Table of Contents

2.5.1 PRODUCT DEVELOPMENT RATIONALE

This Marketing Authorisation Application (MAA) is for a prescription only product licence for a fixed combination of ibuprofen 200 mg and paracetamol (acetaminophen) 500 mg in an immediate release tablet formulation. Throughout this document, the product will be referred to as 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The proposed indications are for the relief of mild to moderate pain.

Background

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) which relieves pain and inflammation by the non-selective inhibition of prostaglandin biosynthesis at the site of tissue injury (peripherally). At a maximum daily dose of ≤ 1.2 g ibuprofen predominately acts as an analgesic. Paracetamol is a weak inhibitor of cyclo-oxygenase (COX) 1 and 2 in peripheral tissues and has no significant anti-inflammatory activity. The analgesic properties of paracetamol are thought to be mediated centrally, although the mechanisms involved are not fully understood (**Section 2.5.3.2**).

Ibuprofen and paracetamol are both widely available as prescription and non-prescription medicines taken for the relief of mild to moderate pain. The efficacy and safety profile of ibuprofen and paracetamol are established and supported by extensive clinical data.

Globally, guidelines recognise the benefit of using analgesics with different modalities in a stepwise approach to control pain (Australian Therapeutic Guidelines Oral and Dental (2007) and Analgesics (2007), and other guidelines for cancer pain, osteoarthritis (OA) and rheumatoid arthritis). The use of paracetamol in conjunction with an NSAID or an opioid for greater analgesia is recommended; however NSAIDs are also recognised as having a significant opioid-sparing effect. Altman (2004) mentions the results of a survey in which 30% of OA sufferers reported using paracetamol and either ibuprofen, naproxen or diclofenac concurrently. Ibuprofen and paracetamol are increasingly used in combination for the relief of pain and fever despite the absence of significant scientific support for this practice.

In countries such as India, Russia, Poland, South Africa and Thailand, the fixed combination of ibuprofen and paracetamol has been licensed at varying maximum daily doses (ibuprofen 1.2–2.4 g and paracetamol 1.3–2.6 g) for the treatment of pain and fever (**Module 2.7 Section 2.7.4.6**).

Product Rationale

The rationale for the development of this fixed combination of ibuprofen and paracetamol was combined efficacy, through the different and complementary mechanisms of action. This resulted in an 'additive' effect, i.e. a level of efficacy above the one achievable by the single actives alone, with an acceptable safety profile. 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was developed as an effective alternative for those patients who suffer from mild to

moderate pain who require stronger analgesia than either paracetamol or ibuprofen alone or for those patients who can not tolerate or prefer not to take codeine-containing products.

The proposed indications are for the relief of mild to moderate pain. The product is intended for adults from 18 years and the proposed posology is for 2 tablets of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' to be taken every 6 to 8 hours not exceeding 6 tablets in a 24 hour period. The proposed maximum daily dose for the product is 3 g of paracetamol and 1.2 g of ibuprofen. In the treatment of mild to moderate pain, the product and the proposed posology reduce the risk of exposure to paracetamol, i.e. paracetamol-sparing.

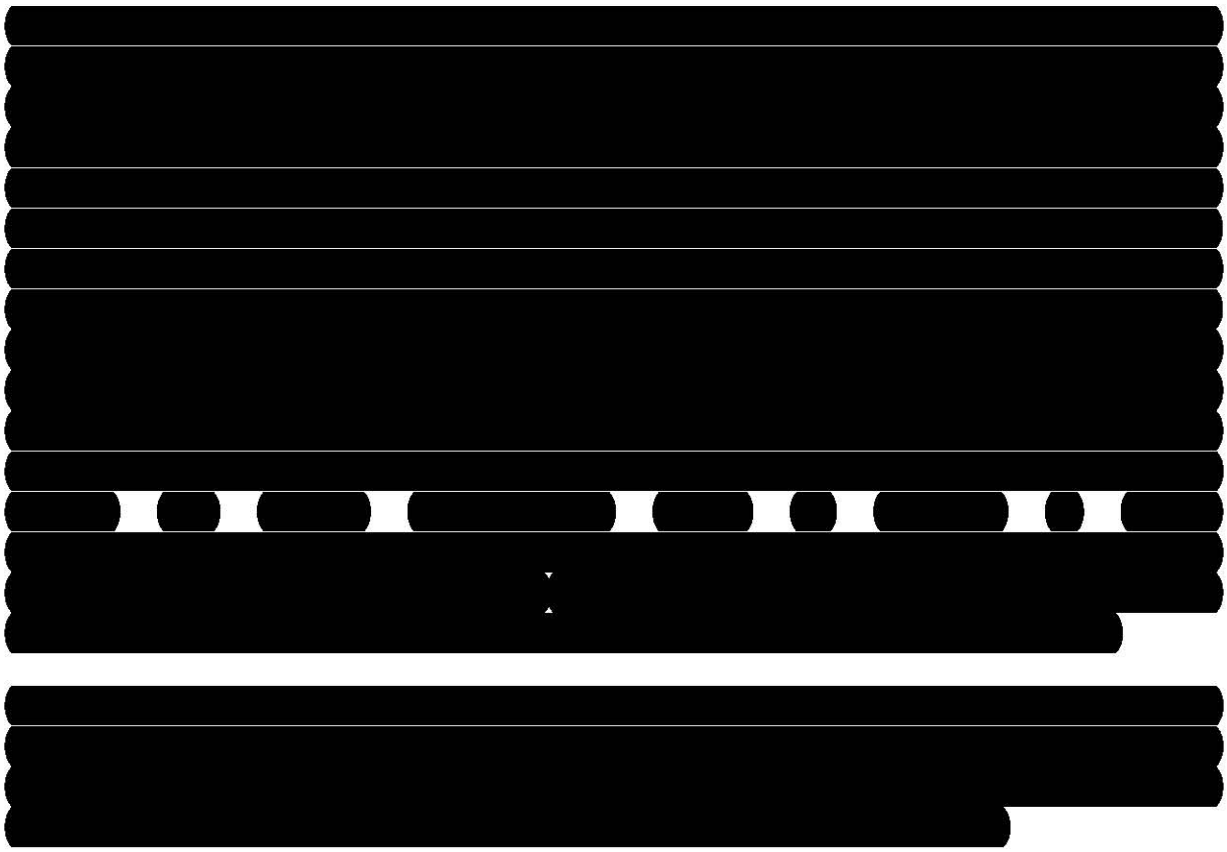
For those patients who are currently co-dosing with ibuprofen and paracetamol, the fixed combination, 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', will simplify dosing thus improving compliance and reducing the risk of medication errors and therefore potential unintentional overdose.

Clinical Programme

The clinical programme was designed to investigate the efficacy and safety of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The unit dose of this fixed combination was chosen based on well documented dose-response and safety data for ibuprofen and paracetamol in the public domain. The maximum dose for ibuprofen and paracetamol were based on the doses currently authorised for the treatment of mild to moderate pain.

The design of the clinical programme employed current standard research approaches and regulatory guidance (CPMP/EWP/QWP/1401/98, CPMP/EWP/612/00, CPMP/EWP/240/95 and revision 1 effect date September 2009). All studies were performed in accordance with GCP. Detailed discussion of the study designs are provided in **Section 2.5.2**, **Section 2.5.3** and **Section 2.5.4**. The comparators used in the studies were the standard routine doses of ibuprofen (400 mg) and paracetamol (1000 mg) used for the treatment of mild to moderate pain.

[redacted]



The clinical programme therefore included the following studies:

- **Pharmacokinetic study NL0602**. An open-label, 4 way crossover, randomised, single centre study in healthy volunteers to assess bioavailability of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in comparison to the single actives. (**Section 2.5.2.1**). The study confirmed the lack of pharmacokinetic drug-drug interaction between ibuprofen and paracetamol and confirmed the effects of food on the pharmacokinetic profiles of ibuprofen and paracetamol.

- **Pharmacokinetic study NL0603**. An open-label, randomised, repeat dose, two-way crossover study in healthy volunteers to examine the steady state pharmacokinetics of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' two or three times a day for 3 days to support the posology (**Section 2.5.3.1.2**). There was no accumulation of ibuprofen and paracetamol following repeat dosing with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. Three times a day dosing provided a more consistent plasma levels with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

- **Exploratory efficacy and tolerability study NL0408 in acute pain**. A double-blind, parallel-group, placebo-controlled randomised, single dose, two centre, modified factorial designed study to compare the analgesic efficacy and tolerability of the concomitant use of 1 or 2 ibuprofen 200 mg tablet(s) and paracetamol 500 mg tablet(s) with the single actives (2 x ibuprofen 200 mg and 2 x paracetamol 500 mg tablets) in the treatment of adults experiencing postoperative dental pain (**Section 2.5.4.5**). The study showed that 'concomitant ibuprofen 400 mg and paracetamol 1000 mg' was

statistically significantly more effective than paracetamol 1000 mg alone and ibuprofen 400 mg alone.

- **Pivotal efficacy and tolerability study NL0604 in acute pain**. A double-blind, parallel-group, placebo-controlled, randomised, single and multiple-dose phase, multicentre factorial design, two-part study examining the analgesic efficacy and tolerability of a 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', 1 x Ibuprofen 100 mg and Paracetamol 250 mg tablet, 1 and 2 ibuprofen 200 mg tablets, and 1 and 2 paracetamol 500 mg tablets in adults experiencing postoperative dental pain (**Section 2.5.4.5**). The study showed that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly more effective than paracetamol 1000 mg alone and ibuprofen 400 mg alone. The product has a fast onset and long duration of action.

- **Confirmatory efficacy and tolerability study NL0605 in chronic pain**. A randomised, double-blind, parallel group, multiple-dose 3-month study to examine the efficacy and tolerability of a 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', 2 x ibuprofen 200 mg caplets and 2 x paracetamol 500 mg caplets, all taken three times a day, in community patients with chronic knee pain. To confirm the efficacy of the fixed combination and to assess tolerability (**Section 2.5.4.5**). At Day 10 and Week 13, a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly more effective than paracetamol 1000 mg alone and was comparable to ibuprofen 400 mg alone.

The Applicant is currently conducting two marketing support studies with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'; a dysmenorrhoea study in the EU and a post-operative dental pain study outside of the EU.

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was well tolerated. There were no deaths or serious treatment-related adverse events with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The overall adverse event profile for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was comparable to the combined adverse event profiles for the single actives. All adverse events were 'expected'.

The clinical programme supports the proposed posology of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' taken every 6 to 8 hours, not exceeding 6 tablets in a 24 hour period, for the treatment of mild to moderate pain. 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provides more effective analgesia than ibuprofen or paracetamol alone with an acceptable safety profile, thus demonstrating a positive benefit/risk profile.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

This section will review and consider the pharmaceutical development of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and the pharmacokinetic data generated from the single dose pharmacokinetic study NL0602.

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is a white pearlescent film coated tablet. The tablet core is formulated with a melt extrudate of ibuprofen, paracetamol and croscarmellose sodium, which is blended with other conventional tablet excipients. The dissolution of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is rapid with approximately 80% of ibuprofen and paracetamol dissolved within 10 minutes (**Module 2.3 Section 2.3.P.2**).

A key criterion for the development of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was that the pharmacokinetic performance of the product was required to be at least comparable to the commercially available reference products ibuprofen tablets (Nurofen®) and paracetamol tablets [redacted]) used in NL0602. In the pivotal efficacy and tolerability study (NL0604) the comparator products were [redacted] tablets and [redacted] caplets. In the confirmatory efficacy and tolerability study (NL0605) all treatments were encapsulated and the comparator products were Nurofen® caplets and [redacted] caplets.

Comparative *in vitro* dissolution data for the fixed combination and commercially available immediate release ibuprofen tablets [redacted] show that at least 70% of ibuprofen and/or paracetamol are dissolved in the first 15 minutes for all products except with [redacted]. The difference in dissolution profile [redacted] can be attributed to either the formulation or the performance of this batch. However, this product complies with the USP/BP requirements that not less than 80% (Q) of the stated content of paracetamol is dissolved at 30 minutes (**Module 3.2.P.2**). These comparative products are considered to be representative of proprietary ibuprofen and paracetamol products available in Europe.

The formulation of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' used in the clinical programme was the 'to-be-marketed' product (**Module 2.3 Section 2.3.P.2**).

Study Design

The single dose pharmacokinetic study NL0602 was designed in accordance with the European notes for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) and fixed combination medicinal products (CPMP/EWP/240/95). The study investigated the relative bioavailability of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and the potential pharmacokinetic drug-drug interaction of ibuprofen and paracetamol by testing for bioequivalence between the fixed combination and the single actives. The study also investigated the food-drug interaction of the fixed combination by comparing the ibuprofen and paracetamol pharmacokinetic profiles of the fixed combination in the fasted state and after a standard meal.

NL0602 had a conventional open-label, four-way crossover, randomised design with a more than adequate wash out period of over 18 plasma half lives between treatment arms. The study was conducted with healthy volunteers to minimise inter-subject variability and therefore allow detection of differences between 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and the commercially available ibuprofen and paracetamol tablets.

The pharmacokinetic studies (NL0602 and NL0603) were conducted with a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The dosing and sampling were conducted at set times of the day for all treatment arms. The sampling was conducted at appropriate times for the plasma half lives of ibuprofen and paracetamol.

NL0602 was adequately powered to detect a 20% difference between the 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and the single active products with a power of 80% and an alpha of 5% based on a ratio of 1.0.

The assay methods used to analyse ibuprofen and paracetamol in human plasma were well characterised and fully validated. The methods were specific, sensitive, accurate, and precise, and had reproducible linearity throughout the calibration range (**Module 2.7 Section 2.7.1.1 Overview of Analytical Methodology**). All analyses were conducted in accordance with Good Laboratory Practice (GLP).

The statistical analysis was conducted in accordance with the European guidelines (CPMP/EWP/QWP/1401/98). The Applicant tested for bioequivalence for the parameters of AUC and C_{max} using ANOVA with a 90% confidence interval (CI) in the range of 80-125% for the logarithmically transformed data. As t_{max} is the actual time to achieve C_{max}, the data for t_{max} are presented as median values, and therefore the median difference. The analysis of t_{max} was non-parametric and applied to untransformed data.

2.5.2.1 Pharmacokinetic Study NL0602 – Singe Dose (Fasted and Fed)

A more detailed summary of these data are presented in **Module 2.7 Section 2.7.1.2.1**.

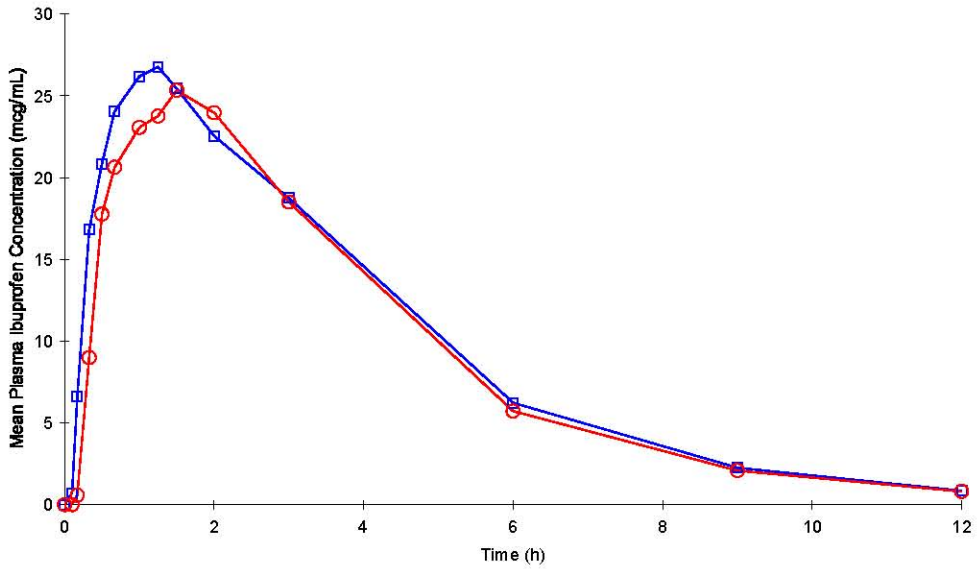
This study was designed to examine the bioavailability of ibuprofen and paracetamol from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', to confirm there was no pharmacokinetic drug-drug interaction between ibuprofen and paracetamol, and to examine the effects of food on bioavailability of the fixed combination in 25 healthy volunteers. The study determined plasma ibuprofen and paracetamol levels. The study was conducted in compliance with GCP.

The primary variables derived from plasma ibuprofen and paracetamol concentrations for each treatment were C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, and $t_{1/2}$, and K_{el}. All the endpoints were defined in the study protocol. In addition, vital signs and adverse events were assessed.

Comparison of ibuprofen pharmacokinetic profiles from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 200 mg tablet in the fasted state

A comparison of the mean plasma concentration curves for ibuprofen from the fixed combination (Treatment C) and ibuprofen tablets (Treatment A) is presented in **Figure 1**.

Figure 1 Mean ibuprofen plasma concentration curves for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 200 mg tablets (fasted)



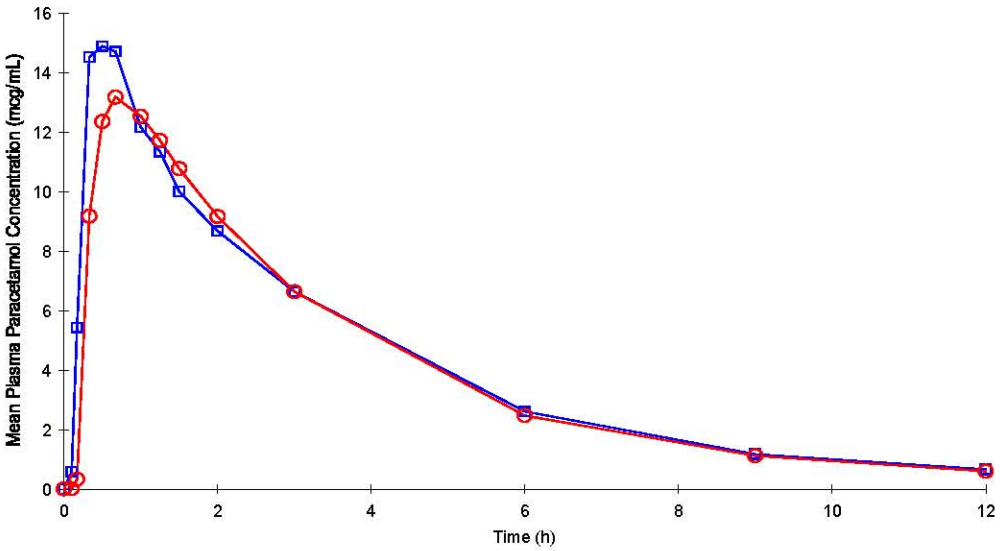
Key: Ibuprofen/A; Ibuprofen/C

The statistical comparison of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and 2 x ibuprofen 200 mg tablets demonstrates bioequivalence for: C_{max} ratio 104.29 (90% CI 95.90, 113.41); AUC_{0-t} ratio 107.08 (90% CI 103.20, 111.11); AUC_{0-inf} ratio 106.99 (90% CI 103.26, 110.85), which are within the 90% CI range 80-125%. The median time to maximum ibuprofen concentrations (t_{max}) was 75 minutes for both products.

Comparison of paracetamol pharmacokinetic profiles from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 500 mg tablet in the fasted state

A comparison of the mean plasma concentration curves for paracetamol from the fixed combination (Treatment C) and paracetamol tablets (Treatment B) is presented in **Figure 2.** The statistical comparison of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and 2 x paracetamol 500 mg tablets demonstrates bioequivalence for: C_{max} ratio 104.14 (90% CI 91.32, 118.76); AUC_{0-t} ratio 104.10 (90% CI 100.08, 108.29); AUC_{0-inf} ratio 104.60 (90% CI 100.56, 108.82), which are within the 90% CI range 80-125%. The median time to maximum paracetamol concentration (t_{max}) was 30 minutes for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to 40 minutes for the paracetamol reference product. The median difference of 15 minutes (95% CI -30–0 minutes) was statistically significant ($p < 0.05$). This difference could be attributed to the formulation difference between the reference product [redacted] and 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (**Section 2.5.2**).

Figure 2 **Mean paracetamol plasma concentration curves for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 500 mg tablet (fasted)**

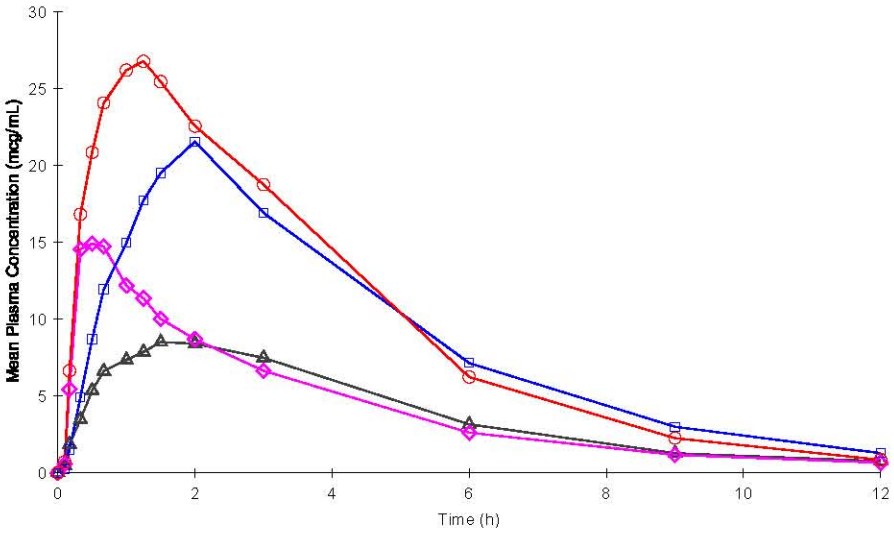


Key: Paracetamol/B; Paracetamol/C

Comparison of pharmacokinetic profiles of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the fed and fasted State

A comparison of the mean ibuprofen and paracetamol plasma concentration curves from 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' administered in the fed (Treatment D) and fasted (Treatment C) states are presented in **Figure 3.**

Figure 3 **Mean ibuprofen and paracetamol plasma concentration curves for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (fed and fasted)**



Key: Ibuprofen/C; Ibuprofen/D; Paracetamol/C; Paracetamol/D

Consistent with the published literature on ibuprofen and paracetamol alone (Davies 1998, Prescott 1996a), the rate of absorption of ibuprofen and paracetamol was significantly delayed when 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was taken after food (**Table 1**).

- In the fed state, ibuprofen and paracetamol t_{max} values were longer and corresponding C_{max} values lower. For ibuprofen in the fed state, t_{max} was delayed by a median of 25 minutes (95% CI 0, 45); compared to the fasted state this difference was not statistically significant (**Table 1**). For paracetamol in the fed state, t_{max} was delayed by a median of 55 minutes (95% CI 30, 80); compared to the fasted state the difference was statistically significant ($p < 0.001$) (**Table 1**).

- The mean plasma half life ($t_{½}$) of ibuprofen was also prolonged from 1.95 hours (range: 1.59–2.83 hours) in the fasted state to 2.25 hours (range: 1.49–3.94 hours) in the fed state. Paracetamol plasma half life was comparable in the fed and fasted state.

