AstraZeneca

Clinical Study Report Synopsis

Drug Substance	PN 400
Study Code	D1120C00024
Edition Number	1
Date	7 December 2009

A Phase I, Open-label, Randomized, 2-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 formulation Naprosyn® E under Fasting (Part A) and Fed (Part B and Part C) Conditions in Healthy Volunteers

Study dates: First healthy volunteer enrolled: 13 May 2009
Last healthy volunteer last visit: 14 September 2009

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 planned to be conducted at 2 centers in Sweden: Quintiles Hermelinen AB, Varvsgatan 53, SE-972 33 Luleå, Sweden, and Quintiles AB, Phase I Services, Box 1543, SE-751 45 Uppsala, Sweden. However, the study was only conducted at 1 of the centers: Quintiles Hermelinen AB. Elisabeth Edén, MD was the Co-ordinating investigator and Aslak Rautio, MD was the Principal investigator.

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 and compare the pharmacokinetics (PK) and relative bioavailability in a fasted state of a single oral dose of 375 mg naproxen administered as a combination product PN 400 (375 mg naproxen/20 mg esomeprazole) to the currently marketed naproxen formulation in Canada, Naprosyn® E, in healthy volunteers	AUC and C_{max}	PK
To assess and compare the PK and relative bioavailability in a fed state of a single oral dose of 375 mg naproxen administered as a combination product PN 400 (375 mg naproxen/20 mg esomeprazole) to the currently marketed naproxen formulation in Canada, Naprosyn® E, in healthy volunteers		
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 Naprosyn® E tablets (marketed in Canada by Hoffman-La Roche Limited) in healthy human volunteers		
	Secondary	
	t_{max}, $AUC_{(0-t)}$, λ_z, $t_{1/2\lambda z}$	PK
Safety	**Secondary**	
To assess safety and tolerability of a single oral dose of naproxen when administered in the fasted and fed state as PN 400 (375 mg naproxen/20 mg esomeprazole) and Naprosyn® E (375 mg), and when administered in the fed state as PN 400 (500 mg naproxen/ 20 mg esomeprazole) and Naprosyn® E (500 mg) to healthy volunteers	Adverse events (AEs), laboratory safety assessments, physical examinations and vital signs	Safety

Study design

This was a Phase I, randomized, open-label, single-dose, 2-way crossover study divided in Part A (conducted in fasted healthy volunteers) and Part B and Part C (conducted in fed healthy volunteers). The study was performed to assess and compare the PK and relative bioavailability in the fasted (Part A) and fed (Part B and Part C) state of a single oral dose of 375 mg (Part A and Part B) and 500 mg (Part C) naproxen administered as PN 400 (test, intended for treatment of arthritis) to the marketed formulation Naprosyn® E (reference).

Target subject 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 72 healthy volunteers were planned to be randomized, ie, 24 in each part of the study, (24 in Part A, 24 in Part B and 24 in Part C) in order to have at least 18 evaluable healthy volunteers in each part (18 in Part A, 18 in Part B and 18 in Part C).

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

Investigational products	Dosage and mode of administration	Batch number
PN 400	Tablet, 375 mg naproxen/20 mg esomeprazole, oral	H1954-01-01-05
PN 400	Tablet, 500 mg naproxen/20 mg esomeprazole, oral	H1939-02-01-06
Marketed Naprosyn® E	Tablet, 375 mg naproxen, oral	H2108-01-01-01
Marketed Naprosyn® E	Tablet, 500 mg naproxen, oral	H2059-03-01-02

Duration of treatment

One (1) single dose was given during each treatment period in Part A, Part B and Part C. The washout period (days without administration of investigational product) was at least 6 days, and the expected total duration of each healthy volunteer's participation was 4 weeks (from the screening visit until the follow-up visit) in all 3 parts of the study.

Statistical methods

The log-transformed parameter values of AUC and C_{max} were analyzed using a mixed effects model. The treatment sequence, period and treatment were treated as fixed effects, and the subjects within sequence was considered as a random effect. Naprosyn® E was considered as reference treatment, and PN 400 was considered as test treatment. The least-squares (LS) means of each treatment and their 95% confidence intervals (CIs), the LS means for the differences between test treatment and the reference treatment and their 90% CIs were calculated from the mixed effects model mentioned above. These LS means and their CIs were then anti-log transformed to obtain the corresponding geometric means and CIs. If the

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

Subject population

In total, 92 healthy volunteers were screened (Part A to Part C). Of these, 24 (15 males and 9 females) aged between 18 and 45 years were randomized to participate in Part A, 24 (17 males and 7 females) aged between 18 and 48 years in Part B and 24 (10 males and 14 females) aged between 18 and 46 years in Part C. The number of healthy volunteers who completed the study was 24, 23 and 23 in Part A, Part B and Part C, respectively. The subject population and sample size were thus in accordance with the clinical study protocol.

