AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1386
Study Code	D5090C00010
Edition Number	1
Date	26 September 2008

A Double-blind, Randomised, Placebo and Naproxen Controlled Study to Investigate the Analgesic Efficacy of a Single Dose of AZD1386, in Patients Undergoing Impacted Mandibular Third Molar Extraction

Study dates: First patient enrolled: 16 April 2008
Last patient completed: 10 June 2008

Phase of development: Therapeutic exploratory (IIa)

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

Study centre(s)

The study was conducted at a single centre at Lifetree Clinical Research, Salt Lake City, USA. The first patient enrolled on16 April 2008, and the last patient completed on 10 June 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate the analgesic efficacy of single dose of orally administered AZD1386 compared to placebo, in patients following impacted mandibular third molar extraction.

Secondary objectives of the study were:

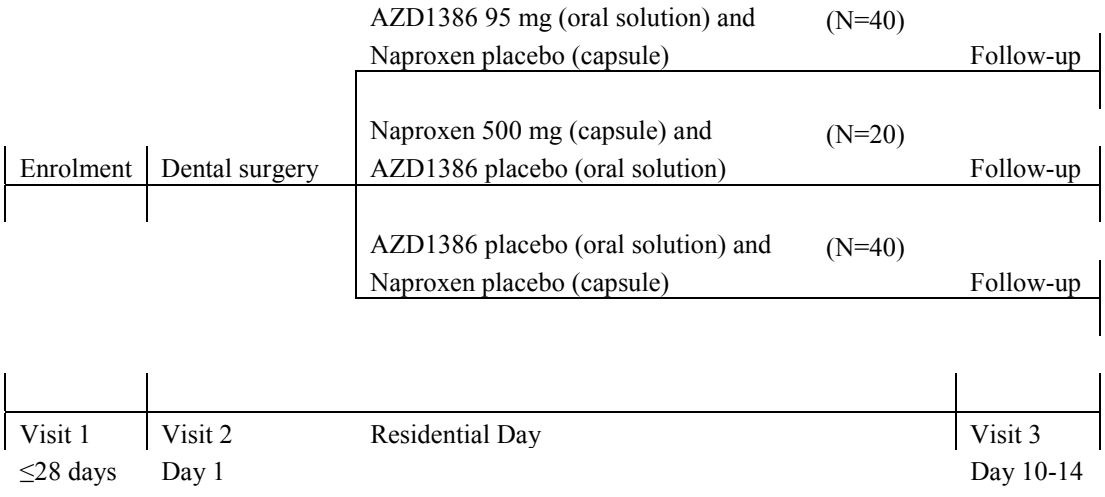
1. To investigate the relationship between analgesic efficacy and plasma concentrations of AZD1386, and

2. to investigate the safety and tolerability of AZD1386.

Study design

This was a single dose, randomised, double blind, double dummy, placebo-controlled study to investigate the analgesic efficacy of AZD1386 95 mg in patients undergoing surgical removal of 1 partially or completely impacted mandibular third molar, where bone removal was judged to be needed. Naproxen 500 mg was included as a treatment arm, for assay sensitivity only. If medically indicated, removal of ipsilateral maxillar third molar at the same time was acceptable. Figure S 1 shows the design of the study and the sequence of treatment periods.

Figure S 1 Flow Chart of Study Design (D5090C00010)



Target healthy volunteer population and sample size

The target population was white, healthy, males or non-fertile females aged ≥18 to ≤45 years, scheduled for surgical removal of one partially or completely impacted mandibular third molar, where bone removal was judged to be needed

The primary aim of the study was to show that AZD1386 leads to larger values of the primary variable, SPID%, than placebo. A Naproxen treatment arm was included to provide evidence of assay sensitivity. To accomplish this, 100 patients considered valid for efficacy evaluation (with sample sizes for treatment groups AZD1386, placebo and Naproxen of 40, 40, and 20 patients, respectively) were judged to be needed in the study. A Naproxen arm with 20 patients was anticipated to be sufficient to establish assay sensitivity with very high power.

