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# Evaluation of the analgesic efficacy of AZD1940, a novel cannabinoid agonist, on post-operative pain after lower third molar surgical removal

Jarkko Kalliomäki[a,*], Märta Segerdahl[a], Lynn Webster[b], Annika Reimfelt[a], Karin Huizar[a], Peter Annas[a], Rolf Karlsten[a], Hans Quiding[a]

[a] AstraZeneca R&D Södertälje, Sweden
[b] Lifetree Clinical Research, 3838 South, 700 East, Suite 202, Salt Lake City, UT 84106, USA

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ABSTRACT

**Aim:** To evaluate the analgesic efficacy of AZD1940, a novel peripherally acting cannabinoid $CB_1/CB_2$ receptor agonist, in patients undergoing third molar surgical removal.
**Methods:** This was a randomized, double-blind, placebo-controlled study in patients scheduled for surgical removal of an impacted lower third molar. Patients received a single oral dose of 800 μg AZD1940, 500 mg naproxen or placebo 1.5 h before surgery. The dose of 800 μg AZD1940 was selected based on earlier data from a single dose study in man, in which it was identified as the highest well tolerated dose. Ongoing post-operative pain (primary variable) and pain on jaw movement were assessed on a visual analog scale (VAS, 0–100 mm) from 0 to 8 h postoperatively, deriving the area under the curve of ongoing pain (VAS $AUC_{0-8\,h}$), and of pain on jaw movement ($VAS_{JM}$ $AUC_{0-8\,h}$). The time to requesting rescue medication (acetaminophen) was recorded. Subjective cannabinoid effects were assessed by the visual analog mood scale (VAMS).
**Results:** In total, 151 patients were randomized to AZD1940 ($n = 61$), placebo ($n = 59$) or naproxen ($n = 31$). There was no statistically significant difference in pain VAS $AUC_{0-8\,h}$ or in $VAS_{JM}$ $AUC_{0-8\,h}$ between AZD1940 and placebo. Naproxen significantly reduced both pain VAS $AUC_{0-8\,h}$ and $VAS_{JM}$ $AUC_{0-8\,h}$ as compared with placebo ($p < 0.0001$ for both). Significantly fewer patients on naproxen requested rescue medication and the duration of time to rescue was greater, as compared with placebo, whereas there were no significant differences between AZD1940 and placebo in these outcome variables. Statistically significant increases in VAMS items "sedated" and "high" were observed after AZD1940 compared with placebo. The increases in VAMS were numerically small compared with previous findings with a centrally acting cannabinoid. The most commonly observed adverse events (AE) on treatment with AZD1940 were postural dizziness (80% of subjects), nausea (26%), hypotension (21%) and headache (13%), most AE being mild to moderate.
**Conclusion:** The $CB_1/CB_2$ receptor agonist AZD1940 did not reduce post-operative pain after lower third molar surgical removal at doses exerting subjective cannabinoid effects.
**Implications:** Activation of peripheral $CB_1/CB_2$ receptors per se is probably of less clinical relevance for the treatment of acute nociceptive pain in man.


## 1. Introduction

Analgesic effects of cannabinoids, the pharmacologically active constituents of cannabis, have been reported in different types of human pain conditions [1,2]. Most of the published studies in chronic neuropathic pain have reported small but statistically significant pain reduction [3–8], whereas the results in acute pain have been more varying [9–17]. CNS side effects at analgesic doses and the risk of drug dependence and abuse have limited the utility of cannabinoids in clinical pain treatment [1,2].

Two types of cannabinoid receptors, $CB_1$ and $CB_2$, have been identified [18,19]. $CB_1$ receptors are expressed on neurons and are widely distributed throughout the CNS, including areas involved in pain processing, whereas $CB_2$ receptors are expressed primarily on immune cells. Most evidence suggests that $CB_1$ receptors located in the CNS mediate both psychoactive and analgesic effects of cannabinoids [20,21]. However, recent research has shown that both $CB_1$ and $CB_2$ receptors are expressed on peripheral sensory nerve fibers [22], and that analgesic effects can be mediated

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* Corresponding author at: AstraZeneca R&D Södertälje, SE-151 85 Södertälje, Sweden. Tel.: +46 733 542089/703 243734; fax: +46 8553 28288.
*E-mail addresses:* jarkko.kalliomaki@astrazeneca.com, jarkko.kalliomaki@telia.com (J. Kalliomäki).

