Clinical Study Report Synopsis

Drug Substance	VIMOVO
Study Code	D1120C00030
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A Phase I, Open-label, Randomised, 3-way Crossover Study to Demonstrate Bioequivalence of a Single Oral Dose of Naproxen Administered as VIMOVO Manufactured at AstraZeneca AB Compared to that of VIMOVO Manufactured by Patheon Pharmaceuticals and a Marketed Enteric-coated Naproxen Formulation (Manufactured by Roche) in Healthy volunteers

Study dates:	First subject enrolled: 22 August 2011 Last subject last visit: 05 October 2011
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To demonstrate the bioequivalence of a single oral dose of naproxen administered as VIMOVO (500-mg naproxen/20-mg esomeprazole) manufactured at a new facility in Sweden (AstraZeneca AB) to that of naproxen administered as VIMOVO manufactured in the United States (Patheon Pharmaceuticals Inc, Cincinnati, Ohio) and to a marketed enteric-coated naproxen formulation (500 mg, manufactured by Roche) in a fasted state in healthy volunteers	Primary: naproxen AUC, and C_{max} Secondary: naproxen $AUC_{(0-t)}$, t_{max}, λ_z, $t_{½\lambda z}$, CL/F, V_z/F, and t_{lag}	PK
Secondary	**Secondary**	
To assess the safety and tolerability of a single oral dose of naproxen administered as VIMOVO (500-mg naproxen/20-mg esomeprazole) manufactured at a new facility in Sweden (AstraZeneca AB), as VIMOVO manufactured in the United States (Patheon Pharmaceuticals Inc, Cincinnati, Ohio) and as a marketed enteric-coated naproxen formulation (500 mg, manufactured by Roche) in a fasted state in healthy volunteers	Adverse events, clinical laboratory parameters, vital signs, and physical examination	Safety

AUC area under the concentration-time curve from time zero to infinity; $AUC_{(0-t)}$ area under the concentration-time curve from time zero to time of last quantifiable concentration; CL/F apparent systemic clearance after extravascular dosing; C_{max} observed maximum plasma concentration; λ_z apparent terminal rate constant; $t_{1/2\lambda z}$, apparent terminal half-life; t_{lag} lag time before observation of first quantifiable plasma concentration; t_{max} time of C_{max}.

Study design

This was a randomised, open-label, single-dose, 3-way crossover study conducted in fasting (at least 10 hours prior to dosing) healthy male and female volunteers, aged 18 to 55 years. Each volunteer received the following 3 single oral-dose treatments (A, B, and C) in randomised order.

- Treatment A: VIMOVO (AstraZeneca) (500-mg naproxen/20-mg esomeprazole)
- Treatment B: VIMOVO (Patheon) (500-mg naproxen/20-mg esomeprazole)
- Treatment C: marketed enteric-coated naproxen formulation (manufactured by Roche) (500-mg tablet)

The study consisted of a screening visit (within 30 days before admission to the first treatment period), 3 treatment periods, and a follow-up visit that was performed at the 72-hour pharmacokinetic sampling in the last treatment period with the flexibility to perform the follow-up physical examination up to 2 days later. Each treatment period was approximately 3.5 days long, including a 2-night stay at the clinic and 3 outpatient visits. There was a washout of at least 7 days between doses.

Target subject population and sample size

Healthy male and female volunteers, aged 18 to 55 years, with a body mass index of 19 to 30 kg/m^2 (inclusive) and weight of 50 to 100 kg (inclusive).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product, dosage and mode of administration

- Treatment A: VIMOVO (AstraZeneca) (500-mg naproxen/20-mg esomeprazole), single dose, oral administration, packaging lot number 11-002-116AZ, formulation lot number 11-001-958AZ.

Comparators, dosage and mode of administration

- Treatment B: VIMOVO (Patheon) (500-mg naproxen/20-mg esomeprazole), single dose, oral administration, packaging lot number 11-002-118AZ, formulation lot number 11-000-643AZ.
- Treatment C: marketed enteric-coated naproxen formulation (manufactured by Roche) (500-mg tablet), single dose, oral administration, packaging lot number 11-002-120AZ, formulation lot number 10-005-422AZ.

Duration of treatment

There were 3 single doses, separated by washout periods of at least 7 days.

The total study duration for each volunteer was approximately 4 to 7 weeks.

Statistical methods

Safety, tolerability, and pharmacokinetic data were summarised descriptively using tables, listings, and graphs, as appropriate. In order to investigate bioequivalence, the log-transformed parameter values of AUC, $AUC_{(0-t)}$, and C_{max} were analysed using 2 mixed-effects models. As a primary analysis, the treatment sequence, period, and treatment were treated as fixed effects, and subject within sequence was considered as a random effect. As a secondary analysis, the treatment sequence, period, treatment, and subject-within-sequence were treated as fixed effects. The type of analysis used was reflected in the table titles when presenting the results. If the 90% confidence intervals for the geometric mean ratios of both AUC and C_{max} (in percent) between the test treatment and each of the reference treatments fell within the interval (80, 125%), then bioequivalence between the test treatment and the corresponding reference treatment was concluded.

