232.9	126.4	2.5	121.9	131.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	127.7	24.9	100.9	205.0	126.4	6.4	113.9	141.5
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	130.1	15.9	98.0	152.4	135.5	4.3	120.9	139.3
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	124.6	18.2	97.4	166.6	123.4	4.9	114.1	135.1
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	128.0	24.8	97.0	191.8	124.8	6.0	115.3	140.8
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	130.9	38.1	62.5	232.9	127.7	9.8	109.7	152.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	120.1	11.4	102.0	139.9	123.1	2.8	114.0	126.2

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(n) Alpha-hydroxybutyrate dehydrogenase (IU/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test
Total	91	0	3.0	23.6	-145.2	88.1	3.0	2.5	-2.0	7.9	0.2351
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	2.0	13.2	-14.4	39.0	0.7	3.4	-5.3	9.3	0.5720
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	11.4	20.5	-23.6	55.2	16.2	5.5	-0.4	23.2	0.0566
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-6.3	41.1	-145.2	25.0	3.8	11.0	-30.1	17.4	0.5735
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	5.7	13.6	-12.9	35.3	4.3	3.3	-1.3	12.7	0.1037
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	7.9	26.0	-14.9	88.1	1.6	6.7	-6.5	22.3	0.2586
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-2.9	17.8	-36.9	28.6	3.0	4.4	-12.4	6.5	0.5192

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(o) Creatinine kinase (IU/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	116.5	99.1	37.6	806.5	89.5	10.4	95.8	137.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	153.0	193.7	45.9	806.5	89.5	50.0	45.8	260.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	136.2	97.6	52.6	443.1	117.3	26.1	79.9	192.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	112.0	67.9	54.5	322.5	92.4	18.1	72.8	151.2
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	102.8	55.2	37.6	241.4	87.1	13.4	74.4	131.2
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	113.2	72.5	41.8	278.5	73.6	18.7	73.1	153.4
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	86.4	23.9	43.2	141.4	81.5	6.0	73.7	99.1

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(o) Creatinine kinase (IU/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	2.4	117.0	-376.1	678.8	-0.1	12.3	-22.0	26.8	0.8459	
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	42.2	196.6	-223.4	678.8	-0.1	50.8	-66.7	151.0	0.4201	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	37.8	117.4	-84.7	387.0	21.4	31.4	-30.0	105.6	0.2497	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-0.0	70.4	-195.9	116.5	4.8	18.8	-40.7	40.6	0.9982	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	-5.9	52.4	-82.5	129.7	-1.0	12.7	-32.9	21.0	0.6466	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	17.6	82.5	-125.1	203.5	1.3	21.3	-28.1	63.3	0.4224	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	-69.2	109.5	-376.1	11.1	-22.8	27.4	-127.5	-10.8	0.0232	*

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(p) Total protein (g/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	76.4	3.0	71.0	84.9	76.6	0.3	75.7	77.0
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	77.1	2.3	73.0	81.4	77.1	0.6	75.8	78.4
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	77.0	3.9	72.5	84.9	75.9	1.0	74.8	79.2
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	76.0	2.7	71.7	79.6	75.5	0.7	74.4	77.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	76.4	2.5	71.7	81.8	76.8	0.6	75.1	77.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	75.7	3.4	71.3	84.9	75.0	0.9	73.8	77.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	76.2	3.5	71.0	83.4	75.9	0.9	74.3	78.0

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(p) Total protein (g/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	1.0	3.3	-8.7	7.6	1.0	0.3	0.3	1.7	0.0068	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.6	3.8	-7.4	7.5	1.2	1.0	-1.6	2.7	0.5817	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	1.8	3.1	-5.6	5.9	2.3	0.8	0.1	3.6	0.0423	*
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.4	2.6	-2.1	5.3	1.0	0.7	-0.1	2.9	0.0708	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.8	2.7	-2.5	6.7	0.3	0.7	-0.6	2.2	0.2624	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.1	3.6	-7.0	5.2	0.1	0.9	-2.1	1.9	0.9000	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.4	3.9	-8.7	7.6	2.1	1.0	-0.7	3.5	0.1706	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(q) Albumin (g/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	46.5	2.0	41.5	51.3	46.5	0.2	46.0	46.9
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	46.5	1.8	42.3	49.4	46.5	0.5	45.5	47.5
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	46.1	2.6	43.2	51.3	45.3	0.7	44.6	47.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	46.9	1.9	44.2	49.6	47.1	0.5	45.8	47.9
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	46.6	1.9	43.4	49.7	46.4	0.5	45.6	47.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	46.2	2.1	41.5	50.0	45.8	0.6	45.0	47.3
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	46.6	2.1	42.9	49.7	47.5	0.5	45.5	47.7

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(q) Albumin (g/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.8	2.3	-5.8	4.7	0.8	0.2	0.3	1.2	0.0019	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.8	2.1	-2.5	4.4	1.4	0.5	-0.4	1.9	0.1673	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	1.4	1.6	-1.3	3.8	1.6	0.4	0.4	2.3	0.0067	**
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.3	2.1	-2.9	3.5	0.2	0.6	-0.9	1.6	0.5537	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	1.0	1.9	-3.0	3.7	1.4	0.5	-0.0	1.9	0.0512	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.2	3.3	-5.8	4.7	-0.3	0.8	-2.0	1.6	0.7855	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.3	2.2	-3.7	4.6	1.7	0.6	0.1	2.5	0.0374	*