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by peripheral $CB_1$ and $CB_2$ receptors [23–26]. This has created interest in new strategies for developing cannabinoids specifically targeting the peripheral $CB_1$ and/or $CB_2$ receptors and having limited access to CNS, thereby avoiding psychoactive side effects [18,19,27].

AZD1940 is a novel synthetic $CB_1/CB_2$ receptor agonist that is orally active in rat models of nociceptive and neuropathic pain. AZD1940 binds with high affinity to human, rat and mouse $CB_1$ and $CB_2$ receptors and displays full agonism at both receptors in all three species [28,29]. Preclinical studies have shown a $CB_1$ receptor dependent peripheral site of action for the reduced pain behavior in both inflammatory and neuropathic rat pain models. Reduced pain behavior in rat pain models were observed from the first day, without any signs of tolerance to analgesia over the course of 10 days [29]. A low brain uptake at analgesic doses has been demonstrated in both rat and primate [29]. The safety, tolerability and pharmacokinetics have been investigated in a single ascending dose study in healthy human volunteers [30]. In that study, doses up to 800 μg were well tolerated.

The aim of this study was to investigate the efficacy of AZD1940 in postoperative pain in patients undergoing third molar surgical removal, which is a well validated human model of nociceptive pain [31]. To confirm assay sensitivity, a treatment arm with naproxen was included. In addition, subjective CNS-related cannabinoid effects were assessed with visual analog mood scale (VAMS) [32]. Brief results of this study have been communicated previously [30].

## 2. Methods

### 2.1. Study population

This study was conducted at Lifetree Clinical Research, Salt Lake City, UT, USA. The study protocol was approved by Compass Institutional Review Board, Mesa, AZ, USA, and by FDA. The study was conducted following current ICH (International Conference on Harmonization) GCP (Good Clinical Practice) guidelines [33], in accordance with the World Medical Association's Declaration of Helsinki.

The study enrolled patients scheduled for 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 in the upper jaw at the same time was also considered acceptable. The patients were to be healthy male or non-fertile females, aged 18–45 years, with a body mass index (BMI) between 18 and 33 $kg/m^2$ and body weight between 50 and 120 kg. Verbal and written informed consent was obtained before any study related procedures were carried out.

### 2.2. Study design

At the first visit, each subject underwent a health examination, including a semi-structured interview by a psychiatrist to judge if it was acceptable to expose the subject to AZD1940, as subjects with previous or ongoing psychiatric conditions were excluded. Subjects with positive tests for Hepatitis B/C, HIV or positive urine drug screen were excluded as well as those with any other disease/condition judged to interfere with the objectives of the study.

A randomized, double-blind, double-dummy, placebo-controlled study was conducted to investigate the analgesic efficacy of AZD1940 following impacted lower third molar surgical removal. Patients were randomized to one of three 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. All study drugs were manufactured and provided by AstraZeneca R&D Södertälje/Mölndal, Sweden.

In a preceding single ascending dose (SAD) study where AZD1940 was administered to healthy volunteers, a dose of 800 μg was found to be the maximal well tolerated dose [30]. The dose-limiting side effects were postural dizziness, hypotension and mild to severe psychiatric adverse events at higher doses. The gold standard and well-documented treatment, naproxen 500 mg, was included for assay sensitivity confirmation [34]. Study treatment was administered 1.5 h before the start of surgery. The timing was based on pharmacokinetic data from the preceding SAD study, as the maximum effect of AZD1940 was expected after $t_{max}$ (approximately 2 h after dosing in fasting condition). At request of pain relief, the patients received 1000 mg acetaminophen as a rescue medication.

