Comparative Bioavailability Study of a New Orodispersible Formulation of Ibuprofen Versus Two Existing Oral Tablet Formulations in Healthy Male and Female Volunteers

Dalma Sugár, DVM[a]; Danielle Francombe, BSc PhD CHP[b]; Tiago da Silva, BSc[a]; Sarah Hanid, BSc[a]; and Simon Hutchings, MPharmacol PhD CHP[b]

[a]Reckitt Benckiser Health Limited, Slough, United Kingdom; and [b]Simbec Research Ltd, Merthyr Tydfil, United Kingdom

ABSTRACT

Purpose: This study aimed to assess the comparative bioavailability between ibuprofen acid orodispersible tablets (Test product) and ibuprofen acid oral tablets (Reference product).

Methods: This was a randomized, single-dose, 3-way crossover, open-label, pharmacokinetic study in 36 healthy male and female volunteers. Blood samples were taken periodically over a 12-h period after dosing to derive total plasma ibuprofen and S(+)/R(−) ibuprofen enantiomer pharmacokinetic parameters; safety profile and tolerability were evaluated throughout the study.

Findings: After a single-dose administration of ibuprofen acid oral tablets (2 × 200 mg), the total ibuprofen C_{max} and AUC_{0-t} (geometric least square [LS] mean) for the Test product was 29.4 μg/mL and 100.6 h/μg/mL, respectively, and for the Reference product it was 30.6 μg/mL and 98.7 h/μg/mL. The geometric LS mean Test/Reference ratio 90% CI for both total ibuprofen C_{max} (90.71−101.77) and AUC_{0-t} (98.72−105.23) was contained entirely within the predefined 80.00%−125.00% lower and upper limits; in addition, no statistically significant difference was found in T_{max} ($P = 0.1819$) after fasted administration of the Test and Reference products. There were 4 mild treatment emergent adverse events, considered unrelated to the study drug, reported by 2 volunteers during the study; no serious adverse events, no suspected unexpected serious adverse events. and no clinically significant changes in laboratory safety, vital signs, or 12-lead ECG measurements were reported. The enantiomer-specific analysis mirrored that of total ibuprofen, with the C_{max} and AUC_{0-t} LS mean Test/Reference ratio 90% CI for both ibuprofen S(+) and R(−) enantiomers contained entirely within the predetermined 80%−125.00% limits.

Implications: This study found that ibuprofen acid 200 mg orodispersible tablets and ibuprofen acid 200 mg tablets met the regulatory criteria for bioequivalence for AUC_{0-t} and C_{max}. Post hoc analysis of ibuprofen both S(+) and R(−) enantiomers mirrored the findings for total ibuprofen. All investigational products were found to be well tolerated. Clinicaltrials.gov identifier: NCT03180879. (*Clin Ther*. 2019;41:1486−1498)

Keywords: bioequivalence, enantiomer, ibuprofen, nonsteroidal anti-inflammatory drug, orodispersible tablet, pain management.

INTRODUCTION

The experience of acute pain is commonplace within the community setting, being defined as pain of recent onset, of limited duration, and usually related to a pathologic process, disease, or injury and is associated with conditions such as headache, backache, dental pain, period pain, and fever and pain associated with common cold.[1] Adequate relief

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of acute pain is regarded as essential to quality clinical care with poor relief a considerable risk factor for the transition from acute to chronic pain.[2] From this, it is widely acknowledged that rapid and effective pain relief is key to the management of acute pain episodes.

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic properties[3] and is administered as a racemate that contains equal quantities of two enantiomers, S(+)- and R(–) ibuprofen.[4]

After oral administration, ibuprofen is rapidly absorbed with peak plasma concentrations generally occurring within 1−2 h after administration.[5] The pharmacologic properties of ibuprofen are shown to be stereoselective,[4] with much of the pharmacologic effect attributed to the S(+) enantiomer.[6,7] When administered to humans, a significant proportion (50%−60%) of R(–) ibuprofen is converted to the S(+) enantiomer that is thought to be 160 times more potent than its antipode.[6−8]

Ibuprofen was initially available as a prescription-only medicine; only launched in 1983 as an over-the-counter (OTC) medication after establishment of a reassuring safety profile, it is now broadly used for fever management and both acute and chronic pain management.[3,4]

Ibuprofen is commonly available over the counter as an acid or as a salt formulation. On absorption, however, the active molecule in the salt formulation is pharmacologically and therapeutically identical to that of the standard ibuprofen formulation. The two formulations therefore have similar overall bioavailability and duration of activity.[4,9,10]

Reckitt Benckiser (RB) Health has developed a 200-mg ibuprofen acid orodispersible tablet (ODT) that may be taken without water and can be used on the go. ODTs are solid in format, similar to conventional tablets, but they are formulated with disintegrants that support more swift dissolution once placed in the mouth. When placed in to the mouth, ODT dosage forms rapidly disintegrate, releasing drug to the saliva to allow absorption from the upper gastrointestinal tract.[11] In addition, the ODT design offers an alternative treatment for children who may be reluctant to swallow a tablet formulation, adults who dislike tablets or have difficulty swallowing, or those who have little or no access to water.[11] The ODT format and ease of administration may offer a suitable alternative analgesic in these populations and for those in search of a more convenient pain relief product. The ibuprofen ODT manufactured by RB Health contains 200 mg of ibuprofen per tablet as the only active ingredient.

The primary objective of this study was to assess comparative bioavailability between the ibuprofen ODT and a Reference formulation of Nurofen ibuprofen acid 200 mg in the fasted state. This product was chosen as a reference product because it meets the European Medicines Agency (EMA) reference product criteria of being granted marketing authorization in the European Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC. Bioavailability was also to be evaluated against a Comparator formulation of Dolormin ibuprofen lysine 342 mg (equivalent to 200 mg ibuprofen per tablet because of increased molecular weight of lysine salt) in the fasted state. A post hoc assessment of ibuprofen enantiomers was also investigated to determine comparative enantiomer bioavailability between Test, Reference, and Comparator formulations; the tolerability of each formulation was also examined.

