AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1940
Study Code	D3120C00006
Edition Number	1
Date	24 September 2008

A Randomised, Double Blind, Placebo-Controlled Study to Investigate the Analgesic Efficacy of a Single Dose of AZD1940, in Patients Undergoing Impacted Mandibular Third Molar Extraction

Study dates: First patient enrolled: 12 February 2008
Last patient completed: 13 May 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)

Lifetree Clinical Research, Salt Lake City, Utah, USA

Study dates

First patient enrolled	12 February 2008
Last patient completed	13 May 2008

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate the analgesic effect of AZD1940 800 µg compared to placebo in dental surgery patients following impacted mandibular third molar extraction.

The secondary objectives of the study were to investigate:

1. The subjective cannabinoid central nervous system (CNS) effects of orally administered AZD1940
2. The safety and tolerability of orally administered AZD1940
3. The pharmacokinetics (PK) of orally administered AZD1940
4. The pharmacokinetics/pharmacodyamics (PK/PD) of orally administered AZD1940

There was also an exploratory objective of this study. A blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK, PD, safety and tolerability related to AZD1940 treatment. Genotyping results are not presented in the Clinical Study Report (CSR).

After the data were unblinded, it was judged that a PK/PD analysis would not be performed because there were no statistically significant differences between the AZD1940 and placebo treatment groups for the primary efficacy variable. Thus, the last secondary objective was not investigated and is not reported in the CSR.

Study design

This was a single dose, randomised, double blind, double dummy, placebo-controlled study to evaluate the analgesic effect of AZD1940 800 µg compared to placebo in patients undergoing surgical removal of one partially or completely impacted mandibular third molar where bone removal was judged to be needed. If medically indicated, removal of the ipsilateral third molar was also acceptable. A gold standard and well-documented treatment, naproxen, was included in a separate treatment arm for assay sensitivity.

Target population and sample size

The patients were to be males or non fertile females between the ages of 18 and 45 years inclusive who were scheduled for the surgical removal of an impacted mandibular third molar where bone removal was judged to be needed. The patients were to be randomised to 1 of 3 treatment arms: 60 patients were to receive AZD1940 800 μg oral solution and naproxen placebo capsule, 60 patients were to receive AZD1940 placebo oral solution and naproxen placebo capsule and 30 patients were to receive naproxen 500 mg (for assay sensitivity only) and AZD1940 placebo oral solution.

The primary variable was Pain AUC_{0-8h} (area under the pain by time curve from end of surgery to 8h post-surgery). With 60 evaluable patients planned in each of the placebo and AZD1940 treatment arms, a standard deviation of 119 and a two-sided significance level of 0.10, the power was to be at least 90% if the true difference (AZD1940-placebo) was at least 64 mm*h.

A naproxen arm was included to confirm assay sensitivity of the study. With 30 patients planned in the naproxen arm it was to be possible to detect a difference between naproxen and placebo with a power >99% at two-sided 10% significance level if the true difference was at least 174 mm*h.

These power calculations were based on the assumptions that AZD1940 would lead to 15% lower AUC_{0-8h} scores than placebo and naproxen to approximately 40% lower AUC_{0-8h} scores than placebo.

An evaluable patient was defined as a patient having at least 50% of all VAS pain assessments and having not more than 1 pain assessment in sequence missing.

Note that the wording of the efficacy variables in the CSR has changed from the original wording in the CSP (Table S1). This change has no effect on the planned analyses but rather only affects the language used to describe these analyses. It was agreed within the CSR delivery team and with the MSD that this new wording would reduce the ambiguity of what was being measured.

Table S1 New wording for efficacy variables

CSP wording	CSR wording
VAS Pain AUC_{0-8h}	Pain AUC_{0-8h}
AUC_{0-4h} VAS Pain	Pain AUC_{0-4h}
Max VAS Pain	Max pain
Mean VAS Pain up until rescue medication or 0-8 h, whichever is applicable in each patient	Mean pain
AUC_{0-8h} VAS Jaw Pain	Pain at jaw movement AUC_{0-8h}
AUC_{0-4h} VAS Jaw Pain	Pain at jaw movement AUC_{0-4h}
Max VAS Jaw Pain	Max pain at jaw movement
Mean VAS Jaw Pain up until rescue medication or 0-8h, whichever is applicable in each patient	Mean pain at jaw movement
VAS Pain at time for rescue medication	Pain at rescue medication
VAS Jaw Pain at time for rescue medication	Pain at jaw movement at rescue medication

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

Table S2 Details of investigational product and any other study treatments

Investigational product or comparator	Dosage form and strength	Manufacturer	Formulation Number	Batch Number
AZD1940	Oral solution, 0.5 mg/mL	AstraZeneca	3973-x-2	3973-3-2
Placebo	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	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 variables)

Primary outcome variable:

Pain AUC_{0-8h} (assessments every 20 min for 4 h and every 60 min between 4-8 h)

Secondary outcome variables:

Secondary: Pain AUC_{0-4h}, Pain at jaw movement $AUC_{0-8\ h}$, Pain at jaw movement $AUC_{0-4\ h}$, Max pain, Max pain at jaw movement, Mean pain, Mean pain at jaw movement, Pain at rescue medication, Pain at jaw movement at rescue medication, Time to rescue medication, Proportion of patients requesting rescue medication

