AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Naloxegol
Study Code	D3820C00018
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A Phase I, Randomised, Open-label, 3-way Cross-over Study in Healthy Volunteers to Demonstrate the Bioequivalence of the Naloxegol 25 mg Commercial and Phase III Formulations and to Assess the Effect of Food Administration on the Pharmacokinetics of the Commercial Formulation

Study dates: First subject enrolled: 03 July 2012
Last subject last visit: 11 September 2012

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 clinical study report (CSR).

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic (PK)	To demonstrate the bioequivalence between two different film-coated tablet formulations of naloxegol, commercial tablet (test) and Phase III tablet (reference), after single-dose administration of a 25 mg tablet to healthy volunteers under fasted conditions	C_{max}, AUC, t_{max}, $t_{1/2\,\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F
Secondary	PK	To assess the effect of food on the PK of naloxegol commercial film-coated tablets	C_{max}, AUC, t_{max}, $t_{1/2\,\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F
	Safety	To investigate safety and tolerability of single oral doses of 25 mg naloxegol administered as two different tablet formulations in healthy volunteers	Adverse events (AEs), laboratory assessments, results of physical examination, electrocardiogram (ECG), vital signs (pulse rate and blood pressure [BP]), and C-SSRS
Exploratory[a]	Pharmacogenetic	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy)	Not applicable
	Safety	To collect plasma samples for safety biomarker testing that will allow future assessment of safety biomarkers	Not applicable

λ_z: terminal rate constant ; AUC: Area under the plasma concentration-time curve from zero extrapolated to infinity; $AUC_{(0-t)}$: Area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; $AUC_{(0-24)}$: Area under the concentration-versus-time curve from time 0 to 24 hours postdose; C_{max}: Maximum observed plasma concentration, obtained directly from the observed concentration versus time data; CL/F: Apparent oral clearance from plasma; DNA: Deoxyribonucleic acid; ECG: Electrocardiogram; t_{max}: Time to maximum plasma concentration obtained directly from the observed concentration versus time data; $t_{1/2\,\lambda z}$: Terminal half-life; V_z/F: Apparent volume of distribution during the terminal phase

[a] Results from the exploratory analyses, if performed, would be reported separately from the Clinical Study Report (CSR).

Study design

This was a single-centre, open-label, randomised, 3-way cross-over Phase I study in healthy volunteers to demonstrate the bioequivalence of the naloxegol 25 mg film-coated commercial and Phase III formulations and to assess the effect of food on the pharmacokinetics (PK) of the naloxegol commercial formulation.

The study comprised of the following visits: Visit 1 (screening; ≤30 days of the first administration of the investigational product [IP] on Day 1), Visits 2, 3 and 4 (treatment period; three randomised single-dose treatment periods with a duration of 3 days, each separated by a washout period of at least 7 days calculated from the time of first administration of naloxegol dose to the next dose administration), and Visit 5 (follow-up; 7 to 10 days after the last administration of IP). Eligible healthy volunteers were randomly assigned to one of the 3 treatments in a crossover design in one of the 6 treatment sequences (ABC, BCA, CAB, CBA, ACB, and BAC)on Day 1 of Period 1: Treatment A (single oral administration of naloxegol film-coated immediate release [IR] tablet 25 mg commercial formulation under fasted conditions), Treatment B (single oral administration of naloxogel film-coated IR tablet 25 mg commercial formulation under fed conditions), and Treatment C (single oral administration of naloxegol film-coated IR tablet 25 mg Phase III formulation under fasted conditions), respectively.

Target subject population and sample size

Healthy male and female (non-pregnant, non-lactating) volunteers aged 18 to 55 years (inclusive) with a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) were randomised in this study.

Planned: 42 healthy volunteers

Enrolled and randomised: 42 healthy volunteers

Completed: 41 healthy volunteers

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

Table S2 Details of the investigational product

Investigational product	Dosage form and strength (mode of administration)	Manufacturer	Batch number
Naloxegol	Commercial formulation 25 mg film-coated IR tablet (oral)	AstraZeneca	P Lot: 12-001566AZ F Lot: 12-001279AZ
Naloxegol	Phase III formulation 25 mg film-coated IR tablet (oral)	Pharmaceutics International Incorporated (PII)	P Lot: WK90884.001 F Lot: 17803.004

IR: Immediate release

Duration of treatment

Single IP administration during each visit (for 3 treatment periods), each separated by a washout period of at least 7 days (calculated from the time of the first administration of naloxegol dose to the next dose administration).

Statistical methods

A sample size of 34 evaluable healthy volunteers provided at least 90% power to demonstrate that naloxegol commercial formulation is bioequivalent to the naloxegol Phase III formulation. Assuming a dropout rate less than 19%, 42 healthy volunteers were enrolled.

Study conduct, safety, and PK data were summarised using descriptive statistics, as appropriate. To make an assessment of the primary objective of the study, Treatment A (naloxegol commercial formulation under fasted conditions, test) and Treatment C (naloxegol Phase III formulation under fasted conditions, reference) were compared statistically. Relative bioavailability in the fasted state was estimated using an analysis of variance model with the logarithm of AUC and C_{max} (primary) as well as $AUC_{(0-t)}$ and $AUC_{(0-24)}$ (secondary) for naloxegol as the response variable; treatment, period, and sequence as fixed effects; and volunteer within sequence included as a random effect. If the 90% CI for the geometric LS means ratios for both AUC and C_{max} fell entirely between the prespecified interval (80.00% to 125.00%), then bioequivalence between the naloxegol commercial formulation and the Phase III formulation under fasted conditions was concluded.