In Part B, 1 healthy volunteer was discontinued due to personal reasons after completing Period 1 in which she received Naprosyn® E. In Part C, 1 healthy volunteer was discontinued due to an AE (common cold) after completing Period 1 in which she received PN 400. In addition, 1 healthy volunteer completed all assessments in Part C but did not eat the entire standard test meal in any of the 2 treatment periods. Furthermore, the healthy volunteer did not eat a comparable amount in the 2 periods, and was thus considered to not have completed the study according to protocol. In Part A and Part B, all randomized healthy volunteers (24 in Part A and 24 in Part B) were included in the safety analysis set and in the PK analysis set. In Part C, all 24 randomized healthy volunteers were included in the safety analysis set. Twenty-one (21) healthy volunteers were included in the PK analysis set for PN 400, whereas 23 healthy volunteers were included in the PK analysis set for Naprosyn® E.

Summary of pharmacokinetic results

In Part A, the geometric mean AUC and C_{max} were 1067 h*µg/mL and 50.9 µg/mL, respectively, following PN 400 treatment and 1074 h*µg/mL and 56.4 µg/mL, respectively, following Naprosyn® E treatment. In Part B, the geometric mean AUC and C_{max} were 1041 h*µg/mL and 56.8 µg/mL, respectively, following PN 400 treatment and 1057 h*µg/mL and 59.8 µg/mL, respectively, following Naprosyn® E treatment. In Part C, the geometric mean AUC and C_{max} were 1261 h*µg/mL and 72.3 µg/mL, respectively, following PN 400 treatment and 1272 h*µg/mL and 69.9 µg/mL, respectively, following Naprosyn® E treatment.

The 90% CIs of the geometric mean ratios comparing AUC and C_{max} of the lower-strength combination product (PN 400) versus the reference formulation (Naprosyn® E), were all contained within the predefined interval for bioequivalence (0.8 to 1.25) in both the fasting (Part A) and fed (Part B) state. The corresponding 90% CIs of the higher-strength combination product (PN 400) versus the reference formulation (Naprosyn® E), were also contained within the predefined interval for bioequivalence (0.8 to 1.25) in the fed (Part C) state.

The geometric mean $AUC_{(0-t)}$ of 375 mg naproxen was comparable for PN 400 and Naprosyn® E in the fasting state (992.8 h*µg/mL and 1004 h*µg/mL, respectively) and comparable for PN 400 and Naprosyn® E in the fed state (953.9 h*µg/mL and 968.0 h*µg/mL, respectively). The geometric mean $AUC_{(0-t)}$ of 500 mg naproxen was

comparable for PN 400 and Naprosyn® E in the fed state (1149 h*µg/mL and 1172 h*µg/mL, respectively).

The 90% CI of the geometric mean ratios comparing AUC_{0-t} of the lower-strength combination product (PN 400) versus the reference formulation (Naprosyn® E), was contained within the predefined interval for bioequivalence (0.8 to 1.25) in both the fasting (Part A) and fed (Part B) state. The corresponding 90% CI of the higher-strength combination product (PN 400) versus the reference formulation (Naprosyn® E), was also contained within the predefined interval for bioequivalence (0.8 to 1.25) in the fed (Part C) state.

The median t_{max} of naproxen (375 mg) was comparable for PN 400 and Naprosyn® E in the fasting state (4.00 h and 2.76 h, respectively) and in the fed state (10.00 h and 8.00 h, respectively). The t_{max} of naproxen (500 mg) was equal for PN 400 and Naprosyn® E in the fed state (12.00 h). The geometric mean $t_{½λz}$ of naproxen was in the same range (17 to 18 h) for PN 400 and Naprosyn® E, irrespective of dose or fasting/fed state.

Summary of safety results

There were no serious AEs. In Part C, there was 1 DAE (nasopharyngitis) after treatment with PN 400. There were few AEs reported after both PN 400 and Naprosyn® E treatment in all 3 study parts, and approximately the same types of AEs were reported after treatment with PN 400 and Naprosyn® E in Part A, Part B and Part C in this open-label study. In Part A, 3 healthy volunteers reported AEs after receiving PN 400 and 4 healthy volunteers after receiving Naprosyn® E. In Part B, 5 healthy volunteers reported AEs after receiving PN 400 and 4 healthy volunteers after receiving Naprosyn® E. The number of healthy volunteers reporting AEs in Part C were 9 after receiving PN 400 and 7 after receiving Naprosyn® E. All AEs were of mild or moderate intensity, except for 1 severe AE (headache) reported by a healthy volunteer after receiving PN 400 in Part C. All AEs in Part A and Part B were judged by the Investigator not to be related to treatment. In Part C, 4 of the AEs reported after PN 400 administration and 1 AE reported after Naprosyn® E administration were judged by the Investigator to be related to treatment.

There were no clinically relevant changes in safety laboratory variables or vital signs during the study.