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(r) Cholesterol (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	4.61	0.85	2.81	7.16	4.56	0.09	4.43	4.79
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	4.71	0.65	3.94	5.99	4.59	0.17	4.35	5.07
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	4.85	1.01	3.29	7.16	4.87	0.27	4.27	5.44
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	4.31	0.77	2.81	5.59	4.48	0.20	3.87	4.75
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	4.61	1.01	3.18	6.71	4.44	0.25	4.09	5.13
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.60	0.98	3.07	6.84	4.41	0.25	4.06	5.14
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	4.58	0.59	3.80	5.48	4.65	0.15	4.26	4.89

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(r) Cholesterol (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.23	0.52	-1.08	1.35	0.22	0.05	0.13	0.34	0.0000	***
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.21	0.56	-0.77	1.29	0.40	0.14	-0.10	0.52	0.1713	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.35	0.50	-0.50	1.35	0.35	0.13	0.06	0.64	0.0201	*
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.32	0.57	-0.72	0.95	0.52	0.15	-0.01	0.65	0.0568	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.29	0.47	-0.64	0.96	0.29	0.11	0.05	0.53	0.0226	*
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.03	0.50	-1.08	0.90	0.11	0.13	-0.31	0.25	0.8360	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.27	0.52	-0.64	1.27	0.26	0.13	-0.01	0.55	0.0576	

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(s) Triglycerides (mmol/L)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	1.29	0.83	0.40	5.10	1.10	0.09	1.12	1.47
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	1.27	0.70	0.50	2.90	1.10	0.18	0.89	1.66
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	1.51	0.94	0.60	4.10	1.10	0.25	0.97	2.06
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.02	0.34	0.50	1.50	1.15	0.09	0.82	1.22
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	1.36	0.96	0.60	4.30	1.00	0.23	0.86	1.85
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	1.34	0.73	0.40	3.30	1.10	0.19	0.93	1.75
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.24	1.09	0.50	5.10	0.90	0.27	0.66	1.82

Table 14.3.7
Change from baseline for biochemistry variables at post-study follow-up
Safety set

(s) Triglycerides (mmol/L) (Cont.)

(ii) Change from baseline

	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean	p-value from paired t-test	
Total	91	0	0.23	0.70	-0.90	3.90	0.00	0.07	0.08	0.37	0.0025	**
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.23	0.55	-0.70	1.30	0.00	0.14	-0.08	0.53	0.1317	
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.41	0.90	-0.50	3.00	0.30	0.24	-0.11	0.94	0.1100	
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.09	0.21	-0.20	0.50	0.05	0.06	-0.03	0.22	0.1267	
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.24	0.70	-0.50	2.10	0.00	0.17	-0.12	0.60	0.1726	
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	0.18	0.44	-0.40	1.40	0.10	0.11	-0.06	0.42	0.1323	
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.22	1.08	-0.90	3.90	-0.05	0.27	-0.36	0.80	0.4321	