The study comprised of three visits: Visit 1 was an enrolment visit (≤28 days prior to a residential period); Visit 2 was the residential period (Day −1, Day 1 (surgery) and Day 2); Visit 3 was a follow up visit (Day 10–Day 14).

### 2.3. Study measurements

The intensity of post-operative pain was rated by the patients on a visual analog scale (VAS, 0–100 mm) from completion of surgery (last stitch) until 8 h thereafter. During the first 4 h assessments were performed every 20 min and thereafter every 60 min. The end points of the VAS were marked "No pain" (0 mm) and "Worst pain imaginable" (100 mm). The VAS $AUC_{0-8\,h}$ (area under pain × time curve from end of surgery to 8 h post-surgery) was derived, being the primary outcome variable.

Pain on jaw movement was rated immediately after the post-operative pain rating and was defined as the pain intensity reported at opening the mouth as wide as possible [35]. It was rated on a VAS (0–100 mm) and pain at jaw movement $VAS_{JM}$ $AUC_{0-8\,h}$ was derived, being a secondary outcome variable.

The time from end of surgery to administration of rescue medication and the proportion of patients taking rescue were also secondary outcome variables.

Subjective CNS-related cannabinoid effects were assessed predose and at 75 min, 2, 3, 4, 5, 6, 7, 9 and 12 h post-study drug. The subjects were asked to rate the extent to which they felt each of the following five experiences signified by the adjectives: 'stimulated', 'high', anxious', 'sedated' and 'down', using a 100 mm visual analog mood scale (VAMS) [32]. The end points of the scale were marked "Not at all" (0 mm) and "Extremely" (100 mm). The maximal change from baseline for each VAMS sub-item score was derived, being a secondary outcome variable.

### 2.4. Safety and tolerability

Adverse events (AE) were recorded and reported according to ICH Good Clinical Practice guidelines. The AE were also classified after intensity (mild, moderate and severe) and causality (yes/no). Vital signs (body temperature, supine and standing blood pressure and pulse and respiratory rate), ECG, standard clinical chemistry, hematology tests, LH, FSH, testosterone and TSH, were monitored before and after administration of study drug.

### 2.5. Pharmacokinetic analysis

Blood samples were taken for pharmacokinetic (PK) analyses before dose, at 30 min, 1 h 15 min, 1 h 45 min, 2 h, 2 h 45 min, 3 h, 4 h, 6 h, 8 h 45 min and 12 h after dose. The PK parameters $C_{max}$ (maximum plasma concentration), $t_{max}$ (time to $C_{max}$), AUC (area

under plasma concentration versus time curve) and $t_{1/2}$ (half-life) of AZD1940 were derived.

### 2.6. Statistical analysis

The primary variable was VAS $AUC_{0-8\,h}$. The power calculations were based on the assumptions that AZD1940 would lead to 15% lower VAS $AUC_{0-8\,h}$ scores than placebo and that naproxen would lead to approximately 40% lower Pain $AUC_{0-8\,h}$ scores than placebo. With 60 evaluable patients in each of the placebo and AZD1940 treatment arms, a standard deviation of 119 mm h and a two-sided 10% significance level, the power would be 90% if the true difference (AZD1940-placebo) was 64 mm h. With 30 patients in the naproxen arm it would 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.

The efficacy evaluation was based on the per protocol principle. In particular, a patient needed to have completed at least 50% of all pain assessments and not more than 1 pain assessment in sequence missing in order to be classified as valid for efficacy evaluation. All patients who received study drug and for whom post-dose information was available were evaluated for safety. PK was evaluated per protocol.

When calculating the derived pain variables, pain ratings obtained after intake of rescue were replaced by the value at rescue. This is also true for scores used in pain curves over time and in summary tables.