- The rate and extent of absorption, determined by C_{max}, was lower in the fed state (**Figure 3**). The statistical comparisons for ibuprofen and paracetamol C_{max} ratios were not bioequivalent, i.e. outside the acceptance range of 80–125%.

- For the more important measures of extent of ibuprofen and paracetamol absorption, $AUC_{0-t,}$ and AUC_{0-inf}, although the fed: fasted ratios were less than 100%, 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was bioequivalent, i.e. within the 90% CI range of 80-125%, for these parameters when taken in the fed and fasted state **Table 1**.

Table 1 Comparison of the pharmacokinetic parameters for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the fed: fasted state

	Treatment Group Comparisons Fed: Fasted State			
	Plasma Ibuprofen		Plasma Paracetamol	
	Ratio (%)	90% CI	Ratio (%)	90% CI
AUC_{0-t} (µg/mL/h)[a]	87.22	84.06, 90.49	90.89	87.38, 94.54
AUC_{0-inf} (µg/mL/h)[a]	89.25	86.14, 92.46	92.01	88.45, 95.71
C_{max} (µg.mL)[a]	76.38	70.25, 83.06	60.92	53.43, 69.46
	Median Difference	**95% CI**	**Median Difference**	**95% CI**
t_{max} (min)[b]	25.0 ($p = 0.0793$)[c]	0.0, 45.0	55.0 ($p = 0.0003$)[c]	30.0, 80.0

[a] Geometric LS Mean; [b] Median; [c] Wilcoxon Matched Pairs Test

Conclusion

Ibuprofen and paracetamol from the fixed combination of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are bioavailable. 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are bioequivalent to commercially available ibuprofen and paracetamol tablets.

Ibuprofen and paracetamol are rapidly released from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' with measurable plasma concentrations being achieved within the first 5 minutes for both paracetamol and ibuprofen. Consequently, onset of analgesia for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is considered to be fast.

The results of NL0602 show the rate of paracetamol absorption (t_{max}) from the fixed combination was significantly faster than the paracetamol reference tablet. This is consistent with the *in vitro* dissolution data for the fixed combination and the reference products where the dissolution of the reference paracetamol product is delayed.

There is no pharmacokinetic drug-drug interaction between ibuprofen and paracetamol when taken as the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

As with the single actives, C_{max} is lower and t_{max} is delayed for ibuprofen and paracetamol from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' following administration after food. Although these are measures of the rate of absorption they are not predictors of onset of clinical efficacy as this is governed by the minimum therapeutic dose. For the more important measure, overall extent of absorption, as measured by area under the plasma concentration curve, ibuprofen and paracetamol from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were bioequivalent in the fed and fasted state.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Pharmacokinetics

Ibuprofen

The pharmacokinetic profile of ibuprofen acid after oral administration is well characterised. Ibuprofen acid is rapidly and almost completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring within 1-2 hours after dosing. Ibuprofen is extensively bound to plasma protein (99%), but clinically this does not appear to be an important issue regarding drug interactions (Baxter 2006). Ibuprofen diffuses into the synovial fluid. Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as the metabolites or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The mean elimination half life is relatively short; 1.9 hours (range 0.9-2.5 hours) (Dollery 1999a). Furthermore, accumulation or time-dependency of ibuprofen does not seem to occur during prolonged therapeutic dosing (Oliary *et al* 1992). No significant differences in pharmacokinetic profile are observed in the elderly (Davies 1998) (**Module 2.7 Section 2.7.2.1**).

Paracetamol

Paracetamol is also rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 10 minutes to 2 hours after ingestion. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentration. Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged as paracetamol (Dollery 1999b).

In addition very small amounts of a hydroxylated metabolite are produced in the liver and kidney which is detoxified by glutathione in the liver. This metabolite may accumulate following paracetamol overdosage and cause liver damage. The elimination half-life varies from about 1 to 4 hours. No significant differences in the pharmacokinetic profile of paracetamol are observed in the elderly (**Module 2.7 Section 2.7.2.1**).

Ibuprofen and Paracetamol in Combination

Wright *et al* 1983 showed that there were no statistically significant differences in the pharmacokinetic parameters of ibuprofen and paracetamol when administered in combination compared to either active alone (**Module 2.7 Section 2.7.1.1**).

Study Design

The design of the single dose pharmacokinetic study NL0602 was reviewed in **Section 2.5.2**. The repeat dose pharmacokinetic study NL0603 was also designed in accordance with the European notes for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). The study investigated differences in the

repeat dose pharmacokinetics of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' taken twice or three times a day for 3 days (Day 2, 3 and 4).

The design of NL0603 was analogous to NL0602. NL0603 utilised a conventional open-label, two-way crossover, randomised design, the same duration of wash out period, the same power calculation and validated assay methods. The study was also conducted in healthy volunteers at the proposed maximum dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', i.e. 2 tablets to standardise the results across both studies (NL0602 and NL0603). The dosing, sampling and standard meals were conducted at set times of the day for both treatment arms. In NL0603, the first dose of treatment and the sampling thereafter was consistent with the single dose study NL0602. The sampling was conducted at appropriate times for the plasma half lives of ibuprofen and paracetamol and in line with the dosing schedule to characterise the time-concentration profile.

The statistical analysis for NL0603 was conducted in accordance with the European guidelines (CPMP/EWP/QWP/1401/98). Logarithmically transformed C_{min} (trough) values on Day 2, 3, 4 and 5 were used to determine whether steady state had been reached for both treatments. The point estimates were then back-transformed to give estimates of the ratios of the geometric means and the corresponding 95% CI. Paired t-tests were also used for the comparison between each treatment.

Following logarithmic transformation C_{max} and AUC_{0-t} values on Day 4 were subjected to an analysis of variance (ANOVA) including terms for sequence, subject nested within sequence, period and treatment. For comparison, point estimates and 90%CIs for the difference between treatments were constructed using the residual mean square error obtained from the ANOVA. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least square means and the corresponding 90% CIs. Additionally, logarithmic AUC_{tau} on Day 4 and AUC_{0-inf} on Day 2 were subjected to an ANOVA (by treatment), including terms for sequence, subject nested within sequence and day. For comparison, point estimates and 90% CIs for the difference between Day 4 and Day 2 were constructed using the residual mean square error obtained from the ANOVA for each treatment. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least square means and the corresponding 90% CIs.

2.5.3.1.1 Pharmacokinetic Study NL0602 – Single Dose (Fasted and Fed)

The design of this study is reviewed in **Section 2.5.2** and the results are reviewed in **Section 2.5.2.1**. A summary of the data can be found in **Module 2.7 Section 2.7.1.2.1.** The results from study NL0602 confirm that the pharmacokinetic parameters of ibuprofen and paracetamol taken as the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are typical of those data reported in the public domain for the single actives. Study NL0602 confirms that there is no pharmacokinetic drug-drug interaction between ibuprofen and paracetamol when taken as the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

2.5.3.1.2 Pharmacokinetic Study NL0603 – Repeat Dose

A more detailed summary of these data are presented in **Module 2.7 Section 2.7.2.2.2**.

This study was designed to examine the repeat dose pharmacokinetics of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' taken twice or three times a day for 3 days by 26 healthy volunteers. The study determined plasma ibuprofen and paracetamol levels. The study was conducted in compliance with GCP.

The primary pharmacokinetic variables for each dosing regimen were area under the plasma concentration curve: AUC_{0-t} (to the last measurable concentration), AUC_{0-inf}, AUC_{tau} (for a dosing interval); plasma concentration: C_{max} (maximum), C_{min} (minimum), C_{av} (average), fluctuation ($[C_{max}-C_{min}]/C_{av}$) and swing ($[C_{max}-C_{min}]/C_{min}$), and t_{max} for ibuprofen and paracetamol. In addition, vital signs and adverse events were assessed.

Comparison of pharmacokinetic parameters after first-dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in NL0603 (Day 2) and with NL0602

The first dose (Day 2) pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}, were comparable for both ibuprofen and paracetamol treatments following administration of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. For ibuprofen there was a slight variation in the rate of absorption (t_{max} 1.25 vs. 1.75 hours) an indication of intra-subject variability, whereas there was no difference in t_{max} values for paracetamol (**Table 2**).

A comparison of the pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, and t_{max} after the first dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in NL0603 (repeat dose) with the fixed combination data from the single dose pharmacokinetic study (NL0602) are summarised in **Table 2**. The results are consistent across both studies, except for the variation in the rate of ibuprofen absorption (t_{max}) in NL0603. However, the t_{max} values for ibuprofen are within 1-2 hours as quoted in the standard texts (Dollery 1999a). In conclusion, the single dose pharmacokinetic parameters for ibuprofen and paracetamol as the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are comparable for studies NL0602 and NL0603.

Table 2: Comparison of ibuprofen and paracetamol pharmacokinetic parameters for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' from NL0602 and NL0603 (first dose)

Pharmacokinetic parameters (Arithmetic means)	Ibuprofen			Paracetamol		
	NL0602 (n = 25)	NL0603 Day 2 First Dose (n = 26)		NL0602 (n = 25)	NL0603 Day 2 First Dose (n = 26)	
	Single Dose	Twice a day	Three a day	Single Dose	Twice a day	Three a day
C_{max} (µg/mL)	32.04	32.53	36.66	18.48	14.73	15.86
AUC_{0-t} (µg/mL.h)	118.32	128.29	124.01	51.69	46.98	47.58
AUC_{0-inf} (µg/mL.h)	120.92	130.67	132.27	54.49	49.23	52.49
t_{max} (h)	1.25[a]	1.75[a]	1.25[a]	0.50[a]	0.67[a]	0.67[a]

[a] Median Value

Steady state pharmacokinetics

A comparison of the mean plasma concentrations for ibuprofen and paracetamol with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' from the first dose (Day 2) and twice a day dosing (Treatment A) and three times a day dosing (Treatment B) on Day 4 are presented in **Figure 4** and **Figure 5** respectively. [redacted] The least square geometric mean ratios and the associated 90% CI fall within the bioequivalence range of 80-125%. In addition, the mean peak plasma concentrations (C_{max}) after single and repeat dosing of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are also comparable (**Table 2** and **Table 4**).

[redacted]

Figure 4: Comparison of ibuprofen and paracetamol mean plasma concentration (µg/mL) curves first dose (Day 2) and twice a day dosing with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Day 4)

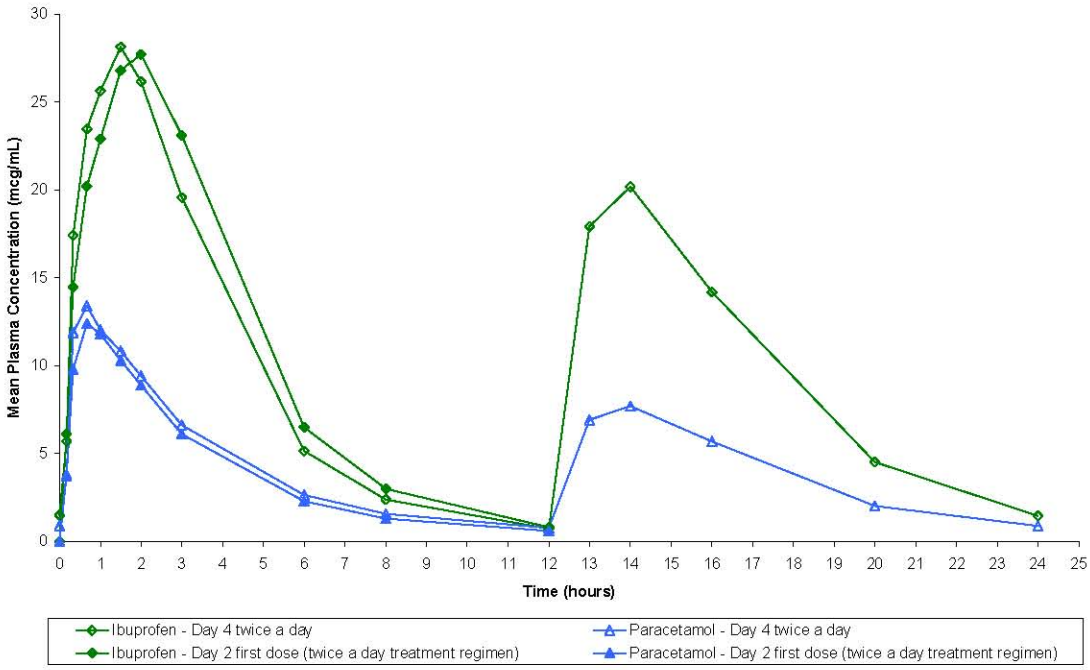
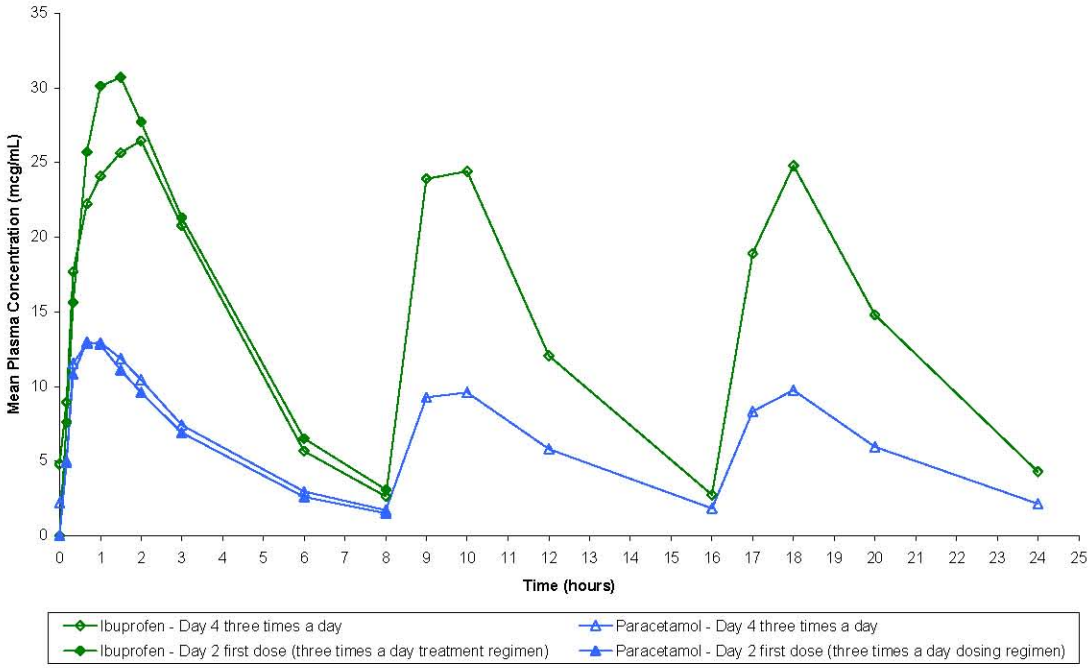


Figure 5: Comparison of ibuprofen and paracetamol mean plasma concentration (µg/mL) curves first dose (Day 2) and three times a day dosing with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Day 4)



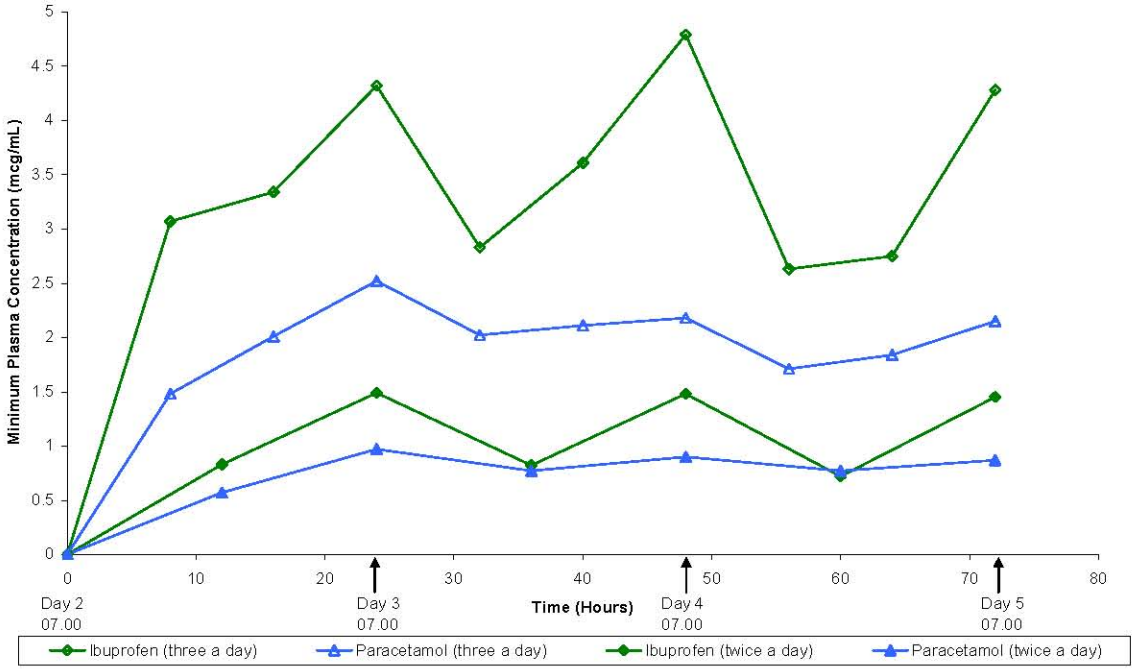
As a comparison of the steady state pharmacokinetics for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' after twice and three times a day dosing the minimum plasma concentrations (C_{min} or trough) values for ibuprofen and paracetamol are plotted from the three treatment days (pre-dosing on Day 2, 3 and 4) and post dose on Day 5 (**Figure 6** and **Module 2.7 Section 2.7.2.2.2 Table 8**). The first pre-dose sample of each day was taken at 07.00 and approximate meal times each day were 09.00 breakfast, 12.00 lunch, 17.00 dinner and 21.00 snack.

Analysis of minimum plasma concentration (C_{min} or trough) data for ibuprofen at the same time of day showed no significant differences irrespective of the dose regimen. The same comparison with paracetamol showed that the C_{min} values on the second day of treatment (Day 3) were significantly higher. However, there was no statistically significant difference between the remaining values on Day 3, 4 and 5 confirming that steady state was achieved (**Module 2.7 Section 2.7.2.2.2 Table 9**).

A comparison of the C_{min} (or trough) values obtained at different times of day, i.e. in the morning (07.00) was significantly different to those obtained in the afternoon (15.00) or evening (19.00 and 23.00) (**Module 2.7 Section 2.7.2.2.2 Table 10**). This variation is expected, as C_{min} (trough) values are higher following the inter-digestive period, i.e. overnight fasting, compared to those obtained in the digestive period during the day.

In conclusion there was no accumulation of either ibuprofen or paracetamol.

Figure 6 **Mean minimum plasma concentrations (C_{min}) for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' from two and three times a day dose regimens over three days**



Comparison of two and three times a day repeat Dose pharmacokinetic parameters with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Day 4)

The arithmetic mean derived pharmacokinetic parameters after repeat dosing on Day 4 with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are presented in **Module 2.7 Section 2.7.2.4 Table 2.7.2.1** and summarised in **Table 4**.

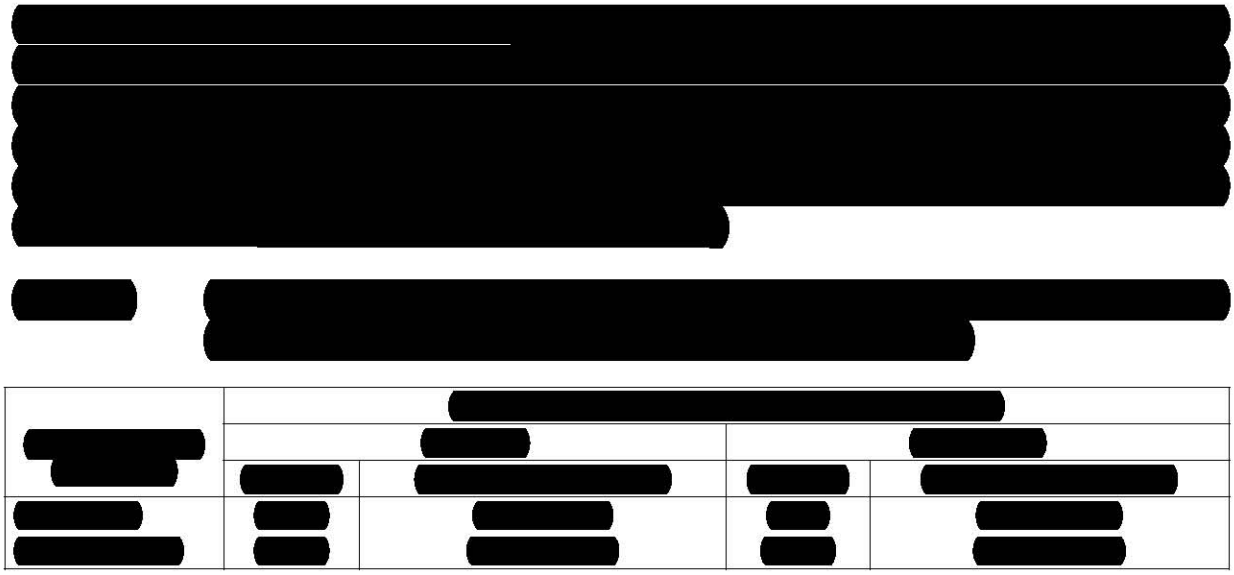
Table 4 **Repeat dose pharmacokinetic parameters for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' after two or three times a day dosing (Day 4)**

	Ibuprofen mean value		Paracetamol mean value	
Pharmacokinetic Parameters	**Twice a day**	**Three times a day**	**Twice a day**	**Three times a day**
N	26	26	26	26
t_{max} (h)	1.50[a]	1.50[a]	0.67[a]	0.67[a]
C_{max} (µg/mL)	33.14	33.55	16.09	15.87
C_{min} (µg/mL)	0.72	2.64	0.74	1.87
C_{av} (µg/mL)	9.61	13.69	4.07	5.86
Fluctuation ($C_{max} - C_{min}$)/ C_{av}	3.44	2.26	3.83	2.47
Swing ($C_{max} - C_{min}$)/ C_{min}	62.47	14.90	22.81	8.73
AUC_{0-t} (µg/mL.h)	230.73	328.60	97.67	140.80
AUC_{tau} (µg/mL.h)	118.12	114.26	51.72	50.74

[a] Median Value

The C_{max} and t_{max} values for both ibuprofen and paracetamol were similar for both treatment regimens. C_{min} and C_{av} values for both ibuprofen and paracetamol were greater following three times a day dosing compared to twice a day. There was, therefore, less fluctuation and swing with ibuprofen and paracetamol plasma concentrations following three times a day

dosing compared to twice a day dosing. AUC_{0-t} values for ibuprofen and paracetamol were greater following three times a day dosing compared to twice a day dosing; however, AUC_{tau} were similar for both dosing regimens.



The three times daily dosing regimen provides more consistent exposure to plasma levels of ibuprofen and paracetamol with less fluctuation and swing which is likely to give sustainable pain relief for the patient. In conclusion, the three times a day dosing gives more consistent plasma levels and is likely to be more effective.