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(a) Haemoglobin (g/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	1 (7.1%)	3 (21.4%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	6 (6.6%)
Within	14 (93.3%)	13 (92.9%)	11 (78.6%)	14 (82.4%)	15 (100.0%)	16 (100.0%)	83 (91.2%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(a) Haemoglobin (g/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Below	1 (6.7%)	1 (7.1%)	3 (21.4%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	6 (6.6%)
Within --> Within	13 (86.7%)	13 (92.9%)	11 (78.6%)	14 (82.4%)	15 (100.0%)	16 (100.0%)	82 (90.1%)
Within --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(b) Red blood cells (10^12/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	14 (87.5%)	87 (95.6%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	12 (85.7%)	14 (100.0%)	15 (88.2%)	14 (93.3%)	16 (100.0%)	84 (92.3%)
Above	2 (13.3%)	2 (14.3%)	0 (0.0%)	2 (11.8%)	1 (6.7%)	0 (0.0%)	7 (7.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(b) Red blood cells (10^12/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
Within --> Within	12 (80.0%)	12 (85.7%)	14 (100.0%)	15 (88.2%)	14 (93.3%)	14 (87.5%)	81 (89.0%)
Within --> Above	2 (13.3%)	1 (7.1%)	0 (0.0%)	2 (11.8%)	1 (6.7%)	0 (0.0%)	6 (6.6%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (2.2%)
Above --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(c) Haematocrit (ratio L/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	14 (100.0%)	14 (100.0%)	13 (76.5%)	15 (100.0%)	15 (93.8%)	85 (93.4%)
Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	4 (23.5%)	0 (0.0%)	1 (6.3%)	6 (6.6%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Within	13 (86.7%)	10 (71.4%)	14 (100.0%)	12 (70.6%)	15 (100.0%)	16 (100.0%)	80 (87.9%)
Above	2 (13.3%)	3 (21.4%)	0 (0.0%)	4 (23.5%)	0 (0.0%)	0 (0.0%)	9 (9.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(c) Haematocrit (ratio L/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Within --> Within	12 (80.0%)	10 (71.4%)	14 (100.0%)	10 (58.8%)	15 (100.0%)	15 (93.8%)	76 (83.5%)
Within --> Above	2 (13.3%)	3 (21.4%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	7 (7.7%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	1 (6.3%)	4 (4.4%)
Above --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(d) Mean cell volume (fL)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	13 (92.9%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	14 (93.3%)	16 (100.0%)	88 (96.7%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(d) Mean cell volume (fL) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	14 (93.3%)	13 (92.9%)	13 (92.9%)	17 (100.0%)	14 (93.3%)	16 (100.0%)	87 (95.6%)
Within --> Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Above --> Within	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(e) Mean cell haemoglobin (pg)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	88 (96.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	87 (95.6%)
Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(e) Mean cell haemoglobin (pg) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Within --> Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	87 (95.6%)
Within --> Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(f) Mean cell haemoglobin concentration (g/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	7 (46.7%)	6 (42.9%)	7 (50.0%)	8 (47.1%)	5 (33.3%)	6 (37.5%)	39 (42.9%)
Within	8 (53.3%)	8 (57.1%)	7 (50.0%)	9 (52.9%)	10 (66.7%)	10 (62.5%)	52 (57.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	7 (46.7%)	8 (57.1%)	9 (64.3%)	8 (47.1%)	6 (40.0%)	7 (43.8%)	45 (49.5%)
Within	8 (53.3%)	6 (42.9%)	5 (35.7%)	9 (52.9%)	9 (60.0%)	9 (56.3%)	46 (50.5%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(f) Mean cell haemoglobin concentration (g/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	5 (33.3%)	3 (21.4%)	5 (35.7%)	5 (29.4%)	3 (20.0%)	3 (18.8%)	24 (26.4%)
Below --> Within	2 (13.3%)	3 (21.4%)	2 (14.3%)	3 (17.6%)	2 (13.3%)	3 (18.8%)	15 (16.5%)
Within --> Below	2 (13.3%)	5 (35.7%)	4 (28.6%)	3 (17.6%)	3 (20.0%)	4 (25.0%)	21 (23.1%)
Within --> Within	6 (40.0%)	3 (21.4%)	3 (21.4%)	6 (35.3%)	7 (46.7%)	6 (37.5%)	31 (34.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(g) White blood cells (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(g) White blood cells (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	89 (97.8%)
Within --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(h) Platelets (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Within	11 (73.3%)	12 (85.7%)	11 (78.6%)	13 (76.5%)	14 (93.3%)	15 (93.8%)	76 (83.5%)
Above	4 (26.7%)	1 (7.1%)	2 (14.3%)	4 (23.5%)	1 (6.7%)	1 (6.3%)	13 (14.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	11 (73.3%)	9 (64.3%)	10 (71.4%)	9 (52.9%)	14 (93.3%)	15 (93.8%)	68 (74.7%)
Above	4 (26.7%)	5 (35.7%)	4 (28.6%)	8 (47.1%)	1 (6.7%)	1 (6.3%)	23 (25.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(h) Platelets (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Within --> Within	10 (66.7%)	8 (57.1%)	8 (57.1%)	8 (47.1%)	13 (86.7%)	15 (93.8%)	62 (68.1%)
Within --> Above	1 (6.7%)	4 (28.6%)	3 (21.4%)	5 (29.4%)	1 (6.7%)	0 (0.0%)	14 (15.4%)
Above --> Within	1 (6.7%)	0 (0.0%)	1 (7.1%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	4 (4.4%)
Above --> Above	3 (20.0%)	1 (7.1%)	1 (7.1%)	3 (17.6%)	0 (0.0%)	1 (6.3%)	9 (9.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(i) Neutrophils (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within	14 (93.3%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	87 (95.6%)
Above	1 (6.7%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(i) Neutrophils (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within --> Within	14 (93.3%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	87 (95.6%)
Above --> Within	1 (6.7%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(j) Lymphocytes (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	89 (97.8%)
Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(j) Lymphocytes (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within --> Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	15 (88.2%)	15 (100.0%)	16 (100.0%)	88 (96.7%)
Within --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(k) Monocytes (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	89 (97.8%)
Above	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	89 (97.8%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(k) Monocytes (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	13 (86.7%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	88 (96.7%)
Within --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(I) Basophils (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(l) Basophils (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Within --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(m) Eosinophils (10^9/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	11 (73.3%)	13 (92.9%)	14 (100.0%)	16 (94.1%)	13 (86.7%)	14 (87.5%)	81 (89.0%)
Above	4 (26.7%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	2 (13.3%)	2 (12.5%)	10 (11.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	13 (92.9%)	14 (100.0%)	15 (88.2%)	15 (100.0%)	14 (87.5%)	84 (92.3%)
Above	2 (13.3%)	1 (7.1%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	2 (12.5%)	7 (7.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(m) Eosinophils (10^9/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	11 (73.3%)	12 (85.7%)	14 (100.0%)	15 (88.2%)	13 (86.7%)	13 (81.3%)	78 (85.7%)
Within --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (6.3%)	3 (3.3%)
Above --> Within	2 (13.3%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	1 (6.3%)	6 (6.6%)
Above --> Above	2 (13.3%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (6.3%)	4 (4.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(n) PT (secs)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	14 (82.4%)	13 (86.7%)	14 (87.5%)	82 (90.1%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	3 (17.6%)	1 (6.7%)	2 (12.5%)	8 (8.8%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	13 (92.9%)	13 (92.9%)	13 (76.5%)	13 (86.7%)	15 (93.8%)	82 (90.1%)
Above	0 (0.0%)	1 (7.1%)	1 (7.1%)	4 (23.5%)	2 (13.3%)	1 (6.3%)	9 (9.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(n) PT (secs) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within --> Within	14 (93.3%)	12 (85.7%)	13 (92.9%)	12 (70.6%)	11 (73.3%)	14 (87.5%)	76 (83.5%)
Within --> Above	0 (0.0%)	1 (7.1%)	1 (7.1%)	2 (11.8%)	2 (13.3%)	0 (0.0%)	6 (6.6%)
Above --> Within	1 (6.7%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	1 (6.3%)	5 (5.5%)
Above --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	1 (6.3%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(o) APTT (secs)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	13 (92.9%)	12 (85.7%)	15 (88.2%)	12 (80.0%)	16 (100.0%)	82 (90.1%)
Above	1 (6.7%)	1 (7.1%)	2 (14.3%)	2 (11.8%)	3 (20.0%)	0 (0.0%)	9 (9.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within	13 (86.7%)	13 (92.9%)	13 (92.9%)	15 (88.2%)	13 (86.7%)	16 (100.0%)	83 (91.2%)
Above	1 (6.7%)	1 (7.1%)	1 (7.1%)	2 (11.8%)	2 (13.3%)	0 (0.0%)	7 (7.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.8
Movement from baseline to post-study follow-up in haematology variables in relation to the normal range
Safety set

