AstraZeneca

Clinical Study Report Synopsis

Drug Substance	VIMOVO
Study Code	D1120C00040
Edition Number	1
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A Phase I, Open-label, Single-center Study to Assess the Pharmacokinetics of a Single Oral Dose of VIMOVO (250 mg Naproxen/20 mg Esomeprazole) in Healthy Adult Subjects

Study dates: First subject enrolled: 23 May 2011
Last subject last visit: 27 June 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 assess the pharmacokinetics of naproxen and esomeprazole following a single oral dose of VIMOVO (250-mg naproxen/20-mg esomeprazole) in a fasted state in healthy adult subjects	C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, λ_z, $t_{1/2,\lambda z}$, CL/F, and V_z/F of naproxen and esomeprazole in plasma	Pharmacokinetic
Secondary	**Secondary**	
To assess the safety and tolerability of a single oral dose of VIMOVO (250-mg naproxen/20-mg esomeprazole) in a fasted state in healthy adult subjects	Adverse events, vital signs, physical examinations, and clinical laboratory measurements	Safety

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

Study design

This was a Phase I, open-label, single-center, single oral dose study to assess the pharmacokinetic properties of VIMOVO (250-mg naproxen/20-mg esomeprazole) in a fasted state in healthy adult volunteers.

Target subject population and sample size

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

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

All volunteers received a single oral dose of VIMOVO (250-mg naproxen/20-mg esomeprazole) on Day 1 in the fasted state. VIMOVO was administered with 240 mL water.

Duration of treatment

The study consisted of 3 visits; Visit 1 (screening) from Day -30 to Day -2, Visit 2 (residential period) from Day -1 to Day 3, and Visit 3 (follow-up) on Day 4. Depending on the length of the screening period, the total study duration for each volunteer was approximately 34 days.

Statistical methods

Plasma concentrations and pharmacokinetic parameters of naproxen and esomeprazole were summarized using descriptive statistics (n, mean, standard deviation, geometric mean, geometric coefficient of variation, 95% confidence interval on the geometric mean, minimum, median, and maximum). Descriptive statistics for naproxen and esomeprazole C_{max}, $AUC_{(0-t)}$, and AUC from this study were qualitatively compared to corresponding descriptive statistics obtained at the higher naproxen dose strengths (375 mg/20 mg to 500 mg/20 mg) in other historical studies of VIMOVO.

Subject population

There were 28 volunteers enrolled and all 28 (100%) received the dose of investigational product and completed the study. All volunteers were included in the safety and pharmacokinetic analyses. There were 16 (57.1%) males and 12 (42.9%) females. Eleven (39.3%) volunteers were white, 13 (46.4%) volunteers were black, 2 (7.1%) volunteers were Asian, and 2 (7.1%) volunteers were American Indian or Alaska native. Three (10.7%) volunteers were Hispanic. The mean (±standard deviation) age of all study participants was 31.1 ±10.28 years (ranged from 18 to 53 years); mean height was 171.4 ±7.14 cm; mean weight was 72.0 ±12.44 kg; and mean body mass index was 24.4 ±3.24 kg/m^2. Medical history was unremarkable and the use of concomitant medication limited to ongoing oral contraception (4 volunteers).

Summary of pharmacokinetic results

Key pharmacokinetic parameters for naproxen and esomeprazole are summarized in Table S2.

Table S2 Summary of pharmacokinetic parameters for naproxen and esomeprazole in plasma

Parameter	n	Geometric mean (CV%)	95% CI
Naproxen			
AUC (µg*h/mL)	28	712 (19.6)	660, 767
C_{max} (µg/mL)	28	36.3 (22.7)	33.2, 39.6
t_{max} (h) [a]	28	4.03 (2.00, 16.25)	ND
Esomeprazole			
AUC (nmol*h/L)	22	894 (123.9)	583, 1370
C_{max} (nmol/L)	28	466 (160.0)	301, 721
t_{max} (h) [a]	28	0.63 (0.33, 2.50)	ND

CI confidence interval on geometric mean; CV% geometric coefficient of variation in percent; ND not determined.

[a] Data presented for this parameter are median (minimum [min], maximum [max]).

Source: Tables 11.2.3 and 11.2.4.

On an approximate dose-adjusted basis, naproxen exposure (AUC and C_{max}) in the current study was similar to exposure for the 375-mg/20-mg VIMOVO dose strength in previous studies (ie, Study D1120C00024 and Study PN400-105). The approximate dose-adjusted geometric means for AUC and C_{max} in the current study were 2.85 µg*h/mL/mg and 0.145 µg/mL/mg, respectively, compared to 2.78 to 2.85 µg*h/mL/mg and 0.136 to 0.152 µg/mL/mg, respectively, across the previous studies). Naproxen exposure in the current study was somewhat higher than mean dose-adjusted exposure for the 500-mg/20-mg VIMOVO dose strength in previous studies (Study PN400-102, Study PN400-103, Study PN400-108, and Study PN400-114). The approximate dose-adjusted geometric means for AUC and C_{max} in these previous studies were 2.43 to 2.62 µg*h/mL/mg and 0.111 to 0.132 µg/mL/mg, respectively. Median t_{max} in the current study was similar to previous studies of VIMOVO (4 hours, compared to 4 to 5 hours in the previous studies of 375 mg/20-mg VIMOVO).

Esomeprazole exposure (AUC and C_{max}) in this study was lower than that reported for previous VIMOVO studies (Study PN400-105, Study PN400-103, and Study PN400-114). Geometric mean AUC in the current study was 894 nmol*h/L (compared to approximately 972 to 1276 nmol*h/L in the previous studies), and geometric mean C_{max} in the current study was 466 nmol/L, which was about half of that observed previously (approximately 861 to 974 nmol/L in the previous studies). Median t_{max} in the current study was slightly longer than in previous studies of VIMOVO (0.63 hours, compared to 0.43 to 0.50 hours in the previous studies).

One volunteer had a much higher esomeprazole exposure than other volunteers in this study (esomeprazole AUC and C_{max} were 13700 nmol*h/L and 6030 nmol/L, which were approximately 15-fold and 13-fold higher than the respective geometric means). The reason for this higher esomeprazole exposure is unknown, but this volunteer had a much longer $t_{1/2,\lambda z}$ and lower CL/F than other volunteers (approximately 140% longer and greater than 90% lower than the means, respectively), suggesting that the volunteer might be a slow metabolizer. This volunteer's naproxen exposure was similar to other volunteers in the study (AUC of 718 µg*h/mL and C_{max} of 51.0 µg/mL).

Summary of safety results

All 28 volunteers enrolled in the study received a single VIMOVO (250-mg naproxen/20-mg esomeprazole) tablet on study Day 1.

There were no deaths, serious adverse events, adverse events of severe intensity, or discontinuations due to adverse events reported during study conduct. Following the single dose of investigational product, there were 5 adverse events reported for 4 (14.3%) volunteers. Catheter site pain was reported by 2 (7.1%) volunteers. Nausea, myalgia (bicep tenderness), and vessel puncture site hemorrhage (ecchymosis) were reported by 1 volunteer each. The event of nausea was 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, or physical examination findings throughout the study.