Subject population

There were 36 volunteers enrolled; 36 (100%) received the 3 single doses of investigational product and completed the study. All volunteers were included in the safety and pharmacokinetic analyses. There were 33 (92%) males and 3 (8%) females. Twenty-eight (78%) volunteers were white, 1 (3%) was black or African American, 4 (11%) were Asian, and 3 (8%) were other. The mean (±standard deviation) age of all study volunteers was 32 ±8.3 years (ranged from 31 to 54 years); mean height was 176 ±6.6 cm; mean weight was 75.6 ±10.2 cm; and mean body mass index was 24.5 ±2.6 kg/m^2. Medical history was unremarkable and the the use of concomitant medication limited to ongoing oral contraception (2 volunteers) and multivitamin and omega 3, 6, 9 capsule (1 volunteer).

Summary of pharmacokinetic results

Naproxen PK parameters for each treatment are summarized in Table S2.

Median t_{max} was 5 hours for Treatment A and 4 hours for Treatments B and C. Mean $t_{1/2,\lambda z}$, CL/F, and V_z/F values were similar across treatments. Due to some volunteers having quantifiable predose plasma concentrations in Periods 2 and 3, median estimates for t_{lag} across all periods were imprecise. However, for Period 1 alone (n=12 for each treatment), median t_{lag} estimates for Treatments A, B, and C were 0.99, 1.00, and 1.00 hour, respectively.

Table S2 Summary of pharmacokinetic parameters for naproxen in plasma

Parameter	Geometric Mean (CV%)		
	Treatment A (N = 36)	Treatment B (N = 36)	Treatment C (N = 36)
AUC (µg*h/mL)	1160 (18.1)	1150 (17.1)	1150 (18.3)
$AUC_{(0-t)}$ (µg*h/mL)	1080 (16.0)	1080 (15.1)	1080 (17.0)
C_{max} (µg/mL)	58.7 (17.6)	62.6 (16.9)	63.2 (24.0)
t_{max} (h)[a]	5.00 (2.50, 12.00)	4.03 (2.50, 11.93)	4.00 (2.00, 10.00)
t_{lag} (h)[a]	0.00 (0.00, 4.00)	0.98 (0.00, 3.98)	1.00 (0.00, 8.00)
$t_{1/2,\lambda z}$ (h)	17.7 (13.0)	17.3 (13.6)	17.7 (14.1)
CL/F (L/h)	0.432 (18.1)	0.435 (17.1)	0.434 (18.3)
V_z/F (L)	11.1 (12.8)	10.9 (10.0)	11.1 (14.4)

CV% geometric coefficient of variation in percent.
[a] Data presented for this parameter are median (minimum, maximum).
Treatments: A = VIMOVO (AstraZeneca) 500-mg naproxen/20-mg esomeprazole; B = VIMOVO (Patheon) 500-mg naproxen/20-mg esomeprazole; C = Marketed enteric-coated naproxen (Roche) 500-mg tablet.
Source: Table 11.2.2.

The results of statistical comparisons of key naproxen pharmacokinetic parameters between treatments are summarized in Table S3.

Table S3 Statistical comparison of key naproxen pharmacokinetic parameters (primary statistical analysis)

Parameter	Treatment	n	Geometric LS Mean	95% CI	Pairwise Comparison		
					Pair	Ratio (%)	90% CI (%)
C_{max}	A	36	58.71	54.98, 62.70			
(µg/mL)	B	36	62.63	58.64, 66.88	A/B	93.75	88.28, 99.57
	C	36	63.25	59.23, 67.55	A/C	92.83	87.41, 98.59
AUC	A	36	1157	1089, 1230			
(µg*h/mL)	B	36	1148	1080, 1220	A/B	100.77	98.04, 103.58
	C	36	1151	1083, 1224	A/C	100.51	97.79, 103.31

CI confidence interval; LS least-squares.
Results based on a linear mixed-effects model with terms for treatment sequence, period, and treatment as fixed effects, and subject-within-sequence as a random effect.
Treatments: A = VIMOVO (AstraZeneca) 500-mg naproxen/20-mg esomeprazole; B = VIMOVO (Patheon) 500-mg naproxen/20-mg esomeprazole; C = marketed enteric-coated naproxen (Roche) 500-mg tablet.
Source: Table 11.2.3.

These results demonstrate that the AstraZeneca VIMOVO formulation (Treatment A) is bioequivalent to the Patheon VIMOVO formulation (Treatment B) and to the Roche marketed enteric-coated formulation (Treatment C) with respect to naproxen pharmacokinetics. The 90% confidence intervals on the geometric least-squares mean ratios for AUC and C_{max} were within the 80% to 125% bioequivalence limits for both comparisons (Treatment B/Treatment A and Treatment C/Treatment A) for the primary and secondary statistical analyses.

Summary of safety results

All 36 volunteers enrolled in the study received a single dose of VIMOVO (AstraZeneca), VIMOVO (Patheon), and naproxen (Roche).

There were no deaths, serious adverse events, adverse events of severe intensity, or discontinuations due to adverse events reported during study conduct. Following single-dose administration of investigational product, there were 18 adverse events reported in 13 (36%) volunteers. Three (18%) volunteers reported 4 adverse events (headache, somnolence, rash, and abdominal pain) that were assessed by the Investigator as causally related to investigational product; all other adverse events were not causally related. All adverse events were of mild intensity.

There were no trends or clinically meaningful changes noted in clinical laboratory, vital sign, electrocardiogram, or physical examination findings throughout the study.