(o) APTT (secs) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Below	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within --> Within	13 (86.7%)	13 (92.9%)	12 (85.7%)	15 (88.2%)	12 (80.0%)	16 (100.0%)	81 (89.0%)
Above --> Within	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (2.2%)
Above --> Above	1 (6.7%)	1 (7.1%)	1 (7.1%)	2 (11.8%)	2 (13.3%)	0 (0.0%)	7 (7.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(a) Sodium (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	11 (73.3%)	13 (92.9%)	12 (85.7%)	14 (82.4%)	11 (73.3%)	14 (87.5%)	75 (82.4%)
Above	4 (26.7%)	1 (7.1%)	2 (14.3%)	3 (17.6%)	4 (26.7%)	2 (12.5%)	16 (17.6%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	11 (78.6%)	15 (88.2%)	11 (73.3%)	15 (93.8%)	81 (89.0%)
Above	0 (0.0%)	0 (0.0%)	3 (21.4%)	2 (11.8%)	4 (26.7%)	1 (6.3%)	10 (11.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(a) Sodium (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	11 (73.3%)	13 (92.9%)	9 (64.3%)	13 (76.5%)	10 (66.7%)	14 (87.5%)	70 (76.9%)
Within --> Above	0 (0.0%)	0 (0.0%)	3 (21.4%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	5 (5.5%)
Above --> Within	4 (26.7%)	1 (7.1%)	2 (14.3%)	2 (11.8%)	1 (6.7%)	1 (6.3%)	11 (12.1%)
Above --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	3 (20.0%)	1 (6.3%)	5 (5.5%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(b) Potassium (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	3 (20.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	6 (6.6%)
Within	12 (80.0%)	14 (100.0%)	13 (92.9%)	17 (100.0%)	13 (86.7%)	16 (100.0%)	85 (93.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	1 (7.1%)	2 (14.3%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	6 (6.6%)
Within	14 (93.3%)	13 (92.9%)	12 (85.7%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	85 (93.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(b) Potassium (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	3 (20.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	6 (6.6%)
Within --> Below	1 (6.7%)	1 (7.1%)	2 (14.3%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	6 (6.6%)
Within --> Within	11 (73.3%)	13 (92.9%)	11 (78.6%)	16 (94.1%)	12 (80.0%)	16 (100.0%)	79 (86.8%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(c) Urea (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(c) Urea (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within --> Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	15 (88.2%)	15 (100.0%)	16 (100.0%)	89 (97.8%)
Above --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(d) Creatinine (umol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	4 (28.6%)	1 (7.1%)	1 (5.9%)	3 (20.0%)	2 (12.5%)	12 (13.2%)
Within	14 (93.3%)	10 (71.4%)	13 (92.9%)	16 (94.1%)	12 (80.0%)	14 (87.5%)	79 (86.8%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	2 (13.3%)	6 (42.9%)	1 (7.1%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	11 (12.1%)
Within	13 (86.7%)	8 (57.1%)	13 (92.9%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	80 (87.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(d) Creatinine (umol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	3 (21.4%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	5 (5.5%)
Below --> Within	1 (6.7%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	2 (13.3%)	2 (12.5%)	7 (7.7%)
Within --> Below	2 (13.3%)	3 (21.4%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (6.6%)
Within --> Within	12 (80.0%)	7 (50.0%)	12 (85.7%)	16 (94.1%)	12 (80.0%)	14 (87.5%)	73 (80.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(e) Uric acid (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	13 (86.7%)	16 (100.0%)	87 (95.6%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within	14 (93.3%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(e) Uric acid (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Below --> Within	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Within --> Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	13 (86.7%)	16 (100.0%)	87 (95.6%)
Above --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(f) Glucose (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	3 (3.3%)
Within	15 (100.0%)	10 (71.4%)	12 (85.7%)	13 (76.5%)	12 (80.0%)	14 (87.5%)	76 (83.5%)
Above	0 (0.0%)	3 (21.4%)	2 (14.3%)	2 (11.8%)	3 (20.0%)	2 (12.5%)	12 (13.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	2 (13.3%)	0 (0.0%)	1 (7.1%)	1 (5.9%)	0 (0.0%)	1 (6.3%)	5 (5.5%)
Within	12 (80.0%)	12 (85.7%)	12 (85.7%)	14 (82.4%)	12 (80.0%)	14 (87.5%)	76 (83.5%)
Above	1 (6.7%)	2 (14.3%)	1 (7.1%)	2 (11.8%)	3 (20.0%)	1 (6.3%)	10 (11.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(f) Glucose (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	3 (3.3%)
Within --> Below	2 (13.3%)	0 (0.0%)	1 (7.1%)	1 (5.9%)	0 (0.0%)	1 (6.3%)	5 (5.5%)
Within --> Within	12 (80.0%)	8 (57.1%)	10 (71.4%)	11 (64.7%)	9 (60.0%)	12 (75.0%)	62 (68.1%)
Within --> Above	1 (6.7%)	2 (14.3%)	1 (7.1%)	1 (5.9%)	3 (20.0%)	1 (6.3%)	9 (9.9%)
