AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	D961FC00012
Edition Number	1
Date	
EudraCT Number	2011-003258-21

A Phase I, Open-label, Randomised, Two-way Crossover Pharmacokinetic Study Comparing the Bioavailability of Acetylsalicylic Acid (ASA) after 5 Days Repeated Once Daily Administration of a Fixed Dose Combination Capsule of ASA 81 mg/Esomeprazole 20 mg and ASA 80 mg (European Aspirin Reference Product) in Healthy Male and Female Volunteers

Study dates: First subject enrolled: 3 November 2011
Last subject last visit: 4 May 2012

Phase of development: Clinical pharmacology (I)

Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centres

The study was conducted at 2 study centres in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetics	The primary objective of this study was to compare the bioavailability of ASA between ASA 81 mg/esomeprazole 20 mg FDC capsule and Acetylsalicylzuur Apotex cardio 80 mg tablet after 5-day once daily administration by the assessment of AUC_{τ} and $C_{ss,max}$ of ASA.	AUC_{τ} and $C_{ss,max}$
Secondary	Pharmacokinetics	To compare the bioavailability of the ASA metabolite, SA, between ASA 81 mg/esomeprazole 20 mg FDC capsule and Acetylsalicylzuur Apotex cardio 80 mg tablet after 5-day once daily administration by the assessment of AUC_{τ} and $C_{ss,max}$ of SA.	AUC_{τ} and $C_{ss,max}$
	Pharmacokinetics	To evaluate the pharmacokinetics of ASA and SA administered as ASA 81 mg/esomeprazole 20 mg FDC capsule and Acetylsalicylzuur Apotex cardio 80 mg tablet by the assessment of $AUC_{0\text{-}t,ss}$, $t_{max,ss}$ and $t_{½\lambda z,ss}$.	$AUC_{0\text{-}t,ss}$, $t_{max,ss}$ and $t_{½\lambda z,ss}$
	Safety	To evaluate the safety and tolerability of esomeprazole and ASA within the study.	Adverse events, clinical laboratory safety variables, physical examination, 12-lead ECGs and vital signs

ASA: acetylsalicylic acid; AUC_{τ}: area under the concentration-time curve during the dosing interval at steady state; $AUC_{0\text{-}t,ss}$: area under the plasma concentration-time curve from time zero to the last quantifiable time point at steady state; $C_{ss,max}$: observed maximum plasma concentration at steady state; ECG: electrocardiogram; FDC: fixed dose combination; SA: salicylic acid; $t_{½\lambda,ss}$: terminal half-life at steady state; $t_{max,ss}$; time to observed maximum plasma concentration at steady state

Study design

This was a Phase I, open-label, randomised, two-way crossover pharmacokinetic (PK) study comparing the bioavailability of a FDC capsule of low dose ASA 81 mg with esomeprazole 20 mg, and a low dose ASA 80 mg tablet (Acetylsalicylzuur Apotex cardio 80 mg), in healthy male and female volunteers.

The healthy volunteers were randomised to 1 of 2 treatment sequences: AB or BA, where Treatment A was ASA 81 mg/esomeprazole 20 mg FDC capsule and Treatment B was the reference Acetylsalicylzuur Apotex cardio 80 mg tablet. The randomisation scheme was generated using the validated global randomisation system (GRand) and randomisation codes were assigned strictly sequentially as healthy volunteers became eligible for randomisation.

Target subject population and sample size

Healthy male and female volunteers aged 20 to 50 years, inclusive, with body mass index of 18.0 to 30.0 kg/m^2, inclusive were included in the study.

This study was planned to be conducted at a single study centre with approximately 54 healthy volunteers to achieve at least 46 evaluable healthy volunteers. However, due to a dose administration error in a different study at the investigational product administration in all AstraZeneca studies at the study centre were placed on temporary hold on 19 December 2011. At the time of this decision this study was ongoing. Twelve healthy volunteers had completed Period 1 and received 3 investigational product administrations in Period 2. These 12 healthy volunteers were withdrawn from the study and did not complete Period 2. These 12 healthy volunteers were included in the safety analysis set. However, since the objective of this study was to compare ASA and SA PK between treatments, analysis of the PK from only 1 treatment would not yield any meaningful results. The PK blood samples for these 12 healthy volunteers were not analysed and were not included in any of the PK summaries or analyses.

In order to meet the study objectives in a timely manner an additional study centre, , was initiated and an additional 12 healthy volunteers were recruited to replace the 12 healthy volunteers withdrawn due to the temporary hold, ie, 66 healthy volunteers were included in the study.

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

Test: Treatment A: ASA 81 mg/esomeprazole 20 mg FDC oral capsules. The capsules were administered once daily for 5 days. Batch number: 11-002701AZ.