AUC variables were analyzed using a *t*-test. Time to first intake of rescue medication was analyzed using survival methods. Kaplan–Meier plots were presented by treatment, and nonparametric 90% confidence intervals were calculated for the median event times. Data were considered censored if the patient had not received rescue medication up until 8 h after surgery. The log-rank test and the chi-squared test were also conducted in the time to rescue medication and the frequency of rescue medication comparisons. Mixed model repeated measurements (MMRM) analyses were used for the VAMS items "sedated" and "high". The models included baseline value as covariate, and time and treatment as fixed effects. An unstructured covariance matrix was used. *P*-Values for comparisons between AZD1940 and placebo and between naproxen and placebo are presented. All tests are one-sided at a 5% significance level (i.e. $\alpha = 0.05$).

## 3. Results

### 3.1. Study subjects

Of 233 patients enrolled, 151 were randomized to treatment out of which all were included in the efficacy and safety analysis sets. The main reasons for not being randomized were abnormal physical findings or abnormalities in vital signs, ECG or in clinical laboratory results. In total, 61 patients received AZD1940, 59 patients received placebo and 31 patients received naproxen.

There were no major imbalances between treatment groups with regard to demographics or dental surgery characteristics. All of the patients were males and the majority were white. The mean age of the study population was 20.7 years (range 18–39 years) and the mean BMI was 24.3 $kg/m^2$ (range 19–33 $kg/m^2$). The surgery was standardized and uniform and was approximately 6–7 min in duration (end of surgery defined as last stitch). Bone removal was performed in 98–100% of the patients in each treatment group. The mean time from drug intake to the start of surgery was 1.5 h, ranging from 1.45 h (placebo group) to 1.47 h (AZD1940 group).

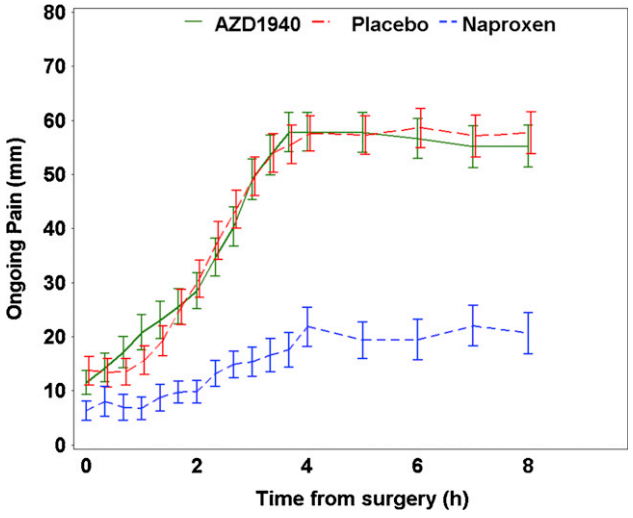


**Fig. 1.** Mean (±s.e.m.) VAS post-operative pain scores from 0 to 8 h post-surgery for patients treated with AZD1940 ($n = 61$ patients), placebo ($n = 59$), and naproxen ($n = 31$). Values after intake of rescue medication are replaced by the VAS score at rescue administration.

### 3.2. Pain measurements

The mean post-operative pain VAS $AUC_{0-8\,h}$ for AZD1940 was 355 mm h (90% c.i. = 316–394), for placebo 356 mm h (90% c.i. = 320–392) and for naproxen 129 mm h (90% c.i. $n = 97$–161). There was no statistically significant difference in the VAS $AUC_{0-8\,h}$ between patients administered AZD1940 and placebo ($p = 0.48$). Patients administered naproxen had significantly reduced VAS $AUC_{0-8\,h}$ compared with patients administered placebo ($p < 0.0001$) (Fig. 1).

The mean pain at jaw movement, $VAS_{JM}$ $AUC_{0-8\,h}$, for AZD1940 was 342 mm h (90% c.i. = 301–383), for placebo 337 mm h (90% c.i. = 300–374) and for naproxen 135 mm h (90% c.i. = 98–171). There was no statistically significant difference between AZD1940 and placebo for $VAS_{JM}$ $AUC_{0-8\,h}$ ($p = 0.56$) whereas a statistically significant difference between naproxen and placebo was observed ($p < 0.0001$).