Above --> Within	0 (0.0%)	3 (21.4%)	2 (14.3%)	1 (5.9%)	3 (20.0%)	2 (12.5%)	11 (12.1%)
Above --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(g) Calcium (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	2 (14.3%)	0 (0.0%)	1 (5.9%)	2 (13.3%)	1 (6.3%)	6 (6.6%)
Within	15 (100.0%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	13 (86.7%)	15 (93.8%)	85 (93.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (6.3%)	2 (2.2%)
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	15 (93.8%)	89 (97.8%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(g) Calcium (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (6.3%)	2 (2.2%)
Below --> Within	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	4 (4.4%)
Within --> Within	15 (100.0%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	13 (86.7%)	15 (93.8%)	85 (93.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(h) Inorganic phosphorus (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	3 (21.4%)	1 (7.1%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	5 (5.5%)
Within	14 (93.3%)	11 (78.6%)	13 (92.9%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	84 (92.3%)
Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	15 (100.0%)	14 (87.5%)	86 (94.5%)
Above	2 (13.3%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	2 (12.5%)	5 (5.5%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(h) Inorganic phosphorus (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	3 (21.4%)	1 (7.1%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	5 (5.5%)
Within --> Within	13 (86.7%)	11 (78.6%)	13 (92.9%)	15 (88.2%)	14 (93.3%)	14 (87.5%)	80 (87.9%)
Within --> Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	2 (12.5%)	4 (4.4%)
Above --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(i) Total bilirubin (umol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	0 (0.0%)	2 (14.3%)	2 (11.8%)	1 (6.7%)	3 (18.8%)	9 (9.9%)
Within	14 (93.3%)	14 (100.0%)	12 (85.7%)	14 (82.4%)	14 (93.3%)	13 (81.3%)	81 (89.0%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	2 (14.3%)	1 (7.1%)	3 (17.6%)	3 (20.0%)	0 (0.0%)	9 (9.9%)
Within	15 (100.0%)	12 (85.7%)	12 (85.7%)	14 (82.4%)	12 (80.0%)	16 (100.0%)	81 (89.0%)
Above	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(i) Total bilirubin (umol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Below --> Within	1 (6.7%)	0 (0.0%)	1 (7.1%)	1 (5.9%)	0 (0.0%)	3 (18.8%)	6 (6.6%)
Within --> Below	0 (0.0%)	2 (14.3%)	0 (0.0%)	2 (11.8%)	2 (13.3%)	0 (0.0%)	6 (6.6%)
Within --> Within	14 (93.3%)	12 (85.7%)	11 (78.6%)	12 (70.6%)	12 (80.0%)	13 (81.3%)	74 (81.3%)
Within --> Above	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(j) Alkaline phosphatase (IU/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	14 (93.3%)	16 (100.0%)	90 (98.9%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(j) Alkaline phosphatase (IU/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	14 (93.3%)	16 (100.0%)	89 (97.8%)
Within --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Above --> Within	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(k) Alanine transaminase (IU/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	14 (93.3%)	15 (93.8%)	87 (95.6%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	13 (92.9%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	88 (96.7%)
Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(k) Alanine transaminase (IU/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Within	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within --> Within	14 (93.3%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	13 (86.7%)	15 (93.8%)	84 (92.3%)
Within --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	3 (3.3%)
Above --> Within	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(I) Aspartate transaminase (IU/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	15 (93.8%)	90 (98.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	15 (93.8%)	90 (98.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(I) Aspartate transaminase (IU/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
Within --> Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	15 (93.8%)	90 (98.9%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(m) Gamma glutamyl transferase (IU/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	1 (6.7%)	3 (21.4%)	3 (21.4%)	3 (17.6%)	1 (6.7%)	3 (18.8%)	14 (15.4%)
Within	13 (86.7%)	10 (71.4%)	11 (78.6%)	14 (82.4%)	14 (93.3%)	13 (81.3%)	75 (82.4%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	2 (14.3%)	1 (7.1%)	3 (17.6%)	1 (6.7%)	1 (6.3%)	8 (8.8%)
Within	15 (100.0%)	11 (78.6%)	13 (92.9%)	14 (82.4%)	14 (93.3%)	15 (93.8%)	82 (90.1%)
Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(m) Gamma glutamyl transferase (IU/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	1 (7.1%)	1 (7.1%)	2 (11.8%)	1 (6.7%)	1 (6.3%)	6 (6.6%)