SUBJECTS AND METHODS

Study Population

Healthy male and female (nonpregnant, nonlactating) volunteers aged 18−50 years and with a body mass index within the range of 18−30 kg/m^2 were eligible to participate in the study. Health of the volunteers was assessed at the screening visit by review of past medical history, physical examination, vital signs, ECG, and laboratory tests. Participants agreed to use an effective method of contraception (unless a woman of nonchildbearing potential, when abstinent from sexual intercourse, or when anatomically sterile), from the first dose until 3 months after the final dose of the study medication.

Key exclusion criteria included a history of allergy or intolerance related to treatment with ibuprofen or other NSAIDs, or the excipients of the formulations; a history and/or presence of significant disease of any body system, including psychiatric disorders and parasuicide; any condition that could have interfered with the absorption, distribution, metabolism, or excretion of drugs; a history of or active peptic or

duodenal ulcers or gastrointestinal bleed or upper gastrointestinal bleed, or other significant gastrointestinal disorders; ingestion of a prescribed drug at any time in the 14 days before the first dose of the study medication or ingestion of an OTC preparation within 7 days before the first dose of the study medication; topical use of ibuprofen within 7 days before the first dose of the study medication; and any deviation from normal parameters in ECG, vital signs, hematology, biochemistry, or urinalysis.

Study Design

This was a randomized, single-dose, 3-way crossover, open-label, comparative bioavailability, pharmacokinetic (PK) study in healthy male and female volunteers conducted at the Clinical Pharmacology Unit, Simbec Research Ltd, Merthyr Tydfil, UK; clinicaltrials.gov identifier NCT03180879. The study consisted of a prestudy screening visit (Day −21 to Day −1), 3 treatment periods (Day −1 to Day 1), and a poststudy follow-up (2−7 days after the final PK blood sample was taken) and was conducted in accordance with the Declaration of Helsinki 2013,[12] International Council on Harmonisation Good Clinical Practice guidelines,[13] and applicable regulatory requirements. The study received Clinical Trial Authorisation from the UK Medicines and Healthcare Products Regulatory Agency and a favorable ethical opinion from Wales Research Ethics Committee 1.

A sample size of 32 volunteers was estimated based on %CV for ibuprofen AUC_{0-t} of 15% and C_{max} of 22.5% taken from previous similar studies that reported bioequivalence assessments under fasted conditions. It was calculated that 32 volunteers contributing complete C_{max} information for the primary study comparison would provide at least 90% power to demonstrate bioequivalence between the RB ibuprofen acid ODTs (Test) and Nurofen ibuprofen acid tablets (Reference).[14] This sample size also satisfied 2010 EMA bioequivalence guideline requirements which specify that the minimum required sample size is 12.[15] To secure 32 volunteers providing key PK parameters and to secure a balanced design of 6 complete blocks, the sample size was increased to 36 volunteers. Sample size calculations were performed with nQuery Advisor 7.0 (Statistical Solutions Ltd, Boston, Mass).

Investigational Medicinal Products

The test product used (ibuprofen acid ODTs [200 mg; Batch No. 05072812; Expiry Oct/2017]) was manufactured by RB. The reference product (Nurofen ibuprofen acid tablets [200 mg; Batch No. CB281; Expiry Oct/2017]) was manufactured by RB. The comparator product (Dolormin ibuprofen lysine tablets [342 mg; each containing 200 mg ibuprofen; Batch No. GFL8500; Expiry Oct/2017]) was manufactured by McNeil GmbH & Co (Neuss, Germany). Volunteers each received a single oral dose of 2 × 200 mg RB ibuprofen acid ODT, 2 × 200 mg Nurofen ibuprofen acid tablets, or 2 × 342 mg Dolormin ibuprofen lysine tablets (ie, equivalent to 2 × 200 mg ibuprofen), as determined by the randomization schedule at Treatment Period 1 (Day 1) and the alternative treatments at Treatment Period 2 (Day 1) and Treatment Period 3 (Day 1) after an overnight fast of 10 h. Both Reference and Comparator Investigational Medicinal Products (IMPs) were swallowed whole with 200 mL water, Test IMP was administered without water after the mouth had been moistened by swallowing 20 mL water; fluids (other than that used for drug administration) were withheld from 1 h before the dose to 1 h after the dose, standardized meals were received at 4.5 h and 10 h after the dose. A 3- to 7-day washout period between each IMP administration was chosen, based on this being >5 times the elimination half-life of the reference product of ~2 h.

Study Assessments and Blood Sampling

Blood samples (2.7 mL) were drawn into lithium heparin tubes via an indwelling cannula placed into a suitable vein up to 2 h before dosing and were collected before the dose and at 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 120, 180, 240, 360, 480, and 720 min after the dose for determination of ibuprofen plasma concentrations. The sampling schedule was based on the known pharmacokinetics of the reference product and exceeded 3 times the elimination half-life of ~2 h. Samples were separated by centrifugation at 1500×*g* and 4 °C for 10 min. The resulting plasma was stored at approximately −20 °C before analysis by Seirian Laboratories, Simbec Research Ltd (Slough, UK), using a validated achiral method. Analysis was