Time to first administration of rescue medication is illustrated in Fig. 2. The difference between placebo and AZD1940 did not reach statistical significance ($p = 0.06$), whereas the difference between placebo and naproxen was highly significant ($p < 0.0001$). There was no statistically significant difference between AZD1940 and placebo in the proportion of patients requesting rescue medication (AZD1940: 61%, placebo: 73%, $p = 0.08$). In contrast, a significantly smaller proportion (23%, $p < 0.0001$) of patients in the naproxen group requested rescue medication than in the placebo group.

### 3.3. Visual analog mood scales (VAMS)

The patients administered AZD1940 reported significantly higher VAMS scores compared with patients administered placebo at all time points up to 7 h post-dose for "high" and up to 9 h post-dose for "sedated" (Fig. 3). The VAMS scores were maximal at 75 min for "high" (LS mean = 14.2 mm) and at 2 h for "sedated" (LS mean = 16.8 mm). The other VAMS scores ("stimulated", "anxious" and "down") were numerically similar for AZD1940 and placebo.

### 3.4. Pharmacokinetics

The average $C_{max}$ for AZD1940 was 9.3 nmol/L with a range of 6.7 and 13.7 nmol/L. The median $t_{max}$ was 2.9 h ranging between 1.2 and 8.8 h. Due to the short sampling time in relation to the $t_{1/2}$, there

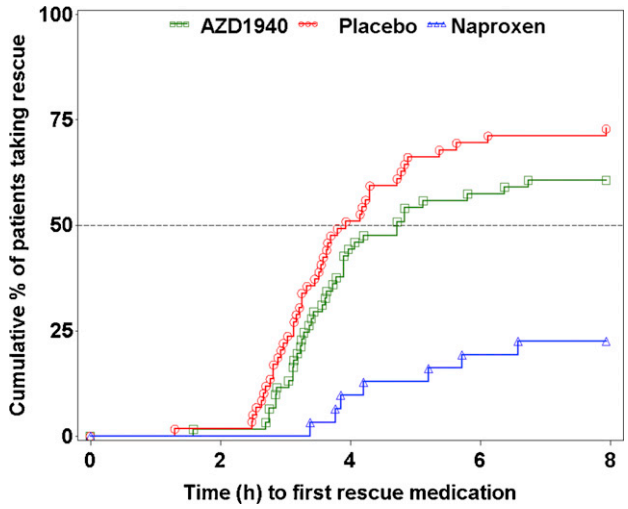


**Fig. 2.** Kaplan–Meier curves of time to first intake of rescue medication for patients treated with AZD1940 ($n = 61$ patients), placebo ($n = 59$), and naproxen ($n = 31$). *P*-Values (one-sided, log-rank tests) indicate comparison of AZD1940 versus placebo and naproxen versus placebo. The *y*-axis indicates the cumulative percentage of patients taking rescue medication from 0 to 8 h post-surgery.

was a large residual AUC (62% on average) and a very large uncertainty of AUC (236 h nmol/L, range 96–865) and $t_{1/2}$ (16.8 h, range 6.2–54.0). The naproxen group was confirmed by naproxen plasma analyses and the placebo group was confirmed by the absence of both naproxen and AZD1940 in plasma.

### 3.5. Safety and tolerability

There were no serious adverse events. The following AE were reported in more than 10% of subjects in any of the respective treatment groups AZD1940, placebo and naproxen: postural dizziness (80%, 32% and 13%), nausea (26%, 14% and 0%), hypotension (21%, 5% and 0%) and headache (13%, 5% and 3%). Presyncope or syncope was reported in three patients treated with AZD1940 and two treated with placebo. Most AE were of mild and moderate intensity. However, one patient in the AZD1940 group had four severe syncope episodes and another patient in this group had 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 hematology results. There were no clinically relevant differences in ECG or body temperature between patients administered AZD1940 and placebo. AZD1940 had hemodynamic effects with a reduction in mean standing