Reference: Treatment B: Acetylsalicylzuur Apotex cardio 80 mg oral tablets. The tablets were administered once daily for 5 days. Batch number: 11-002703AZ.

Duration of treatment

The study consisted of 2 treatment periods. The investigational products were administered once daily for 5 days in each treatment period. The 2 treatment periods were separated by a washout period of at least 14 days, counted from the day of the last investigational product administration in Period 1 to the day of the first investigational product administration in Period 2.

Statistical methods

Safety analyses:

Continuous safety data were summarised by time point, for the absolute value at each scheduled assessment and for the corresponding change from baseline, using descriptive statistics. Extra measurements (such as unscheduled or repeat assessments) were not included in the descriptive statistics by scheduled time point, but were included in data listings. All adverse events (AEs) and clinical laboratory outliers that occurred following the first administration of the ASA 81 mg/esomeprazole 20 mg FDC capsule or the Acetylsalicylzuur Apotex cardio 80 mg tablet were included in the tabulations of AEs and outlier events, including episodes that occurred at unscheduled evaluations.

All available data from healthy volunteers in the safety analysis set were included in the safety analyses. No adjustment or imputation were utilised for missing values or for healthy volunteers who withdrew prior to completing the study, neither was analyses restricted to healthy volunteers with complete data.

Adverse events were summarised by Preferred Term (PT) and System Organ Class using Medical Dictionary for Regulatory Activities vocabulary by treatment. Furthermore, listings of serious adverse events (SAEs) and AEs that lead to withdrawal were made and the number of healthy volunteers who had any AEs, SAEs, AEs that lead to withdrawal and AEs with severe intensity were summarised.

Listings of data for vital signs, clinical laboratory tests, ECGs and physical examination findings are presented. All continuous safety data were summarised for the absolute value at each scheduled assessment and for the corresponding change from baseline to the follow-up visit. For clinical laboratory tests, listings of values for each healthy volunteer are presented with abnormal or out-of-range values flagged. Clinical laboratory data were reported in Système International units.

Pharmacokinetic analyses:

The plasma concentrations of ASA and SA and the derived PK parameters were summarised by treatment using descriptive statistics.

The PK parameters of AUC_{τ}, $AUC_{0\text{-}t,ss}$ and $C_{ss,max}$ for ASA and SA were compared between the ASA 81 mg/esomeprazole 20 mg FDC capsule (test) (Treatment A) and the Acetylsalicylzuur Apotex cardio 80 mg tablet (reference) (Treatment B). These PK

parameters were analysed on log scale using a linear mixed effect analysis of variance model with fixed effects for sequence, period and treatment, and random effect for healthy volunteer nested within sequence. Transformed back from the logarithmic scale, geometric means together with 2-sided 95% confidence intervals (CIs) for AUC_{τ}, $AUC_{0\text{-}t,ss}$ and $C_{ss,max}$ were estimated. Ratios of geometric means together with 2-sided 90% CIs for Treatment A/Treatment B were estimated. If the lower bound of the 2-sided 90% CIs did not fall below 80.00% then no difference in the bioavailability of ASA between the 2 treatments was concluded.

The secondary parameter time to observed maximum plasma concentration at steady state ($t_{max,ss}$), was analysed for each analyte non-parametrically using the Wilcoxon signed-rank test which does not account for period effects. A Hodges-Lehmann estimator of the median differences and 90% CIs for the difference of $t_{max,ss}$ between the ASA 81 mg/esomeprazole 20 mg FDC capsule (test) (Treatment A) and the Acetylsalicylzuur Apotex cardio 80 mg tablet (reference) (Treatment B) was calculated. The CIs were calculated using the method of Hahn and Meeker.

Subject population

Overall, 66 healthy volunteers received investigational product. Sixteen healthy volunteers discontinued investigational product administration and were withdrawn from the study. A total of 50 healthy volunteers completed the study. All 66 healthy volunteers were included in the safety analysis set and 54 healthy volunteers were included in the PK analysis set.

The demographic and volunteer characteristics were according to the inclusion and exclusion criteria for the study and were similar for the safety analysis set and the PK analysis set. No relevant medical or surgical histories were reported. All concomitant medications administered during the study were for the treatment of AEs.