Patients requesting pain relief, due to pain from the dental surgical area, within 6 hours after the end of the administration of the local anaesthetic (last anaesthetic dose) were randomised to 1 of 3 treatment arms: 40 patients received AZD1386 95 mg oral solution and Naproxen placebo capsule, 40 patients received AZD1386 placebo oral solution and Naproxen placebo capsule and 23 patients received AZD1386 placebo oral solution and Naproxen 500 mg (for assay sensitivity only).

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

The details of the investigational product and any study treatment are given in Table S 1.

Table S 1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD1386	Oral solution, 2.5 mg/mL	AstraZeneca	4059-x-2	4059-3-2
Placebo (AZD1386)	Oral solution	AstraZeneca	4073-x-2	4073-2-2
Naproxen	500 mg capsule	Under the responsibility of AstraZeneca	4105-x-1	4105-2-1
Placebo (Naproxen)	Capsule	Under the responsibility of AstraZeneca	H 2016-01-01-	H 2016-01-01-01

Duration of treatment

Single dose

Criteria for evaluation - efficacy and pharmacokinetics (main variable

Primary outcome variable

Sum of pain intensity difference in percent (SPID%), derived from the pain intensity ratings.

Secondary outcome variables

Efficacy: Sum of pain intensity difference (SPID); pain intensity difference (PID); pain intensity difference in percent (PID%); maximum PID; maximum PID%; time to maximum PID; mean pain intensity difference (MPID); mean pain intensity difference in percent (MPID%); maximum pain at jaw movement; mean Pain at jaw movement; SPID% for pain at jaw movement; SPID for pain at jaw movement; time to first perceptible pain relief; time to first meaningful pain relief; time to first administration of rescue medication

PK/PD: SPID% vs $AUC_{0\text{-}8h}$; PID% vs plasma concentration; PID vs plasma concentration; MPID% vs $AUC_{0\text{-}8h}$; Maximum PID% vs C_{max}; maximum pain at jaw movement vs C_{max}; SPID% pain at jaw movement vs $AUC_{0\text{-}8h}$; time to maximum PID vs t_{max}.

Criteria for evaluation - safety (main variables)

Assessment of AEs, vital signs, oral body temperature, ECG and standard laboratory variables.

Statistical methods

The primary outcome variable, SPID%, was analysed on the efficacy analysis set using the Wilcoxon test. The Hodges-Lehmann estimator, corresponding p-value and two-sided 90% confidence interval of the treatment difference between AZD1386 and placebo was calculated. A plot of the Hodges-Lehmann point estimator of the treatment difference with corresponding 90% confidence interval for the difference was used to illustrate the result. A comparison of naproxen and placebo was made to assess the assay sensitivity.

The Wilcoxon test was used to analyse the variables derived from pain intensity and pain at jaw movement, on the efficacy analysis set. The Cox Proportional Hazards Regression model was used for the time to event variables, with factor for treatment group and a covariate for baseline pain measurement. The hazard ratio for treatment group comparison is presented with corresponding 90% confidence interval and p-value.

The relationship of clinical assessments to plasma concentration and estimated PK parameters were investigated in terms of descriptive statistics. The statistical analysis of all laboratory, vital signs, AE and ECG data was primarily descriptive.

Subject population

The treatment groups were well balanced in terms of demography and baseline characteristics. The patients in the study comprised healthy male patients with a mean age of 21.5 years (range 18 to 38 years), as shown in Table S 2. This patient population could be considered appropriate for this type of study using human pain models. The usage of additional (non-

rescue) medication was reasonable in the clinical context and was judged not to influence the study results. The 4 dropouts that occurred during the study were considered not to be a major protocol deviation. All patients received the correct allocated investigational product.

