AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: PN 400
ACTIVE INGREDIENT: 500 mg enteric-coated naproxen and 20 mg immediate-release esomeprazole

Study No: D1120C00035
A single centre, two treatment, two period, two sequence, randomized crossover steady-state relative bioavailability study of naproxen in two tablet formulations given twice daily (PN 400 tablets containing 500 mg of naproxen plus 20 mg of esomeprazole versus Naprosyn® containing naproxen 500 mg)

Developmental Phase: Phase I
Study Completion Date: 27 October 2009
Date of Report: 22 March 2010

OBJECTIVES:

The primary objective of the study is to determine the relative naproxen bioavailability of AstraZeneca PN 400 (naproxen 500 mg plus esomeprazole 20 mg) compared to an immediate release Naprosyn® 500 mg tablet by assessment of area under the plasma concentration-time curve from time zero to 12 hours (AUC_{12}) maximum observed plasma concentration ($C_{ss,max}$), minimum plasma concentration ($C_{ss,\ min}$) and average plasma concentration over the dosing interval ($C_{ss,ave}$) on Day 9 of repeated bid administration.

The secondary objectives are to evaluate the pharmacokinetic (PK) properties of the naproxen component of AstraZeneca PN 400 tablet and immediate release Naprosyn® 500 mg tablet, by assessment of $C_{ss,max}/C_{ss,min}$, $C_{ss,max}/C_{ss,ave}$ and time to maximum plasma concentration (t_{max}) on Day 9 of repeated bid administration. Terminal elimination half-life ($t_{1/2}$), terminal elimination rate constant (k_e) and fluctuation will also be assessed for information.

The safety objective is to compare the adverse event profile from the AstraZeneca PN 400 to that from the Naprosyn® 500 mg tablet.

METHODS:

The clinical study was randomised, two treatment, two period, two sequence, balanced crossover pharmacokinetic comparison of naproxen from the two formulations under study in healthy volunteers. The analytical study used a validated HPLC method for the determination of naproxen in plasma samples.

It was planned to recruit 26 subjects in order to enrol 24 healthy volunteers. Thirty subjects were screened and 24 healthy volunteer subjects were enrolled in the study. Twenty-three subjects completed both study periods after one subject withdrew after the first dose in Period 1. Plasma samples from 23 subjects were analysed for naproxen.

Test Product (AstraZeneca PN 400 tablets): Batch No. H 1939-02-01-06

One tablet of AstraZeneca PN 400 was administered orally to each subject, each morning and evening (at approximately 12 hour intervals) for a total of 17 doses.

Reference (Roche 500mg naproxen tablet [Naprosyn®]): Batch No. E0009E1

One tablet of Naprosyn® was administered orally to each subject, each morning and evening (at approximately 12 hour intervals) for a total of 17 doses.

Seventeen doses of the test and reference product were administered to each subject on two occasions separated by at least 13 days between the final dose in Period 1 and the first dose in Period 2. Blood samples were collected in each period for the determination of steady-state pharmacokinetics of naproxen, and data was analysed to provide a comparison of the naproxen pharmacokinetics for the two formulations.

A nested ANOVA model was applied to the logarithmically transformed data with the fixed effects model: Dependent Variable = Intercept + Sequence +Formulation (i.e. treatment) + Period; and the random effects model: Subject (Sequence) for the primary pharmacokinetic variables. The assessment of comparative pharmacokinetics was based upon the 90% CI for the ratio of the geometric means (test/ref) for these parameters.

An analogues statistical comparison was conducted for $C_{ss,max}/C_{ss,min}$, $C_{ss,max}/C_{ss,ave.}$

The Wilcoxon Test was used to test for differences between formulations for t_{max}.

RESULTS:

Primary Pharmacokinetic Parameters

$C_{ss,max}$

Summary results are presented below:

Test formulation	(arithmetic mean ± SD):	106 ± 19.4 µg/mL
	(geometric mean):	104 µg/mL
Reference formulation	(arithmetic mean ± SD):	106 ± 10.1 µg/mL
	(geometric mean):	106 µg/mL
Ratio of Geometric Means (T/R):		0.985
90% C.I.		0.923 to 1.052

There were no statistically significant ($p < 0.05$) effects for the factors of period sequence or formulation.

The 90% confidence interval for $C_{ss,max}$ was within the bioequivalence acceptance interval of 0.80 to 1.25 as specified in the protocol for this bioequivalence study.

$C_{ss,min}$

Summary results are presented below:

Formulation T	(arithmetic mean ± SD):	59.7 ± 13.8 µg/mL
	(geometric mean):	58.2 µg/mL
Formulation R	(arithmetic mean ± SD):	50.3 ± 7.65 µg/mL
	(geometric mean):	49.7 µg/mL
Ratio of Geometric Means (T/R)		1.170
90% C.I.:		1.086 to 1.261

There were no statistically significant ($p < 0.05$) effects for the factors of period or sequence. There was a statistically significant ($p < 0.05$) difference between formulations for $C_{ss,min}$ ($p=0.0015$).