Conclusion

The pharmacokinetic data from studies NL0602 and NL0603 confirm that there is no pharmacokinetic drug-drug interaction between ibuprofen and paracetamol when taken as the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

The twice and three times a day repeat dose pharmacokinetics parameters for ibuprofen and paracetamol after administration of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' for 3 days were comparable to the corresponding first dose pharmacokinetic parameters confirming that steady state was achieved and there was no accumulation of ibuprofen or paracetamol.

The three times a day dosing regimen of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provided more consistent plasma concentrations of ibuprofen and paracetamol compared to twice daily dosing without the risk of accumulation. This supports the posology for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' of 2 tablets to be taken every 6 to 8 hours, i.e. six tablets a day.

2.5.3.1.3 Special Groups

No specific pharmacokinetic studies were conducted in children, the elderly or high risk special populations such as patients with renal, hepatic or cardiac impairment. No specific pharmacokinetic drug-drug interaction studies were conducted.

Children

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is not indicated for children or adolescents below the age of 18 years.

Elderly

Age has minimal influence on the pharmacokinetics of ibuprofen and paracetamol, and repeated administration of ibuprofen and paracetamol does not result in drug accumulation. Therefore no dosage modifications are required for the elderly. However caution should be exercised with this population because they also suffer from hepatic, renal and cardiac impairment and the morbidity associated with any adverse reactions may be greater hence the inclusion of contraindications and caution statements in the Summary of Product Characteristics (SPC) and product labelling.

Renal, Hepatic and Cardiac Impairment

Patients with renal, hepatic or cardiac impairment are at increased risk of adverse reactions when taking ibuprofen and paracetamol containing products. Therefore the SPC and product labelling for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' contra-indicates patients with severe renal, hepatic or cardiac impairment and cautions all patients with renal, hepatic and cardiac dysfunction to seek medical advice before taking this product.

Pregnancy and Lactation

In animal studies, ibuprofen at high doses may have a weak effect on ovulation and as a result, impair fertility; however this finding has doubtful relevance to humans (**Module 2.4 Section 2.4.5**). However a caution appears in the SPC and product labelling.

Animal studies have not demonstrated a foetal risk with ibuprofen, but there have been no studies in pregnant women (**Module 2.4 Section 2.4.5**). Therefore ibuprofen containing products should be avoided during pregnancy. The use of ibuprofen in the third trimester has been associated with the inhibition of uterine contraction, premature closure of ductus arteriosus and pulmonary hypertension of the neonate, an increased bleeding tendency in mother and child, and increased formation of oedema in the mother. Therefore, a statement has been included in the SPC and product labelling that 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' should be avoided during pregnancy except with doctor's advice and contra-indicated in the last trimester.

Ibuprofen and paracetamol can pass in very small non-clinically significant amounts into the breast milk. No harmful effects to infants are known, so it is not necessary to interrupt breast-feeding for short-term treatment with the recommended dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. In long-term treatment, if possible, 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' should be avoided when breastfeeding.

2.5.3.1.4 Drug Interactions

No drug-drug interactions studies have been conducted with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'; however it is considered prudent to contra-indicate the taking of this product in combination with other paracetamol-containing products and NSAIDs, including COX-2 selective inhibitors and aspirin at doses above 75 mg because of the risk of serious adverse effects.

Caution should be exercised or medical advice sought before taking 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' with any of the following:

- Anticoagulant effects of warfarin and other coumarins may be prolonged by regular use with paracetamol or an NSAID increasing the risk of bleeding.
- Antihypertensives and diuretics effects may be reduced with NSAIDs, whereas diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs) may increase the risk of gastrointestinal bleeding with NSAIDs
- Cardiac glycosides taken with an NSAID may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma glycoside levels.
- Chloramphenicol because plasma concentration may be increased
- Cholestyramine as it reduces the speed of absorption of paracetamol
- Ciclosporin taken with an NSAID may increase the risk of nephrotoxicity.
- Corticosteroids taken with an NSAID may increase the risk of adverse effects, especially of the gastrointestinal tract.
- Lithium taken with an NSAID may increase the plasma levels of lithium.
- Methotrexate taken with an NSAID may increase the plasma levels of methotrexate.
- Metoclopramide and Domperidone increase the absorption of paracetamol
- Mifepristone effect can be reduced when taken with NSAIDs. NSAIDS should be avoided for 8-12 days after mifepristone administration.
- Quinolone antibiotics taken concurrently with NSAIDS may increase the risk of developing convulsions.
- Tacrolimus taken with an NSAID may increase the risk of nephrotoxicity.
- Zidovudine taken with an ibuprofen may increase the risk of haemarthroses and haematoma in HIV (+) haemophiliacs.

2.5.3.2 Pharmacodynamics

Mechanism of Action

Ibuprofen, a propionic acid derivative, is a NSAID which relieves pain and inflammation by the non-selective inhibition of prostaglandin biosynthesis at the site of tissue injury. Therefore ibuprofen prevents the sensitisation of tissues to other pain mediators e.g. histamine, 5-hydroxytryptamine and bradykinin. Ibuprofen is a potent inhibitor of COX 1 and 2 and experimentally inhibits induced-leucocyte migration into inflamed areas (Dollery 1999a). Sandrini *et al* (1992) has shown that ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. At a maximum

daily dose of ≤ 1200 mg ibuprofen predominately acts as an analgesic and antipyretic (**Module 2.7 Section 2.7.2.1**).

Paracetamol is a weak inhibitor of COX 1 and 2 in peripheral tissues and has no significant anti-inflammatory activity (Brunton 2006). The analgesic and antipyretic mechanism of action of paracetamol are still considered to be unknown, however the following mechanisms have been proposed: the inhibition of COX in the central nervous system by reversible, non-competitive binding preventing the production of prostaglandin from arachidonic acid; interaction with spinal 5-hydroxtryptamine ($5\text{-}HT_3$) receptors; interference with spinal substance P; inhibition of neurons excited by substance P, activation of suprasegmental descending inhibitory pathways, increase in pituitary β–endorphin secretion or direct effects on neuronal membrane potentials, COX 3, a splice variant of COX 1, has also been considered. (Bannwarth *et al* 1995, Bonnefont *et al* 2003 Breivik *et al* 1999, Chandasrasekharan *et al* 2002, Pelissier *et al* 1995, Pini *et al* 1996; Raffa and Codd 1996, Sandrini *et al* 2003) (**Module 2.7 Section 2.7.2.1**).

Pharmacodynamics

There is a clear and positive relationship between ibuprofen plasma levels and the degree of measured pain relief (Laska *et al* 1986) and there is an indication that minimum therapeutic effects are associated with plasma levels of 10–50 µg/mL (Davies 1998). The relationship between plasma concentrations and therapeutic effects of paracetamol is not straight forward. There is a marked counter-clockwise hysteresis loop for analgesia and plasma concentration curve due to a lag between plasma concentration and effect (Seymour and Rawlins 1981, Kelley *et al* 1992). Delayed therapeutic effects are accounted for by an 'effect compartment' and the need for paracetamol concentrations to reach this 'effect compartment'. Despite this delay in effect, the literature indicates that plasma levels of between 5–10 µg/mL are required for analgesic effects of paracetamol (Kelley *et al* 1992, Rumack 1978, Brown 1998, Anderson 1999).

Dose – response relationship

There is a clear dose-response relationship of ibuprofen 50, 100, 200, 400, and 600/800 mg in the treatment of acute pain, as efficacy increases with an increase in dose, e.g. with ibuprofen 200 mg 48% of patients with initial pain of moderate or severe intensity had at least 50% pain relief over 4-6 hours, as did 55% with ibuprofen 400 mg and 79% with ibuprofen 600 mg (**Module 2.7 Section 2.7.2.1**). This is reflected in the NNT (number-needed-to-treat for at least one additional patient to have at least 50% pain relief in 4-6 hours) compared to placebo of 2.5, 2.7 and 1.7 for ibuprofen 200 mg, 400 mg and combined 600/800 mg respectively.

The dose-response relationship of paracetamol in the treatment of acute pain is flat, as with paracetamol 500 mg 61% of patients with initial pain of moderate or severe intensity had at least 50% pain relief over 4-6 hours compared to 38% with paracetamol 600/650 mg, 46% with paracetamol 1000 mg and 65% with paracetamol 1500 mg (**Module 2.7 Section 2.7.2.1**). This is reflected in flat NNT compared to placebo of 3.5, 4.6, 3.8 and 3.7 for paracetamol 500 mg, 600/650 mg, 1000 mg and 1500 mg respectively.

McQuay and Moore (2006) investigated the dose-response relationship for analgesia by direct comparison of different doses of ibuprofen and paracetamol within the same study and then pooling the extractable efficacy data from these studies. The extractable data comparing ibuprofen 200 mg to 400 mg, from 994 patients, showed that 59% of patients had at least 50% pain relief with 200 mg compared to 68% of patients with 400 mg. The relative benefit was 1.2 (95% CI 1.1, 1.3) and the NNT for one additional patient to obtain more than 50% pain relief with 400 mg rather than 200 mg was 10 (6, 23). The pooled extractable data comparing paracetamol 500 mg/650 mg to 1000 mg, from 933 patients, showed that 52% of patients had at least 50% pain relief with 500/650 mg compared to 64% of patients with 1000 mg. The relative benefit was 1.2 (95%CI 1.1, 1.4) and the NNT for one additional patient to obtain more than 50% pain relief with 1000 mg rather than 500/650 mg was 9 (6, 20).

The unit dose of the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was chosen based on well documented dose-response data and safety data for ibuprofen and paracetamol alone in the public domain. The clinical efficacy of ibuprofen alone at a dose of 400 mg, and paracetamol alone at dose of 1000 mg, are well established in the treatment of mild to moderate pain.

2.5.3.2.1 Dose-Response Studies

Dose-response with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was investigated as part of the pivotal efficacy and tolerability study NL0604 using the post-surgical dental pain model, which is sensitive, validated and discriminating. The design of this study is reviewed in **Section 2.5.4** and the results are reviewed in **Section 2.5.4.5.1**. A summary of the data can be found in **Module 2.7 Section 2.7.3.2.2.** The results from this study confirm that there was a dose-response between the three doses of the fixed combination test (Ibuprofen 100 mg and Paracetamol 250 mg tablet, and a 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'). The 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were statistically significantly more effective than Ibuprofen 100 mg and Paracetamol 250 mg tablet, and the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective from hour 7 than 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 Brief Introduction

This section contains an analysis of the clinical data that supports the efficacy of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' as a treatment for mild to moderate pain. The product is intended for adults from 18 years. The proposed posology is 2 tablets to be taken every 6 to 8 hours not exceeding 6 tablets (i.e. a maximum daily dose of ibuprofen 1.2 g and paracetamol 3.0 g) in a 24-hour period.

A systematic bibliographic review was conducted to investigate the overall efficacy and tolerability of ibuprofen and paracetamol used in combination, or alternated, in the treatment of pain and fever (**Module 2.7 Section 2.7.3.1.2**). Two systematic searches of the literature identified 212 unique papers 15 of which met the search criteria. A further two papers were identified published as electronic versions only. None of the eleven surgical pain studies were conducted in a well characterised and sensitive acute pain model, i.e. extraction of impacted third molars. The unit dose of the combination used in the adult studies was different to 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. Despite these differences, it can be concluded that the combination of ibuprofen and paracetamol was more effective than placebo and paracetamol alone; there was no clear difference between the combination and ibuprofen at the doses studied.

The unit dose of the fixed combination was chosen based on well documented dose-response data and safety data for ibuprofen 400 mg and paracetamol 1000 mg alone in the public domain (Bandolier 2008 and 2002, McQuay 2006).

The clinical programme has established that ibuprofen and paracetamol, from the fixed combination, are bioavailable; there is no pharmacokinetic drug-drug interaction, no accumulation on repeat dosing, and the three times a day dosing regimen provides more consistent plasma levels.

[redacted]

The Applicant designed and conducted three well-controlled, randomised, double-blind, parallel group efficacy and tolerability studies: an exploratory study (NL0408), the pivotal study (NL0604) and the confirmatory study (NL0605) (**Table 6**).

Table 6 Summary of efficacy and tolerability studies

Study ID	Test treatment	Dosing	Subject Population	Number of Subjects	
				Randomised	Completed
Exploratory study in acute pain **NL0408**	1. Concomitant tablets – dose: 2 x ibuprofen 200 mg and 2 x paracetamol 500 mg 2. Concomitant tablets – dose: 1 x ibuprofen 200 mg and 1 x paracetamol 500 mg	Single dose	Adults (16-31 years)	234	222
Pivotal Study in acute pain **NL0604** **Part 1 and 2**	1. 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' 2. 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' 3. 1 x Ibuprofen 100 mg and Paracetamol 250 mg tablet	Part 1 – Single dose Part 2 – multiple dose up to 3 days	Adults (16-39 years)	735 715	715 678
Confirmatory Study in chronic pain **NL0605**	1. 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' 2. 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'	Multiple dose for 13 weeks	Adults (40-84 years)	892	615

Although the Notes for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Nociceptive Pain (CPMP/EWP/612/00) states that models such as tooth extraction, sprains, minor surgery (e.g. cutaneous surgery, hernia), headache (other than migraine), sore throat, low back pain and primary dysmenorrhoea are suitable for assessment of mild to moderate acute pain; these models lack sensitivity to develop sufficient pain so the fixed combination can show additional pain relief over the single substances, especially ibuprofen 400 mg. Therefore to comply with the fixed combination guidance (CPMP/EWP/240/95) the Applicant sought advice as to the most appropriate model where a sufficient increase in pain occurs so additional pain relief with the fixed combination could be determined over ibuprofen 400 mg and paracetamol 1000 mg. Post-operative dental pain is a widely accepted, validated pain model (Cooper and Beaver 1976) used to evaluate and compare analgesic efficacy. The model is robust as it produces moderate to severe acute pain that is predictable in character, duration and intensity. In addition, the model is sensitive and has a proven record of separating treatments from each other and placebo (Cooper *et al* 1989). The post-operative dental pain model has been widely used to assess and compare the efficacy of ibuprofen and paracetamol (McQuay and Moore 2006). The exploratory (NL0408) and pivotal study (NL0604) were conducted in this acute pain model.

The exploratory study (NL0408) was of a conventional single dose factorial design, which utilised proprietary ibuprofen [redacted] and paracetamol [redacted] products to demonstrate the contribution of the individual actives to the combination, whilst assessing efficacy and tolerability (**Module 2.7 Section 2.7.3.2.1**). The pivotal and confirmatory studies (NL0604 and NL0605) investigated the efficacy of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', the product which is the subject of this MAA.

Traditionally, the pivotal study NL0604 may have been designed as four separate studies, i.e. a factorial study for a single tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', a factorial study for a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', a single dose assessment of dose response, and the efficacy and tolerability of three

different doses of the fixed combination tablet. In study NL0604, all of these comparisons were incorporated in a two part study (**Module 2.7 Section 2.7.3.2.2**).

The pivotal study (NL0604 Part 1) was the only full factorial study designed to establish superior efficacy of the fixed combination over the single substances. Part 1 also investigated dose-response and included an Ibuprofen 100 mg and Paracetamol 250 mg tablet. Part 2 investigated the efficacy and tolerability of 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', Ibuprofen 100 mg and Paracetamol 250 mg tablet and placebo after multiple dosing over 3 days.

The confirmatory study NL0605 was conducted in a chronic mild to moderate pain model over 13 weeks. Following scientific advice sought from the FDA, EMEA (CHMP) and MHRA the Applicant agreed to include efficacy assessments in this study. This study was not designed as a full factorial study as there is no evidence that chronic knee pain provides enough 'sensitivity' to show a benefit of paracetamol over and above that of an NSAID or that knee pain (surgical or OA) is a good model to discriminate between a fixed combination and the single substances (Rømsing *et al* 2002), Hyllested *et al* 2002, Dahl *et al* 2004, Kjaersgaard-Andersen *et al* 1990). The study was designed to generate confirmatory efficacy data with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the relief of mild to moderate pain, but to principally generate tolerability data compared to ibuprofen and paracetamol alone (**Module 2.7 Section 2.7.3.2.3**).

2.5.4.2 Patient Population Studied

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is intended for adults from 18 years for mild to moderate pain.

The demographic profiles for studies NL0408, NL0604 and NL0605 are summarised in **Module 2.7 Section 2.7.3.3.1.3** and the overall demographic profile from studies NL0408, NL0604 and NL0605 are presented in **Module 2.7 Section 2.7.4.7 Appendix Table 2.7.4.2.**

Both the exploratory (NL0408) and the pivotal (NL0604) efficacy studies were conducted in young subjects (16-39 years) who were otherwise well, but suffering from moderate to severe acute pain associated with dental surgery. Overall 87.7% of subjects were aged 18 years or over. The majority of the participants were: female (74.4% in NL0408 and 62.6% in NL0604); race classified as white (76.5% in NL0408 and 91.3% in NL0604). The patient population from these studies can be considered to be representative of patients who suffer from mild to moderate pain.

The demographics by treatment groups were balanced across studies NL0408 and NL0604 with respect to age, gender, race, site, weight and height. The mean vital sign values, on screening, were within the normal ranges and similar across treatment groups. The medical history, physical examination, concomitant medications were also similar. The mean baseline VAS pain scores were 74.1 mm (NL0408) and 76.9 mm (NL0604).

By comparison the subject population from the confirmatory study NL0605 differed from the subjects who participated in studies NL0408 and NL0604. In NL0605, the subjects were older (40-84 years) and a greater proportion of subjects drank alcohol. Subjects in NL0605

were allowed to continue to drink alcohol during the study. The overall proportion of subjects experiencing an ongoing medical condition was comparable across all three studies. However, the type of conditions was different, i.e. in NL0408 and NL0604 ongoing conditions included allergies/drug sensitivities, urogenital conditions and neurological disorders, whereas in NL0605 44% had musculoskeletal disorders and 37% had cardiovascular disorders.

In study NL0605 the demographics by treatment group were balanced with respect to age, race, weight, height, medical history, ongoing medical condition, OA, and baseline pain and QoL scores. There was an imbalance between treatment groups with respect to gender, therefore gender was used as a subgroup analyses for the primary efficacy endpoints. There was also a 15% difference in subjects taking concomitant medication with paracetamol 1000 mg compared to a single dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The mean baseline WOMAC (VAS) pain score was 43.6 mm.

Patients were excluded from the studies if they had: a current history of significant disease, ongoing painful condition, or were taking specific concomitant medication that may have confounded the efficacy results from the studies (**Module 2.7 Section 2.7.3.3.1.2**). This is in line with accepted study design practice.

2.5.4.3 Implications of the Study Designs

The exploratory (NL0408) and the pivotal (NL0604) acute pain studies had a similar study design, i.e. double-blind, parallel-group, placebo-controlled, randomised, factorial conducted using post-operative dental pain (**Section 2.5.4.1** and **Module 2.7 Section 2.7.3.1.4**). To ensure the studies were able to demonstrate additional pain relief with the combination of ibuprofen and paracetamol compared to the reference products (ibuprofen 400 mg and paracetamol 1000 mg), a minimum of three bony impacted third molars were removed (of which two had to be mandibular impacted molars requiring bone removal). With a greater number of surgical sites there is a corresponding increase in the pain that arises (Woolf 1983), so called 'upside sensitivity'. The model is relevant to the indication of mild to moderate acute pain as the pain from the model is transient.

The primary endpoint for NL0408 and NL0604 Part 1 was the sum of pain relief and pain intensity differences over the 0 to 8 hour interval ($SPRID_{0-8h}$), which combines the validated and widely used variables of 'pain relief' (PAR) and 'pain intensity difference' (PID). PAR and PI were determined using validated scale evaluations. Key secondary endpoints included assessments of 'time to confirmed perceptible pain relief', 'time to meaningful pain relief', 'time to pain half gone', 'duration of effect' (time to use of rescue medication or next dose of study medication) and the 'subject's global assessment' of the study medication. These are conventional endpoints routinely used in the assessment of pain and are in accordance with those proposed in the European guidance (CPMP/EWP/612/00).

The primary endpoint in NL0604 Part 2 was based on a similar principle to 'pain half gone', i.e. defining a 'responder variable' for a set of well defined time intervals for the total follow-up period and then counting the number of time intervals for which the 'responder variable' was positive for a patient. In NL0604 the 'responder variable' was positive when a

patient completed a 24-hour period with no more than one dose of rescue medication and provided a response of 'at least good' for the subjects overall assessment at the end of each 24-hour period. In Part 2 there was three consecutive 24-hour periods (72 hours), therefore the number of 24-hour periods for which the 'responder variable' could be positive was 0, 1, 2, or 3.

NL0605 was a double-blind, parallel-group, placebo-controlled randomised study in chronic knee pain. Initially the study was to be conducted in patients with osteoarthritis (OA). Following consultation with external experts, the patient population was broadened to include patients in the community with chronic knee pain rather than just a "sub population" with a specific degree of OA. During the study a patient was assessed or confirmed as having OA. These patients are typical of those who are likely to seek medical advice and require long-term analgesia. A placebo control was considered inappropriate for a study where patients with a painful condition participated for 13 weeks.

NL0605 had two primary efficacy endpoints and a primary tolerability endpoint after long-term use (**Section 2.5.5.4.2**). The primary efficacy endpoints were:

- Short-term efficacy at Day 10 assessed using the pain element of the Western Ontario McMaster Universities Osteoarthritis (WOMAC) Index subscale for pain (normalised to 0-100 mm scale).

- Long-term efficacy was the patient global assessment of study medication at Week 13 (where Week 13 data was unavailable the last observation was carried forward (LOCF)) assessed on the 5-point Likert scale in response to the question "overall, taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for your painful knee?" as excellent, good, fair, poor or unacceptable.

The above measures have been defined and validated in patients with OA of the knee (Tubach *et al* 2005a and 2005b, Ehrich *et al* 2000). The minimum clinically relevant changes for the above measures have been defined and supported. Todd *et al* (1996) and Kelly (2001) present evidence that the minimum clinically significant meaningful change in a 100 mm VAS with acute pain is 12-13 mm, irrespective of whether the subject has mild (≤ 30 mm), moderate (> 30 mm < 70 mm) or severe pain (≥ 70 mm) as predetermined by VAS pain scores (Kelly 2001). Tubach *et al* (2005b) presented evidence that in knee OA patients a minimum clinically important improvement in pain was a reduction of 19.9 mm, where the baseline pain intensity was 59.3 mm, Tubach noted that the higher the baseline score the greater the change required in VAS.

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In all studies randomisation was according to a computer generated schedule. In studies NL0408 and NL0604 randomisation was stratified according to sex and pain intensity, whereas in NL0605 it was stratified by diagnosis of OA to ensure equal distribution across the treatment groups. All studies were double blind.

The studies were conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in European Union (EU) Directive 2001/20/EC. The studies complied with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the Code of Federal Regulations (CFR) of the United States (US) Food and Drug Administration (FDA) (21 CFR Part 56, IRBs, and 21 CFR Part 50, Protection of Human Subjects).

2.5.4.4 Statistical Methods

Sample Size

As there were no available data at the proposed combination dose of ibuprofen 400 mg and paracetamol 1000 mg versus placebo, the sample size calculation for the exploratory study (NL0408) was based on a previous dental pain study (Sunshine 1997). The Sunshine study reported a difference in total pain relief (TOTPAR) 0 to 6 hours between ibuprofen 400 mg compared to placebo of 10 units (standard deviation (SD) 8). This was considered to be a clinically meaningful effect. For the primary endpoint ($SPRID_{0-8h}$) in NL0408, the effect size between a combined dose of ibuprofen 400 mg and paracetamol 1000 mg, and ibuprofen 400 mg was 9 units (SD 15) this was also clinically meaningful. The data generated from NL0408 was used to determine the sample size for NL0604.

