AstraZeneca

Clinical Study Report Synopsis

Drug Substance	PN 400
Study Code	D1120C00001
Edition Number	1
Date	16 July 2009

A Phase I, Open-label, Randomized, 3-way Crossover Study to Assess the Relative Bioavailability of a Single Oral Dose of Naproxen Administered as PN 400 (Naproxen/Esomeprazole) Compared to the Marketed Naproxen Formulations Proxen® S and Naprosyn® E in Healthy Human Volunteers

Study dates: First healthy volunteer enrolled: 9 September 2008
Last healthy volunteer completed: 15 December 2008

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

The study was conducted at 2 centers: Quintiles Hermelinen, Varvsgatan 53, SE-972 33 Luleå, Sweden, and Quintiles Phase I Services, Box 1543, SE-751 45 Uppsala, Sweden.

The first healthy volunteer was enrolled on 9 September 2008 and the last healthy volunteer completed the study on 15 December 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to assess and compare the pharmacokinetics (PK) and relative bioavailability in a fasted state of a single oral dose of 500 mg naproxen administered as a combination product PN 400 (500 mg naproxen/20 mg esomeprazole) to the currently marketed naproxen formulations Proxen® S (marketed in Germany by Roche Pharma AG) and/or Naprosyn® E tablets (marketed in Canada by Hoffman-La Roche Limited) in healthy human volunteers.

The secondary objective was to assess and compare the PK and relative bioavailability in a fed state of a single oral dose of 500 mg naproxen administered as a combination product PN 400 (500 mg naproxen/20 mg esomeprazole) to the currently marketed naproxen formulation Proxen® S (marketed in Germany by Roche Pharma AG) in healthy human volunteers.

Study design

This was a Phase 1, randomized, open-label, multi-center study conducted both in fasted (Part A) and fed (Part B) healthy volunteers.

Part A had a 3-way crossover design and was performed to assess the relative bioavailability of a single oral dose of 500 mg naproxen administered as PN 400 compared to the marketed formulations Proxen® S and/or Naprosyn® E. Each healthy volunteer received 1 oral single-dose treatment during each period: 1 dose of PN 400, 1 dose of Proxen® S and 1 dose of Naprosyn® E in randomized order.

Part B had a 2-way crossover design and was performed to assess the relative bioavailability of a single oral dose of 500 mg naproxen administered as PN 400 compared to the marketed formulation Proxen® S. Each healthy volunteer received 1 oral single-dose treatment during each period: 1 dose of PN 400 and 1 dose of Proxen® S in randomized order.

Target healthy volunteer population and sample size

Healthy females (using appropriate birth control) and males aged 18 to 55 years with a body mass index of ≥19 to ≤30 kg/m^2 and weight of ≥50 to ≤100 kg.

A total of 38 healthy volunteers were planned to be randomized in Part A to obtain a sample size of at least 32 healthy volunteers who completed the study. In Part B, a total of 44 healthy volunteers were planned to be randomized to obtain a sample size of at least 38 healthy volunteers who completed the study.

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

Investigational products	Dosage and mode of administration	Batch number
PN 400	Tablet, 500 mg naproxen/20 mg esomeprazole, oral	H 1939-01-01-06
Marketed Proxen® S	Tablet, 500 mg naproxen, oral	H 2059-02-01-01
Marketed Naprosyn® E	Tablet, 500 mg naproxen, oral	H 2059-03-01-01

Duration of treatment

One (1) single dose was given during each period. The 3 and 2 doses in Part A and Part B, respectively, were separated by a washout of 7 days.

Criteria for evaluation - pharmacokinetics (main variables)

The following PK parameters were calculated for naproxen in plasma:

AUC	Area under the plasma concentration-time curve from 0 to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from 0 to time t
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration
$t_{1/2\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
λ_z	Smallest (slowest) disposition (=hybrid) rate constant

Criteria for evaluation - safety (main variables)

Adverse events (AEs), clinical chemistry and hematology evaluations, vital signs measurements (blood pressure, temperature and heart rate) and physical examinations were used to monitor safety.

Statistical methods

The log-transformed parameter values of AUC and C_{max} were analyzed using a mixed effects model. Treatment sequence, period and treatment were treated as fixed effects, while subject within sequence was considered as a random effect. In Part A, Treatment B and C (Proxen® S and Naprosyn® E) were considered as reference treatments, and Treatment A (PN 400) was considered as test treatment. In Part B, Treatment E (Proxen® S) was considered as reference treatment, and Treatment D (PN 400) was considered as test treatment. The least squares (LS) means of each treatment and their 95% confidence intervals (CIs), and the LS means for the differences between test treatment and each of the reference treatments and their 90% CIs were calculated. The results were then anti-log transformed back to the original scale to obtain the corresponding geometric means and CIs.

If the 90% CIs for the geometric mean ratios of AUC and C_{max} between the test treatment and each of the reference treatments fell into the interval (0.8, 1.25), then bioequivalence was to be concluded.

Subject population

In total, 107 healthy volunteers were screened, 38 (23 females and 15 males) aged between 18 and 51 years were randomized to participate in Part A and 44 (27 females and 17 males) aged between 19 and 38 years were randomized to participate in Part B. The number of healthy volunteers who completed the study was 37 and 42 in Part A and Part B, respectively. The subject population and sample size were thus in accordance with the clinical study protocol. Twenty-one (21) healthy volunteers participated in both Part A and Part B of the study.