performed by LC-MS/MS detection, using the instrument in turbo ionspray negative ion MRM mode. The LC-MS/MS system consisted of an Applied Biosystems (Foster City, Calif) MDS Sciex API 5000 triple quadrupole, atmospheric pressure ionization mass spectrometer. Automated injection of samples took place with an Agilent (Santa Clara, Calif) 1200 Series pump and autosampler. LC-MS/MS analysis was performed on a Phenomenex (Torrance, Calif) Gemini C18 column, using an isocratic method. The following multiple reaction monitoring (MRM) transitions were monitored in negative ion mode: ibuprofen: $^{m}/_{z}$ 205.2 → $^{m}/_{z}$ 161.2, typical retention time 2.1−2.4 min; flurbiprofen: $^{m}/_{z}$ 243.1 → $^{m}/_{z}$ 199.2, typical retention time 1.4−1.6 min. Instrument control, data acquisition, and integration were achieved with proprietary Applied Biosystems MDS Sciex Analyst software Version 1.4.2. Each test, standard, and quality control plasma samples were extracted with a solution that contained internal standard flurbiprofen, using a protein precipitation method before the LC-MS/MS analysis. The lower limit of quantitation (LLOQ) for ibuprofen was 0.102 μg/mL, with a validated calibration range of 0.102−99.892 μg/mL. Throughout the study sample analysis, assay performance was acceptable with demonstrated intra-assay accuracy that ranged from 94.8% (S7 calibration standard) to 103.9% (S2 calibration standard) and intra-assay precision (% CV) that ranged from 2.8% (S8 calibration standard) to 5.6% (S2 calibration standard).

Additional exploratory samples were analysed with a validated chiral method. Analysis was performed by LC-MS/MS, using the instrument in turbo ionspray, positive ion MRM mode. The LC-MS/MS system consisted of an Applied Biosystems MDS Sciex API 5000 triple quadrupole atmospheric pressure ionization mass spectrometer. Automated injection of samples took place with an Agilent 1200 series pump and autosampler. LC-MS/MS analysis was performed on a Phenomenex Kinetex F5 column, using an isocratic method. The following MRM transitions were monitored in positive ion mode: R(−) and S(+) ibuprofen: $^{m}/_{z}$ 360.3→ $^{m}/_{z}$ 154.9, typical retention times 3.9 and 4.3 min; R(−) and S(+)ibuprofen d_3: $^{m}/_{z}$ 363.3 → $^{m}/_{z}$ 155.0, typical retention times 3.9 and 4.3 min. Instrument control, data acquisition, and integration were achieved with the use of proprietary Applied Biosystems MDS Sciex Analyst software Version 1.4.2. Each test, standards and quality control matrix samples were extracted with an IS solution that contained ibuprofen d_3 using a liquid−liquid extraction method before LC-MS/MS analysis. The LLOQ for S(+) ibuprofen was 48.86 ng/mL and R(−) ibuprofen was 55.20 ng/mL, with a validated calibration range of 48.86−75046.90 ng/mL (S(+) enantiomer) and 55.20−75317.07 ng/mL (R(−) enantiomer). Throughout the study sample analysis, S(+) enantiomer assay performance was acceptable with demonstrated intra-assay accuracy that ranged from 96.1% (S6 calibration standard) to 102.4% (S2 calibration standard), and intra-assay precision (%CV) that ranged from 1.3% (S5 calibration standard) to 5.7% (S2 calibration standard); R(−) enantiomer assay performance demonstrated intra-assay accuracy that ranged from 93.3% (S6 calibration standard) to 104.3% (S2 calibration standard) and intra-assay precision (% CV) that ranged 1.3% (S10 calibration standard) to 7.1% (S2 calibration standard).

Safety assessments were conducted at predetermined times throughout the study through recording of adverse events, vital signs, ECG, and safety laboratory test measurements. Adverse events were solicited once daily throughout the study period by a standard nonleading question; safety assessments were performed according to local standard operating procedures as per study protocol.

PK Methods and Statistical Analysis

Noncompartmental PK analysis was performed with the use of validated Phoenix WinNonlin v6.3 software (Certara USA, Inc, Princeton, N J) to derive PK parameters from plasma ibuprofen versus time data; primary end points were C_{max} and AUC_{0-t}. The following secondary end points were derived: T_{max}, AUC_{0-inf}, $AUC_{\%extrap}$ (residual area), k_e, and $t_{½}$. Actual sampling times were used for all PK analyses, and the predose timepoint was set to 0 h. For all LLOQ concentrations, plasma concentration was set to 0 μg/mL, and in the instance of missing samples the trapezoidal rule was used between the samples immediately before and after the missing sample for AUC calculations.

After logarithmic transformation, an ANOVA model was fitted to naturally log-transformed AUC_{0-t} and C_{max} with fixed effects for treatment,

period, and treatment with volunteer nested within sequence. The exponentiated least square (LS) means from each ANOVA model were presented as the LS geometric means for each treatment. The exponentiated differences and 90% CIs for the differences between LS means were presented as the LS geometric mean ratios and corresponding 90% CIs. Bioequivalence was found between the Test and Reference IMPs and Test and Comparator IMPs if each 90% CI for the ratio between LS geometric means (Test/Reference) (Test/Comparator) lay within 80.00% and 125.00% for both AUC_{0-t} and C_{max} as specified in 2010 EMA Guidelines for Investigation of Bioequivalence.[15] Statistical analysis was performed with SAS version 9.3 (SAS Institute, Cary, N C).

Post Hoc Analysis

Noncompartmental PK analysis was performed with the use of validated Phoenix WinNonlin v6.3 software (Certara USA, Inc) to derive PK parameters from plasma S(+) and R(−) ibuprofen enantiomer versus time data; primary end points for each enantiomer were those derived for total ibuprofen (C_{max} and AUC_{0-t}). The following secondary end points were derived for each enantiomer: T_{max}, AUC_{0-inf}, $AUC_{\%extrap}$, k_e, and t½. Actual sampling times were used for all PK analyses, and the predose timepoint was set to 0 h. For all LLOQ concentrations, plasma concentration was set to 0 ng/mL, and in the instance of missing samples the trapezoidal rule was used between the samples immediately before and after the missing sample for AUC calculations.