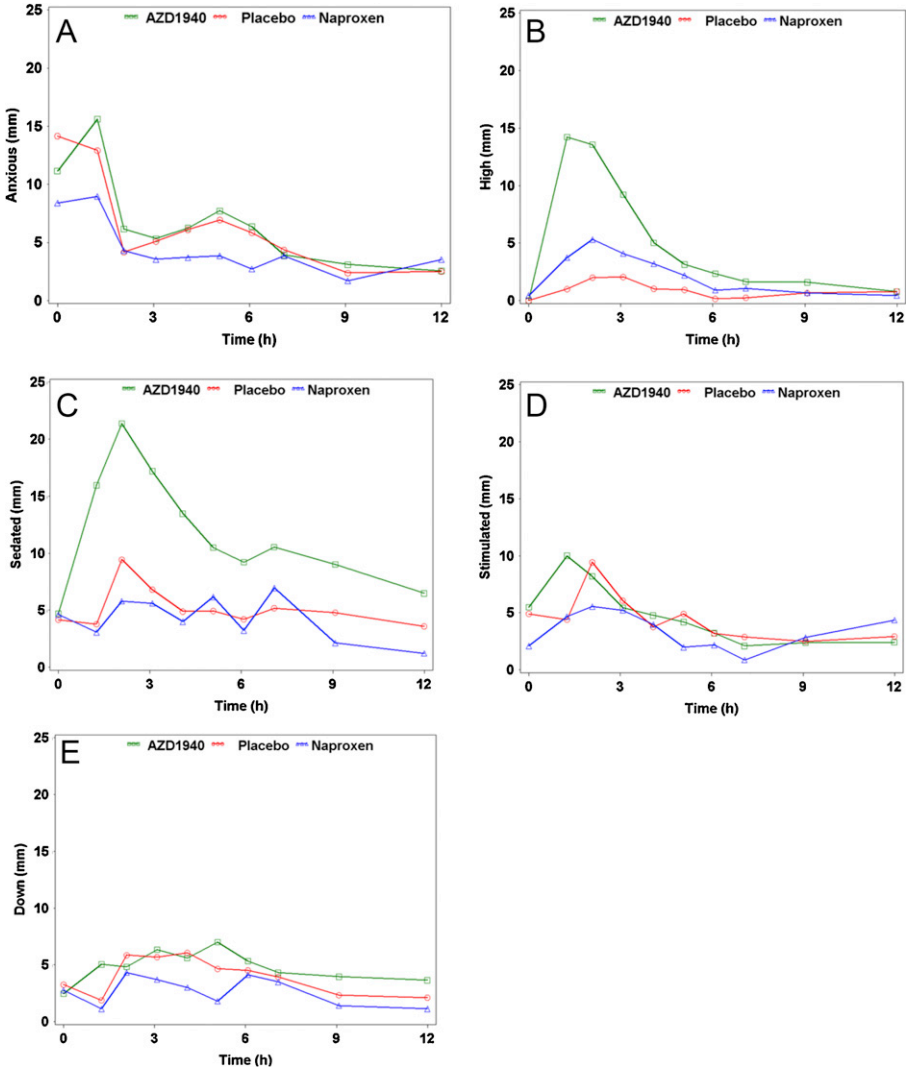


**Fig. 3.** Mean VAMS scores for (a) anxious, (b) high, (c) sedated, (d) stimulated, and (e) down, plotted versus time for AZD1940 ($n = 61$ patients), placebo ($n = 59$), and naproxen ($n = 31$).

systolic and diastolic blood pressure (BP) and a corresponding mean pulse increase. The greatest difference between AZD1940 and placebo in mean standing (for 2 min) blood pressure was recorded at 4 h post-dose, with mean standing systolic/diastolic BP change from baseline after AZD1940 being −12.5/−10.5 mmHg (placebo 3.4/2.1 mmHg) and mean standing pulse rate change of 20.3 bpm (placebo 3.4 bpm).