In Part A, 1 healthy volunteer was discontinued from the study for safety reasons. In Part B, 2 healthy volunteers were discontinued from the study. One (1) of the 2 healthy volunteers was discontinued due to an AE and the other healthy volunteer was discontinued due to being lost to follow-up. All 38 (Part A) and 44 (Part B) randomized healthy volunteers were included in the safety population. All randomized healthy volunteers were included in the PK population, except for 1 healthy volunteer in Part A who had anomalous predose concentration values and 1 healthy volunteer in Part B who was incorrectly enrolled in the study.

Summary of pharmacokinetic results

The mean naproxen plasma concentration profiles were similar for the combination product PN 400 (500 mg naproxen/20 mg esomeprazole) and the two currently marketed naproxen formulations Proxen® S and Naprosyn® E tablets during both fasting and fed conditions. Mean AUC and C_{max} in the fasting state were 1300 h*µg/mL and 69.8 µg/mL during PN 400 treatment, 1327 h*µg/mL and 70.6 µg/mL during Proxen® S treatment and 1318 h*µg/mL and 70.5 µg/mL during Naprosyn® E treatment. Mean AUC and C_{max} in the fed state were 1321 h*µg/mL and 66.5 µg/mL during PN 400 treatment and 1328 h*µg/mL and 64.9 µg/mL during Proxen® S treatment.

The 90% CIs of the geometric mean ratios comparing AUC and C_{max} of the test product (PN 400) versus the two marketed reference products (Proxen® S and Naprosyn® E), were all contained within the predefined interval for bioequivalence (0.8 to 1.25) in both the fasting (Table S1) and fed (Table S2) state. The inter-subject variability in the fasting state was 14.8% for AUC and 6.6% for C_{max} and the corresponding intra-subject variability was 5.9% and 16.8%, respectively. The inter-subject variability was 20.2% for AUC and 13.3% for C_{max} in the fed state and the corresponding intra-subject variability was 6.6% and 17.2%, respectively.

Table S1 Statistical comparison of key PK parameters, Part A

						Comparisons		
Parameter (unit)	**Treatment**	**n**	**Arithmetic Mean**	**Geometric LS Mean**	**95% CI**	**Comparison**	**Ratio**	**90% CI**
AUC (µg*h/mL)	PN 400	36	1300	1312	(1229, 1400)			
	Naprosyn® E	37	1318	1326	(1244, 1414)	PN 400/Naprosyn® E	0.9895	(0.9667, 1.013)
	Proxen® S	36	1327	1341	(1257, 1431)	PN 400/Proxen® S	0.9781	(0.9556, 1.001)
C_{max} (µg/mL)	PN 400	36	69.8	66.0	(61.0, 71.4)			
	Naprosyn® E	37	70.5	66.8	(62.1, 71.8)	PN 400/Naprosyn® E	0.9882	(0.9253, 1.055)
	Proxen® S	36	70.6	67.1	(62.0, 72.6)	PN 400/Proxen® S	0.9838	(0.9214, 1.051)

Results based on linear mixed model with terms for treatment sequence, period, and treatment as fixed effects and subjects within sequence as a random effect.
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Table S2 Statistical comparison of key PK parameters, Part B

						Comparisons		
Parameter (unit)	**Treatment**	**n**	**Arithmetic Mean**	**Geometric LS Mean**	**95% CI**	**Comparison**	**Ratio**	**90% CI**
AUC (µg*h/mL)	PN 400	42	1321	1218	(1049, 1415)			
	Proxen® S	40	1328	1227	(1058, 1425)	PN 400/Proxen® S	0.9926	(0.9676, 1.018)
C_{max} (µg/mL)	PN 400	42	66.5	64.5	(55.0, 75.7)			
	Proxen® S	40	64.9	62.6	(53.7, 73.0)	PN 400/Proxen® S	1.0302	(0.9654, 1.099)

Results based on linear mixed model with terms for treatment sequence, period, and treatment as fixed effects and subjects within sequence as a random effect.
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The median value of t_{max} was equal for PN 400, Proxen® S and Naprosyn® E in the fasted state (4.0 h) and comparable for PN 400 and Proxen® S in the fed state (12.0 and 11.0 h respectively).

Summary of safety results

There were no serious adverse events. In Part B, 1 healthy volunteer discontinued due to an AE (pyrexia) after treatment with Proxen® S. In Part A, 12 healthy volunteers reported AEs after receiving PN 400, 16 healthy volunteers after receiving Proxen® S and 10 healthy volunteers after receiving Naprosyn® E. In Part B, 21 healthy volunteers reported AEs after receiving PN 400 and 19 healthy volunteers after receiving Proxen® S. All reported AEs were of mild or moderate intensity, except for 1 AE of severe intensity (depressed mood) after administration of Proxen® S in Part A. In Part A, the most common AEs after treatment with PN 400 were headache and fatigue. The most common AEs after treatment with Proxen® S and Naprosyn® E were diarrhea and nasopharyngitis, and abdominal pain and headache, respectively. In Part B, the most common AEs after treatment with PN 400 were fatigue, nasopharyngitis, headache and dysmenorrhoea. Similar AEs were reported after treatment with Proxen® S.

One (1) healthy volunteer had high alanine transaminase and aspartate transaminase values on Day -1 in Period 2 (Part A) and was excluded from the study. There were no other clinically relevant or significant changes in safety laboratory variables or vital signs during the study.