Contemporary Clinical Trials 37 (2014) 189–199

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Experiences with an adaptive design for a dose-finding study in patients with osteoarthritis

Frank Miller *[,1], Marcus Björnsson, Ola Svensson [2], Rolf Karlsten [3]

AstraZeneca, Södertälje, Sweden

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised 26 December 2013
Accepted 29 December 2013
Available online 3 January 2014

Keywords:
Adaptive design
AZD1386
Data Monitoring Committee
Dose-finding
Interim analysis
Osteoarthritis

ABSTRACT

Dose-finding studies in non-oncology areas are usually conducted in Phase II of the development process of a new potential medicine and it is key to choose a good design for such a study, as the results will decide if and how to proceed to Phase III. The present article has focus on the design of a dose-finding study for pain in osteoarthritis patients treated with the TRPV1 antagonist AZD1386. We describe different design alternatives in the planning of this study, the reasoning for choosing the adaptive design and experiences with conduct and interim analysis.

Three alternatives were proposed: one single dose-finding study with parallel design, a programme with a smaller Phase IIa study followed by a Phase IIb dose-finding study, and an adaptive dose-finding study. We describe these alternatives in detail and explain why the adaptive design was chosen for the study. We give insights in design aspects of the adaptive study, which need to be pre-planned, like interim decision criteria, statistical analysis method and setup of a Data Monitoring Committee.

Based on the interim analysis it was recommended to stop the study for futility since AZD1386 showed no significant pain decrease based on the primary variable. We discuss results and experiences from the conduct of the study with the novel design approach. Huge cost savings have been done compared to if the option with one dose-finding design for Phase II had been chosen. However, we point out several challenges with this approach.

1. Introduction

Many new potential medicines fail in early clinical development. Following preclinical studies to characterize the compound, translational studies and first time in man studies the challenge is great to select the right doses and study population for the first clinical studies on efficacy. The aim is not only to demonstrate the intended effect, but also to be able to evaluate the dose–response relationship regarding both efficacy and potential side effects to select the right doses for the forthcoming confirmatory trials in Phase III. Dose-finding studies in non-oncology areas are usually conducted in Phase II of the drug-development process and it is key to choose a good design for such a study.

In the Phase II programme for chronic pain, the most commonly used design is a randomised, placebo-controlled parallel group trial. As pointed out in the review by Kalliomäki et al. [1], difficulties to select an appropriate study population and/or appropriate doses are common for new drug candidates with novel pharmacological mechanism. Alternative design options to address this may therefore be considered. One of these alternative options is an adaptive dose-finding design, which gives the opportunity to obtain information on the most interesting part of the dose response curve even in situations where there is large uncertainty about the dose-effect-relation prior to the study.

* Corresponding author at: Department of Statistics, Stockholm University, SE10691 Stockholm, Sweden. Tel.: +46 816 2976.
E-mail address: frank.miller@stat.su.se (F. Miller).
[1] Present address: Stockholm University, Sweden.
[2] Present address: Pain Clinic, St. Göran Hospital, Capio, Stockholm, Sweden.
[3] Present address: Department of Surgical Sciences/Anaesthesiology & Intensive Care, Uppsala University, Uppsala, Sweden.

1551-7144/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cct.2013.12.007

For a new chemical entity AZD1386, an early phase clinical programme had been successfully conducted. Based on this early phase data, it was decided to conduct a Phase II dose-finding study in patients with osteoarthritis of the knee. Results of this study are presented by Svensson et al. [2].

Adaptive dose-finding designs have been discussed (e.g. Gaydos et al. [3]). Bretz et al. [4] highlight that adaptive trials can be applied to all stages of drug discovery and development including dose-finding studies. Statistical characteristics of adaptive dose-finding studies were evaluated by Bornkamp et al. [5] and Dragalin et al. [6] and efficiency considerations compared to fixed design have been conducted (e.g. Miller et al. [7], Dette et al. [8]). Clinical studies with adaptive dose-finding design are still rare. Examples include the ASTIN study for treatment of stroke (Krams et al. [9]), the INHANCE study for treatment of chronic obstructive pulmonary disease (Donohue et al. [10]) and a study for treatment of neuropathic pain (Smith et al. [11]).