The 90% confidence interval for the $C_{ss,min}$ was not wholly within the bioequivalence acceptance interval of 0.80 to 1.25.

C_{min}

Summary results for this parameter are presented below:

Formulation T	(arithmetic mean ± SD):	47.9 ± 9.72 µg/mL
	(geometric mean):	46.9 µg/mL
Formulation R	(arithmetic mean ± SD):	44.6 ± 7.07 µg/mL
	(geometric mean):	44.1 µg/mL
Ratio of Geometric Means (T/R)		1.062
90% C.I.:		0.985 to 1.146

There were no statistically significant ($p < 0.05$) effects for the factors of period, sequence or formulation. The 90% confidence interval for the C_{min} was within the bioequivalence acceptance interval of 0.80 to 1.25.

$C_{ss,av}$

Summary results are presented below:

Formulation T	(arithmetic mean ± SD):	71.3 ± 11.1 µg/mL
	(geometric mean):	70.5 µg/mL
Formulation R	(arithmetic mean ± SD):	69.0 ± 8.69 µg/mL
	(geometric mean):	68.5 µg/mL
Ratio of Geometric Means	(T/R)	1.031
90% C.I.:		0.978 to 1.087

There were no statistically significant ($p < 0.05$) effects for the factors of period, sequence or formulation. The 90% confidence interval for the $C_{ss,av}$ was within the bioequivalence acceptance interval of 0.80 to 1.25.

AUC_T

Summary results are presented below:

Formulation T	(arithmetic mean ± SD):	855.7 ± 133.2 µg/mL.hr
	(geometric mean):	845.4 µg/mL.hr
Formulation R	(arithmetic mean ± SD):	828.0 ± 104.3 µg/mL.hr
	(geometric mean):	821.8 µg/mL.hr
Ratio of Geometric Means	(T/R)	1.031
90% C.I.:		0.978 to 1.087

There were no statistically significant ($p < 0.05$) effects for the factors of period, sequence or formulation. The 90% confidence interval for the AUC_T was within the bioequivalence acceptance interval of 0.80 to 1.25.

Secondary Pharmacokinetic Parameters

T_{max}

Median values were:

Test formulation:	3.52 hr
Reference formulation:	1.53 hr

It was shown by the Wilcocon Test that the median values were significantly different (P = 0.0002).

$C_{ss,max}/C_{min}$

Summary results are presented below:

Formulation T	(arithmetic mean ± SD):	2.30 ± 0.70
	(geometric mean):	2.22
Formulation R	(arithmetic mean ± SD):	2.42 ± 0.28
	(geometric mean):	2.40
Ratio of Geometric Means (T/R)		0.928
90% C.I.:		0.838 to 1.027

There were no statistically significant ($p < 0.05$) effects for the factors of period, sequence or formulation. The 90% confidence interval for $C_{ss,max}$ / C_{min} was within the bioequivalence acceptance interval of 0.80 to 1.25.

$C_{ss,max}$ / $C_{ss,av}$

Summary results are presented below:

Formulation T	(arithmetic mean ± SD):	1.48 ± 0.14
	(geometric mean):	1.48
Formulation R	(arithmetic mean ± SD):	1.55 ± 0.11
	(geometric mean):	1.55
Ratio of Geometric Means (T/R)		0.956
90% C.I.:		0.911 to 1.003

There were no statistically significant ($p < 0.05$) effects for the factors of period, sequence or formulation. The 90% confidence interval for $C_{ss,max}$ / $C_{ss,av}$ was within the bioequivalence acceptance interval of 0.80 to 1.25.

Additional Pharmacokinetic Parameters

Terminal elimination rate constant (k_e)
The mean values (± SD) were:

Formulation T:	0.03860 ± 0.00438 hr^{-1}
Formulation R:	0.03797 ± 0.00543 hr^{-1}

Terminal elimination half-life ($t_{½}$)
The mean values (± SD) were:

Formulation T:	18.19 ± 2.13 hr
Formulation R:	18.58 ± 2.45 hr

Fluctuation
The mean values (± SD) were:

Formulation T:	80.79 ± 21.93%
Formulation R:	90.40 ± 13.52%

Safety
Both PN400 and naproxen were well tolerated, with few adverse events, of which were mild and moderate in severity and none of which was serious or led to withdrawal from the study. There was no clinically significant changes in laboratory test results or vital signs.

Summary of Pharmacokinetic Results
The results of the study show that there was no statistically significant difference between the test and reference formulations with respect to rate/extent of absorption of naproxen as assessed in terms of all of the primary pharmacokinetic parameters for naproxen at steady state, apart from $C_{ss,min.}$ These results supported a conclusion of bioequivalence for naproxen in the PN 400 and Naprosyn formulations.

Summary of Safety Results
There were few adverse events reported in the study, with no obvious difference between the two formulations.