After logarithmic transformation, an ANOVA model was fitted to naturally log-transformed AUC_{0-t} and C_{max} with fixed effects for treatment, period, and treatment with volunteer nested within sequence. The exponentiated LS means from each ANOVA model were presented as the LS geometric means for each treatment. The exponentiated differences and 90% CIs for the differences between LS means were presented as the LS geometric mean ratios and corresponding 90% CIs. Treatments could be considered bioequivalent if each 90% CI for the ratio between LS geometric means (Test/Reference) (Test/Comparator) lay within 80.00% and 125.00% for both AUC_{0-t} and C_{max}.[15] Statistical analysis was performed with SAS version 9.3 (SAS Institute).

RESULTS

Study Population

Ninety volunteers gave their consent. Of these, 40 failed the screen, 5 withdrew consent, 7 declined to participate, 2 were reserve volunteers, and 36 (23 men and 13 women) were randomly assigned according to a randomization schedule generated with SAS version 9.3 (SAS Institute). There were 4 withdrawals due to protocol deviations, and 32 volunteers completed all treatment periods; however, 33 volunteers completed the Test, Reference, or Comparator Treatment Periods and were included in the derivation of parameters C_{max} and AUC_{0-t}; 32 volunteers had sufficient data within the elimination phase of the concentration−time profile to allow calculation of λ_z and associated parameters (including AUC_{0-inf}) (Tables 2 and 3). Volunteer disposition is summarized in Figure 1. The mean age of volunteers who completed the study and were included in the PK analysis was 27.1 years (range, 18−48 years) and mean BMI was 24.97 kg/m^2 (range, 20.5−29.7 kg/m^2); a summary of volunteer demographic characteristics is presented in Table I. One volunteer reported clinically significant concurrent/ongoing

Table I. Summary of volunteer demographic characteristics.

Parameter	Value
Age, y	
n	32
Mean (SD)	27.1 (7.59)
Weight, kg	
n	32
Mean (SD)	76.79 (13.606)
Height, m	
n	32
Mean (SD)	1.748 (0.0964)
Body mass index, kg/m^2	
n	32
Mean (SD)	24.97 (2.804)
Race, n (%)	
White	30 (93.75)
Other	2 (6.25)
Sex, n (%)	
Male	21 (65.625)
Female	11 (34.375)

Table II. Summary of statistical analysis of derived plasma pharmacokinetic parameters.*

Parameter	Geometric LS Mean			Geometric %CV Based on ANOVA Model
	Test	Reference	Test/Reference Ratio (90% CI)	
C_{max}, μg/mL (n = 33)†				
Reference	29.4	30.6	96.08 (90.71–101.77)	13.8
Comparator	29.8	40.2	74.21 (69.37–79.38)	16.1
AUC_{0-t}, h/μg/mL (n = 33)†				
Reference	100.6	98.7	101.92 (98.72–105.23)	7.6
Comparator	101.7	99.8	101.89 (98.05–105.87)	9.1
AUC_{0-inf}, h/μg/mL (n = 32)†				
Reference	102.7	99.2	103.49 (100.70–106.36)	6.4
Comparator	104.1	100.2	103.86 (100.16–107.70)	8.4
	Test Median	Reference Median	Median Difference (95% CI)‡	*P*§
T_{max}, h (n = 33)				
Reference	2.00	1.17	0.42 (0.00–0.83)	0.1819
Comparator	2.00	0.67	1.08 (0.67–1.50)	<0.0001

Comparator = Dolormin ibuprofen lysine tablets (2 × 342 mg); LS = least square; Reference = Nurofen ibuprofen acid tablets (2 × 200 mg); Test = Reckitt Benckiser ibuprofen acid orodispersible tablets (2 × 200 mg).

* Results were obtained with a fixed effects ANOVA with fixed effects of treatment, study period, treatment sequence, and volunteer nested within sequence.

† Thirty-three volunteers completed the Test, Reference, or Comparator treatment periods and were included in the derivation of parameters C_{max} and AUC_{0-t}; 32 volunteers had sufficient data within the elimination phase of the concentration–time profile to allow calculation of λz and associated parameters (including AUC_{0-inf}).

‡ CI was obtained with the Hodges-Lehman method.

§ *P* value was obtained with the Wilcoxon signed-rank test.

chondromalacia patellae, no concomitant medication was received for this condition during the study; with the exception of contraception, no volunteer who reported a concurrent/ongoing condition was receiving concomitant medication. There were no positive pregnancy test results during the study and no volunteer took concomitant medication throughout.

Plasma Pharmacokinetics

Plasma ibuprofen concentrations were sufficient to allow derivation of primary and secondary PK parameters. The mean plasma concentration versus time profiles for ibuprofen after single administration of the Test (RB ibuprofen acid ODTs), Reference (Nurofen ibuprofen acid tablets), and Comparator (Dolormin ibuprofen lysine tablets) IMPs are presented in Figure 2A and B. Mean plasma versus time profiles for the primary comparison of Test and Reference IMPs is also presented by sex in Figure 3A and B. Although formal statistical analysis of any differences in pharmacokinetics between men and women was not an objective of the study, there do not seem to be any appreciable differences in the plasma concentration versus time profiles for Test and Reference IMP in men and women. Review of the primary PK end points (C_{max} and AUC_{0-t}) indicated that the Test IMP (RB ibuprofen acid ODTs) was considered bioequivalent to the Reference IMP (Nurofen ibuprofen acid tablets) with the geometric LS mean Test/Reference ratio 90% CI for C_{max} of 90.71–101.77 and AUC_{0-t} of 98.72–105.23 were contained entirely within the predefined 80.00%–125.00% lower and upper limits[15] when

Table III. Summary of statistical analysis of derived plasma S(+) and R(−) ibuprofen pharmacokinetic parameters.*