Time to max deterioration in Visual Analogue Mood Scale (VAMS) scores, Maximum deterioration in VAMS scores and Change from baseline in VAMS Scores

PK parameters included: C_{max}, t_{max}, t_{lag}, AUC_{0-t}, AUC, λ_z, $t_{½\lambda z}$, CL/F, V_z/F, MRT

Criteria for evaluation - safety (main variables)

Adverse events (frequency and severity), vital signs (supine and standing blood pressure, pulse, respiratory rate and oral body temperature), clinical chemistry, haematology laboratory tests, urine analysis, hormone analysis and ECG

Statistical methods

In general, all efficacy, PK, PD and safety variables are presented using descriptive statistics and graphs as appropriate, or frequency tables where applicable.

The statistical analysis of the primary outcome variable, Pain AUC_{0-8h}, was performed using t-test. The comparisons of interest was the difference between AZD1940 and placebo. In addition, a comparison of naproxen and placebo were also made to assess the assay sensitivity.

The secondary efficacy variables (Pain AUC_{0-4h}, Pain at jaw movement $AUC_{0-8\ h}$, Pain at jaw movement $AUC_{0-4\ h}$, Max pain, Max pain at jaw movement, Mean pain up until rescue medication or 8 h, , Mean pain at jaw movement up until rescue medication or 8 h, Pain at rescue medication, Pain at jaw movement at rescue medication, Time to rescue medication, Proportion of patients requesting rescue medication) were analysed with t-tests.

Subject population

The patient population consisted of 151 randomised males between the ages of 18 and 39 years old (mean age 20). In total, 61 patients received AZD1940, 59 patients received placebo and 31 patients received naproxen. There were no patients excluded from the PD or safety analyses. Only patients administered AZD1940 were to be included in the PK analysis set, however, 1 of these patients was excluded due to a mix-up of his blood samples. There were

no imbalances between treatment groups with regards to demographics or dental surgery characteristics that were expected to have an influence on the results and their interpretation.

Summary of efficacy results

There was no statistically significant difference in the primary variable, Pain $AUC_{0\text{-}8h}$, between patients administered AZD1940 and placebo (p=0.48) (Table S3). Patients administered naproxen had significantly reduced Pain $AUC_{0\text{-}8h}$ scores compared to patients administered placebo (p<0.0001). There were no statistically significant differences between the AZD1940 and placebo treatment groups for any of secondary efficacy variables in this study.

Table S3 Comparison of Pain $AUC_{0\text{-}8h}$ (mm*h) for AZD1940 vs placebo and Naproxen vs placebo (PD analysis set)

	Pain $AUC_{0\text{-}8h}$ (mm*h)							Difference from placebo		
Treatment	n	Mean	90% CI	SD	Min	Median	Max	Estimate	90% CI	One-sided p-value
AZD1940	61	354.71	315.72, 393.70	182.28	28.68	336.13	745.36	-1.46	-54.23, 51.31	0.48
Naproxen	31	128.74	96.60, 160.88	105.44	1.58	117.53	367.77	-227.43	-281.98, -172.87	<0.0001
Placebo	59	356.17	320.11, 392.23	165.70	15.69	360.19	631.92			

Differences less than 0 show AZD1940 treatment to have favorable outcome compared with Placebo
T-tests (equal variances assumed) were used to generate the p-values.
P-values are one-sided and to be compared with alpha=0.05.
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Summary of pharmacokinetic results

The PK of AZD1940 was characterized by a mean C_{max} of 9.3 nmol/L and a median t_{max} of 2.9 h. Due to the short sampling time in relation to the $t_{½}$, there was a large residual AUC (62% on average) and large uncertainty of AUC, $t_{½}$, CL/F and Vz/F.

Summary of pharmacodynamic results

The patients were asked to rate the extent to which they felt stimulated, sedated, anxious, high and down on the Visual Analogue Mood Scale (VAMS) following the administration of AZD1940, placebo or naproxen. There were statistically significant differences in the max deterioration of the VAMS adjectives “sedated” and “high” between the AZD1940 treatment group and the placebo group. There were no statistically significant differences in the max deterioration for any of the 5 adjectives between those patients administered naproxen and placebo.

Summary of safety results

In this study, the administration of a single dose of AZD1940 showed an acceptable safety profile and did not produce any unexpected safety findings based on preclinical data, previous experience with AZD1940 and findings from other cannabinoids. There were no deaths, other SAEs or DAEs. The most common AEs were postural dizziness, nausea, hypotension and headache which were all reported more frequently in the AZD1940 treatment group than in the placebo or naproxen groups. Most AEs were of mild and moderate intensity. However, 1 patient in the AZD1940 group had 4 severe syncopic episodes and another patient in this group had a severe headache. Apart from a numerical reduction in the mean plasma levels of testosterone, LH and TSH, the patients administered AZD1940 had in general normal clinical chemistry and haematology results. There were no clinically significant changes in ECG and body temperature between patients administered AZD1940 or placebo. AZD1940 had haemodynamic effects with a reduction in mean standing SBP and DBP at 2 and 5 minutes compared to placebo and a corresponding mean pulse increase was also observed in this treatment group.