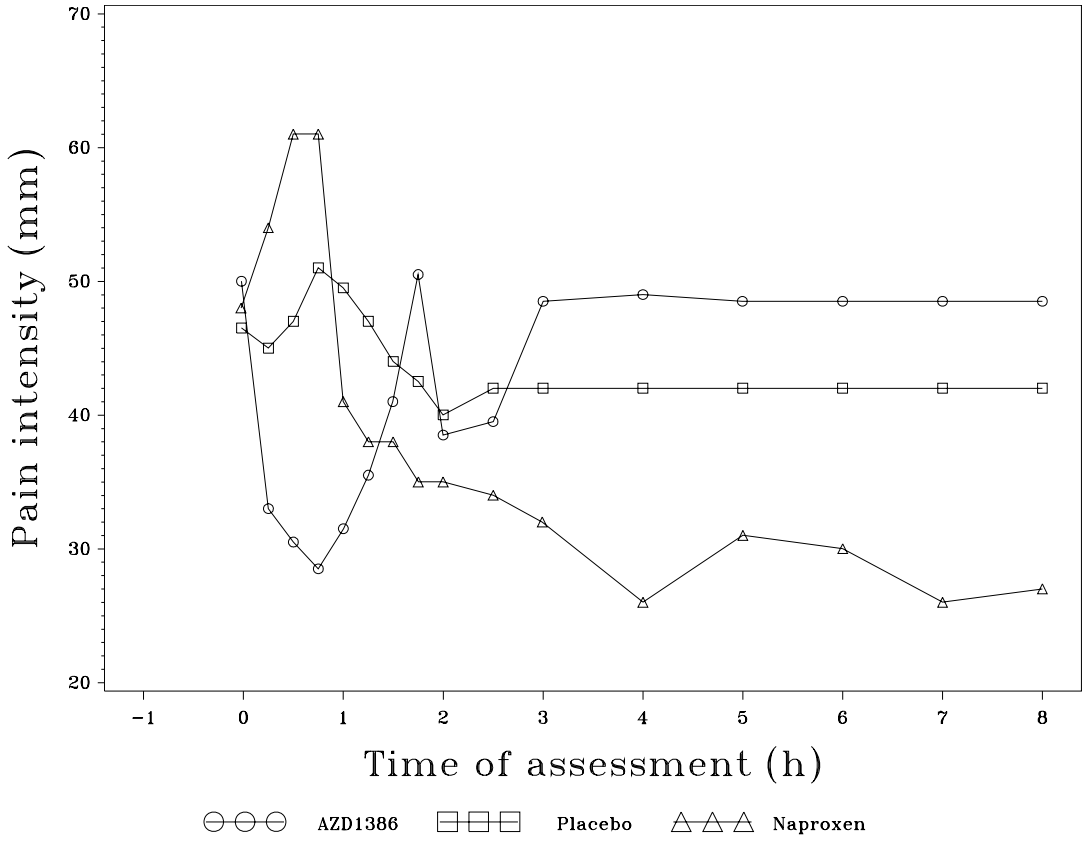
Table S 2 Subject population and disposition (D5090C00010)

Demographic or baseline characteristic		Study population			
		AZD1386	Placebo	Naproxen	Total
Population					
N of enrolled				135	
N of randomised		40 (100%)	40 (100%)	23 (100%)	103 (100%)
Demographic characteristics					
Sex	Male	40 (100%)	40 (100%)	23 (100%)	103 (100%)
Age (years)	Mean ±SD	21.5±4.4	21.9±4.8	21.0±4.8	21.5±4.6
	Range	18-32	18-35	18-38	18-38
BMI (kg/m2)	Mean ±SD	24.3±3.9	24.5±3.1	24.2±3.2	24.4±3.4
	Range	19.0-33.2	19.6-32.0	19.5-32.6	19.0-33.2
Body weight (kg)	Mean ±SD	75.6±11.1	76.8±12.0	75.9±12.5	76.1±11.7
	Range	58-101	54-106	59-109	54-109
Race n(%)					
	White	35 (87.5%)	34 (85.0%)	18 (78.3%)	87 (84.5%)
	Black or African American	0	1 (2.5%)	0	1 (1.0%)
	Asian	0	0	1 (4.3%)	1 (1.0%)

Summary of efficacy results

The efficacy variables related to pain intensity are calculated from the pain intensity scores over time, which are illustrated in terms of median pain intensity over time for all treatment groups in Figure S 2. Similarly, the secondary efficacy variables, related to pain intensity at jaw movement, are derived from the pain at jaw movement scores over time.