Parameter	Geometric LS Mean			Geometric %CV Based on ANOVA Model
	Test	Reference	Test/Reference Ratio (90% CI)	
C_{max}, ng/mL (n = 33)†				
Reference				
S(+) ibuprofen	15,113.3	15,955.4	94.72 (88.69−101.17)	15.8
R(−) ibuprofen	14,314.5	14,995.8	95.46 (88.92−102.47)	17.0
Comparator				
S(+) ibuprofen	15,234.8	20,387.2	74.73 (70.28−79.45)	14.7
R(−) ibuprofen	14,458.3	19,090.3	75.74 (69.46−82.58)	20.8
AUC_{0-t}, h/ng/mL (n = 33)†				
Reference				
S(+) ibuprofen	58,139.6	57,247.3	101.56 (98.66−104.54)	6.9
R(−) ibuprofen	43,609.5	42,731.3	102.05 (96.90−107.48)	12.4
Comparator				
S(+) ibuprofen	58,630.6	56,887.1	103.06 (99.17−107.12)	9.2
R(−) ibuprofen	43,834.9	42,210.3	103.85 (97.72−110.37)	14.5
AUC_{0-inf}, h/ng/mL (n = 33)†				
Reference				
S(+) ibuprofen	60,698.5	59,015.8	102.85 (100.30−105.47)	6.0
R(−) ibuprofen†	44,195.1	42,842.6	103.16 (98.01−108.57)	12.0
Comparator				
S(+) ibuprofen	61,318.9	58,271.0	105.23 (101.37−109.27)	8.9
R(−) ibuprofen	44,554.1	42,142.7	105.72 (99.76−112.04)	13.5
	Test Median	Reference Median	Median Difference (95% CI)‡	P§
T_{max}, h (n = 33)				
Reference				
S(+) ibuprofen	2.00	1.33	0.42 (0.00−0.83)	0.1103
R(−) ibuprofen	2.00	1.33	0.42 (0.00−0.83)	0.2026
Comparator				
S(+) ibuprofen	2.00	0.67	1.21 (0.83−1.58)	<0.0001
R(−) ibuprofen	2.00	0.50	1.21 (0.83−1.58)	<0.0001

Comparator = Dolormin ibuprofen lysine tablets (2 × 342 mg); LS Mean = least square; Reference = Nurofen ibuprofen acid tablets (2 × 200 mg); Test = Reckitt Benckiser ibuprofen acid orodispersible tablets (2 × 200 mg).

* Results were obtained with a fixed effects ANOVA with fixed effects of treatment, study period, treatment sequence, and volunteer nested within sequence.

† Thirty-three volunteers completed the Test, Reference, or Comparator treatment periods and were included in the derivation of parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}. For R(−) ibuprofen only, 32 volunteers had sufficient data within the elimination phase of the concentration−time profile to allow calculation of λz and associated parameters.

‡ CI was obtained with the Hodges-Lehman method.

§ *P* was obtained with the Wilcoxon signed-rank test.

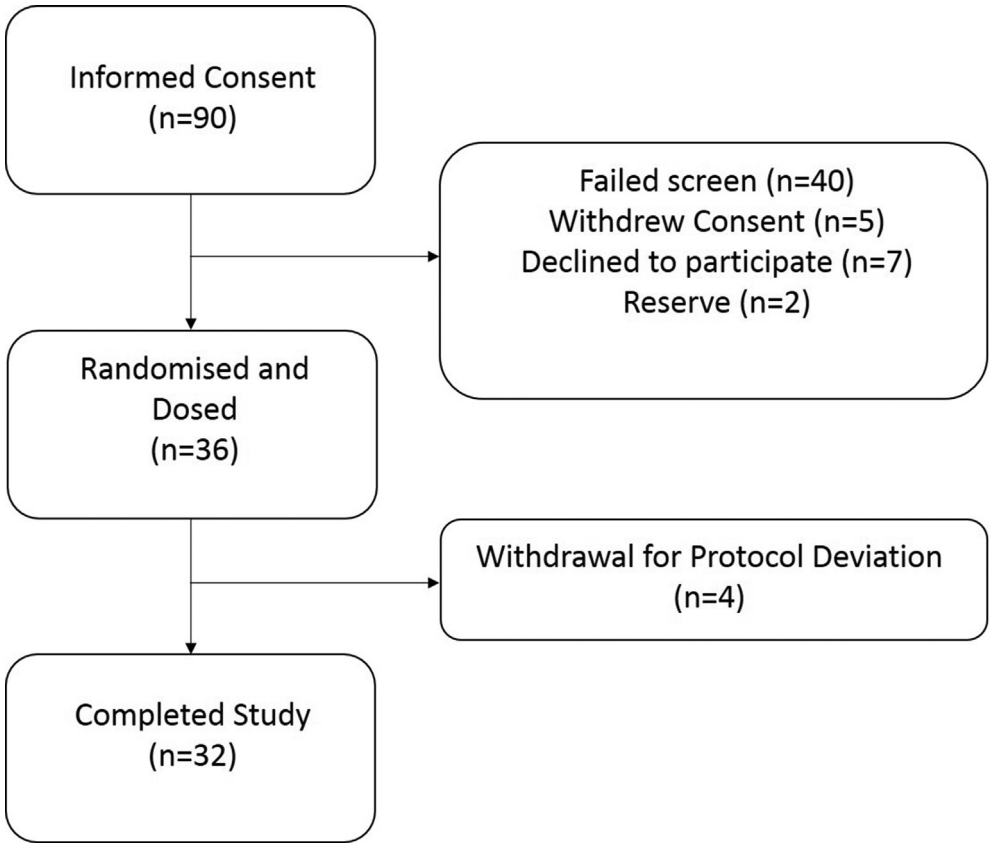

Figure 1. Consort diagram for volunteer disposition.

administered fasted. Review of PK end points demonstrate that the Test IMP (RB ibuprofen acid ODTs) was found not to be bioequivalent to the Comparator IMP (Dolormin ibuprofen lysine tablets) for the parameter C_{max} with the geometric LS mean Test/Comparator ratio 90% CI of 69.37−79.38 not contained within 80.00%−125.00%. However, the geometric LS mean Test/Comparator ratio 90% CI calculated for ibuprofen AUC_{0-t} indicated that the formulations were bioequivalent for this parameter, with upper and lower limits contained within the prespecified 80.00%−125.00% range[15] (Table II).