Below --> Within	1 (6.7%)	2 (14.3%)	2 (14.3%)	1 (5.9%)	0 (0.0%)	2 (12.5%)	8 (8.8%)
Within --> Below	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	2 (2.2%)
Within --> Within	13 (86.7%)	9 (64.3%)	11 (78.6%)	13 (76.5%)	14 (93.3%)	13 (81.3%)	73 (80.2%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Above --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(n) Alpha-hydroxybutyrate dehydrogenase (IU/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within	15 (100.0%)	14 (100.0%)	13 (92.9%)	17 (100.0%)	14 (93.3%)	16 (100.0%)	89 (97.8%)
Above	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within	14 (93.3%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	12 (80.0%)	16 (100.0%)	86 (94.5%)
Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	2 (13.3%)	0 (0.0%)	4 (4.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(n) Alpha-hydroxybutyrate dehydrogenase (IU/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Below --> Below	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (1.1%)
Within --> Within	14 (93.3%)	14 (100.0%)	13 (92.9%)	16 (94.1%)	12 (80.0%)	16 (100.0%)	85 (93.4%)
Within --> Above	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	2 (13.3%)	0 (0.0%)	4 (4.4%)
Above --> Within	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(o) Creatine kinase (IU/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	14 (100.0%)	12 (85.7%)	17 (100.0%)	15 (100.0%)	13 (81.3%)	85 (93.4%)
Above	1 (6.7%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	3 (18.8%)	6 (6.6%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	13 (92.9%)	13 (92.9%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	85 (93.4%)
Above	2 (13.3%)	1 (7.1%)	1 (7.1%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	6 (6.6%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(o) Creatine kinase (IU/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	12 (80.0%)	13 (92.9%)	12 (85.7%)	16 (94.1%)	14 (93.3%)	13 (81.3%)	80 (87.9%)
Within --> Above	2 (13.3%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	5 (5.5%)
Above --> Within	1 (6.7%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	3 (18.8%)	5 (5.5%)
Above --> Above	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(p) Total protein (g/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	13 (92.9%)	14 (100.0%)	17 (100.0%)	14 (93.3%)	15 (93.8%)	87 (95.6%)
Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.3%)	4 (4.4%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	14 (87.5%)	84 (92.3%)
Above	1 (6.7%)	2 (14.3%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	2 (12.5%)	7 (7.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(p) Total protein (g/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	13 (86.7%)	12 (85.7%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	13 (81.3%)	82 (90.1%)
Within --> Above	1 (6.7%)	1 (7.1%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	2 (12.5%)	5 (5.5%)
Above --> Within	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (2.2%)
Above --> Above	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(q) Albumin (g/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	14 (100.0%)	10 (71.4%)	16 (94.1%)	11 (73.3%)	14 (87.5%)	78 (85.7%)
Above	2 (13.3%)	0 (0.0%)	4 (28.6%)	1 (5.9%)	4 (26.7%)	2 (12.5%)	13 (14.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	11 (78.6%)	10 (71.4%)	13 (76.5%)	13 (86.7%)	14 (87.5%)	74 (81.3%)
Above	2 (13.3%)	3 (21.4%)	4 (28.6%)	4 (23.5%)	2 (13.3%)	2 (12.5%)	17 (18.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(q) Albumin (g/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	11 (73.3%)	11 (78.6%)	8 (57.1%)	13 (76.5%)	9 (60.0%)	12 (75.0%)	64 (70.3%)
Within --> Above	2 (13.3%)	3 (21.4%)	2 (14.3%)	3 (17.6%)	2 (13.3%)	2 (12.5%)	14 (15.4%)
Above --> Within	2 (13.3%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	4 (26.7%)	2 (12.5%)	10 (11.0%)
Above --> Above	0 (0.0%)	0 (0.0%)	2 (14.3%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	3 (3.3%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(r) Cholesterol (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	13 (86.7%)	12 (85.7%)	13 (92.9%)	15 (88.2%)	11 (73.3%)	16 (100.0%)	80 (87.9%)
Above	2 (13.3%)	2 (14.3%)	1 (7.1%)	2 (11.8%)	4 (26.7%)	0 (0.0%)	11 (12.1%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	12 (80.0%)	9 (64.3%)	13 (92.9%)	12 (70.6%)	12 (80.0%)	13 (81.3%)	71 (78.0%)
Above	3 (20.0%)	5 (35.7%)	1 (7.1%)	5 (29.4%)	3 (20.0%)	3 (18.8%)	20 (22.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(r) Cholesterol (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	12 (80.0%)	9 (64.3%)	12 (85.7%)	12 (70.6%)	9 (60.0%)	13 (81.3%)	67 (73.6%)
Within --> Above	1 (6.7%)	3 (21.4%)	1 (7.1%)	3 (17.6%)	2 (13.3%)	3 (18.8%)	13 (14.3%)
Above --> Within	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	4 (4.4%)
Above --> Above	2 (13.3%)	2 (14.3%)	0 (0.0%)	2 (11.8%)	1 (6.7%)	0 (0.0%)	7 (7.7%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(s) Triglycerides (mmol/L)