The pivotal study (NL0604) utilised a partially balanced design where fewer subjects were assigned to treatment groups expected to be less effective (i.e., placebo and the Ibuprofen 100 mg and Paracetamol 250 mg tablet) and for the groups who received the four single actives in Part 1. This sample size provided sufficient statistical power to address the key objectives in Part 1 and 2.

In NL0605, the sample size calculation for the primary short-term efficacy endpoint assumed 90% power, SD of 17 and a 5% significance level (Miceli-Richard *et al* 2007) with 200 subjects in each treatment group ensured a difference of 5.5 between 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg with a two-sample t-test. This specification was also applied to the comparison of 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' to paracetamol 1000 mg. The actual variability was close to the predicted 16.1 (root mean square error from the ANCOVA model – ITT population), and the actual mean difference was 5.3 between 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg, therefore this endpoint was adequately powered.

For the long-term efficacy endpoint, from NL0605, the integer scores for the global assessment scale outcomes were expected to have a respective treatment distribution with an SD of about 1.2 (larger than 25% of the range of 1 to 5 for excellent to unacceptable). Thus, with 200 subjects per treatment group, a two-sided 95% CI for the pairwise difference

between treatments for corresponding means of this endpoint was expected to be about ± 0.24. The sample size of 200 subjects per treatment group provided about 90% power to detect a treatment difference of 0.4 or more at the two-sided 5% significance level, therefore treatments that differed by at least 0.4 would have 90% power for their two-sided 95% CI to exclude 0, and that equivalent treatments had at least 80% power for their two-sided 95% CI to be within ± 0.4. The actual variability for this endpoint was 1.22 (root mean square error from the ANCOVA model – ITT population) therefore this endpoint was adequately powered.

Statistical Analysis

In the exploratory study (NL0408), pivotal study (NL0604) and the confirmatory study (NL0605) the null hypothesis was equivalence. All statistical tests performed were two-tailed with 5% overall significance level. All efficacy analyses were performed using Analysis of Covariance (ANCOVA). In studies NL0408 and NL0604 factors were included for centre, gender and treatment and a covariate for baseline pain intensity, whereas in NL0605 factors were included for treatment group, presence of OA, site and a covariate for baseline WOMAC pain score (continuous). In NL0408 and NL0604 Kaplan-Meier descriptions for time to events; Cox's proportional hazards model; and a logistic regression model were also used.

In addition in NL0604, Cochran-Mantel-Haenszel (CMH) correlation (row mean scores Analysis of Variance [ANOVA]) statistic with integer valued table scores and strata according to the cross-classification of gender and baseline pain severity at the start of Part 1 [moderate or severe] were conducted. In NL0604 and NL0605, the multiple treatment comparisons and the hierarchy involved in testing pairwise differences between the treatment groups was handled using a closed testing procedure with a fixed sequence for treatment comparisons. Within the fixed sequence of treatment comparisons, stages with two parallel assessments used the Hochberg method to manage multiple comparisons.

Normality assumptions were tested by an examination of the residual plots and the Shapiro-Wilk test of normality. For continuous variables, the mean, SD, median, minimum and maximum for the population and for the individual treatment groups was determined.

In NL0604, all scheduled Part 1 diary assessments completed after a subject had taken rescue medication were treated as missing. For PAR, PID and 'duration of pain half gone', missing values between two available assessments were linearly interpolated. Missing readings that could not be interpolated were replaced with the baseline PI, zero PAR, or 'duration pain half gone' equal to zero.

[redacted]

In NL0605, additional efficacy endpoints to those proposed in the study protocol were performed. These were presence and size of effusion in the signal knee, and time taken for sit-to-stand test (seconds) at Day 10, Week 7, Week 13 and at Endpoint (LOCF). Post database lock, gender was added to the subgroup analyses for the two primary efficacy endpoints because of the treatment group gender imbalance.

In conclusion, studies NL0408 and NL0604 demonstrated a high level of assay sensitivity with clear discrimination between the single actives and placebo for virtually every efficacy measure. The pairwise comparisons show statistically significant differences in favour of all active treatment groups versus placebo for the majority of measurements of analgesic efficacy, thereby demonstrating sensitivity of the assay. Study NL0605 was conducted primarily to generate tolerability data and with the knowledge that the knee pain model was not sufficiently sensitive to discriminate between the most effective treatments (2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 400 mg). All treatments were effective; however the only consistent statistically significant differences were observed between 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg.

2.5.4.5 Clinical Relevance of Data

The exploratory study (NL0408) and the pivotal study (NL0604) were well controlled and of a clinically representative design appropriate to assess the efficacy of the combination of ibuprofen and paracetamol in the treatment of mild to moderate acute pain. Study NL0408 was a smaller study conducted with proprietary ibuprofen and paracetamol products dosed concomitantly, whereas the pivotal study NL0604 was conducted with the product which is the subject of this MAA ('Ibuprofen 200 mg and Paracetamol 500 mg tablet').

The confirmatory study NL0605 was also a well controlled study and of a clinically representative design to confirm the efficacy of the fixed combination in the treatment of mild to moderate chronic pain.

2.5.4.5.1 Acute Pain Studies (NL0408 and NL0604 Part 1) - Single Dose

A more detailed summary of these data are presented in **Module 2.7 Section 2.7.3.2.1** (NL0408), **Section 2.7.3.2.2** (NL0604) **and Section 2.7.3.3.2** (Combined Dataset).

Primary Endpoint

For studies NL0408 and NL0604 Part 1 the protocol pre-defined primary endpoint was the area-under-the-curve for the sum of pain relief and pain intensity difference from 0 to 8 hours

($SPRID_{0-8h}$). The results for the primary endpoint are presented in **Table 7** for the ITT population along with an analysis of the Combined Dataset.

Table 7 Summary of the primary endpoint results from NL0408, NL0604 Part 1 and a Combined Dataset (ITT population)

Treatment Groups	AUC (0-8h) of SPRID – ITT Population					
	Exploratory NL0408		Pivotal NL0604 Part 1		Combined Dataset	
	n	LS Mean	n	LS Mean	n	LS Mean
Ibuprofen 400 mg and Paracetamol 1000 mg	67	3.74	149	3.83	216	3.72
Ibuprofen 200 mg and Paracetamol 500 mg	33	2.94	143	3.76	176	3.45
Ibuprofen 100 mg and Paracetamol 250 mg	-	-	71	3.26	71	3.03
Ibuprofen 400mg	69	2.40	74	3.36	143	2.90
Ibuprofen 200mg	-	-	75	2.95	75	2.72
Paracetamol 1000 mg	34	2.07	74	2.20	108	2.09
Paracetamol 500 mg	-	-	76	1.64	76	1.41
Placebo	31	0.49	73	1.03	104	0.77

The numerical results for the primary endpoint ($SPRID_{0-8h}$) from the pivotal study (NL0604 Part 1) confirm the results of the exploratory study (NL0408) and show a clear increase in effect with dose of ibuprofen and paracetamol in combination (**Table 7**).

The results of the pairwise comparison for the primary endpoint from NL0604 Part 1 show that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than ibuprofen 400 mg alone and paracetamol 1000 mg alone (**Table 8**). In comparison to the other doses of the fixed combination, the single dose was more effective than Ibuprofen 100 mg and Paracetamol 250 mg tablet, but was not statistically significantly different to the 1 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. These results confirm the findings of the exploratory study NL0408, where concomitant ibuprofen 400 mg and paracetamol 1000 mg was more effective than ibuprofen 400 mg alone and paracetamol 1000 mg alone (**Table 8**). However, in the exploratory study the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than the single tablet dose ($p = 0.0209$). All pairwise comparisons separated from placebo.

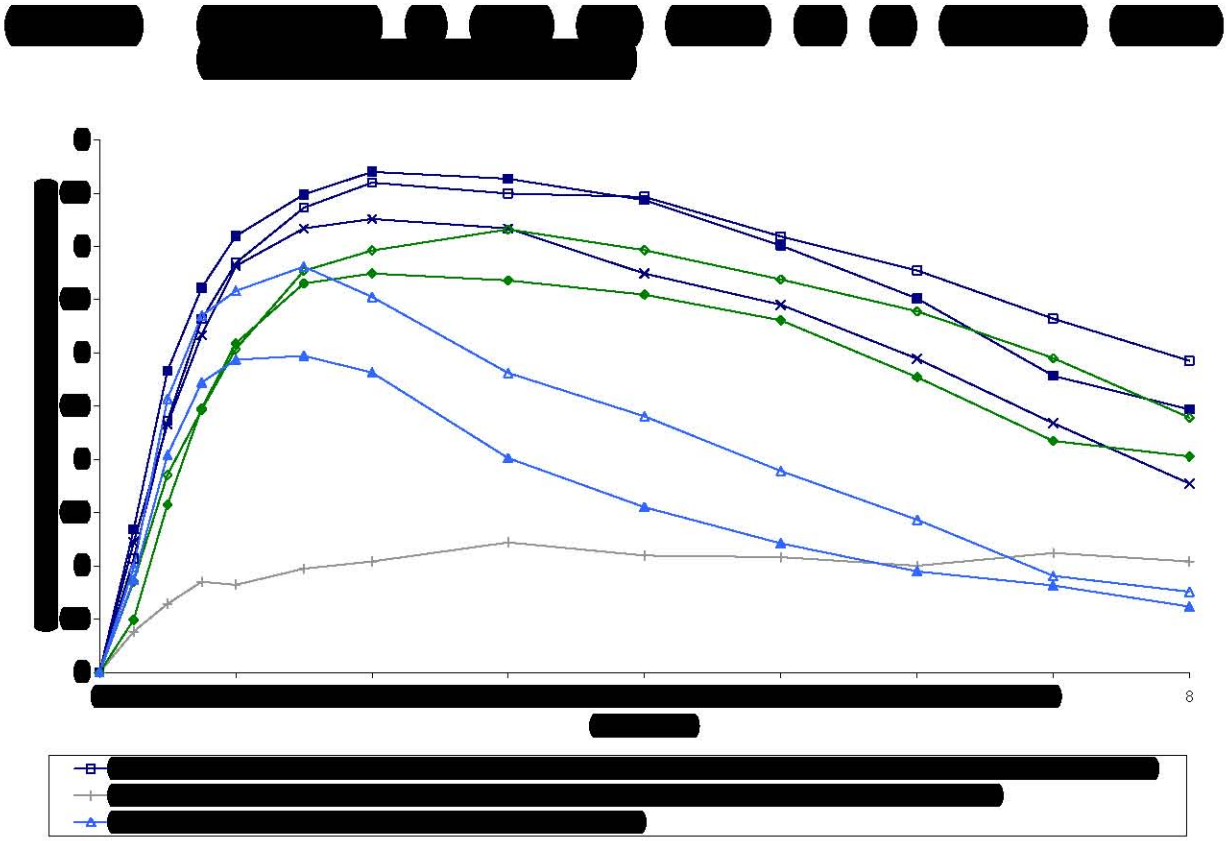
Table 8: Results of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg' pairwise treatment comparisons for the primary endpoint (ITT population)

Study	2 x 'Ibuprofen 200 mg and Paracetamol 500 mg' Primary endpoint SPRID 0-8h pairwise treatment comparisons [a]:				
	Ibuprofen and Paracetamol			Ibuprofen	Paracetamol
	200 mg / 500 mg	100 mg / 250 mg	Placebo	400 mg	1000 mg
NL0408	0.0209*	NA	<0.0001***	<0.0001***	<0.0001***
NL0604 Part 1	NS	0.0068**	<0.0001***	0.0221*	<0.0001***
Combined Dataset	NS	0.0010**	<0.0001***	<0.0001***	<0.0001***

[redacted]

200 mg and Paracetamol 500 mg tablet' compared to ibuprofen 400 mg now becomes highly significant.

The timepoint analysis of mean change from baseline for 'pain relief and pain intensity difference' scores (PRID) for all treatments from the pivotal study (NL0604 Part 1) are presented in **Figure 7**. The results of the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' pairwise treatment comparisons by timepoint for PRID are presented in **Table 9**.



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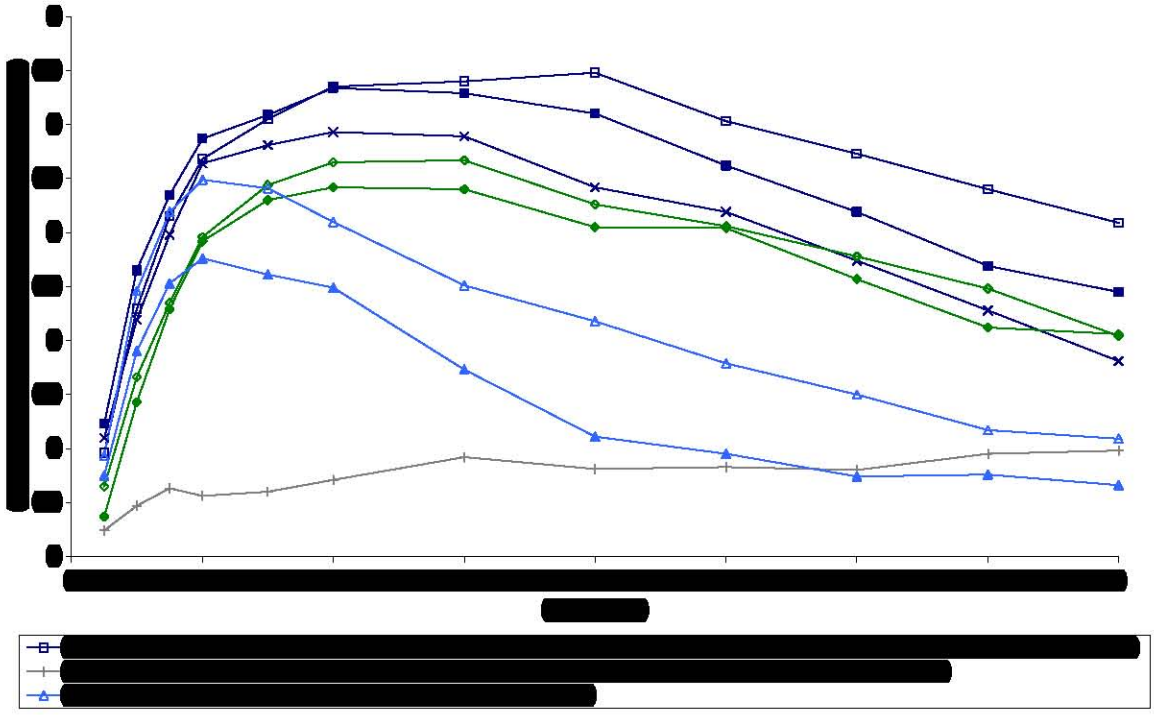


Secondary Efficacy Endpoints

The secondary efficacy endpoints for the pivotal study (NL0604 Part 1) included sum of pain intensity difference (SPID) measured using a categorical scale and VAS, TOTPAR, 'time to confirmed perceptible pain relief', 'time to meaningful pain relief', 'time of pain half gone', 'duration of effect' and the 'subject overall assessment' of the study medication. A summary of the results and the pairwise treatment comparisons are presented in **Module 2.7 Section 2.7.3.2.2**. For the secondary efficacy endpoints in NL0604 Part 1 statistical comparisons were only performed against the equivalent dose of the single actives (i.e. ibuprofen 400 mg and paracetamol 1000 mg).

The results of the pairwise treatment comparisons from NL0604 Part 1 show that:

- **For SPID 0-4 hours, 0-6 hours and 0-8 hours**, the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than placebo ($p < 0.0001$), ibuprofen 400 mg ($p < 0.05$) and paracetamol 1000 mg ($p < 0.0001$). There was no statistically significant difference between the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. These results were similar for **SPID VAS**; however the only statistical difference between 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 400 mg was at 0-4 hours. For the same endpoints in NL0408 the 2 tablet dose of the combination was more effective than paracetamol 1000 mg, ibuprofen 400 mg and placebo ($p < 0.0001$) (**Module 2.7 Section 2.7.3.2.1**).

- **For TOTPAR 0-4 hours, 0-6 hours and 0-8 hours**, the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than placebo ($p < 0.0001$), ibuprofen 400 mg ($p < 0.05$) and paracetamol 1000 mg ($p < 0.0001$). For the same endpoints in NL0408 the 2 tablet dose of the combination was more effective than paracetamol 1000 mg, ibuprofen 400 mg and placebo ($p < 0.0001$) and 'Ibuprofen 200 mg and Paracetamol 500 mg 0-8 hours ($p < 0.05$) (**Module 2.7 Section 2.7.3.2.1**).

- The Kaplan-Meier estimates for median **'time to confirmed perceptible pain relief'** shows a fast onset of action for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' of 18.3 minutes, and has a statistically significantly more rapid onset of action than ibuprofen 400 mg ($p < 0.01$). There were no statistically significant differences between the combination tablets. These results confirm the findings of the exploratory study (NL0408), where the 2 tablet dose of the combination was statistically significantly superior to ibuprofen 400 mg ($p < 0.05$) and paracetamol 1000 mg ($p < 0.05$) (**Module 2.7 Section 2.7.3.2.1**).

- The Kaplan-Meier estimates for median **'time to meaningful relief'** also support the fast onset of action of the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' with a time of 44.6 minutes. The 'time to meaningful relief' was more rapid with the 2 tablet dose of the combination than ibuprofen 400 mg ($p < 0.001$). There were no statistically significant differences between the combination tablets.

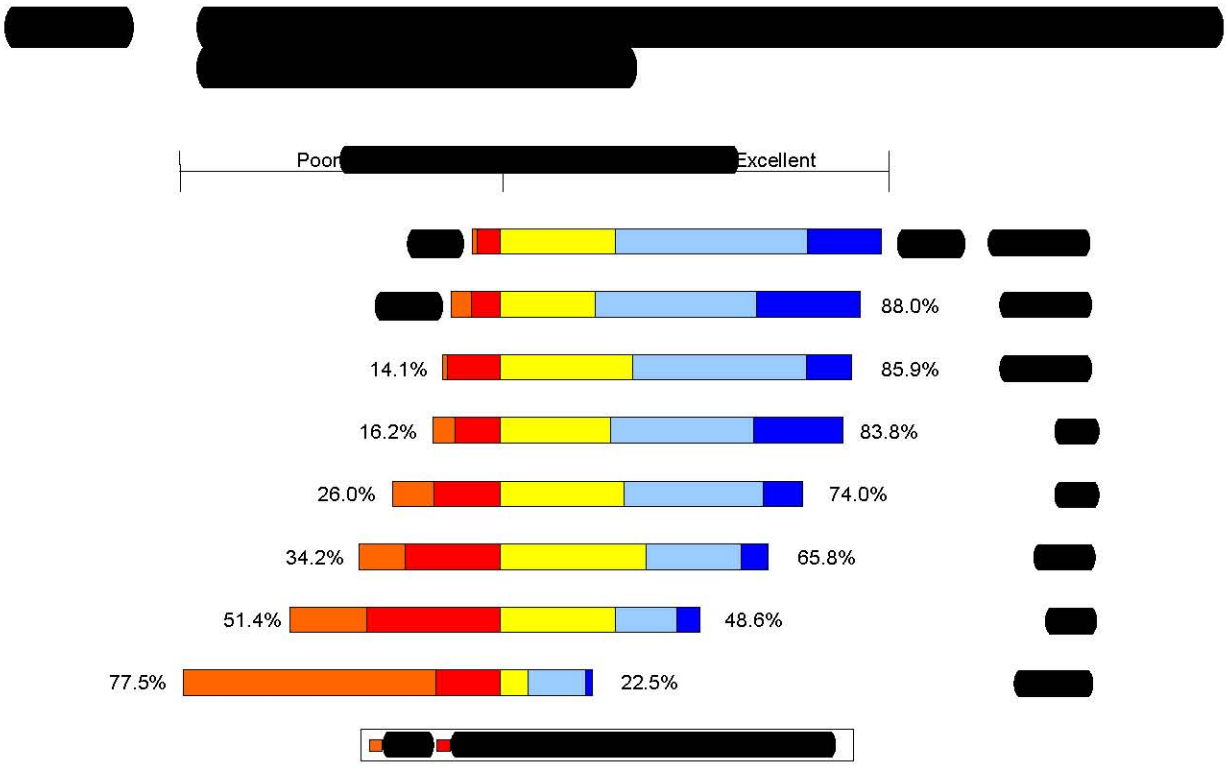
- For the measure **'pain half gone'** the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than ibuprofen 400 mg ($p < 0.05$) and paracetamol 1000 mg ($p < 0.0001$). There were no statistically significant differences between the combination tablets. These results confirm the findings of the exploratory study (NL0408) (**Module 2.7 Section 2.7.3.2.1**).

- For the more appropriate measure of **'duration of effect'** (i.e. time to first administration of rescue medication or first dose of Part 2 study medication) the duration of action of the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was 9.1 hours compared to 5.2 hours for paracetamol 1000 mg, 8.4 hours for ibuprofen 400 mg and the single dose of the combination, and 8.2 hours with Ibuprofen 100 mg and Paracetamol 250 mg tablet. The pairwise treatment comparisons show that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' had a significantly longer duration of action than paracetamol 1000 mg ($p < 0.0001$) and Ibuprofen 100 mg and Paracetamol 250 mg tablet ($p < 0.05$).

- [redacted]

  The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly superior to paracetamol 1000 mg ($p < 0.0001$). There was no statistically significant difference compared to the other doses of the fixed combination

or ibuprofen 400 mg. These findings confirm the results of exploratory study NL0408, although the 2 tablet dose of the combination was statistically significantly superior to ibuprofen 400 mg in that study($p < 0.01$) (**Module 2.7 Section 2.7.3.2.1**).



Abbreviations: I = ibuprofen; P = paracetamol

As expected the Combined Dataset confirms the findings from the exploratory and pivotal studies (NL0408 and NL0604 Part 1) and shows that the combination of ibuprofen 400 mg and paracetamol 1000 mg (e.g. 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') was now also preferred to ibuprofen 400 mg ($p < 0.01$) and Ibuprofen 100 mg and Paracetamol 250 mg tablet ($p < 0.05$) (**Module 2.7 Section 2.7.3.3.2**).

Additional Exploratory Analysis - Number-needed-to-treat

To enable comparison between the efficacy data generated as part of the clinical programme and the data in the public domain an exploratory analysis was conducted to determine the number-needed-to-treat (NNT) for one subject to achieve at least 50% of the maximum pain relief available (i.e. AUC for total pain relief (TOTPAR)) for 0-4, 0-6 and 0-8 hours compared to placebo (**Module 2.7 Section 2.7.3.3.2**). NNT was determined for all treatments in studies NL0408, NL0604 Part 1 and the Combined Dataset and results are summarised in **Table 10**. The NNT for at least 50% relief with the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and Ibuprofen 100 mg and Paracetamol 250 mg tablet were lower than for the single substances alone in studies NL0408, NL0604 Part 1 and the Combined Dataset. The results show that for every three patients treated with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' two patients would achieve at least 50% pain relief over 6 hours.