Figure S 2 **Median Pain intensity versus time, all treatments groups (Efficacy analysis set)**



The pain intensity scores after intake of rescue medication are assigned to the pain intensity at baseline.
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As shown in Table S 3, using a dental extraction pain model a single 95mg dose of AZD1386 treatment did not reach a statistically significant difference from placebo as assessed by the primary endpoint SPID% over 8 hours (p=0.132). Assay sensitivity was demonstrated by the superiority of Naproxen over placebo in SPID% (p=0.038).

Table S 3 **Wilcoxon test of difference between AZD1386 and placebo, SPID% (Efficacy analysis set)**

Variable	n (Placebo)	n (AZD1386)	Hodges-Lehmann estimate	90% CI	p-value
SPID%	40	40	38.06	(-5.23, 75.91)	0.132

Positive Hodges-Lehmann estimate implies that the treatment has favourable outcome in comparison with placebo.
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However, AZD1386 rapidly and significantly reduced pain intensity, as demonstrated by statistically significant difference from placebo in PID% and PID within 15 minutes. The effect of AZD1386 remained significant at the measurements up to the 1h timepoint for PID% ($p \leq 0.026$) and the 1hr15min timepoint for PID ($p \leq 0.065$). AZD1386 significantly reduced pain in comparison to placebo as assessed by secondary pain intensity variables, ie SPID (p=0.071), maximum PID% (p=0.040), maximum PID (p=0.006), MPID% (p=0.059) and MPID (p=0.020).

AZD1386 significantly reduced SPID% pain at jaw movement (p=0.089) and mean pain at jaw movement (p=0.077) in comparison to placebo, but was not significantly better than placebo in reducing SPID pain at jaw movement or maximum pain at jaw movement. AZD1386 also significantly reduced the time to first perceptible pain relief (p=0.002) and the time to first meaningful pain relief (p=0.031) compared to placebo. AZD1386 was not statistically different from placebo regarding the time interval from dose to first rescue medication.

Summary of pharmacokinetic results

Following administration of AZD1386, 95 mg as an oral solution at fasting conditions, median t_{max} was found at 1 h (range 0.5-4 h). Geometric mean C_{max} was 1771 nmol/L (CV 31%) and geometric mean AUC_{0-8h} was 7,346 nmol*h/L (CV 34%). There was an approximately 3.5-fold difference between the highest and lowest C_{max} and AUC_{0-8h}, respectively.

Summary of pharmacokinetic/pharmacodynamic relationships

The relationships between plasma concentrations and efficacy variables were explored. The increase in PID% was rapid, and peaked before the maximum plasma concentrations of AZD1386. After the peak, the PID% decreased rapidly despite sustained high concentrations of AZD1386. Despite the early onset and offset of effect there seemed to be a relationship between PK variables and effects. There seemed to be a trend towards larger effects with higher AUC_{0-8h}, although the variability in the response was large.

Summary of pharmacogenetic results

Not reported in this CSR.

Summary of safety results

Treatment with AZD1386 was well tolerated. All AEs were either mild or moderate in intensity. The only AE occurring more than once and uniquely in the AZD1386 group was "chills", recorded in 2 patients. There were no deaths, SAEs or discontinuations due to adverse effects. AZD1386 treatment resulted in an increase in mean oral body temperature compared with placebo treatment (≤ 0.4 ºC at all timepoints), but this was not considered clinically relevant on either the group or individual level. The highest individual body temperature recorded was 38.1 °C, recorded in 2 patients at single timepoints. AZD1386 treatment also resulted in a decrease in QTc interval with maximum effects seen at 45 minutes

post-dose. An increase in RR interval was seen in all groups, and was slightly larger in the AZD1386 group than in the placebo group.

One patient in the AZD1386 group (patient E0101214) had an increase of S-ALAT, S-ASAT and LD at follow–up. There were no other apparent clinically relevant AZD1386 treatment emergent effect on haematology, clinical chemistry or vital signs.