(i) Baseline

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	15 (100.0%)	14 (100.0%)	14 (100.0%)	16 (94.1%)	14 (93.3%)	16 (100.0%)	89 (97.8%)
Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(ii) Post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within	14 (93.3%)	12 (85.7%)	14 (100.0%)	15 (88.2%)	13 (86.7%)	15 (93.8%)	83 (91.2%)
Above	1 (6.7%)	2 (14.3%)	0 (0.0%)	2 (11.8%)	2 (13.3%)	1 (6.3%)	8 (8.8%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.9
Movement from baseline to post-study follow-up in biochemistry variables in relation to the normal range
Safety set

(s) Triglycerides (mmol/L) (Cont.)

(iii) Change from baseline to post-study follow-up

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Within --> Within	14 (93.3%)	12 (85.7%)	14 (100.0%)	15 (88.2%)	13 (86.7%)	15 (93.8%)	83 (91.2%)
Within --> Above	1 (6.7%)	2 (14.3%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	1 (6.3%)	6 (6.6%)
Above --> Above	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (6.7%)	0 (0.0%)	2 (2.2%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(a) Systolic blood pressure (mmHg)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	125.1	12.3	100.0	178.0	123.0	1.3	122.6	127.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	126.2	12.9	101.0	146.0	126.0	3.3	119.1	133.3
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	127.0	17.0	111.0	178.0	125.0	4.5	117.2	136.8
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	124.2	9.8	107.0	142.0	125.5	2.6	118.5	129.9
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	126.1	13.5	100.0	149.0	124.0	3.3	119.1	133.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	126.8	9.3	107.0	144.0	123.0	2.4	121.7	131.9
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	120.7	10.6	103.0	139.0	120.0	2.6	115.0	126.3

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(a) Systolic blood pressure (mmHg) (Cont.)

(ii) Change from baseline

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.1	12.6	-37.0	37.0	-1.0	1.3	-2.5	2.7
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.4	15.6	-37.0	20.0	2.0	4.0	-8.3	9.1
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	1.6	12.5	-9.0	37.0	-3.5	3.3	-5.6	8.8
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-5.2	11.5	-37.0	9.0	-2.5	3.1	-11.9	1.4
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	1.2	11.3	-26.0	23.0	1.0	2.7	-4.6	7.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.1	12.1	-23.0	18.0	-1.0	3.1	-6.9	6.6
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	2.4	12.6	-17.0	27.0	-0.5	3.1	-4.3	9.1

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(b) Diastolic blood pressure (mmHg)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	75.1	9.8	54.0	109.0	74.0	1.0	73.0	77.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	75.5	10.0	60.0	97.0	77.0	2.6	69.9	81.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	77.1	10.8	60.0	107.0	75.5	2.9	70.9	83.4
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	73.4	9.0	60.0	94.0	71.0	2.4	68.2	78.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	77.6	13.3	54.0	109.0	78.0	3.2	70.8	84.4
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	75.9	7.4	65.0	89.0	75.0	1.9	71.9	80.0
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	70.8	6.5	62.0	85.0	69.5	1.6	67.3	74.3

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(b) Diastolic blood pressure (mmHg) (Cont.)

(ii) Change from baseline

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	3.2	13.9	-78.0	24.0	3.0	1.5	0.3	6.1
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-0.5	22.9	-78.0	18.0	3.0	5.9	-13.2	12.2
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	6.2	7.1	-4.0	24.0	5.5	1.9	2.1	10.3
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	-1.0	18.7	-61.0	16.0	3.0	5.0	-11.8	9.8
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	7.1	9.5	-12.0	24.0	6.0	2.3	2.2	12.0
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	5.9	9.4	-7.0	23.0	6.0	2.4	0.6	11.1
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	1.0	8.6	-23.0	14.0	1.0	2.2	-3.6	5.6

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(c) Heart rate (bpm)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	78.4	13.5	53.0	129.0	77.0	1.4	75.6	81.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	76.1	12.5	58.0	102.0	77.0	3.2	69.1	83.0
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	79.2	14.3	59.0	119.0	77.5	3.8	70.9	87.5
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	79.3	14.2	57.0	110.0	78.0	3.8	71.1	87.5
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	80.6	16.7	62.0	129.0	76.0	4.0	72.0	89.2
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	80.2	11.9	64.0	100.0	82.0	3.1	73.6	86.8
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	75.0	11.8	53.0	102.0	73.5	3.0	68.7	81.3

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(c) Heart rate (bpm) (Cont.)