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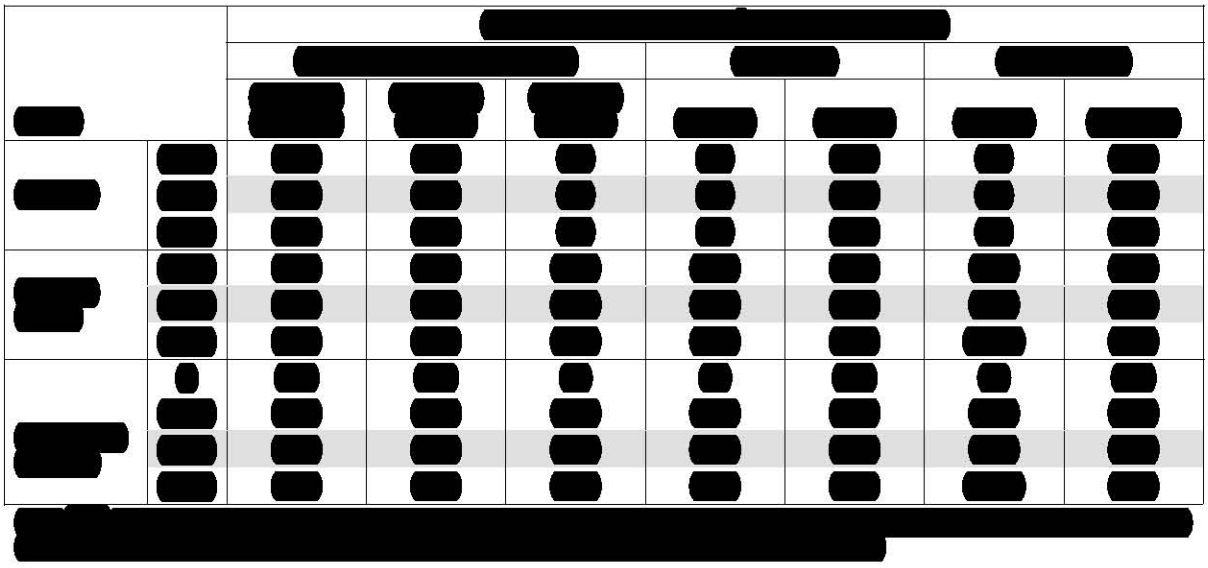


This NNT analysis is consistent with that used by Bandolier to generate the "Oxford League Table of Analgesic Efficacy" where analgesic efficacy is expressed as NNT (**Table 11**). NNT was calculated for the proportion of patients with at least 50% pain relief compared to placebo over 4-6 hour treatment period in randomised, double-blind, single-dose studies in patients with moderate to severe pain. The league table shows that effective relief can be achieved with oral non-opioids and NSAIDs. The most effective drugs have a low NNT of just over 2, i.e. for every two patients who receive the drug one patient will get at least 50% relief because of the treatment (the other patient may or may not obtain relief but it does not reach the 50% level). The key limitation of the league table is the small datasets, which cannot accurately estimate the magnitude of the analgesic effect; therefore the dataset has been limited to analgesics where there have been three or more studies or greater than 200 patients exposed. As NNT is treatment-specific it is useful for comparison of relative efficacy.

The NNT determined for ibuprofen 400 mg alone and paracetamol 1000 mg alone in studies NL0408, NL0604 Part 1 and Combined Dataset are broadly comparable to those from the published literature, thus giving confidence in the reliability of the NNT values for the combination products.

A total of 216 subjects were exposed to the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the Combined Dataset. Of these subjects 164 (75.9%) achieved at least 50% pain relief over 6 hours. The NNT was 1.51 (95% CI 1.43, 1.59). In comparison to the data presented in the "Oxford League Table of Analgesic Efficacy" the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has comparable efficacy to etoricoxib 180/240 mg and 120 mg (**Table 11**) and is more effective than other analgesics used routinely including ibuprofen 400 mg alone and paracetamol alone.

Table 11 Oxford league table of analgesic efficacy (adapted to introduce the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet')

The 2007 Oxford league table of analgesic efficacy (at least 3 trials or 200 patients)					
Analgesic and dose (mg)	**No. of patients in comparison**	**Percent of patients with at least 50% pain relief over 4-6 hours**	**NNT**	**95% Confidence Interval**	
Placebo	>10,000	18	NA	NA	NA
Etoricoxib 180/240	248	77	1.5	1.3	1.7
2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'	**216**	**76**	**1.5**	**1.4**	**1.6**
Etoricoxib 120	500	70	1.6	1.5	1.8
Diclofenac 100	545	69	1.8	1.6	2.1
Celecoxib 400	298	52	2.1	1.8	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Rofecoxib 50	675	54	2.3	2.0	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Ibuprofen 400	5456	55	2.5	2.4	2.7
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Diclofenac 25	502	53	2.6	2.2	3.3
Ketorolac 10	790	50	2.6	2.3	3.1
Naproxen 400/440	197	51	2.7	2.1	4.0
Piroxicam 20	280	63	2.7	2.1	3.8
Lumiracoxib 400	370	48	2.7	2.2	3.5
Naproxen 500/550	784	52	2.7	2.3	3.3
Diclofenac 50	1296	57	2.7	2.4	3.1
Ibuprofen 200	3248	48	2.7	2.5	2.9
Pethidine 100 (intramuscular)	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 200/220	202	45	3.4	2.4	5.8
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Paracetamol 500	561	61	3.5	2.2	13.3
Celecoxib 200	805	40	3.5	2.9	4.4
Ibuprofen 100	495	36	3.7	2.9	4.9
Paracetamol 1000	2759	46	3.8	3.4	4.4
Paracetamol 600/650 + Codeine 60	1123	42	4.2	3.4	5.3
Paracetamol 650 + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5	5.6
Aspirin 600/650	5061	38	4.4	4.0	4.9
Paracetamol 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	32	4.7	3.3	8.0
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 + Codeine 60	598	25	5.3	4.1	7.4
Paracetamol 300 + Codeine 30	379	26	5.7	4.0	9.8
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0

Key: NA = not applicable; Source: After http://www.medicine.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html

Conclusion

The pivotal efficacy study (NL0604 Part 1) supports the conclusion that the fixed combination of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is effective in the treatment of mild to moderate acute pain. This factorial study demonstrates the superior efficacy of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to ibuprofen 400 mg alone and paracetamol 1000 mg alone. The NNT analysis shows that the analgesic efficacy of the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is more effective than many of the routinely used analgesics.

There was a dose-response between the three doses of the fixed combination. A 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than Ibuprofen 100 mg and Paracetamol 250 mg tablet. In addition, the 2 tablets dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective from hour 7 than a single dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' as a 2 tablet dose has a fast onset of action with 'time to confirmed perceptible pain relief' in a median of 18.3 minutes. The onset of action was more rapid than for ibuprofen or paracetamol alone. 'Meaningful pain relief' for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was achieved in 44.6 minutes. For the measure 'time to pain half gone' the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was significantly more effective than ibuprofen and paracetamol alone. 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has a long duration of action lasting 9.1 hours. This is significantly longer than paracetamol alone.

The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' as 'good', 'very good' or 'excellent' in achieving pain relief.

2.5.4.5.2 Acute Pain Study (NL0604 Part 2) - Multiple Dose

A more detailed summary of these data are presented in **Module 2.7 Section 2.7.3.2.2**.

Primary Efficacy Endpoint (Primary Population)

The primary endpoint was the number of completed 24-hour periods (as 0, 1, 2, 3) with no more than one dose of rescue medication and with the subject's overall assessment always rated as at least 'good' (i.e., 3, 4, 5). The primary analysis was conducted in those subjects randomised to receive combination treatment or placebo throughout Part 1 and 2 of the study (primary population). The secondary population included all subjects who received a single active in Part 1 and took the corresponding combination in Part 2.

The mean number of completed periods for the primary endpoint were 2.40, 2.29, 2.31 and 1.00 for 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', Ibuprofen 100 mg and Paracetamol 250 mg tablet and placebo, respectively. The multiple treatment comparisons, using the Hochberg method for the parallel assessments, showed that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol

500 mg tablet' was highly statistically significantly superior to placebo ($p < 0.0001$). However there were no statistically significant differences between the three fixed combination doses.

Secondary Efficacy Endpoint (Primary Population)

The secondary endpoints from the pivotal study (NL0604 Part 2) included 'time to treatment failure', 'subjects' overall assessment', 'number of doses of study or rescue medication', 'duration between doses of study or rescue medication', 'peak pain relief scores per 24-hour period'. A summary of the results and the pairwise treatment comparisons are presented in **Module 2.7 Section 2.7.3.2.2.**

The results from NL0604 Part 2 show that:

- **The incidence of 'treatment failure'** was very low and there were no statistically significant differences between the three fixed combination doses and placebo for 'time to treatment failure'.

- **'Subjects' overall assessment'** of the study medication (from 'poor' to 'excellent') in each 24-hour period improved slightly with time. The mean responses for the three combination doses were similar for each 24-hour period. Subjects receiving placebo had lower mean scores that were highly statistically significantly inferior ($p < 0.0001$) to the three fixed combination doses.

- The comparison of the mean **'number of doses of study or rescue medication'** between the three fixed combinations and placebo were not statistically significantly different during the three separate 24-hour periods or during the whole of Part 2. Even though subjects in the placebo group took considerably more rescue medication compared to the fixed combination treatments, the number of combined doses of study and rescue medication was slightly less in the placebo group. Indicating that the rescue medication 'Lortab' was effective.

- **The mean 'duration between doses of study or rescue medication'** was statistically significantly longer for placebo compared to 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' for the first ($p < 0.05$), third ($p < 0.05$) and combined 24-hour periods ($p < 0.01$); for 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' for the first ($p < 0.05$) and combined 24-hour periods ($p < 0.01$); for Ibuprofen 100 mg and Paracetamol 250 mg tablet for the combined 24 hour period ($p < 0.01$). Indicating that the rescue medication 'Lortab' was effective.

- **For 'peak pain relief scores per 24-hour period'** there were no statistically significant differences between the three fixed combination doses and placebo, except for 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and placebo in the first 24-hour period ($p < 0.05$). In the last 24 hour period of the study 34.2%, 31.4%, 31.9% and 22.9% reported complete pain relief in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', Ibuprofen 100 mg and Paracetamol 250 mg tablet and placebo groups, respectively.

Primary and Secondary Efficacy Endpoints (Secondary Population)

For the secondary population (subjects who received a single active in Part 1 and the corresponding dose of the fixed combination in Part 2) the results for the primary endpoint were comparable to those for the primary population. However, subjects in the paracetamol 500 mg group in Part 1 had fewer 'mean complete periods with no more than one dose of rescue medication and an overall assessment of at least good' (1.89).

Overall subjects switching from either ibuprofen 400 mg or paracetamol 1000 mg in Part 1 to 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in Part 2 recorded an improvement in pain relief of 49.3% and 54.4% respectively.

Conclusion

The pivotal efficacy study (NL0604 Part 2) supports the conclusion that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is an effective multiple dose treatment for mild to moderate acute pain.

2.5.4.5.3 Chronic Pain Study (NL0605) - Multiple Dose

A more detailed summary of these data are presented in **Module 2.7 Section 2.7.3.2.3**.

Primary Efficacy Endpoints

Short-term efficacy: the protocol pre-defined primary endpoint was signal knee pain at Day 10 using the WOMAC pain subscale (ITT population). The results for the mean change from baseline, the mean differences between treatments and 95% CI, plus the treatment pairwise comparisons for this primary endpoint are presented in **Table 12**.

The absolute pain reduction (**Table 12**) achieved with the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 400 mg were considered clinically meaningful with respect to acute pain (12-13 mm on a VAS (Todd *et al* (1996), Kelly (2001)). There were no statistically significant differences between treatments, except for the pairwise comparison between the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg (mean difference -5.3; p = 0.0012).

The per-protocol pairwise comparisons supported the results from the ITT population. The results of the sensitivity analyses to account for missing data using BOCF were consistent with the principal analysis.

Long-term efficacy: the protocol pre-defined primary endpoint was 'patient global assessment at Endpoint' (Week 13 using LOCF at withdrawal for missing data) using a 5-point Likert scale where a lower score is preferable (ITT population). The results for the percentage of patients that rated the treatment as 'excellent' or 'good', the LS mean, the mean differences between treatments and 95% CI, plus the closed test procedure treatment comparisons for this primary endpoint are presented in **Table 12**.

The results of the closed test procedure using Hochberg's methodology show that the 1 tablet and 2 tablet (**Table 12**) doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were statistically significantly superior to paracetamol 1000 mg alone. However, 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was not statistically significantly different to ibuprofen 400 mg. Therefore a non-inferiority comparison of 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' to ibuprofen 400 mg was conducted to assess whether this treatment preserved at least 50% of the effect of ibuprofen relative to paracetamol. The results met the requirements for the closed procedure, i.e. 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was not inferior to ibuprofen 400 mg. Ibuprofen 400 mg alone was statistically significantly superior to paracetamol 1000 mg alone ($p = 0.013$).

Table 12 Summary of the results for the primary short-term efficacy and primary long-term efficacy endpoints

Primary Efficacy Endpoint	'Ibuprofen and Paracetamol tablet'		Ibuprofen 400 mg	Paracetamol 1000 mg
	2 x 200 mg/500 mg	1 x 200 mg/500 mg		
Short-term Efficacy (Pain in the Signal knee at Day 10[a])				
n	204	201	193	188
Mean change from baseline[a]	-15.0	-12.8	-13.3	-10.1
2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. (mean difference (95% CI); p-value)[b]	NA	-2.9 (-6.0, 0.3); NS	-2.2 (-5.4, 1.0); NS	-5.3 (-8.5, -2.1); p = 0.0012**
Long-term Efficacy (Patients' global assessment of treatment at Endpoint (LOCF)[c]				
n	221	220	219	220
% rating treatment as excellent or good	60.2	54.1	50.7	45.5
LS Mean	2.54	2.69	2.68	2.97
2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. (mean difference (95% CI); p-value)[b]	NA	-0.15 (-0.38, 0.08); NS	-0.14 (-0.37, 0.09); NS	-0.43 (-0.66,-0.20); p = 0.0002***

Key: [a] Mean WOMAC OA Index pain sub-scale scores (normalised 0-100 mm), a lower score is preferable; [b] Estimated from ANCOVA model with factors for treatment, presence of OA and site and a covariate for baseline score. *p < 0.05, **p < 0.01, ***p < 0.001; [c] Patient global assessment in response to the question "taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for painful knee?" This was recorded on a 5-point scale where 1 = Excellent, 2 = Good, 3 = Fair, 4 = Poor and 5 = Unacceptable; Endpoint (LOCF) = Week 13 data plus LOCF for missing data; NA – not applicable; NS – not statistically significant.

A sensitivity analysis was conducted to replace missing data with the worst possible score and the results were consistent with the principal analysis, i.e. the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were statistically significantly superior to paracetamol 1000 mg (-0.34; $p = 0.02$, and -0.51; $p = 0.0003$ respectively). A mixed-effect model repeated measures analysis was also performed, where the only statistically significant pairwise difference was between 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg (-0.37; $p = 0.005$).

Secondary Efficacy Endpoints

The secondary endpoints from the confirmatory study (NL0605) included 'acceptability of knee pain', 'WOMAC pain score', 'WOMAC physical function score', 'WOMAC stiffness score', 'WOMAC composite score', 'patient global assessment of study medication', Quality of Life (QoL) questionnaire SF 36, QoL Patient Generated Index (PGI), signal knee effusion,

and sit-to-stand test. A summary of the results and the pairwise treatment comparisons are presented in **Module 2.7 Section 2.7.3.2.3.**

The results of the pairwise treatment comparisons for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' from NL0605 show:

- **For acceptability of knee pain in the last 48 hours** at Day 10 the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.01$) and the 1 tablet dose ($p < 0.01$). There was no statistically significant difference compared to ibuprofen 400 mg or with the other treatments at Week 7, Week 13 or at Endpoint (LOCF).

- **For WOMAC pain score** at Endpoint (LOCF) the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.01$). There was no statistically significant difference compared to the other treatments at Week 7, Week 13 and Endpoint (LOCF).

- **For WOMAC physical function score** at Day 10, Week 7, and Endpoint (LOCF) the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.001$, $p < 0.05$ and $p < 0.05$ respectively) and at Day 10 the 2 tablet dose of the combination was superior to the 1 tablet dose ($p < 0.01$). There were no other statistically significant differences compared to the other treatments.

- **For WOMAC stiffness score** at Day 10, Week 7, Week 13 and Endpoint (LOCF) the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.001$, $p < 0.05$, $p < 0.05$ and $p < 0.01$ respectively). There were no other statistically significant differences compared to the other treatments.

- **For WOMAC composite score** at Day 10, Week 7, and Endpoint (LOCF) the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.001$, $p < 0.05$ and $p < 0.05$ respectively) and at Day 10 the 2 tablet dose of the combination was superior to the 1 tablet dose ($p < 0.05$). There were no other statistically significant differences compared to the other treatments.

- **For patient global assessment of the study medication** at Day 10, Week 7 and 13 the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.001$, $p < 0.05$ and $p < 0.01$ respectively). There were no other statistically significant differences compared to the other treatments.

- **For QoL SF 36 questionnaire** at Day 10, Week 7, Week 13 and Endpoint (LOCF) for the vast majority of measures there was no statistically significant differences compared to the other treatments (**Module 2.7 Section 2.7.3.2.3 Table 28**).

- **For QoL PGI** at Day 10, Week 13 and Endpoint (LOCF) the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was superior to paracetamol 1000 mg ($p < 0.01$) and at Day 10 the 2 tablet dose of the combination was superior to the

1 tablet dose ($p < 0.05$). There were no other statistically significant differences compared to the other treatments.

- **Signal Knee Effusion** occurred in significantly fewer subjects with the 2 tablet dose of 'ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to the 1 tablet dose at Day 10, Week 13 and Endpoint (LOCF) ($p < 0.05$, $p < 0.01$ and $p < 0.05$ respectively). There were no other statistically significant differences compared to the other treatments.

- **For the sit-to-stand test** the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly superior to paracetamol 1000 mg at Day 10, Week 13 and Endpoint (LOCF) ($p < 0.05$, $p < 0.05$ and $p < 0.01$ respectively) and ibuprofen 400 mg and the 1 tablet dose of the combination at Week 13 ($p < 0.05$). There were no other statistically significant treatment differences at the other timepoints.

Conclusion

The confirmatory efficacy study (NL0605) supports the conclusion that the fixed combination of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is effective in the treatment of pain.

Short-term treatment (at Day 10) with 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was comparable to paracetamol 1000 mg and ibuprofen 400 mg alone in the reduction of knee pain. However, for the primary endpoint the long-term efficacy of 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly superior compared to paracetamol 1000 mg alone. The efficacy of 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was comparable to ibuprofen 400 mg alone.

Although this study was conducted in a chronic pain model, the data support the efficacy of the 1 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' taken every 6 to 8 hours for the short-term and long-term treatment of moderate pain.

Overall Efficacy Conclusion

The exploratory, pivotal and confirmatory efficacy studies (NL0408, NL0604 and NL0605) support the conclusion that the fixed combination of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is an effective single and multiple dose treatment for mild to moderate pain.

These factorial studies (NL0408 and NL0604) demonstrate the superior efficacy of combining ibuprofen and paracetamol and demonstrated a dose response between the three doses of the fixed combination.

The pivotal study (NL0604) confirmed that the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' at a dose of 2 tablets is statistically significantly more effective than ibuprofen 400 mg alone and paracetamol 1000 mg alone.

The NNT analysis, in comparison to the data presented in the "Oxford League Table of Analgesic Efficacy", shows that the analgesic efficacy of the 2 tablet dose of 'Ibuprofen

200 mg and Paracetamol 500 mg tablet' is more effective than many of the routinely used analgesics.

The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 18.3 minutes and 'meaningful pain relief' achieved in 44.6 minutes. Numerically the onset of action was more rapid than paracetamol 1000 mg alone and statistically significantly faster than ibuprofen 400 mg alone.

The duration of action of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was sustained lasting a median of 9.1 hours. This was numerically longer than ibuprofen 400 mg alone and statistically significantly longer than paracetamol 1000 mg alone.

The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination performed statistically significantly better than paracetamol 1000 mg alone.

The confirmatory efficacy study (NL0605) supports the conclusion that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is statistically significantly more effective than paracetamol 1000 mg alone in the treatment of mild to moderate chronic pain. In addition, statistically significantly more patients preferred the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' to paracetamol 1000 mg.

The clinical programme supports the proposed posology of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' to be taken every 6 to 8 hours for the treatment of mild to moderate pain. 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provides more effective analgesia than ibuprofen 400 mg or paracetamol 1000 mg alone.

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 Brief Introduction

The safety profiles of ibuprofen and paracetamol as single actives are well characterised. This section of the overview will briefly review the background and supportive safety and tolerability in the public domain, a bibliographic review of the literature on the combination, a General Practice Research Database (GPRD) study, as well as the data generated as part of the clinical programme for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is intended for adults from 18 years and the proposed posology is for 2 tablets of product to be taken every 6 to 8 hours not exceeding 6 tablets in a 24 hour period. The proposed maximum daily dose for the product is 3 g of paracetamol and 1.2 g of ibuprofen.

Clinical Programme

To assess the tolerability and safety of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' the Applicant included safety assessments in the pharmacokinetic studies (NL0602 and NL0603), the exploratory study (NL0408), pivotal study (NL0604) and the confirmatory study (NL0605). A primary objective of study NL0605 was to generate 3 months of exposure data with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and to compare the tolerability profile to the single actives (ibuprofen 400 mg alone and paracetamol 1000 mg alone).

All healthy volunteers and subjects in the reported studies were included in the safety analysis. The safety dataset includes a total of 52 healthy volunteers (NL0602 and NL0603), 969 subjects with acute pain (NL0408 and NL0604). In study NL0604, 735 subjects participated in Part 1 and 715 subjects continued on into the multiple dose phase (Part 2) of the study of which 658 subjects received study medication. In study NL0605, 892 subjects with chronic knee pain received multiple doses of study medication.

The clinical programme has demonstrated that there is no pharmacokinetic drug-drug interaction between ibuprofen and paracetamol and that 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is well tolerated.

2.5.5.2 Adverse Events Characteristic of Pharmacological Class

The safety and tolerability profiles of paracetamol and ibuprofen have been well characterised over decades by the considerable prescription and non-prescription usage of both medicines. This established use of ibuprofen and paracetamol has negated the need to conduct modern long-term clinical safety/tolerability studies or studies such as prescription event monitoring, in the UK, with these medicines to establish the frequency of reporting of adverse reactions.

Moore *et al* (1999) conducted a large tolerability study with ibuprofen (up to 1.2 g daily) and paracetamol (up to 3 g daily) in the treatment of mild to moderate pain for up to 7 days and established that the tolerability profiles were similar. The most frequently reported (i.e. ≥ 1/1000 to < 1/10) adverse events for ibuprofen and paracetamol included abdominal pain,

dyspepsia, nausea, headache, diarrhoea, asthenia, somnolence, vomiting, dizziness and flatulence.