Throughout all treatment periods, the observed maximum $AUC_{\%extrap}$ was 6.80%, indicating that AUC_{0-t} covered >80% of AUC_{0-inf} for each volunteer in the sample. No statistically significant difference was found in T_{max} after fasted administration of the Test and Reference IMP ($P = 0.1819$); ibuprofen T_{max} was, however, more rapid for the Comparator IMP compared with the Test IMP ($P < 0.0001$). The k_e (mean values) was 0.350/hour, 0.353/hour and 0.342/hour after fasted administration of Test, Reference, and Comparator IMPs, respectively, indicating little difference in the rate of elimination between the 3 formulations, with t½ (mean values) of 2.01, 2.01, and 2.06 h, respectively. The PK parameters for ibuprofen are summarized in Table II.

Post Hoc Plasma Pharmacokinetics

Plasma ibuprofen enantiomer concentrations were sufficient to allow derivation of primary and secondary PK parameters. The mean plasma concentration versus time profiles for ibuprofen S(+) and R(−) enantiomers after single administration of the Test (RB ibuprofen acid ODTs), Reference (Nurofen ibuprofen acid tablets), and Comparator (Dolormin ibuprofen lysine tablets) IMPs are

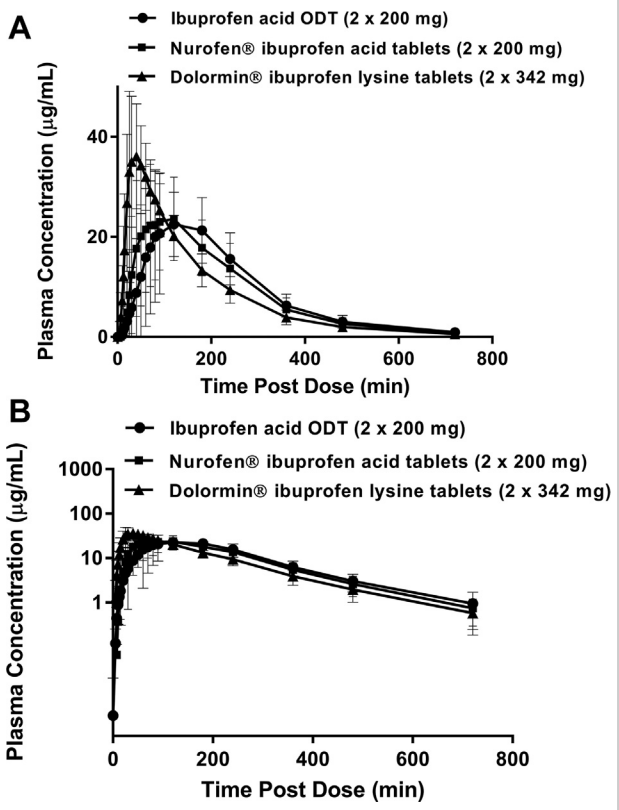

Figure 2. (A) Mean plasma concentration versus time curve with SD error bars for ibuprofen after single oral administration of the Test (2 × 200 mg ibuprofen acid orodispersible tablet [ODT]), Reference (2 × 200 mg Nurofen ibuprofen acid tablets), or Comparator (2 × 342 mg Aleve ibuprofen lysine tablets) products in healthy male and female volunteers. (B) The same data are shown on a log-linear plot.

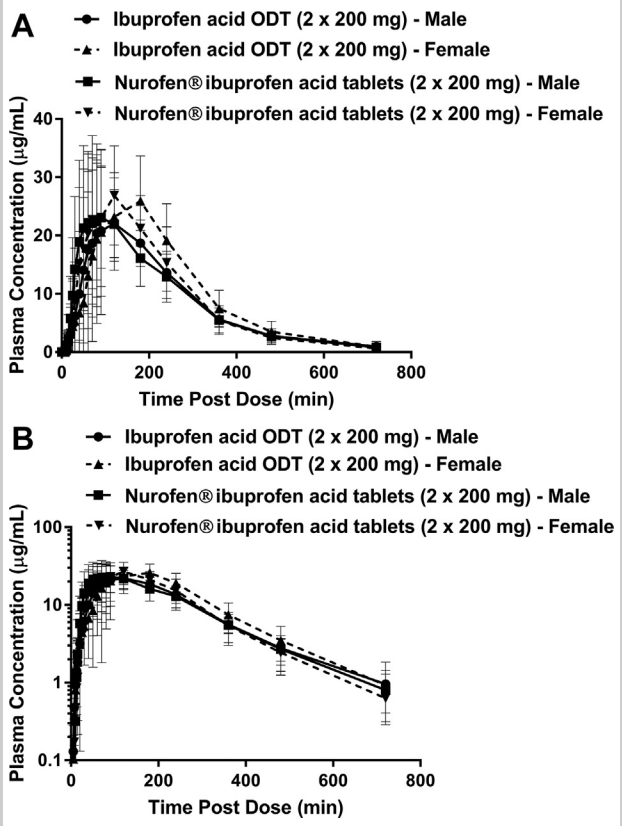

Figure 3. (A) Mean plasma concentration versus time curve with SD error bars for ibuprofen after single oral administration of the Test (2 × 200 mg ibuprofen acid orodispersible [ODT]), Reference (2 × 200 mg Nurofen ibuprofen acid tablets), or Comparator (2 × 342 mg Aleve ibuprofen lysine tablets) product plotted by sex in healthy male (solid line) and female (dashed line) volunteers. (B) The same data are shown on a log-linear plot.