(ii) Change from baseline

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	2.5	12.9	-38.0	41.0	2.0	1.4	-0.2	5.2
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	-2.4	9.2	-26.0	7.0	1.0	2.4	-7.5	2.7
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.2	12.7	-21.0	29.0	-0.5	3.4	-7.1	7.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	1.7	16.6	-38.0	36.0	2.0	4.4	-7.9	11.3
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	7.8	14.2	-13.0	41.0	6.0	3.4	0.5	15.1
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	4.5	12.9	-18.0	25.0	3.0	3.3	-2.6	11.7
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	2.1	10.3	-12.0	25.0	-1.5	2.6	-3.4	7.6

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(d) Temperature (degrees C)

(i) Post-study follow-up

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	36.3	0.7	34.0	38.6	36.5	0.1	36.1	36.4
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	36.4	0.7	34.9	37.0	36.7	0.2	36.0	36.8
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	36.2	0.7	34.0	36.8	36.5	0.2	35.8	36.6
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	36.3	0.6	34.7	37.0	36.5	0.2	35.9	36.7
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	36.2	0.7	34.0	36.9	36.4	0.2	35.8	36.6
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	36.1	0.7	34.4	37.0	36.3	0.2	35.7	36.5
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	36.5	0.9	34.8	38.6	36.7	0.2	36.0	36.9

Table 14.3.10
Change from baseline for vital signs recorded at post-study follow-up visit
Safety set

(d) Temperature (degrees C) (Cont.)

(ii) Change from baseline

Treatment sequence	n	miss.	mean	s.d.	min	max	median	s.e.m.	lower limit of 95% CI for mean	upper limit of 95% CI for mean
Overall	91	0	0.2	0.9	-2.2	2.7	0.2	0.1	0.0	0.4
Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg/Placebo	15	0	0.3	0.9	-1.5	2.1	0.4	0.2	-0.2	0.8
Ibu. 200mg + Para. 500mg/Placebo/Ibu. 400mg + Para. 1000mg	14	0	0.1	0.6	-0.6	1.6	-0.1	0.2	-0.2	0.4
Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg/Placebo	14	0	0.1	0.8	-1.5	1.2	0.1	0.2	-0.4	0.6
Ibu. 400mg + Para. 1000mg/Placebo/Ibu. 200mg + Para. 500mg	17	0	0.0	0.9	-2.2	1.7	0.1	0.2	-0.5	0.5
Placebo/Ibu. 200mg + Para. 500mg/Ibu. 400mg + Para. 1000mg	15	0	-0.0	0.7	-1.9	0.7	0.2	0.2	-0.4	0.4
Placebo/Ibu. 400mg + Para. 1000mg/Ibu. 200mg + Para. 500mg	16	0	0.6	1.1	-1.2	2.7	0.5	0.3	0.0	1.2

Table 14.3.11
Physical examination at post-study follow-up visit
Safety set

(a) ANY ABNORMALITIES

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
No	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(b) SKIN

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.11
Physical examination at post-study follow-up visit
Safety set

(c) EYES

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(d) EARS

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(e) NOSE

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(f) CHEST AND LUNGS

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.11
Physical examination at post-study follow-up visit
Safety set

(g) LYMPH NODES

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

(h) MOUTH AND THROAT

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.11
Physical examination at post-study follow-up visit
Safety set

(i) OTHER

	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg	Total
Normal	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)
Total	15 (100.0%)	14 (100.0%)	14 (100.0%)	17 (100.0%)	15 (100.0%)	16 (100.0%)	91 (100.0%)

Table 14.3.12
Concomitant medication commencing after the first dose of study medication
Safety set

ATC level 2 category	Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg\Placebo (n=16)	Ibu. 200mg + Para. 500mg\Placebo\Ibu. 400mg + Para. 1000mg (n=15)	Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg\Placebo (n=14)	Ibu. 400mg + Para. 1000mg\Placebo\Ibu. 200mg + Para. 500mg (n=18)	Placebo\Ibu. 200mg + Para. 500mg\Ibu. 400mg + Para. 1000mg (n=15)	Placebo\Ibu. 400mg + Para. 1000mg\Ibu. 200mg + Para. 500mg (n=16)	Total (n=94)
ANY	2 (12.5%)	8 (53.3%)	4 (28.6%)	5 (27.8%)	4 (26.7%)	8 (50.0%)	31 (33.0%)
ANALGESICS	2 (12.5%)	6 (40.0%)	1 (7.1%)	3 (16.7%)	1 (6.7%)	7 (43.8%)	20 (21.3%)
ANTIANEMIC PREPARATIONS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
ANTIBACTERIALS FOR SYSTEMIC USE	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (2.1%)
ANTIHISTAMINES FOR SYSTEMIC USE	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0 (0.0%)	0 (0.0%)	2 (14.3%)	2 (11.1%)	2 (13.3%)	0 (0.0%)	6 (6.4%)
ANTIPROTOZOALS	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
ANTIPRURITICS,INCL ANTIHIST,ANESTHET,ETC.	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (1.1%)
NASAL PREPARATIONS	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
PSYCHOANALEPTICS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (2.1%)
UNSPECIFIED HERBAL	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
UROLOGICALS	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
VITAMINS	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)