As with all NSAIDs serious undesirable effects of gastrointestinal bleeding, ulceration and perforation have been reported. These events can be fatal at any time during treatment without warning symptoms or a previous history of serious gastrointestinal events. The risk of these events increases with increased dose, history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. However, the relative risk of an upper gastrointestinal complication differs by NSAID. Henry *et al* (1996) established that up to 1.2 g daily (low dose) of ibuprofen had the lowest risk of serious gastrointestinal complications compared to other traditional or non-selective NSAIDs (tNSAIDs).

Garcia Rodriguez and Hernández-Diaz (2001) conducted a nested case control GPRD study and estimated the overall relative risk of an upper gastrointestinal complication with paracetamol was 1.3 (95% CI 1.1, 1.5); for current users of paracetamol (≥ 2 g daily) the relative risk was 3.6 (95% CI 2.6, 5.1); for ibuprofen the relative risk was 2.5 (95% CI 1.9, 3.4) which was relatively low compared to other tNSAIDs. A comparison of non-NSAID users with concurrent users of tNSAIDs and paracetamol (≥ 2 g daily) had a relative risk of an upper gastrointestinal event of 13.2 (95% CI 9.2, 18.9), whereas, if the dose of paracetamol was < 2 g the relative risk was 4.1 (95% CI 3.1, 5.5). This study showed that the relative risk of an upper gastrointestinal complication with a tNSAID was lower with: low/medium doses of tNSAID; a tNSAID with a plasma half-life < 12 hours; an immediate release formulation. Also the relative risk of experiencing an upper gastrointestinal event was independent of duration of treatment. Hippisley-Cox *et al* (2005) conducted a UK based observational study using the QResearch GP database and reported an adjusted odds ratio for adverse gastrointestinal events with current use of ibuprofen of 1.42 (95% CI 1.27, 1.59). This may reflect the changes in prescribing practice with time, i.e. the use of low doses.

Rahme *et al* (2008) in a population based retrospective cohort study compared the rates of hospitalisation because of upper or lower gastrointestinal ulceration, perforation, or bleeding in elderly patients (≥ 65 years old) dispensed tNSAIDs with or without paracetamol. The crude rates of hospitalisation were 3.4, 4.0, 4.4 and 7.2 per 1000 patient years for ≤ 3 g/day paracetamol, > 3 g/day paracetamol, tNSAIDs and concurrent tNSAIDs plus paracetamol, respectively. The adjusted hazard rates compared to ≤ 3 g/day paracetamol were 1.23 (95% CI 1.04, 1.46), 1.66 (95% CI 1.44, 1.91) and 2.56 (1.94, 3.37) for > 3 g/day paracetamol, tNSAIDs and concurrent tNSAIDs plus paracetamol, respectively. The adjusted hazard rate for concurrent tNSAID and paracetamol compared to tNSAID alone was 1.53 (95% CI 1.16, 2.03). This study suggests that elderly patients are at increased risk of hospitalisation due to gastrointestinal complications when a tNSAID and paracetamol are taken concurrently. However, Rahme *et al* do not specify which tNSAIDs and at what doses they were prescribed.

Recently there has been concern regarding the cardiovascular safety of tNSAIDs. Chan *et al* (2006) investigated in a prospective study the influence of tNSAIDs and paracetamol on the risk of major cardiovascular events (non-fatal myocardial infarction, fatal coronary heart disease, non-fatal and fatal stroke) in women (44-69 years). Women who took tNSAIDs or paracetamol for ≤ 21 days/month did not experience a significant increase in the risk of

cardiovascular events compared to non-users. However, tNSAIDs use ≥ 22 days/month had a relative risk of 1.44 (95% CI 1.27, 1.65) compared to non-users, whereas paracetamol use at the same frequency had a relative risk of 1.35 (95% CI 1.14, 1.59). For non-ibuprofen NSAID users, regular use had an observed multivariate risk of a cardiovascular event of 1.62 (95% CI 1.21, 2.15) compared to non-regular use. Age, aspirin use, BMI, physical activity, or presence or absence of hypertension, hypercholesterolemia or diabetes mellitus did not significantly influence the risk of a cardiovascular event with tNSAIDs or paracetamol. However, the elevated risk of a cardiovascular event associated with frequent tNSAID use was influenced by whether the user was a current smoker 1.82 (95% CI 1.38, 2.42). There was a significant dose-response relationship, compared to non-users, the relative risk of a cardiovascular event among women who used ≥ 15 tablets/week was 1.86 (95% CI 1.27, 2.73) for tNSAIDs and 1.68 (95% CI 1.10, 2.58) for paracetamol. In conclusion the use of tNSAIDs or paracetamol at high frequency or dose is possibly associated with an increased risk of a major cardiovascular event.

Other risks with tNSAIDs include haematuria, acute renal failure, interstitial nephritis and nephritic syndrome. These effects occur very rarely and are particularly associated with dehydrated subjects, patients with compromised renal function and / or a massive overdose (Volans and Fitzpatrick 1999). Unlike phenacetin, regular use of paracetamol is not associated with renal failure except in overdose. This occurs in about 1-2% of all patients hospitalised with paracetamol poisoning and is generally secondary to liver failure (Prescott 1996b and Pakravan *et al* 2007). The risk of this occurring also increases with dose and dehydration. In the literature, there has been one case report (Granese *et al* 2007) of a 38 year old woman with intermittent left side flank pain who was taking diphenhydramine hydrochloride, conjugated estrogens, metoclopramide, fenofibrate, venafaxine and pantoprazole, as well as naproxen 325 mg daily and paracetamol 500 mg twice daily (the latter two drugs for 2-3 years). She developed unilateral analgesic neuropathy in her non-functioning kidney with no affect on the contra-lateral normally developed kidney. Pre-existing renal insufficiency appears to be a pre-requisite of analgesic nephropathy; the normally functioning kidney was resistant to the chronic nephrotoxicity. This case illustrates the importance of class contraindications and warnings associated with pre-existing renal insufficiency and using the product with other NSAIDs and paracetamol containing products.

Skin rashes have been reported occasionally and other hypersensitivity reactions have been reported more rarely, e.g. angioedema and anaphylaxis, with ibuprofen and paracetamol. In common with all NSAIDs exacerbation of asthma and bronchospasm, especially in patients with aspirin-sensitive asthma, has been reported. Haematological reactions have been reported with ibuprofen and paracetamol; they can include thrombocytopenia, leucopenia, pancytopenia, neutropenia and agranulocytosis. Other central nervous system related events have also been reported with ibuprofen and paracetamol, which can include headache, dizziness, somnolence and visual disturbance.

The greatest concern with paracetamol is toxicity in overdose, hepatic disease and alcoholism.

Post-marketing suspect adverse drug reaction reports for ibuprofen and paracetamol as single actives are available in the public domain from the UK. These reports are from

healthcare professionals and patients have been collated by the MHRA and the Commission on Human Medicines since 1963. The cumulative listings of these data are confounded by the following factors: combined prescription and non-prescription usage; no stratification by dose or duration of treatment; causality based on suspicion not confirmation; no direct exposure data; rate of adverse drug reaction reporting is affected by the medicines position in the product lifecycle, severity of the reaction and reporter. However, these data provide useful information on the adverse drug reactions likely to be reported with paracetamol and ibuprofen containing products. These data should be considered in context with prescription and non-prescription usage data (**Module 2.7 Section 2.7.4.6**).

The most frequently reported adverse drug reactions, i.e. accounting for at least 5% of reports; by system organ class for paracetamol were injuries, gastrointestinal disorders, skin disorders, hepatic disorders, nervous system disorders, general disorders, psychiatric disorders, investigations, respiratory disorders and cardiac disorders. For ibuprofen these were gastrointestinal disorders, skin disorders, general disorders, nervous system disorders, blood disorders, psychiatric disorders, renal and urinary disorders, and respiratory disorders.

The mostly frequently reported adverse drug reactions, i.e. accounting for at least 1% of reports, with paracetamol were overdoses (25.3%), vomiting (8.5%), urticaria (7.3%), nausea (7.0%), liver injury (7.0%), hepatic necrosis (6.1%), rash (5.5%), acute hepatic failure (5.0%), dizziness (3.9%), visual impairment (2.1%) and analphylactic responses (2.0%). For ibuprofen these were haematemesis (6.1%), gastrointestinal haemorrhage (6.0%), rash (5.8%), melaena (5.4%), duodenal ulcers, haemorrhage and/or perforation (4.8%), urticaria (4.0%), gastric ulcers, haemorrhage and/or perforation (3.4%), angioedema (2.7%), abdominal pain (2.6%), dizziness (2.6%), diarrhoea (2.6%), pruritus (2.5%), dyspepsia (2.4%), nausea (2.3%), asthma (2.2%), thrombocytopenia (2.1%), vomiting (2.0%), and stomatitis and ulceration (2.0%).

Exposure data for ibuprofen and paracetamol from first launch in the UK to the present day is not available. However, data in the public domain show that prescriptions dispensed for systemic preparations in the UK were approximately 123.2 million for paracetamol and approximately 51.9 million for ibuprofen (Department of National Statistics for England 1998-2007). Non-prescription products sold in the UK were 3.6 billion doses of paracetamol and 2.3 billion doses of ibuprofen (Nielsen for 3 years ending 24th February 2009). These data suggest that over the last 40 years the patient exposure, in UK, to both of these medicines has been very high. Although there is likely to have been considerable under-reporting of adverse drugs reactions for paracetamol and ibuprofen to the MHRA it can still be concluded that adverse drug reactions are very rare with less than one report per 10000 prescriptions (**Module 2.7 Section 2.7.4.6**).

Ibuprofen and Paracetamol in Combination

Combinations of ibuprofen and paracetamol are licensed in a number of countries (e.g. India, Russia, Poland, South Africa and Thailand). The products contain various dose ratios of ibuprofen and paracetamol and the posology vary from country to county with maximum daily doses ranging from 1.2-2.4 g for ibuprofen and 1.3-2.6 g for paracetamol. One product in India and one in Thailand contain the same dose combination as 'Ibuprofen 200 mg and

Paracetamol 500 mg tablet'; however accurate pharmacovigilance data on the Indian product is not in the public domain and the data is not collected by the authorities in Thailand (**Module 2.7 Section 2.7.4.6**).

Bibliographic Review

The Applicant therefore commissioned a systematic review to assess the overall tolerability of ibuprofen and paracetamol used in combination, or alternated, in comparison to ibuprofen or paracetamol alone in the treatment of pain and fever. The bibliographic search identified 212 unique papers, 15 of which met the search criteria. A further two papers were identified that were published as electronic versions only. Fifteen of these trials provide adverse event information. The overall reporting of adverse event data in the published literature is poor. However, in the surgical pain studies, where the combination of ibuprofen and paracetamol was compared to placebo or the single actives, the adverse event profile was comparable. The adverse events reported in these studies were 'expected' either in relation to the surgical procedure or the treatment taken. In the fever studies, either no adverse events were reported or there was no difference in the tolerability profile between the combination of ibuprofen and paracetamol and both of the single actives (**Module 2.7 Section 2.7.4.1.1.2**).

In addition to the above review, three case reports in the published literature (McIntire *et al* 1993, Del Vecchio and Sundel 2001 and Zaffanello *et al* 2009) describe three cases of reversible acute renal failure in volume depleted children, who had taken alternating doses of ibuprofen and paracetamol. In the latter case the child also suffered from acute liver failure. McIntire *et al* proposed that tubular toxicity was caused by NSAIDs inhibiting glutathione and renal ischaemia (associated with NSAID use or dehydration) which may lead to the accumulation of paracetamol in the renal medulla. Del Vecchio and Sundel suggest that there is an additive mechanism as paracetamol and NSAIDs both inhibit urinary prostaglandin synthesis; however this seems to be clinically irrelevant unless the child also has mild to moderate dehydration. Whereas Zaffanello *et al*, suggests that the renal and hepatic effects in sensitive and volume depleted patients are those attributed to ibuprofen and paracetamol alone. There are no epidemiological data to suggest that the fixed combination of paracetamol and ibuprofen increase the risk of nephrotoxicity, other than the theoretical arguments (Baxter 2007 in Stockley Drug Interactions).

General Practice Research Database Study

A full summary is presented in **Module 2.7 Section 2.7.4.1.1.3**.

The Applicant, anecdotally, was aware of the practice of co-prescribing ibuprofen and paracetamol in the UK. Therefore the Applicant commissioned a pharmacoepidemiology study utilising data from the UK General Practice Research Database (GPRD). This database is maintained by, and the study was conducted by a division of the MHRA in the UK. The GPRD collects prescribing data for medicines, rather than patient actual use data; however data is also captured on disease and safety outcomes, e.g. gastrointestinal events, cardiac and renal failure, stroke, overdose and mortality.

The study investigated and compared the patient populations who were prescribed ibuprofen alone, paracetamol alone or had a co-prescription, and then reviewed the safety outcomes, listed above. Hepatic failure was not evaluated because of lack of data in the GPRD. An estimate of the relative risks (RR) by dose, duration, number of prescriptions and current or past use, and time between prescriptions was determined using time-dependent Cox-regression and adjusted for relevant population differences and confounding factors associated with the safety outcomes. Patterns of hazard rates (absolute risk) were also evaluated to determine whether they changed with the number of prescriptions.

The study population included 382404 patients prescribed paracetamol (4767409 prescriptions), 806381 patients prescribed ibuprofen (3244798 prescriptions), and 13079 patients co-prescribed ibuprofen and paracetamol (165607 prescriptions). The patient population was heterogeneous. Patients prescribed paracetamol alone or co-prescribed ibuprofen and paracetamol compared to ibuprofen alone were older, had a higher prescribing rate in patients 65 years and older, were more likely to have a disease history and had greater morbidity. This pattern is indicative of the different patterns of prescribing in the UK for the three treatments.

Analysis of the data most closely aligned with the proposed usage of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' suggest that patients were more likely to have had an upper gastrointestinal event and were more likely to have a myocardial infarction if they had more than 20 previous NSAID prescriptions. For the other comparisons (stroke, heart failure, renal failure, suicide, overdose and mortality) the RR and 95% CI for paracetamol alone were contained within the results for co-prescribed ibuprofen and paracetamol showing that there was no difference. The safety outcomes were also analysed by frequency of prescribing (exposure) where 'first-time' users of paracetamol or co-prescription had the highest RRs. This finding could be associated with a protopathic bias (i.e. when a drug is prescribed before the disease is diagnostically detected). For the remaining safety outcomes by exposure no conclusions could be drawn because of the small number of cases with co-prescribed ibuprofen and paracetamol. The 95% CIs for co-prescribed ibuprofen and paracetamol were wide and contained those for paracetamol and ibuprofen alone.

The pattern hazard rate analysis performed for the safety outcomes (upper gastrointestinal events, myocardial infarction, stroke, heart failure, renal failure, suicidal behaviour, overdose and mortality) for the 3 years following a prescription show that the patterns for co-prescribed ibuprofen and paracetamol are between those for paracetamol and ibuprofen alone. To test whether the hazard rates for co-prescription remained stable over time compared to ibuprofen and paracetamol alone Cox proportional hazards analysis was performed to test the interaction between relative rate and time since last prescription. There were some minor differences between co-prescribing, ibuprofen alone and paracetamol alone. The Author considered these findings to be spurious, as chance dictates that 10 % of the interaction terms in repeated measures ANCOVA models are significant. In conclusion, there is no change in hazard rate following co-prescribing with ibuprofen and paracetamol.

Scientific advice regarding the findings of the GPRD study was received by the Applicant from the MHRA in a meeting held in April 2008. MHRA commented that a number of important covariates were missing from the statistical analysis for various outcomes. These

factors have been taken into account in the updated version of the GPRD report included in the MAA. Other comments from MHRA related to imbalances in the groups leading to a potential impact on outcomes and the overall interpretation of the data, leading MHRA to the conclusion that some of the hazard rates may suggest worse safety in the combination. These conclusions were at odds with those of the report Author who concluded that the concomitant use of paracetamol and ibuprofen does not modify the risk of the various safety outcomes over that of paracetamol or ibuprofen alone.

2.5.5.3 Extent of Exposure

The safety dataset includes a total of 52 healthy volunteers, 969 subjects with acute pain and 892 subjects with chronic pain who participated in the clinical programme (**Table 13**). A more detailed summary of these data can be found in **Module 2.7 Section 2.7.4.1.2.**

The 52 healthy volunteers in the crossover designed pharmacokinetic single and repeat dose studies (NL0602 and NL0603) took a total of 441 doses of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The overall exposure to 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was 147 days assuming a maximum daily dose of 1.2 g of ibuprofen and 3 g of paracetamol.

In the single dose acute pain studies (NL0408 and NL0604 Part 1), a total of 463 subjects took a dose of the ibuprofen and paracetamol in combination (**Table 13**). In the multiple dose acute pain study (NL0604 Part 2) a total of 602 subjects (**Table 13**) took 3212 doses of ibuprofen and paracetamol in combination. The total overall exposure from the single and

multiple dose acute pain studies (taking into account that some subjects took half or a quarter of the proposed dose rather than 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') is equivalent to 858.3 days of treatment assuming a maximum daily dose of 1.2 g of ibuprofen and 3 g of paracetamol.

In the chronic pain study (NL0605) a total of 446 subjects took the fixed combination (**Table 13**). The mean number of days exposure was 72.4 with 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and 74.1 days with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The total exposure was 16074 days with 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and 16600 days with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. This is equivalent to 24637 days of treatment assuming a maximum daily dose of 1.2 g of ibuprofen and 3.0 g of paracetamol.

2.5.5.4 Adverse Events – Overview

Presentation of the adverse event data in **Module 2.7 Section 2.7.4.2** is by healthy volunteer studies (NL0602 and NL0603), individual single dose studies in acute pain (NL0408 and NL0604 Part 1), a multiple dose study in acute pain (NL0604 Part 2), and a multiple dose study in chronic pain (NL0605). The Applicant has also generated a Pooled Safety Dataset with the objective of assessing the overall tolerability profile of the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

The Pooled Safety Dataset includes all subjects and treatment-emergent adverse events from the acute pain studies NL0408 and NL0604 (Part 1 and 2), and the chronic pain study NL0605. In pooling the data from NL0604, the Applicant has taken a conservative approach, i.e. for all subjects who received the fixed combination or placebo in Part 1 and continued on this treatment in Part 2 the subjects were counted once, whereas for those subjects who received a single active product in Part 1 and the fixed combination product in Part 2, the subjects were attributed to the treatment taken and therefore counted twice. The Pooled Safety Dataset includes 2127 subjects of which 1861 are unique.

2.5.5.4.1 Pharmacokinetic Studies (NL0602 and NL0603)

For the healthy volunteers the frequency of adverse event reporting was 0.31 reports per volunteer exposed to the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (**Table 14** and **Module 2.7 Section 2.7.4.2.1 (i)**).

Four events were considered to be related to the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (dyspepsia, nasopharyngitis and two reports of rash from the same participant). Dyspepsia and rash have been previously reported with ibuprofen and paracetamol and as such are considered as 'expected' adverse events.

2.5.5.4.2 Efficacy and Tolerability Studies (NL0408, NL0604, NL0605 and Pooled Safety Dataset)

For the acute and chronic pain studies, the frequency of adverse events, i.e. the number of adverse events reported per subject at risk by treatment are summarised in **Table 15**. For a full summary of these data refer to **Module 2.7 Section 2.7.4.2.1 (ii), (iii), (iv), (v)** and **(vi)**.

[redacted]

In the single dose acute pain studies, NL0408 and NL0604 Part 1, the frequency of adverse events reported was considerably lower in the groups taking the combination of ibuprofen and paracetamol compared to the subjects taking placebo or the single actives.

In the multiple dose acute pain study (Part 2 of NL0604) the frequency of adverse events for the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (0.82 and 0.84) were comparable, but slightly higher than the frequency for placebo (0.73).

In the multiple dose chronic pain study (NL0605) the frequency of events reported, for all treatment groups, was higher compared to the other studies with the increase in exposure; however overall the chi-square test and the individual pairwise comparisons for the proportion of subjects reporting treatment-emergent adverse events was not statistically significantly different between treatments. For the primary tolerability endpoint, the incidence of all 'moderate' and 'severe' adverse events regardless of relationship to treatment, expressed as 'persons days exposure'; the incidence of subjects experiencing at least one event was similar for the 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg

tablet' (62% and 68% respectively), ibuprofen 400 mg (58%) and paracetamol 1000 mg (59%). The median incidence for all treatment groups was 1.1 per person day (i.e. one 'moderate' or 'severe' adverse event during the 13 week study). The frequency distribution of the number of 'moderate' or 'severe' events was comparable for all treatment groups. The pairwise comparisons indicated that there was a higher incidence of 'moderate' or 'severe' adverse events with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to ibuprofen 400 mg ($p = 0.03$).

For the Pooled Safety Dataset, the results show that the frequency of adverse event reporting was highest with the paracetamol 1000 mg group (2.01 events per subject at risk); however overall the frequencies are similar across all treatment groups.

Common Adverse Events

The most common adverse events, i.e. adverse events reported by at least 5% (1 in 20) of the study population, in the efficacy and tolerability studies NL0408, NL0604 (Part 1 and 2) and the Pooled Safety Dataset were nausea, vomiting, alveolar osteitis (dry socket), headache, dizziness and swelling face. These adverse events are 'expected' as surgical removal of impacted third molars is often associated with swelling, bruising, dry sockets, a limited ability to open the mouth, as well as pain. In addition, the subjects received fentanyl and diazepam to induce conscious sedation during the procedure, which can cause nausea, vomiting, headache and dizziness. Likewise, in study NL0605 and the Pooled Safety Dataset arthralgia (joint pain) is common and consistently reported adverse event, which is 'expected' with chronic knee pain (**Module 2.7 Section 2.7.4.2.1.1**).

In NL0408, subjects on placebo were more likely to experience nausea (35.5%) compared to either dose of the combination. Subjects receiving paracetamol 1000 mg were more likely to vomit (29.4%), have a headache (20.6%) or dizziness (20.6%) compared to those taking the combination of ibuprofen and paracetamol (e.g. 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') at either dose. The adverse event profile for the combination of ibuprofen and paracetamol was similar or better than those for the single actives.