presented in Figure 4A and B. Review of the primary PK end point, C_{max}, found that ibuprofen S(+) and R(−) enantiomers from Test IMP (RB ibuprofen acid ODTs) were considered bioequivalent to the Reference IMP (Nurofen ibuprofen acid tablets) with the geometric LS mean Test/Reference ratio 90% CIs of 88.69−101.17 and 88.92 to 102.47, S(+) and R(−) enantiomers, respectively, contained entirely within the predefined 80.00%−125.00% lower and upper limits[15] when administered fasted. Ibuprofen S(+) and R(−) enantiomers from the Test IMP were also considered bioequivalent to the Reference IMP for the primary end point AUC_{0-t}; the geometric LS mean Test/Reference ratio 90% CIs of 98.66−104.54 and 96.90 to 107.48 for S(+) and R(−) enantiomers, respectively, were contained entirely within the 80.00%−125.00% range.[15]

The Test IMP was found not to be bioequivalent to the Comparator IMP (Dolormin ibuprofen lysine tablets) for the parameter C_{max}; the difference between the Test and Comparator formulations was

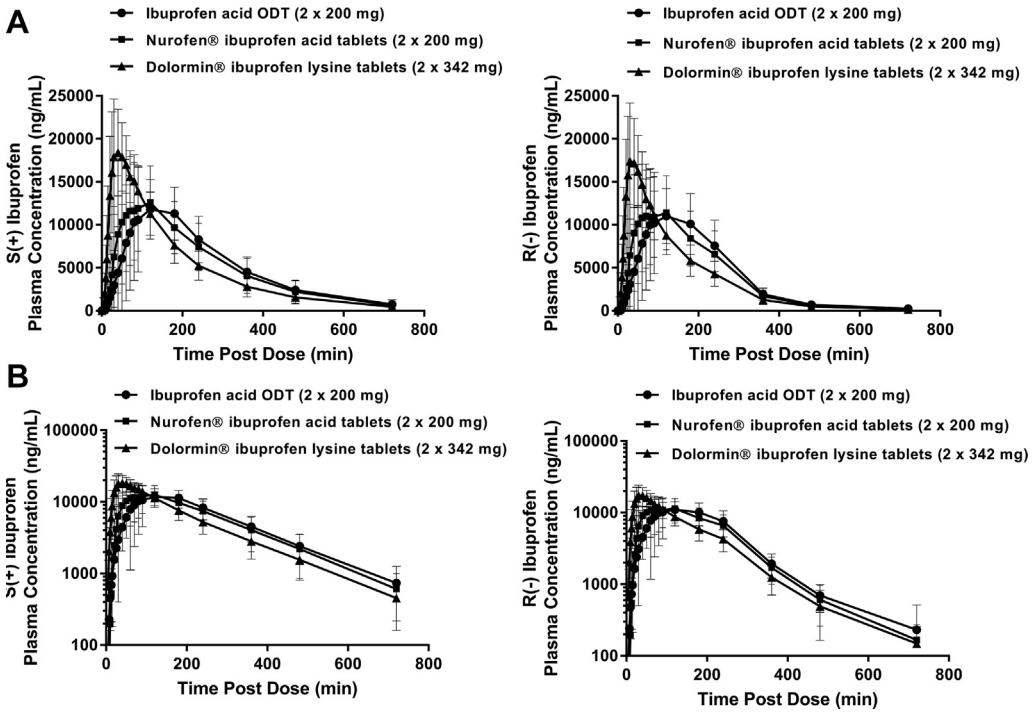

Figure 4. (A) Mean plasma concentration versus time curve with SD error bars for ibuprofen enantiomers after single oral administration of the Test (2 × 200 mg ibuprofen acid orodispersible [ODT]), Reference (2 × 200 mg Nurofen ibuprofen acid tablets), or Comparator (2 × 342 mg Aleve ibuprofen lysine tablets) product in healthy male and female volunteers. (B) The same data are shown on a log-linear plot.

statistically significant for both enantiomers ($P \leq 0.0001$). However, for both S(+) and R(−) enantiomers, the Test IMP formulation and Comparator IMP formulation were comparable for the parameter AUC_{0-t}, with test/reference geometric LS mean ratio 90% CIs for S(+) and R(−) enantiomers of 99.17−107.12 and 97.72 to 110.37, respectively, contained entirely within the prespecified 80.00%−125.00% lower and upper limits.[15] In addition, the Test and Reference formulations and Test and Comparator formulations were comparable for the parameter AUC_{0-inf} for both S(+) and R(−) ibuprofen enantiomers.

For both S(+) and R(−) enantiomers C_{max} was reached faster for the Reference formulation than for the Test formulation (S(+) enantiomer at 1.33 h versus 2.00 h, respectively, and R(−) enantiomer at 1.33 h versus 2.00 h, respectively; for each enantiomer, there was no strong statistical evidence of a difference in T_{max} between the Reference and Test formulations. C_{max} was also reached faster for the Comparator formulation than for the Test formulation; (S(+) enantiomer at 0.67 h versus 2.00 h, respectively, and R(−) enantiomer at 0.50 h versus 2.00 h, respectively). For each enantiomer, the difference was considered statistically significant with the use of the Wilcoxon signed-rank test for the Test and Comparator formulations ($P < 0.0001$).

The k_e (mean values) for S(+) ibuprofen was 0.321/hour, 0.332/hour, and 0.327/hour after fasted administration of the Test, Reference, and Comparator formulations, respectively, with t½ (mean values) of 2.23 h, 2.14 h, and 2.16 h, respectively. The mean k_e values for R(−) ibuprofen was 0.463/hour, 0.474/hour, and 0.457/hour after fasted administration of the Test, Reference, and

Comparator formulations, respectively, with mean t½ of 1.52 h, 1.50 h, and 1.56 h, respectively, indicating similarity in the rate of elimination of each enantiomer for all 3 formulations. The PK parameters for S(+) and R(−) ibuprofen are summarized in Table III.