To make an assessment of the effect of food on the naloxegol commercial formulation, the PK parameters (AUC and C_{max} [primary] as well as $AUC_{(0-t)}$ and $AUC_{(0-24)}$ [secondary]) from the fed arm, Treatment B (test), were compared to that of the fasted arm, Treatment A (reference). The comparisons were made using analysis of variance model utilising similar methodology as described in the preceding paragraph.

Continuous variables (haematology, clinical chemistry, and vital signs) were summarised using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) by treatment group. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment group. Tabulations and listings of data for vital signs and clinical laboratory tests are presented. Listings are presented for electrocardiogram (ECG) data and physical examination results. Results from the Columbia-Suicide Severity Rating Scale (C-SSRS) were presented separately in a listing only.

Subject population

All 42 healthy volunteers enrolled, were randomised in the study. All 42 subjects received Treatments A and B and 41 subjects received Treatment C. One subject (E0001039), who received Treatments A and B, was withdrawn from the study due to a positive cotinine test result on admission to the study centre on Day -1 and did not receive Treatment C. The demographic and baseline characteristics of all subjects were in accordance with the inclusion/exclusion criteria of the Clinical Study Protocol (CSP).

Summary of pharmacokinetic results

Under fasted conditions, naloxegol absorption was rapid with peak concentrations in plasma being achieved within 1 hour post-dose (median value). The mean naloxegol plasma concentration-time profiles following administration of naloxogel film-coated IR tablet 25 mg commercial formulation (Treatment A) and naloxegol film-coated IR tablet 25 mg Phase III formulation (Treatment C) in the fasted state seemed similar. Naloxegol PK parameters were similar in mean value between the commercial and Phase III formulations (Treatments A and C). Following C_{max} the decline in naloxegol mean plasma concentration was rapid with a geometric mean $t_{1/2\,\lambda z}$ of 6.99 hours and 6.55 hours for Treatments A and C, respectively. The results of the statistical comparisons of PK parameters for treatments A and C are presented in Table S3.

Table S3 Statistical comparison of primary pharmacokinetic parameters for treatments A and C (fasted state)

						Comparisons		
Parameter (Units)	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI (%)**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC	A	Fasted	42	144.6	(126.56, 165.33)	A/C	94.38	(89.13, 99.94)
(ng·h/mL)	C	Fasted	41	153.3	(134.05, 175.22)			
$AUC_{(0-t)}$	A	Fasted	42	142.4	(124.48, 162.80)	A/C	93.98	(88.67, 99.60)
(ng·h/mL)	C	Fasted	41	151.5	(132.42, 173.28)			
$AUC_{(0-24)}$	A	Fasted	42	140.5	(123.16, 160.20)	A/C	93.66	(88.38, 99.25)
(ng·h/mL)	C	Fasted	41	150.0	(131.46, 171.10)			
C_{max}	A	Fasted	42	38.35	(33.13, 44.39)	A/C	92.38	(82.42, 103.54)
(ng/mL)	C	Fasted	41	41.51	(35.82, 48.10)			

CI: confidence interval; Geo: geometric; IR immediate release; LS least squares; Tmt: treatment
Results based on linear mixed effect analysis of variance model with terms for sequence, period, and treatment as fixed effects, and volunteer within sequence as a random effect

[a] Treatment A: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fasted condition).

[a] Treatment C: Single oral administration of naloxegol film-coated IR tablet 25 mg Phase III formulation (fasted condition).

Under fed conditions (Treatment B), the t_{max} for the commercial formulation was prolonged to 2 hours (median value) while mean naloxegol plasma concentration-time profiles showed higher exposure compared to naloxegol film-coated IR tablet 25 mg commercial formulation administered in the fasted state (Treatment A). Naloxegol AUC and C_{max} were higher, indicating greater exposure in the presence of food for the commercial formulation. The geometric mean $t_{1/2\,\lambda z}$ was 7.72 hours. The results of statistical comparison of primary PK parameters of the naloxogel commercial formulation in the fed state (Treatment B) compared to the fasted state (Treatment A) are shown in Table S4.

Table S4 Statistical comparison of primary pharmacokinetic parameters for Treatments A and B (fed versus fasted state)

							Comparisons	
Parameters	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI (%)**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC	A	Fasted	42	144.6	(126.56, 165.33)	B/A	145.09	(137.09, 153.56)
(ng·h/mL)	B	Fed	42	209.9	(183.62, 239.87)			
$AUC_{(0-t)}$	A	Fasted	42	142.4	(124.48, 162.80)	B/A	145.72	(137.56, 154.35)
(ng·h/mL)	B	Fed	42	207.4	(181.39, 237.22)			
$AUC_{(0-24)}$	A	Fasted	42	140.5	(123.16, 160.20)	B/A	143.60	(135.58, 152.10)
(ng·h/mL)	B	Fed	42	201.7	(176.86, 230.05)			
C_{max}	A	Fasted	42	38.35	(33.13, 44.39)	B/A	129.51	(115.66, 145.02)
(ng/mL)	B	Fed	42	49.66	(42.90, 57.49)			

CI: Confidence intervals; Geo: Geometric; IR: Immediate release; LS: Least squares; n: Number of observations; Tmt: Treatment

Results based on linear mixed effect analysis of variance model with terms for sequence, period, and treatment as fixed effects, and volunteer within sequence as a random effect.

[a] Treatment A: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fasted condition).

[a] Treatment B: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fed condition).

Summary of safety results

There were no deaths, serious adverse events (SAEs) or AEs leading to discontinuation (DAEs) reported during the study. All the AEs were considered to be mild in severity and resolved before the end of the study. The number of healthy volunteers with at least 1 AE was similar across all treatment groups. No clinically relevant changes were reported in any laboratory measurements, vital signs, ECGs, or physical examination findings. Overall, the IP under study was considered well tolerated in the population studied.