## 4. Discussion

The main finding was that a single dose of the $CB_1/CB_2$ receptor agonist AZD1940 was not efficacious for treatment of post-operative dental pain, while naproxen was efficacious, thus demonstrating assay sensitivity.

Surgical removal of impacted mandibular third molars has been used extensively as a model for the evaluation of analgesic drugs for acute pain. Treatments are usually administered post-operatively at moderate or severe pain intensities, thereby decreasing the dispersion of pain intensity measures by only including patients in need of analgesics. However, using this pain model, treatments have also been administered around or before surgery in order to study preemptive effects of analgesics [35,36]. In the present study, a relatively late maximum effect of AZD1940 was expected, i.e. approximately 2 h after drug administration [30], and could also be confirmed. In order to avoid intake of rescue analgesics before the onset of an effect, AZD1940 was administered before surgery, as was placebo and naproxen, the half-life of the latter allowing a sustained reliable analgesia during the study period.

In a previous dental extraction pain study, an AMPA/kainate antagonist showed an analgesic effect exclusively on pain evoked by jaw opening, but not on ongoing spontaneous pain [37]. Therefore it is conceivable that these two pain measures may differ depending on the analgesic mechanism of a compound. However, in the present study, no efficacy was seen on either of these two pain measures.

Patients receiving 800 μg of AZD1940 reported being more "sedated" and "high" on the VAMS than the placebo group. However, the VAMS scores were in general rather small compared with what has been observed with the centrally acting cannabinoid nabilone at clinically recommended doses [12,38]. Healthy volunteer subjects also reported more pronounced psychiatric AE after nabilone than what was observed with AZD1940 [12].

AZD1940 induced orthostatic effects with a reduction in mean blood pressure on standing compared with placebo and a corresponding increase in mean pulse rate. One patient in the AZD1940 group had severe syncope episodes after initial orthostatic testing. The two most common AE, postural dizziness and nausea, were observed more frequently in the AZD1940 treatment group than in the placebo group.

The numerical reduction in the mean plasma levels of testosterone, LH and TSH is consistent with an effect on the hypothalamic–pituitary axis. This is also a well-known finding from studies on other natural and synthetic cannabinoids indicating a potential acute effect on hypothalamic hormone release [39,40].

Preclinical studies have shown that the site of action for analgesic effects of AZD1940 in both inflammatory and neuropathic rat pain models is dependent on peripheral $CB_1$ receptors. Stable analgesic effects were observed in rat pain models from the first day, without any signs of tolerance to analgesia over the course of 10 days. AZD1940 has a low brain uptake and a low propensity of adverse CNS effects at analgesic doses in the rat, consistent with a window for analgesic effects before adverse CNS effects are observed [28,29]. Since the selected dose of 800 μg of AZD1940 induces mild psychoactive effects, it is likely to be within the analgesic window suggested by the preclinical data on AZD1940.

Thus, the present study seems to provide a valid pain model as well as an appropriate dose of AZD1940 to investigate its efficacy in acute nociceptive pain. Therefore it implies that activation of peripheral $CB_1/CB_2$ receptors per se may be of less clinical relevance for the treatment of acute nociceptive pain in man. However, it is as yet unknown to what extent peripheral cannabinoid receptors might be of importance in more chronic pain conditions.

In conclusion, the new $CB_1/CB_2$ receptor antagonist AZD1940 did not attenuate pain after third molar surgical removal at single doses exerting subjective cannabinoid effects.

## Disclosure statement

J. Kalliomäki, M. Segerdahl, A. Reimfelt, K. Huizar, P. Annas, R. Karlsten and H. Quiding are employees of AstraZeneca R&D Södertälje, Sweden and L. Webster is an employee of Lifetree Clinical Research, Salt Lake City, UT, USA.

## Role of the funding source

The study was sponsored by AstraZeneca R&D Södertälje, Sweden and conducted at Lifetree Clinical Research, Salt Lake City, UT, USA. The authors are responsible for the study design, collection, analysis, and interpretation of the data, and the decision to submit the paper for publication.

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