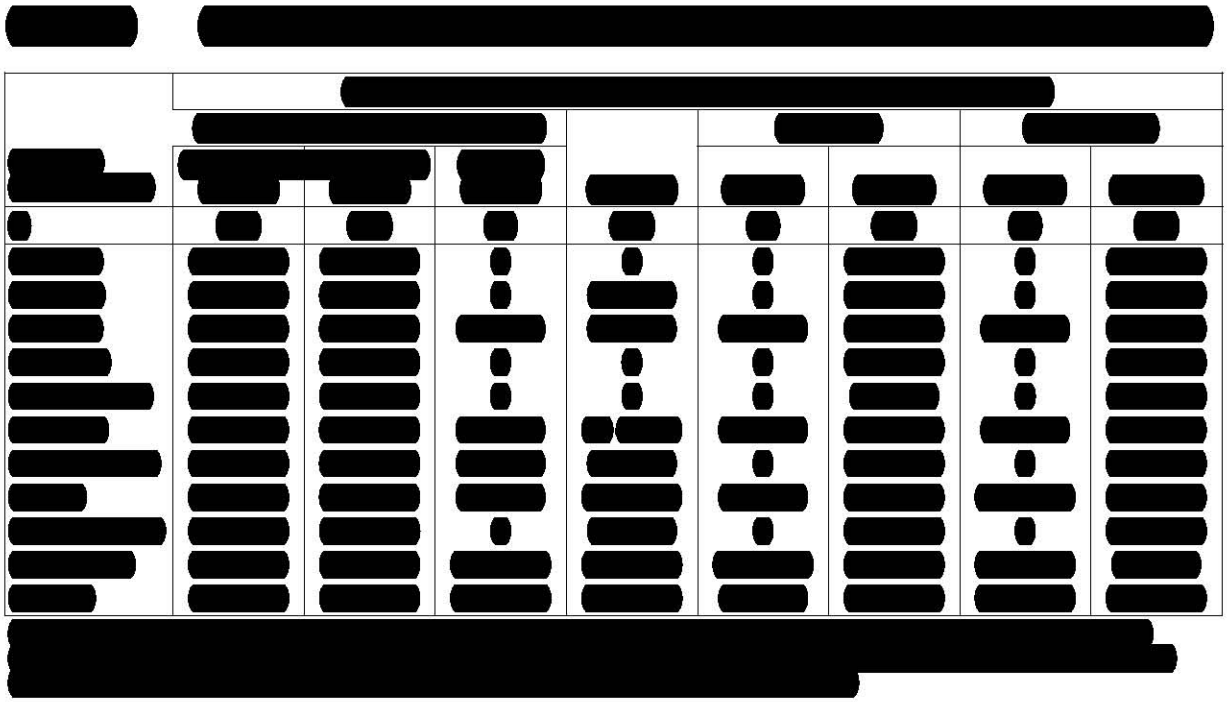
In NL0604 Part 1, the overall incidence of nausea, vomiting, headache and swelling face was lower than in NL0408. Subjects on placebo were more likely to experience headache (15.1%), whereas subjects taking ibuprofen 400 mg were more likely to have a swelling face (21.6%) compared to those taking a 1 or 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. Subjects taking paracetamol 500 mg were more likely to be nauseous (18.4%) or vomit (18.4%) compared to the 1 or 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. There was no real difference in the incidence of common adverse events between 1 or 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The adverse event profiles for the combination products were similar or better than those for the single actives.

In NL0604 Part 2, subjects in the placebo group were more likely to have a headache (14.3%), whereas subjects taking 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were more likely to have a swelling face (11.7%). The incidence of nausea and vomiting and was highest in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group (8.9% and

5.6% respectively), whereas subjects taking Ibuprofen 100 mg and Paracetamol 250 mg tablet were more likely to be dizzy (7.6%).

In NL0605, overall the most common adverse events reported were arthralgia, dyspepsia and headache. At least 5% of subjects reported arthralgia, back pain, cough, diarrhoea, dyspepsia, headache, nasopharyngitis, nausea and pain in extremity in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group. Compared to the other treatment groups subjects taking 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were more likely to report diarrhoea (12.5%), headache (12.1%) and cough (5.8%). Subjects taking 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were more likely to report arthralgia (17.1%), dyspepsia (17.1%), nausea (9.0%), back pain (7.7%) and blood urea increased (5.9%); subjects taking ibuprofen 400 mg were more likely to report constipation (5.4%) and pharyngolaryngeal pain (5.4%); subjects taking paracetamol 1000 mg were more likely to report arthralgia (17.1%), nasopharyngitis (9.9%), pain in extremity (8.6%), gamma-glutamyltransferase (GGT) increased (8.1%) and liver function test abnormalities (6.3%) compared to the other treatment groups.

In the Pooled Safety Dataset, the most common adverse events reported and the frequency of reporting, i.e. the number of events per subject exposed, are summarised in **Table 16**. The most common adverse events reported by at least 5% of subjects in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group were headache, nausea, swelling face, vomiting, diarrhoea, dyspepsia and arthralgia. The overall adverse event profile of the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was 'expected' and comparable to the combined adverse event profiles of the single actives (ibuprofen 400 mg and paracetamol 1000 mg).



Causality

Treatment-related adverse events were considered to be those classified as 'definitely', 'probably' or 'possibly' related to treatment. In studies NL0408, NL0604 Part 1 and 2 no adverse events were classed as 'definitely' related to treatment. The majority of adverse events reported in the efficacy and tolerability studies were considered by the Investigator to be 'unlikely' or 'not-related to treatment'. The number and frequency of treatment-related adverse events reported by treatment, study and Pooled Safety Dataset are summarised in **Table 17**.

In NL0408 and NL0604 Part 1 the frequency of reporting with the combination of ibuprofen and paracetamol (e.g. 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') was at most half the number of reports compared to placebo and the single active treatments. In NL0408 and NL0604 Part 1, the number of subjects reporting treatment-related adverse events for 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly lower than those reported with placebo ($p < 0.01$) and paracetamol 1000 mg ($p < 0.05$). In the multiple dose phase of NL0604 (Part 2), the frequency of reporting with 2 x 'Ibuprofen 200 mg and paracetamol 500 mg tablet' was comparable to placebo.

In the chronic pain study (NL0605) treatment-related adverse events were reported by 50%, 51%, 42% and 45% of subjects in the 1 and 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' groups, ibuprofen 400mg group, and paracetamol 1000 mg group respectively. Subjects in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group reported more treatment-related adverse events than in the ibuprofen 400 mg group ($p = 0.04$).

[redacted]

In the Pooled Safety Dataset, the incidence of subjects reporting treatment-related adverse events was lowest with ibuprofen 200 mg (16.0%) and highest in the paracetamol 1000 mg group (37.7%). The incidence of subjects reporting at least one treatment-related adverse

event was 27.7% in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group, which was comparable to the ibuprofen 400 mg group (32.7%) and placebo (29.8%). The frequency of treatment-related adverse events was lowest with ibuprofen 200 mg (0.213 adverse events per subject at risk) and highest in the paracetamol 1000 mg group (0.712). The frequency was 0.526 for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to 0.621 for ibuprofen 400 mg and 0.519 with placebo (**Table 17**).

The treatment-related adverse events reported with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the single dose studies (NL0408 and NL0604 Part 1) included nausea, vomiting, headache, dizziness, somnolence and tremor. These adverse events and the associated frequencies were lower than those reported for placebo and the corresponding doses of ibuprofen and paracetamol. These adverse events are consistent with the known adverse event profile for ibuprofen and paracetamol alone and as such are 'expected' (**Module 2.7 Section 2.7.4.2.1 (ii)** and **(iii)**).

In the multiple dose study (NL0604 Part 2), the most frequently reported treatment-related adverse events for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' also included nausea, vomiting, headache, somnolence and dizziness. In addition, there were reports of upper abdominal pain and diarrhoea, and rash. The treatment-related adverse events and associated frequencies are consistent with the known adverse event profile for ibuprofen and paracetamol alone and as such are 'expected' (**Module 2.7 Section 2.7.4.2.1 (iv)**).

In the multiple dose study NL0605, overall the most frequently reported treatment-related adverse events during the 13 weeks of the study were dyspepsia, diarrhoea, nausea, and gastrointestinal adverse events such as abdominal discomfort, distension, and pain, epigastric pain and stomach discomfort (**Module 2.7 Section 2.7.4.2.1 (v)**). For 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' the reported treatment-related adverse events and associated incidence are consistent with the known adverse event profile of ibuprofen and paracetamol taken alone and are therefore considered as 'expected'.

In the Pooled Safety Dataset, the most frequently reported treatment-related adverse events were nausea, dyspepsia, vomiting and headache. The incidence of subjects reporting nausea, vomiting and headache were highest in the placebo group, where as dyspepsia was highest with the 1 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. These data are presented in **Module 2.7 Section 2.7.4.2.1 (vi) and 2.7.4.7**. The incidence of subjects reporting treatment-related adverse events with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet was comparable or less than ibuprofen 400 mg alone or paracetamol 1000 mg alone. These adverse events and the associated frequencies are consistent with the well characterised tolerability profiles of ibuprofen and paracetamol and are considered to be 'expected'.

The treatment-related adverse event data from the Pooled Safety Dataset combined with the information from the 'Minimum Clinical Particulars for Non-selective POM NSAIDs for Systemic Administration (November 2007)' and UK post-marketing suspect adverse drug reaction data were used to generate the Undesirable Effects Section 4.8 of the SPC for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (**Appendix 1**). In

conclusion, the adverse event profile of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is reflected in the proposed SPC and product labelling.

Withdrawals

For a full summary of these data refer to **Module 2.7 Section 2.7.4.2.1 (vii)**.

In summary there were no adverse events that lead to subject withdrawal in NL0408. In NL0604, 19 subjects withdrew from the study due to an adverse event, 11 in Part 1 and eight in Part 2. In Part 1, 11 subjects withdrew because of vomiting within 30 minutes of taking the study medication, 2 of these reports were considered to be related to treatment. All the adverse events resolved. In Part 2, eight subjects reported 10 adverse events. Two events were considered to be related to treatment (vomiting and urticaria) in subjects taking 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. All treatment-related adverse events resolved.

In study NL0605, 145 subjects withdrew from the study due to an adverse event. These subjects reported 192 adverse events of which 115 were considered by the Investigator to be at least 'possibly related to treatment. Of the treatment-related reports there were 33 in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group, 25 in the 1 tablet group, 27 in the ibuprofen 400 mg group and 30 in the paracetamol 1000 mg. The treatment-related adverse events that led to withdrawal in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group included: abdominal discomfort, distension or pain (4 reports; severity: 2 mild, 2 moderate; outcome: 1 ongoing, 3 resolved), nausea (4 reports; severity: 4 moderate; outcome: 1 ongoing, 3 resolved), diarrhoea (3 reports; severity: 3 moderate; outcome: 1 ongoing, 2 resolved), dyspepsia (3 reports; severity: 3 moderate; outcome: 2 ongoing, 1 resolved), alanine aminotransferase increased (2 reports; severity: 1 mild, 1 moderate; outcome: 2 ongoing), haemoglobin decreased (2 reports; severity: 2 moderate; outcome: 1 ongoing, 1 resolved), headache (2 reports; severity: 2 severe; outcome: 1 ongoing, 1 resolved), rash (2 reports; severity: 1 severe, 1 moderate; outcome: 1 ongoing, 1 resolved) and one report each of anal haemorrhage, angioedema, asthma, constipation, dizziness, epigastric discomfort, flatulence, liver function test abnormal, malaise, pollakiuria, proteinuria (asthma, proteinuria and liver function test abnormal were also ongoing at study completion). In general, the adverse events that led to withdrawal were broadly similar for all the treatment groups in NL0605.

Overall the adverse events that led to withdrawal are typical of adverse events associated with ibuprofen and paracetamol. None of these events raised significant safety concerns with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

Conclusion

No additional safety issues have been identified from the adverse event data with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The adverse event profile for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' can be considered to be comparable to the combined profiles for ibuprofen and paracetamol alone. Therefore the Applicant has proposed that the safety information in the SPC and product

labelling for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is line with the 'Minimum Clinical Particulars for Non-selective POM NSAIDs for Systemic Administration (November 2007)' and data for paracetamol alone.

2.5.5.5 Serious Adverse Events

There were no deaths reported in the clinical studies NL0602, NL0603, NL0408, NL0604 and NL0605 with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. However, there was one death reported in study NL0605 in a subject randomised to the ibuprofen 400 mg treatment group. The subject suffered a ruptured abdominal aortic aneurysm; the Investigator assessed the causality as 'possible' (**Module 2.7 Section 2.7.4.2.1.2**).

There were no serious adverse events reported in studies NL0602, NL0603, NL0408, NL0604 with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. However, in study NL0605, there were 13 treatment-emergent serious adverse events of which two had causality assessed as 'possible' by the Investigator (one report of moderate renal impairment in the ibuprofen 400 mg treatment group and one report of moderate angina pectoris in the paracetamol 1000 mg treatment group), both adverse events were reported as 'ongoing' at the time the clinical study report was completed (**Module 2.7 Section 2.7.4.2.1.3**). There were no serious treatment-related adverse events reported with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

There were no other significant adverse events reported in studies NL0602, NL0603, NL0408 and NL0604. However, in study NL0604, one subject one month after completing their participation in the study reported developing a blood clot in their arm where the IV had been placed for surgery. This adverse event was not related to treatment and resolved (**Module 2.7 Section 2.7.4.2.1.4**).

In study NL0605, 56 subjects (25.0%) in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' treatment group reported 73 clinically significant abnormal laboratory findings, of which 47 had causality assessed by the Investigator of at least 'possible'. These findings are discussed in **Section 2.5.5.6.**

2.5.5.6 Vital Signs and Haematology Serum Biochemistry

Vital signs and physical findings in studies NL0602, NL0603, NL0408, NL0604 and NL0605 were unremarkable and raised no safety concerns with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (**Module 2.7 Section 2.7.4.4**).

Haematology

For a full summary of these data refer to **Module 2.7 Section 2.7.4.3**.

An unexpected finding of study NL0605 was that some subjects had a decrease in haemoglobin, although not necessarily out of the normal range. This prompted further analysis of relevant haematological parameters.

At baseline, mean haemoglobin values were of the order of 14.1 g/dL. During the course of the study the mean group values decreased in all treatment groups. A total of a 112 subjects had a shift in haemoglobin from high-to-normal, normal-to-low, or high-to-low (normal range: males 13.6-17.1 g/dL and females 12.0-5.2 g/dL). The mean value for 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was lower than the mean values for ibuprofen 400 mg and paracetamol 1000 mg treatment groups. A total of 223 subjects had a decrease in haemoglobin ≥ 1 g/dL of which 29 had a decrease of at least 2 g/dL. There were 17 subjects in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group, six in the 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group, and two each in the ibuprofen 400 mg group and paracetamol 1000 mg group who had a haemoglobin decrease of ≥ 2 and < 3 g/dL. Two subjects (one each in the 1 and 2 tablet 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' treatment groups) had a decrease of 3 g/dL.

As the number of subjects with a decrease of at least 2 g/dL of haemoglobin was small the between group analysis was conducted in subjects with a decrease of at least 1 g/dL. A logistic regression model was fitted to these data. At Day 10, the terms for treatment ($p = 0.014$) and baseline haemoglobin ($p = 0.0008$) were statistically significant but the factors for site, baseline aspirin use, age and smoking status were not statistically significant. The pairwise treatment comparisons showed no statistically significant difference between the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 400 mg; however more subjects had a decrease with the 2 tablet dose of the combination compared to paracetamol 1000 mg ($p < 0.01$). Only one subject in the 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group had a haemoglobin decrease of at least 2 g/dL; however this subject's haemoglobin level increased by 1 g/dL by Week 7 and 13 without clinical intervention. At Endpoint (LOCF), the terms for treatment ($p < 0.0001$), site ($p = 0.003$) and baseline haemoglobin ($p < 0.0001$) were statistically significant whereas the factors for baseline aspirin use, age and smoking status were not significant. The pairwise comparisons show that significantly more subjects had a haemoglobin decrease (≥ 1 g/dL) with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to the other treatments.

A subgroup analysis of these data was also conducted using a stepwise multivariate logistic regression model fitted on the proportion of subjects reporting at least 1 g/L decrease in haemoglobin between baseline and Day 10, and baseline and Endpoint (LOCF). The model included factors for randomised treatment group, site, gender, baseline aspirin use, smoker (current versus former/never), baseline concomitant glucosamine use, baseline alcohol drinker, ongoing haematological condition at baseline, ongoing gastrointestinal conditions at baseline, ongoing cardiovascular conditions at baseline and ongoing endocrine/metabolic conditions at baseline and with continuous covariates for age at baseline and baseline haemoglobin value. For baseline and Day 10, baseline haemoglobin, treatment group and gender were the three significant predictors in the model. For baseline and Endpoint (LOCF), there were five statistically significant predictors in the model: baseline haemoglobin, treatment group, site, gender and concomitant glucosamine use at baseline. Further investigation of these baseline predictors shows:

- Subjects 65 years and older taking 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group were more likely to experience a haemoglobin decrease of at least 1g/dL

compared to the single actives; however the combined number of subjects affected taking the single actives was similar to the number of subjects taking the combination.

- Subjects exposed to 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' for up to 13 weeks are more likely to experience a haemoglobin decrease of at least 1 g/dL compared to the single actives; however the combined number of subjects affected taking the single actives was similar to the number of subjects taking the combination.

- Gender and baseline haemoglobin values are significant predictive factors in haemoglobin decrease. The normal haemoglobin range for males (13.6-17.1 g/dL) is higher than the range for females (12.0-15.2 g/dL), which provides males with greater scope for a haemoglobin decrease. In addition, study NL0605 also had a gender imbalance therefore the results are difficult to interpret.

- The presence of baseline cardiovascular disease, gastrointestinal disease, endocrine or metabolic disorders did not influence the decrease in haemoglobin.

Within subject pattern analysis of subjects with either a haemoglobin decrease of at least 1 g/dL or a level below the normal range showed for each treatment approximately a third of subjects first experienced the decrease at Day 10, a third at Week 7 and a third at Week 13. In the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group the absolute number of subjects who experienced a decrease of at least 1 g/dL at Day 10 was approximately the sum of the numbers for the ibuprofen 400 mg and paracetamol 1000 mg groups whereas at Week 7 and Week 13 the numbers in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group were less than the sum of the single actives.

A small number of subjects in each treatment group had plasma haemoglobin levels below the normal range at baseline. The percentage of these potentially vulnerable subjects that then experienced a decrease of at least 1 g/dL was lower than the study population as a whole. These data support the finding that higher baseline haemoglobin levels are a significant factor in predicting haemoglobin decreases with subjects as the haemoglobin level has further to fall (regression toward the mean).

For other haematological parameters, i.e. mean cell volume and mean cell haemoglobin there were no obvious differences between treatment groups apparent during the study. For red blood cell count, the mean decrease by Endpoint (LOCF) was greater for the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group compared to the other treatment groups, but this was not clinically significant. The mean change from baseline in platelet counts was highest with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' at Week 7, Week 13 and Endpoint (LOCF); however these values were less than the combined values for the ibuprofen 400 mg and paracetamol 1000 mg groups.

Although, the laboratory findings from study NL0605 highlighted the decrease in haemoglobin only seven cases were considered by the Investigator to be clinically significant and reported as adverse events, as well as 12 cases of anaemia. Of these a total of 15 reports were considered to be treatment-related according to the Investigator. Eight subjects had below normal range haemoglobin values at baseline, which remained so

throughout the study; however all differences at Day 10, Week 7 and Week 13 were ≤ 1 g/dL. One subject had borderline values and five subjects had a decrease in haemoglobin > 1 g/dL (two subjects in each combination group and one in the paracetamol 1000 mg group). The two subjects in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group withdrew from the study. There were four treatment emergent reports of increased platelet count, i.e. higher than the normal range (male: 152-351 x 10^9 /L and female: 169-357 x 10^9 /L), and considered by the Investigator to be clinically significant. Three of which were recorded as treatment-related adverse events, one each in the paracetamol 1000 mg group, and the 1 and 2 tablet 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' groups.

In conclusion, the decrease in mean blood haemoglobin was observed in all four treatment groups. The maximum observed decrease in haemoglobin was similar for all treatment groups; however the greatest decreases were experienced by subjects with higher baseline levels demonstrating regression to the mean. A greater number of subjects in the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group had a decrease in haemoglobin level of at least 1 g/dL, which was approximately the same as the sum of the number of subjects who experienced this decrease when taking ibuprofen 400 mg alone or paracetamol 1000 mg alone. This additive effect relates to the number of subjects with a decrease in haemoglobin rather than severity. These decreases in haemoglobin levels in NL0605 were not associated with clinically significant sequelae.

In studies with NSAIDs, reporting a 2 or 3 g/dL decrease of haemoglobin is a more common practice. In a meta-analysis Moore *et al* (2005) reported a haemoglobin decrease of 2 g/dL or more in 1-2 % of patients on placebo or NSAIDs. A search of the published literature found no reports of haemoglobin monitoring in clinical trials of paracetamol. Of the 29 subjects in NL0605 that experienced at least 2 g/dL decrease, three reports were considered by the Investigator as clinically significant and were reported as adverse events (one subject in 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group and two subjects in the 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group). Two subjects (one in each combination treatment group) had a decrease of 3 g/dL with no clinical manifestations. The data from study NL0605 suggests that there is an additive effect of taking ibuprofen and paracetamol in combination in subjects sensitive to a fall in haemoglobin.

As a precaution the SPC contra-indicates the use of this product in patients with a history of gastrointestinal ulceration, perforation or bleeding, the elderly and in patients already taking NSAIDs. The SPC also cautions patients about the risks and warning signs of gastrointestinal toxicity.

Biochemistry

There was a higher incidence of clinically significant liver function test abnormalities reported with paracetamol 1000 mg compared to the 1 or 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' or ibuprofen 400 mg alone. There were also reports of clinically significant changes in some of the individual markers used to assess liver function; of note were the elevated levels of GGT with the paracetamol containing products which was most pronounced in the paracetamol 1000 mg treatment group. There were mean increases in

alanine transaminase (ALT) values of a similar magnitude in all paracetamol containing treatment groups, but there was no real difference between treatment groups in the shift tables. For total bilirubin, aspartate aminotransferase, alkaline phosphatase, albumin and prothrombin time there was no difference between treatment groups.

There were reports of clinically significant changes in some of the individual markers used to assess renal function. Further analysis of these parameters by assessment of shift tables from baseline to Endpoint (LOCF) shows that:

- For urea, there was no real difference in the number of subjects with an increase from baseline for all the ibuprofen containing treatment groups (17-18%) compared to 11% with paracetamol 1000 mg group.

- For uric acid, there were a greater number of subjects with a decrease from baseline in the combination groups (5.9% 1 tablet dose and 9.3% 2 tablet dose) compared to ibuprofen 400 mg (2.3%) and paracetamol 1000 mg (3.7%).

- No treatment group differences in the numbers of subjects with changes in creatinine, creatinine kinase or electrolytes.

The only other biochemistry parameter of note was a shift increase from baseline to Endpoint (LOCF) for triglycerides. However, for the treatment groups containing paracetamol 1000 mg the results are comparable, i.e. 22.3% (2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') and 20.3% (paracetamol 1000 mg).

Urinalysis findings between treatment groups were unremarkable. In the 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' group there was one report of an abnormal urinalysis adverse event at Week 7; this was mild, resolved and the Investigator considered that the relation-to-treatment as 'unlikely'.

In conclusion, the changes in biochemistry were consistent with the known safety profiles of ibuprofen and paracetamol, and are therefore unremarkable and raise no new safety concerns with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. As a precaution the SPC contra-indicates the use of this product in patients with severe hepatic failure and severe renal failure and cautions all patients with renal and hepatic failure to ensure that they seek medical advice before taking this product.

2.5.5.7 Overdose, Potential for Dependence, Rebound and Abuse

There was no evidence of overdose, dependence, rebound and abuse from the clinical programme. It is not expected that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' would differ from the single active products of paracetamol and ibuprofen with respect to the incidence and consequences associated with overdose, dependence, rebound and abuse.

In overdose, hepatic toxicity is possible in adults who have taken 10 g or more of paracetamol. However, if patients have other risk factors, e.g. taking liver enzyme inducing drugs, consume excessive amounts of alcohol or are likely to be glutathione depleted the

toxic dose can be as low as 5 g. Acute renal failure has been reported in approximately 1-2% of unselected patients hospitalised with paracetamol overdose (Prescott 1996b). In the majority of overdose cases renal failure is secondary to liver failure, although there are isolated reports of renal failure without significant liver involvement. The prevalence of acute renal failure increases to 10% in patients who are severely poisoned (Pakravan *et al* 2007).