Safety Assessments

During the study, a total of 4 treatment emergent adverse events (TEAEs) were reported by 2 volunteers, both after dosing with the Comparator IMP. All 4 TEAEs were mild in severity and were considered unrelated to the study drug; all events resolved without sequelae. There were no TEAEs of note, and, given the low TEAE incidence without causal link to the study drug, there was considered to be little difference in the TEAE profile observed between the Test, Reference, and Comparator IMPs. There were no serious adverse events, or suspected unexpected serious adverse reactions reported during the study.

DISCUSSION

Acute pain can occur after injury, as a result of surgery, or in association with tissue damage or infection; the importance of timely treatment and relief from which is widely recognized within clinical practice and literature.[10] As a result, prescription of NSAIDs is made on a routine basis for alleviation from mild-to-moderate pain; worldwide, NSAIDs are the most commonly prescribed analgesic agent, their efficacy for treatment of acute pain being well-established.[10,16]

Of these, ibuprofen is one of the most used analgesic, anti-inflammatory drug, ranking also as one of the most commonly used OTC treatments for the relief of acute pain. Described as "the mildest NSAID with the fewest side effects,"[17] ibuprofen offers a favorable safety profile compared with other common OTC analgesics such as paracetamol and aspirin.[18]

Within the United Kingdom, it is estimated that upward of 80% of households keep a supply of pain medication readily available, the most common format being tablet and caplet formulations[19]; however, studies have indicated that, in the case of ibuprofen, the rate and extent of absorption from a standard oral formulation may be compromised during a pain event, suggesting fast-dissolving formulations to perform more favorably.[20,21]

RB Health has developed an ibuprofen ODT that contains 200 mg ibuprofen acid per tablet with proposed therapeutic indications, including muscular pain, back pain, and acute pain and fever associated with cold and flu; these are similar to that for Nurofen 200 mg tablets which have been authorized for marketing in the European Union for >3 decades. The ODT format developed by RB Health is a fast-dissolving formulation that can be administered without water for added convenience; this alternative formulation may also aid improved treatment adherence in children and adults who dislike standard tablet formats or have difficulty swallowing.[22] Consequently, the availability of a pharmaceutically equivalent variant in ibuprofen formulation has the potential to affect the market, resulting in greater choice and improved compliance for this treatment.[23]

This study sought to examine the comparative bioavailability of RB ibuprofen acid ODTs with the commercially available Nurofen ibuprofen acid and Dolormin ibuprofen lysine products. The findings from this study found that there were no statistically significant differences between the Test and Reference ibuprofen acid tablet formulations with respect to PK parameters, representing peak and extent of exposure; this finding was applicable for both total ibuprofen and S(+) and R(−) ibuprofen enantiomers. Analysis of the primary PK end points (C_{max} and AUC_{0-t}) found that the differences in the geometric LS mean Test/Reference ratio was <15% for both parameters. When measuring total or enantiomer ibuprofen, the Test IMP was also considered comparable with the Comparator IMP for the parameter AUC_{0-t} but not the parameter C_{max}, however, because the Test product was not comparable with the Comparator product in both rate (C_{max}) and extent (AUC_{0-t}) of absorption; bioequivalence was not reached for this comparison.

The $t_{½}$ (mean value, total ibuprofen) of 2.01 h seen for the Test ibuprofen product is in line with the usual human plasma half-life (1.8−2 h) seen in other studies with ibuprofen.[24] The median T_{max} of 2 h also supports its rapid onset of action and is statistically comparable ($P = 0.1819$) with the Reference product. The Comparator product had a faster median T_{max} of 0.67 h, which is supported by the known pharmacokinetics of ibuprofen lysine and associated rapid onset of analgesia.[25,26] Analysis of

S(+) and R(−) ibuprofen found similar profiles for each enantiomer compared with total ibuprofen; this was applicable for the Test, Reference, and Comparator products.

The overall PK profile (racemate and enantiomer) for RB ibuprofen acid ODTs was comparable with that of Nurofen ibuprofen acid, presenting the RB ibuprofen ODT as a potential alternative to the currently marketed Nurofen originator product; comparative pharmacokinetics allow bridging of data to the Test RB ibuprofen acid ODT.

The study was designed and powered sufficiently to allow recognition of differences in primary PK parameters and complied with the regulatory requirements of the EMA.[15]

CONCLUSIONS

This single-dose study found that the Test and Reference products met the regulatory criteria for bioequivalence in these fasted healthy male and female volunteers. Statistical analysis of AUC_{0-inf} data indicated that the Test, Reference, and Comparator products have similar bioavailability. Further, review of ibuprofen enantiomer PK profiles found that the Test, Reference, and Comparator products each reflected the findings observed with total ibuprofen. The results of this study support the bridging of ibuprofen ODT data to the core clinical data available for ibuprofen oral tablets.

All formulations were well tolerated, the incidence of TEAEs was low during the study, and there was little difference in the TEAE profile observed between the Test, Reference, and Comparator products. These results support the use of RB ibuprofen acid ODT as an alternative ibuprofen tablet formulation.

CONFLICTS OF INTEREST

Dalma Sugár, Tiago da Silva, and Sarah Hanid were employees of Reckitt Benckiser Health at the time of this publication. At the time of publication Simon Hutchings and Danielle Francombe were employees of Simbec Research, Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Address correspondence to: Simon Hutchings, MPharmacol, PhD, CHP, Simbec Research Ltd, Pentrebach, Merthyr Tydfil, CF48 4DR, UK. E-mail: simon.hutchings@simbec.com