AstraZeneca

Clinical Study Report Synopsis

Drug Substance	NKTR-118
Study Code	D3820C00032
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EudraCT Number	

An Open-label, sequential, 3-period study to Assess the Effects of Diltiazem on the Pharmacokinetics of Naloxegol in Healthy Subjects

Study dates: First subject enrolled: 18 May 2012
Last subject last visit: 06 August 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 report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the effect of coadministration of diltiazem on the pharmacokinetics of naloxegol in healthy volunteers	Primary variables: C_{max} and AUC Secondary variables: t_{max}, $t_{1/2\ \lambda z}$, λ_z, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, CL/F, and V_z/F	Pharmacokinetic
Secondary	**Secondary**	
To assess the safety and tolerability of naloxegol when administered alone and in combination with diltiazem extended-release tablets	Adverse events, clinical laboratory assessments (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse rate), physical examinations, 12-lead electrocardiograms, and Columbia-Suicide Severity Rating Scale assessments	Safety
Exploratory	**Exploratory**	
To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy)	These data do not form part of the main report for this study.	Pharmacogenetic
To collect blood samples for safety biomarker testing that will allow future assessment of safety biomarkers	These data do not form part of the main report for this study.	Biomarker

λ_z: terminal rate constant; AUC: area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-}24)}$: area under the plasma concentration-time curve from time zero to 24 hours postdose; $AUC_{(0\text{-}t)}$: area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; CL/F: apparent oral clearance from plasma; C_{max}: maximum observed plasma concentration; $t_{1/2\ \lambda z}$: apparent terminal half-life; t_{max}: time to maximum observed plasma concentration; V_z/F: apparent volume of distribution during the terminal phase.

Study design

This was an open-label, nonrandomized, fixed-sequence study conducted at a single center to assess the effect of diltiazem XR on the pharmacokinetics of naloxegol in healthy volunteers.

In Period 1, a single 25-mg dose of naloxegol (Treatment A) was administered orally on the morning of Day 1 followed by a 2-day washout (Days 2 and 3). In Period 2, once-daily doses of 240-mg diltiazem XR (Treatment B) were administered from Days 4 through Day 6. In Period 3, a single dose of 240-mg diltiazem XR plus a single dose of 25-mg naloxegol (Treatment C) was administered on the morning of Day 7 and a single dose of 240-mg diltiazem XR was administered on Day 8. Serial blood samples for the determination of naloxegol pharmacokinetics were collected up to 72 hours following naloxegol dosing on Days 1 and 7. Volunteers were admitted to the clinic on Day -1 and remained confined until completion of Day 10 procedures. A follow-up visit was conducted 7 to 10 days following clinic discharge.

Target subject population and sample size

Healthy males and females of nonchildbearing potential (nonpregnant and nonlactating) between the ages of 18 and 55 years, inclusive, with a minimum weight of 50 kg and a body mass index between 18 and 30 kg/m^2, inclusive, were eligible for study participation.

Forty-three volunteers were to be enrolled to assure a minimum of 34 volunteers completed the study.

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

Naloxegol, a 25-mg white, film-coated tablet (batch number 17803.004), was administered orally after a fasting period of at least 10 hours on Days 1 and 7.

Diltiazem XR 240-mg tablets (lot number 11J049P) were sourced locally and were administered on the mornings of Days 4 through 6. On Day 7, diltiazem XR was administered in combination with naloxegol following a minimum 10-hour fast with an additional dose of 240-mg diltiazem XR administered on Day 8; there were no food restrictions when diltiazem XR was administered alone.

Duration of treatment

The total duration of the study was approximately 48 days, including a screening period (Visit 1) of 28 days or less, 1 residential treatment period (Visit 2) of 11 days (from check-in on Day -1 until discharge on Day 10), and a follow-up visit (Visit 3) 7 to 10 days after discharge.

Statistical methods

Pharmacokinetic variables (naloxegol plasma concentrations and pharmacokinetic parameters) were summarized by treatment using appropriate descriptive statistics and graphical figures.

The effect of diltiazem extended release (XR) on the pharmacokinetics of naloxegol, utilizing data from naloxegol plus diltiazem extended-release administration (Treatment C) as the test and naloxegol administered alone (Treatment A) as the reference, was assessed using an analysis of variance model for the primary (AUC and C_{max}) and secondary [$AUC_{(0-t)}$ and

$AUC_{(0-24)}$] pharmacokinetic parameters on a logarithmic scale. Treatment was included as a fixed effect and volunteer was included as a random effect in the model. Additionally, the t_{max} between Treatment groups A and C was compared and the median difference was calculated.

Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities and summarized by treatment. Clinical laboratory parameters and vital signs were summarized using descriptive statistics. Electrocardiograms and physical examination findings as well as the Columbia-Suicide Severity Rating Scale assessments were presented in listings.

Subject population

The 43 volunteers had a mean age of 29 years (range 18 to 52 years), a mean height of 176.5 cm (range 163.1 to 188.3 cm), a mean weight of 78.4 kg (range 57.1 to 97.4 kg), and a mean body mass index of 25.13 kg/m^2 (range 20.0 to 29.86 kg/m^2). There were 42 (97.7%) males and 1 (2.3%) female. The race for 24 (55.8%) volunteers was white; for 17 (39.5%) volunteers was black; and for 2 (4/7%) volunteers was American Indian or Alaska native. Two (4.7%) volunteers reported their ethnicity as Hispanic or Latino. All volunteers were considered healthy and no concomitant medications were reported for ongoing medical conditions.

All 43 (100%) volunteers received all planned doses of investigational product, completed all study procedures, and were included in the pharmacokinetic and safety analysis sets. There were no important protocol deviations.

Summary of pharmacokinetic results

Table S2 summarizes key naloxegol pharmacokinetic parameters in the presence and absence of diltiazem.

There was an increase in naloxegol primary exposure parameters, AUC and C_{max}, and a decrease in CL/F following a single dose of NKTR-118 in the presence of the moderate *CYP3A* inhibitor, diltiazem. This indicated that the *CYP3A4*-mediated metabolism of naloxegol was inhibited by ditiazem. Diltiazem did not appear to have a consistent effect on naloxegol t_{max}.

Table S2 Summary of geometric mean (CV%) naloxegol pharmacokinetic parameters

Treatment[a]	AUC (ng·h/mL)	C_{max} (ng/mL)	t_{max}[b] (h)	$t_{1/2,\lambda z}$ (h)	CL/F (L/h)
Treatment A	140	32.9	1.00	6.13	179
(n=43) (CV%)	(49.0)	(46.2)	(0.25-5.00)	(44.1)	(49.0)
Treatment C	478	94.0	3.00	8.04	52.3
(n=43) (CV%)	(35.1)	(36.5)	(0.50-5.00)	(35.1)	(35.0)

CV geometric coefficient of variation.

[a] Treatment A: naloxegol 25 mg on Day 1 only (Note: Days 2 and 3 were washout period from naloxegol). Treatment C: diltiazem XR 240 mg plus naloxegol 25 mg on Day 7 followed by one additional diltiazem XR 240-mg tablet on the morning of Day 8.

[b] t_{max} presented as median (range).

Results from the statistical analysis showed that in the presence of diltiazem, geometric least-squares mean naloxegol AUC was 3.41-fold that of naloxegol administered alone (ratio%, 341.29, 90% CI: 316.00% to 368.60). In the presence of diltiazem, geometric least-squares mean naloxegol C_{max} was 2.86-fold that of naloxegol administered alone (ratio% 285.74 90% CI: 259.48 to 314.66). These were completely outside the prespecified limits of 80.00% to 125.00%. The intra-subject variability for AUC and C_{max} were estimated to be 21.5% and 21.6%, respectively. There was no significant difference in t_{max} between the 2 treatments based on the statistical analysis.

Summary of safety results

There were no deaths, serious adverse events, discontinuations due to adverse event, other significant adverse events, or adverse events of severe intensity. Overall, 18 (41.9%) volunteers experienced at least 1 adverse event during the study; 3 (7.0%) volunteers had adverse events during naloxegol alone (Treatment A); 10 (23.3%) had adverse events during diltiazem XR alone (Treatment B); and 7 (16.3%) volunteers had adverse events during the combination therapy (Treatment C).

The most frequently occurring adverse events overall were headache in 5 (11.6%) volunteers and abdominal pain, occurring in 2 (4.7%) volunteers. All adverse events were assessed by the Investigator as mild in intensity. One volunteer in the naloxegol plus diltiazem XR group had an adverse event of abdominal pain which was assessed by the Investigator as causally related to naloxegol. No volunteers in the naloxegol-alone group had adverse events assessed as causally related to investigational product.

There were no trends or clinically relevant changes in clinical laboratory, vital sign, electrocardiogram, or Columbia-Suicide Severity Rating Scale findings following dosing.