Pakravan *et al* (2007) reported experimental evidence of dose-dependent serum potassium decrease of less than 24 hours and kaliuresis in the first 12 hours only following paracetamol overdose (> 200 mg/L). No data was presented as to whether potassium values were within the normal range. The authors state that there was no correlation between changes in serum bicarbonate and serum potassium, or between serum bicarbonate and serum paracetamol concentration. There was no change in serum creatinine or serum sodium, or in fractional excretion of sodium, and no significant changes in blood pressure. The authors report that three cases had developed features of liver injury (rise in ALT) at 24 hours, although serum creatinine was in the normal range; no mention is made of the dose of paracetamol that these patients had taken. In conclusion, the changes reported are of experimental interest; however these changes are rarely clinically significant and do not merit specific actions.

Renal toxicity with ibuprofen is more likely to occur in subjects who take a massive overdose, i.e. greater than 400 mg/kg or with a plasma ibuprofen concentration greater than 280 mg/L within the first 10 hours following ingestion (Volans and Fitzpatrick 1999) or are dehydrated. There has been one case report in the published literature (Nelson *et al* 2007) where 250 g of paracetamol (serum level at admission to hospital was 316 µg/mL) and an unknown quantity of ibuprofen (no serum levels given) was ingested. The patient had acute renal failure, fulminant liver failure (requiring transplantation), rhabdomyolysis and necrotic bowel. The cause of acute renal failure could be associated with one or all the following effects: direct toxicity of paracetamol and ibuprofen, the liver failure, prolonged and frequent hypotension and the rhabdomyolysis.

In the Applicant commissioned study with Guy's and St Thomas' Poisons Unit (GPTU). The risk of toxicity from overdose with paracetamol and ibuprofen as single substances was compared to concomitant ingestion, with or without alcohol, by analysing five years of case data (2003-2007). This report was then independently reviewed by Dr GN Volans Consultant Clinical Pharmacologist **(Module 2.7 Section 2.7.4.5.5**). There were 11968 cases involving paracetamol, 5812 involving ibuprofen and 1633 involving paracetamol plus ibuprofen. There are limitations of the GTPU data; however the results show that there were no severe/life threatening or deaths with concomitant paracetamol and ibuprofen. There was no evidence that paracetamol and ibuprofen overdoses were more severe when taken with alcohol. There was little difference between the single substances and concomitant paracetamol plus ibuprofen in overdose with the majority of cases being asymptomatic or mild. In conclusion there were no new or unexpectedly severe toxic effects.

The proposed posology for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has a maximum single dose of 1000 mg and a maximum daily dose of 3 g of paracetamol. This is consistent with the doses for existing paracetamol containing products, but reduces the risk of daily exposure to paracetamol by 1 g, i.e. paracetamol-sparing. The SPC contains relevant information about overdose with 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

The SPC and the product labelling for the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' contraindicates the concomitant use of this product with other paracetamol containing products to minimise the risk of unintentional or accidental overdose.

Excessive use of analgesics, such as phenacetin, has been associated with analgesic nephropathy (Mihatsch *et al* 2006); however since withdrawal of phenacetin cases have declined significantly, whilst paracetamol, paracetamol combinations with aspirin and ibuprofen are widely used. There are no case reports in the published literature of analgesic nephropathy when paracetamol and ibuprofen are taken concomitantly although these drugs are often co-prescribed (**Section 2.7.4.1.1.3**). The abuse potential is considered not to be significant. The SPC and product labelling contain relevant warnings and precautions, as well as instructing the patient's physician to monitor at risk groups. This is in line with other prescribed ibuprofen and paracetamol containing products.

2.5.6 BENEFITS AND RISKS CONCLUSIONS

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has been developed as an effective alternative for the treatment of mild to moderate pain. The efficacy and safety profiles of ibuprofen and paracetamol as single actives are well characterised.

'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is intended for adults from 18 years and the proposed posology is 2 tablets to be taken every 6 to 8 hours as required, with at least 6 hours between doses and not exceeding 6 tablets in any 24-hour period. The proposed indication is for the treatment of mild to moderate pain, which is consistent with the indication already approved for both ibuprofen and paracetamol alone.

The proposed posology for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has a maximum daily dose of 1.2 g of ibuprofen and 3.0 g of paracetamol. The product and the proposed posology therefore reduce the risk of exposure to paracetamol, i.e. paracetamol-sparing, thus minimising the risk of unintentional or accidental overdose with paracetamol.

The clinical programme has established that ibuprofen and paracetamol administered as 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are bioavailable, the pharmacokinetic profiles are comparable to the single actives, and there is no pharmacokinetic interaction between ibuprofen and paracetamol. The repeat dose pharmacokinetic study shows that there is no accumulation of ibuprofen or paracetamol and that three times a day dosing provides more consistent plasma levels than twice a day dosing regimen.

The exploratory and pivotal factorial efficacy studies in the sensitive and widely recognised postoperative dental pain model confirm the 'additive' efficacy of ibuprofen and paracetamol and demonstrate a dose response between the three doses of the fixed combination. The studies demonstrate that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provides statistically significantly more effective pain relief than ibuprofen 400 mg alone and paracetamol 1000 mg alone. The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' has a faster onset of action than ibuprofen 400 mg and a long duration of action than paracetamol 1000 mg. The 93.2% of subjects rated the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' as 'good', 'very good' or 'excellent' in achieving pain relief. The confirmatory efficacy study supports the conclusion that the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is statistically significantly more effective than paracetamol 1000 mg alone in the treatment of mild to moderate pain.

The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was well tolerated. There were no deaths or serious treatment related adverse events reported from the studies. The overall adverse event profile for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was comparable to the combined profiles for the single actives. All adverse events were 'expected'.

The data presented support the proposed summary of product characteristics and product labelling for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The indications, posology

and warning statements are in line with those for prescription ibuprofen and paracetamol containing products.

The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provides a higher level of effective analgesia than ibuprofen or paracetamol alone with an acceptable safety or tolerability profile, thus demonstrating a positive benefit/risk profile.

All sections are redacted under section 43 of FOI act

2.5.7 LITERATURE REFERENCES

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Appendix 1

Justification of the Proposed Summary of Product Characteristics Section 4.8 Undesirable Effects

To define a list of undesirable effects and the associated frequency of a patient experiencing such an effect when taking the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet.

The document 'Minimum Clinical Particulars for Non-selective POM NSAIDs for Systemic Administration (November 2007)' describes the standard safety information including a list of undesirable effects that should be included in Section 4.8 of the Summary of Product Characteristics (SPC) for any non-selective NSAID. This document does not describe the frequency of such effects as this is dependent on the NSAID. This list has formed the basis of information in the proposed SPC. The full list is presented, highlighted in 'bold', as part of **Table 18**.

The clinical programme where 574 patients, in the Pooled Safety Dataset, were exposed to the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provides data on potential undesirable effects and the associated frequencies (**Module 5 Section 5.3.5.3**). The Pooled Safety Dataset includes all subjects from NL0408, all subjects from NL0604 Part 1, plus all subjects who switched from the single active treatment in Part 1 to the corresponding dose of the combination treatment in Part 2, and all subjects from NL0605. For this analysis Investigator determined treatment-related adverse events were used to determine the frequency of undesirable effects attributable to 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. Although there may be inconsistencies in assignment of causality by the Investigators, these data are more likely to be representative of adverse drug reactions reported with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in actual use.

All adverse events from the clinical programme experienced by subjects taking a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' up to the maximum daily dose of 6 tablets (equivalent to 1.2 g of ibuprofen and 3.0 g of paracetamol) are detailed in (**Table 18**). All the treatment-related adverse events reported in the clinical programme were considered to be either 'common' (experienced by ≥ 1/100 to < 1/10 subjects) or 'uncommon' (experienced by ≥ 1/1000 to < 1/100 subjects) in frequency.

The data from the clinical programme does not provide frequency information for all undesirable effects described in the 'Minimum Clinical Particulars for Non-selective POM NSAIDs for Systemic Administration (November 2007)' nor does it provide information on paracetamol specific adverse reactions. Therefore additional data from the UK post-marketing suspect adverse drug reaction reports for ibuprofen alone and paracetamol alone have been used (**Module 2.7 Section 2.7.4.6**). These reports are from healthcare professionals and patients and are collated by the MHRA and the Commission on Human Medicines since 1963. The cumulative listings of these data are confounded by the following factors: combined prescription and non-prescription usage; no stratification by dose or duration of treatment; causality based on suspicion not confirmation; no direct exposure

data; rate of adverse drug reaction reporting is affected by the medicines position in the product lifecycle, severity of the reaction and reporter. However, these data provide useful information on the adverse drug reactions likely to be reported with paracetamol and ibuprofen containing products (**Table 18**).

Exposure data for ibuprofen and paracetamol from first launch in the UK to the present day is not available. However, data in the public domain show that prescriptions dispensed for systemic preparations in the UK were approximately 123.2 million for paracetamol and approximately 51.9 million for ibuprofen (Department of National Statistics for England 1998-2007). Non-prescription products sold in the UK were 3.6 billion doses of paracetamol and 2.3 billion doses of ibuprofen (Nielsen for 3 years ending 24th February 2009). These data suggest that over the last 40 years the patient exposure, in UK, to both of these medicines has been very high. Although there is likely to have been considerable under-reporting of adverse drugs reactions for paracetamol and ibuprofen to the MHRA it can still be concluded that adverse drug reactions are 'rare' or 'very rare' with less than one report per 1000 to 10000 prescriptions.

These combined data, presented in **Table 18**, support the proposed Section 4.8 of the SPC for a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

Table 18 Proposed SPC Section 4.8 Undesirable Effects for a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'

Section 4.8 Undesirable Effects **PRIMARY SYSTEM ORGAN CLASS** Preferred term	**Pooled Safety Dataset No. of treatment-related adverse events reported for 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (frequency)**	**UK DAP – No. of reactions (as a % of total no. of reports)**		**Proposed Summary of Product Characteristics description**
		Paracetamol (single active products only)	**Ibuprofen** (single active products only)	
n	574	-	-	-
Total number of subjects or reports	159	1291	4378	-
No. of adverse events or reactions	302	2810	7248	-
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**3 (0.005)**	**61 (4.7)**	**281 (6.4)**	
Aplastic anaemia	0	9 (0.7)	30 (0.7)	Very rare
Anaemia	3 (0.005)	5 (0.4)	41 (0.9)	Uncommon
Agranulocytosis	0	2 (0.2)	13 (0.3)	Very rare
Haemolytic anaemia	0	1 (0.1)	9 (0.2)	Very rare
Neutropenia	0	1 (0.1)	6 (0.1)	Very rare
Thrombocytopenia	0	9 (0.7)	94 (2.1)	Very rare
CARDIAC DISORDERS	**0**	**71 (5.5)**	**115 (2.6)**	
Myocardial Infarction	0	3 (0.2)	7 (0.2)	Very rare
Stroke	0	0	0	Very rare
EAR AND LABYRINTH DISORDERS	**0**	**12 (0.9)**	**57 (1.3)**	
Tinnitus	0	3 (0.2)	22 (0.5)	Very rare
Vertigo	0	6 (0.5)	26 (0.6)	Very rare
EYE DISORDERS	**0**	**60 (4.6)**	**157 (3.6)**	
Visual disturbance (impairment)	0	27 (2.1)	35 (0.8)	Very rare

Section 4.8 Undesirable Effects PRIMARY SYSTEM ORGAN CLASS Preferred term	Pooled Safety Dataset No. of treatment-related adverse events reported for 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (frequency)	UK DAP – No. of reactions (as a % of total no. of reports)		Proposed Summary of Product Characteristics description
		Paracetamol (single active products only)	Ibuprofen (single active products only)	
GASTROINTESTINAL DISORDERS	**170 (0.296)**	**371 (28.7)**	**2229 (50.9)**	
Abdominal pain and discomfort [a]	31(0.054)	14 (1.0)	113 (2.6)	Common
Anal or rectal haemorrhage	1 (0.002)	2 (0.2)	22 (0.5)	Uncommon
Colitis	0	1 (0.1)	15 (0.3)	Very rare
Constipation	5 (0.009)	2 (0.2)	11 (0.3)	Uncommon
Diarrhoea	26 (0.045)	17 (1.3)	112 (2.6)	Common
Dry mouth	2 (0.003)	6 (0.5)	12 (0.3)	Uncommon
Dyspepsia	48 (0.084)	2 (0.2)	104 (2.4)	Common
Epigastric discomfort	1 (0.002)	0	2 (0.0)	Uncommon
Faeces discoloured	2 (0.003)	2 (0.2)	20 (0.5)	Uncommon
Flatulence	4 (0.007)	0	9 (0.2)	Uncommon
Gastritis	1 (0.002)	0	69 (1.6)	Uncommon
Gastrointestinal haemorrhage	0	11 (0.9)	263 (6.0)	Rare
Haematemesis	0	13 (1.0)	268 (6.1)	Rare
Melaena	0	8 (0.6)	238 (5.4)	Rare
Nausea	29 (0.051)	90 (7.0)	101 (2.3)	Common
Pancreatitis	0	1 (0.1)	6 (0.1)	Very rare
Peptic ulcers, haemorrhage and/or perforation also described as:	0	1 (0.1)	30 (0.7)	Rare
Duodenal	0	6 (0.5)	212 (4.8)	
Gastric	0	4 (0.3)	148 (3.4)	
Gastrointestinal	0	0	8 (0.2)	
Stomatitis and ulceration	0	7 (0.5)	86 (2.0)	Very rare
Vomiting	15 (0.026)	110 (8.5)	87 (2.0)	Common
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	**10 (0.017)**	**212 (16.4)**	**559 (12.8)**	
Chest pain	4 (0.007)	3 (0.2)	27 (0.6)	Uncommon
Face Oedema	0	18 (1.4)	70 (1.6)	Very rare
Fatigue	1 (0.002)	6 (0.5)	19 (0.4)	Uncommon
Feeling hot	1 (0.002)	2 (0.2)	3 (0.1)	Uncommon
Malaise	2 (0.003)	18 (1.4)	50 (1.1)	Uncommon
Oedema peripheral	1 (0.002)	12 (0.9)	59 (1.3)	Uncommon
Pain	1 (0.002)	5 (0.4)	23 (0.5)	Uncommon
HEPATOBILIARY DISORDERS	**0**	**330 (25.6)**	**106 (2.4)**	
Acute hepatic failure	0	65 (5.0)	0	Very rare
Hepatic failure	0	20 (1.5)	2 (0.0)	Very rare
Hepatic function abnormal	0	8 (0.6)	10 (0.2)	Very rare
Hepatic necrosis	0	79 (6.1)	3 (0.1)	Rare
Hepatitis	0	6 (0.5)	23 (0.5)	Very rare
Hepatotoxicity	0	14 (1.1)	1 (0.0)	Very rare
Jaundice	0	14 (1.1)	31 (0.7)	Very rare
Liver injury	0	90 (7.0)	0	Rare
INFECTIONS AND INFESTATIONS	**1 (0.002)**	**33 (2.6)**	**78 (1.8)**	
Influenza	1 (0.002)	0	0	Uncommon
IMMUNE SYSTEM DISORDERS	**0**	**42 (3.3)**	**135 (3.1)**	
Allergic reactions (hypersensitivity)	0	15 (1.2)	53 (1.2)	Very rare
Analphylactic responses (HLT)	0	26 (2.0)	81 (1.9)	Very rare

Section 4.8 Undesirable Effects PRIMARY SYSTEM ORGAN CLASS Preferred term	Pooled Safety Dataset No. of treatment-related adverse events reported for 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (frequency)	UK DAP – No. of reactions (as a % of total no. of reports)		Proposed Summary of Product Characteristics description
		Paracetamol (single active products only)	Ibuprofen (single active products only)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**1 (0.002)**	**380 (29.4)**	**69 (1.6)**	
Contusion	1 (0.002)	3 (0.2)	15 (0.3)	Uncommon
INVESTIGATIONS	**46 (0.080)**	**119 (9.2)**	**167 (3.8)**	
Alanine aminotransferase increased	8 (0.014)	8 (0.6)	5 (0.1)	Common
Aspartate aminotransferase increased	1 (0.002)	3 (0.2)	2 (0.0)	Uncommon
Blood alkaline phosphatase increased	1 (0.002)	3 (0.2)	3 (0.1)	Uncommon
Blood creatine phosphokinase increased	1 (0.002)	2 (0.2)	0	Uncommon
Blood creatinine increased	1 (0.002)	2 (0.2)	13 (0.3)	Uncommon
Blood urea increased	11 (0.019)	2 (0.2)	14 (0.3)	Common
Gamma-glutamyltransferase increased	11 (0.019)	4 (0.3)	1 (0.0)	Common
Haemoglobin decreased	3 (0.005)	0	17 (0.4)	Uncommon
Hepatic enzyme increased	2 (0.003)	1 (0.1)	1 (0.0)	Uncommon
Liver function test abnormal	6 (0.010)	16 (1.2)	19 (0.4)	Common
Platelet count increased	1 (0.002)	0	0	Uncommon
METABOLISM AND NUTRITION DISORDERS	**2 (0.003)**	**35 (2.7)**	**95 (2.2)**	
Enzyme abnormality	1 (0.002)	0	0	Uncommon
Increased appetite	1 (0.002)	1 (0.1)	1 (0.0)	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**7 (0.012)**	**27 (2.1)**	**111 (2.5)**	
Arthralgia	2 (0.003)	2 (0.2)	17 (0.4)	Uncommon
Back pain	1 (0.002)	1 (0.1)	13 (0.3)	Uncommon
Joint swelling	2 (0.003)	1 (0.1)	10 (0.2)	Uncommon
Neck pain	1 (0.002)	1 (0.1)	0	Uncommon
Pain in jaw	1 (0.002)	0	0	Uncommon
NERVOUS SYSTEM DISORDERS	**37 (0.064)**	**264 (20.4)**	**558 (12.7)**	
Dizziness	7 (0.012)	50 (3.9)	112 (2.6)	Common
Headache	21 (0.037)	22 (1.7)	74 (1.7)	Common
Hepatic encephalopathy	0	19 (1.5)	0	Very rare
Lethargy	1 (0.002)	4 (0.3)	19 (0.4)	Uncommon
Migraine	1 (0.002)	1 (0.1)	9 (0.2)	Uncommon
Optic neuritis	0	0	6 (0.1)	Very rare
Paraesthesia	0	14 (1.1)	46 (1.1)	Very rare
Somnolence	6 (0.010)	19 (1.5)	61 (1.4)	Common
Tremor	1 (0.002)	21 (1.6)	17 (0.4)	Uncommon
PSYCHIATRIC DISORDERS	**3 (0.005)**	**180 (13.9)**	**341 (7.8)**	
Confusion	0	16 (1.2)	43 (1.0)	Very rare
Depression	0	13 (1.0)	54 (1.2)	Very rare
Hallucinations	0	17 (1.3)	26 (0.6)	Very rare
Initial insomnia	1 (0.002)	0	0	Uncommon
Insomnia	2 (0.003)	5 (0.4)	22 (0.5)	Uncommon

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		Paracetamol (single active products only)	Ibuprofen (single active products only)	
RENAL AND URINARY DISORDERS	**5 (0.009)**	**60 (0.2)**	**283 (6.5)**	
Haematuria	2 (0.003)	2 (0.2)	19 (0.4)	Uncommon
Interstitial nephritis	0	0	25 (0.6)	Very rare
Nephrotic syndrome	0	0	8 (0.2)	Very rare
Nephrotoxicity (nephropathy toxic)	0	2 (0.2)	0	Very rare
Pollakiuria	1 (0.002)	3 (0.2)	19 (0.4)	Uncommon
Proteinuria	1 (0.002)	0	3 (0.1)	Uncommon
Renal failure	0	19 (1.5)	42 (1.0)	Very rare
Renal failure acute	0	3 (0.2)	47 (1.1)	Very rare
Renal impairment	1 (0.002)	5 (0.4)	17 (0.4)	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**9 (0.016)**	**81 (6.3)**	**356 (8.1)**	
Asthma	1 (0.002)	6 (0.5)	97 (2.2)	Uncommon
Bronchospasm	0	5 (0.4)	66 (1.5)	Very rare
Dyspnoea	1 (0.002)	16 (1.2)	66 (1.5)	Uncommon
Epistaxis	2 (0.003)	5 (0.4)	15 (0.3)	Uncommon
Hiccups	1 (0.002)	0	1 (0.0)	Uncommon
Pharyngeal haemorrhage	1 (0.002)	0	0	Uncommon
Pharyngolaryngeal pain	3 (0.005)	0	0	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**7 (0.012)**	**365 (28.3)**	**1351 (30.9)**	
Angioedema	1 (0.002)	22 (1.7)	119 (2.7)	Uncommon
Bullous dermatoses	0	1 (0.1)	14 (0.3)	Very rare
Erythema multiforme	0	0	23 (0.5)	Very rare
Exfolative dermatoses (HLT)	0	1 (0.0)	18 (0.4)	Very rare
Hyperhidrosis	1 (0.002)	18 (1.4)	35 (0.8)	Uncommon
Periorbital oedema	0	7 (0.5)	45 (1.0)	Very rare
Photosensitivity	0	1 (0.1)	49 (1.1)	Very rare
Pruritus	1 (0.002)	22 (1.7)	110 (2.5)	Uncommon
Pruritus generalised	0	4 (0.3)	10 (0.2)	Very rare
Purpura	0	17 (1.3)	59 (1.3)	Very rare
Rash	2 (0.003)	71 (5.5)	256 (5.8)	Uncommon
Rash erythematous	0	22 (1.7)	69 (1.6)	Very rare
Rash generalised	1 (0.002)	2 (0.2)	12 (0.3)	Uncommon
Rash maculo-papular	0	13 (1.0)	59 (1.3)	Very rare
Rash pruritic	0	3 (0.2)	19 (0.4)	Very rare
Stevens Johnson Syndrome	0	3 (0.2)	9 (0.2)	Very rare
Swelling face	1 (0.002)	6 (0.5)	27 (0.6)	Uncommon
Urticaria	0	94 (7.3)	174 (4.0)	Rare
Toxic epidermal necrolysis	0	2 (0.2)	7 (0.2)	Very rare
VASCULAR DISORDERS	**1 (0.002)**	**55 (4.3)**	**108 (2.5)**	
Hot flush	1 (0.002)	0	1 (0.0)	Uncommon

UK DAP (Drug Analysis Print out Paracetamol 17 Dec 08 and Ibuprofen 18 Dec 08; **Bold** = Undesirable Effects listed in the Minimum Clinical Particulars for non-selective POM NSAID for systemic administration; [a] Includes abdominal discomfort, distension, pain upper, pain lower, gastrointestinal reflux disease and stomach discomfort from the Pooled Safety Dataset; [b]In the SPC these are described as 'uncommon' because the incidence is similar to placebo; common = ≥ 1/100 to < 1/10 patients; uncommon = ≥ 1/1000 to < 1/100 patients; rare = ≥ 1/10000 to < 1/1000 patients; very rare ≤ 1/10000 patients.