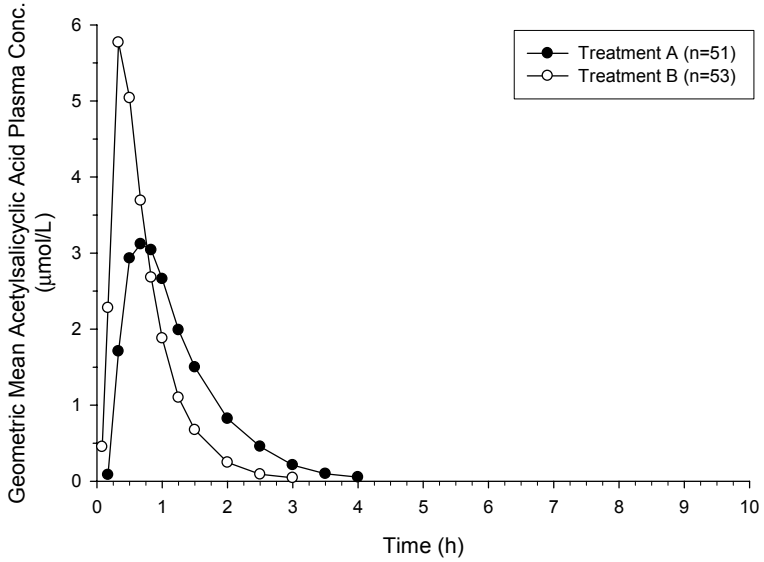
Summary of pharmacokinetic results

Plasma concentrations

<u>Acetylsalicylic acid</u>

Geometric mean and generally individual ASA concentrations were higher during the first hour following dosing with the reference Acetylsalicylzuur Apotex cardio 80 mg tablet; however, ASA concentrations at each subsequent time point were slightly higher for the ASA 81 mg/esomeprazole 20 mg FDC capsule.

Figure S1 Geometric mean acetylsalicylic acid plasma concentration-time profiles by treatment

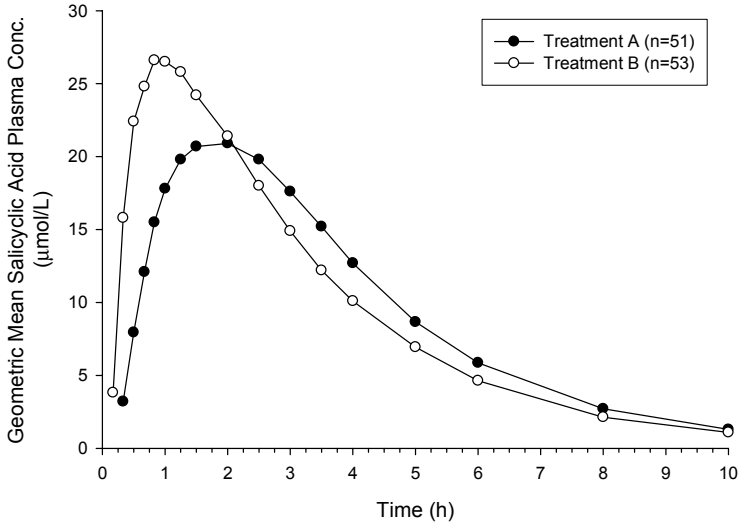


Treatment A = ASA 81 mg/esomeprazole 20 mg fixed dose combination capsule
Treatment B = ASA 80 mg tablet (Acetylsalicylzuur Apotex cardio 80 mg)

Salicylic acid

Geometric mean and generally individual SA concentrations were higher during the first 2 hours following dosing with the reference Acetylsalicylzuur Apotex cardio 80 mg tablet; however, SA concentrations at each subsequent time point were slightly higher for the ASA 81 mg/esomeprazole 20 mg FDC capsule.

Figure S2 Geometric mean salicylic acid plasma concentration-time profiles by treatment



Treatment A = ASA 81 mg/esomeprazole 20 mg fixed dose combination capsule
Treatment B = ASA 80 mg tablet (Acetylsalicylzuur Apotex cardio 80 mg)

Pharmacokinetic parameters

Acetylsalicylic acid

The least squares mean AUC_{τ} and $AUC_{0\text{-}t,ss}$ values for ASA were similar between the ASA 81 mg/esomeprazole 20 mg FDC capsule (Treatment A) and the reference Acetylsalicylzuur Apotex cardio 80 mg tablet (Treatment B). The lower limit of the 90% CI for the least squares mean ratio comparing AUC_{τ} and $AUC_{0\text{-}t,ss}$ values between treatments was above 80%.

The least squares mean $C_{ss,max}$ value for ASA was approximately 44% lower following the ASA 81 mg/esomeprazole 20 mg FDC capsule (Treatment A) compared to the reference Acetylsalicylzuur Apotex cardio 80 mg tablet (Treatment B). The lower limit of the 90% CI for the least squares mean ratio comparing $C_{ss,max}$ values between treatments was below 80%.

Median $t_{max,ss}$ for ASA occurred approximately 20 minutes later for the ASA 81 mg/esomeprazole 20 mg FDC capsule (Treatment A) compared to the reference Acetylsalicylzuur Apotex cardio 80 mg tablet (Treatment B).

Table S2 Statistical comparison of key acetylsalicylic acid pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric LS Mean	Pair	Ratio (%)	90% CI
AUC_{τ} (µmol·h/L)	A	51	4.719			
	B	53	4.848	A/B	97.35	(92.38, 102.58)
$AUC_{0\text{-}t,ss}$ (µmol·h/L)	A	51	4.694			
	B	53	4.835	A/B	97.09	(92.13, 102.32)
$C_{ss,max}$ (µmol/L)	A	51	3.817			
	B	53	6.805	A/B	56.09	(51.31, 61.32)
			Median	**Pair**	**Difference**	**90% CI**
$t_{max,ss}$ (h)	A	51	0.67			
	B	53	0.33	A-B	0.33	(0.17, 0.34)

Treatment A = ASA 81 mg/esomeprazole 20 mg fixed dose combination capsule (test)
Treatment B = ASA 80 mg tablet (Acetylsalicylzuur Apotex cardio 80 mg) (reference)
CI confidence interval; LS least squares; N number of volunteers/observations.

Salicylic acid

The least squares mean AUC_{τ} and $AUC_{0\text{-}t,ss}$ values for SA were similar between the ASA 81 mg/esomeprazole 20 mg FDC capsule (Treatment A) and the reference Acetylsalicylzuur Apotex cardio 80 mg tablet (Treatment B). The lower limit of the 90% CI for the least squares mean ratio comparing AUC_{τ} and $AUC_{0\text{-}t,ss}$ values between treatments was above 80%.

The least squares mean $C_{ss,max}$ value for SA was approximately 22% lower following the ASA 81 mg/esomeprazole 20 mg FDC capsule (Treatment A) compared to the reference Acetylsalicylzuur Apotex cardio 80 mg tablet (Treatment B). The lower limit of the 90% CI for the least squares mean ratio comparing $C_{ss,max}$ values between treatments was below 80%.

Median $t_{max,ss}$ for SA occurred approximately 43 minutes later for the ASA 81 mg/esomeprazole 20 mg FDC capsule (Treatment A) compared to the reference Acetylsalicylzuur Apotex cardio 80 mg tablet (Treatment B).

Table S3 Statistical comparison of key salicylic acid pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric LS Mean	Pair	Ratio (%)	90% CI
AUC_{τ} (µmol·h/L)	A	51	97.88			
	B	53	100.8	A/B	97.09	(94.87, 99.35)
$AUC_{0\text{-}t,ss}$ (µmol·h/L)	A	51	95.96			
	B	53	99.06	A/B	96.87	(94.66, 99.12)
$C_{ss,max}$ (µmol/L)	A	51	24.02			
	B	53	30.60	A/B	78.48	(74.38, 82.81)
			Median	**Pair**	**Difference**	**90% CI**
$t_{max,ss}$ (h)	A	51	2.00			
	B	53	0.83	A-B	0.71	(0.50, 1.00)

Treatment A = ASA 81 mg/esomeprazole 20 mg fixed dose combination capsule (test)
Treatment B = ASA 80 mg tablet (Acetylsalicylzuur Apotex cardio 80 mg) (reference)
CI confidence interval; LS least squares; N number of volunteers/observations.

Summary of safety results

The incidence of healthy volunteers reporting AEs was similar for Treatment A (12 [19.0%] healthy volunteers) and Treatment B (12 [18.5%] healthy volunteers.

The AEs, by PT, reported by the highest number of healthy volunteers after Treatment A were flatulence (3 [4.8%] healthy volunteers), nasopharyngitis (2 [3.2%] healthy volunteers) and increase aspartate aminotransferase (AST, 2 [3.2%] healthy volunteers). By PT, the AEs reported by the highest number of healthy volunteers after Treatment B were increased AST, increased alanine aminotransferase (ALT) and oropharyngeal pain (each reported by 2 [3.1%] healthy volunteers).

One healthy volunteer experienced an SAE of severe anal abscess 4.45 days after the last administration of Treatment B in Period 1 which led to her withdrawal from the study. The SAE was considered to be not related to Treatment B by the investigator and resolved.

Two more healthy volunteers were prematurely withdrawn from the study (1 after Treatment A and 1 after Treatment B) both due to AEs of mild increased AST and mild increased ALT. Both events for both healthy volunteers were considered to be related to the investigational product by the investigator.

Mean increases in ALT and AST were observed from baseline at Day 1 for both Treatment A (4.91 U/L and 11.31 U/L, respectively) and Treatment B (4.39 U/L and 8.52 U/L, respectively). A mean increase in alkaline phosphatase (ALP) from baseline to Day 1 was observed for Treatment A only (4.28 U/L). All the mean ALT, AST and ALP values were

within the normal ranges at all visits and did not raise any safety concerns. No relevant changes were observed for bilirubin.

No clinically relevant changes in vital signs or 12-lead ECG results were observed.