The purpose of this article was to describe different design alternatives in the planning of the AZD1386 OA study, the reasoning for choosing the adaptive design and experiences with conduct and interim analysis. Experiences from this study can help for planning and conduct of future adaptive dose-finding studies.

2. Background

AZD1386, developed by AstraZeneca, is a potent and efficacious antagonist at the human TRPV1. AZD1386 was primarily being developed for oral treatment of chronic nociceptive pain. A proof-of-mechanism study was conducted to investigate the pharmacodynamic effects of a single dose, 95 mg of AZD1386, on intradermal capsaicin evoked pain symptoms and heat sensitivity in healthy volunteers. The study showed significant effects on increasing heat pain threshold and decreasing maximal pain after intradermal capsaicin injection (Karlsten et al. [12]). In Phase I studies several variables showed evidence of target engagement. Heat pain threshold (HPT) was chosen to select doses for the osteoarthritis (OA) study as it is a measure of pain and was available after both single and multiple dosing of several different dose levels. A pharmacokinetic/pharmacodynamic (PK/PD) model for HPT was developed and used to simulate the response in HPT after different dose levels.

Despite the dose–response information from the PK/PD model for HPT, there was considerable uncertainty about the dose levels for the OA study. The PK/PD model was based on healthy volunteers in the Phase I studies and these subjects have normal physiology in contrast to OA patients with pathological pain. It was therefore not clear if these HPT results would be predictive for pain of OA patients. The necessary dose in OA patients could be lower or higher compared to the doses suggested by the PK/PD model.

In a single dose study on pain after molar extraction (Quiding et al. [13]), patients randomly received 95 mg AZD1386, placebo or 500 mg Naproxen in a double-blind manner. The primary variable (sum of pain intensity difference over an 8 h period) did not differ significantly between AZD1386 and placebo, however AZD1386 showed a rapid on-set and short lasting analgesia compared to Naproxen. The pain reduction compared to placebo was statistically significant at 15, 30, 45 and 60 min after drug administration. This significant reduction was encouraging; however the implication of the short lasting effect in the acute pain model for chronic pain of OA patients was not clear.

The primary endpoint in the present OA-study was change from baseline to mean of weeks 2 and 4 using the pain subscale from the Western Ontario and McMaster Universities Arthritis Index (WOMAC) with a 48 hour recall where each item was rated with a Visual Analogue Scale (0–100 mm). Secondary endpoints were Numerical Rating Scale NRS (0–10) pain intensity in the morning and evening, 12 hour recall, and the WOMAC function and stiffness subscales. The treatment duration chosen for the study was 4 weeks. The patient population for the study were patients with OA of the knee that had unsatisfactory pain relief from past or on-going non-selective (ns) NSAIDs/COX-2s and paracetamol/acetaminophen treatment, or with intolerability to nsNSAIDs/COX-2s.

In the next section, we describe different options considered for the AZD1386 Phase II development programme. Since there were uncertainties around appropriate doses to use in the study, programmes with adaptive design options were included and compared with other development programmes.

3. Design options for the Phase II osteoarthritis programme

Preliminary plans for the osteoarthritis programme had been developed prior to the results of the tooth extraction study. At this point of time, Option 1 as described below was favoured. After the readout of the tooth extraction study, alternative options (see Options 2 and 3) were developed.

3.1. Option 1 (one dose-finding study)

It was judged that placebo and three doses AZD1386 were necessary in a double-blinded randomised parallel group dose-finding study in osteoarthritis patients. The dose 90 mg twice daily was chosen as the highest dose based on the results from the Phase I safety studies in healthy volunteers. See Fig. 1 for a flow diagram for this parallel design. For sample size calculation, a treatment effect of 8 mm on WOMAC pain for the highest dose compared to placebo and a standard deviation of 22 were assumed based on published results from other studies (Bjordal et al. [14], Lohmander et al. [15], Schnitzer et al. [16], Karlsson et al. [17]). A sample size of 110 evaluable patients per treatment group yields a power of 90% for the primary test (linear trend test, with contrasts based on ordinal doses according to Tukey et al. [18]) at a significance level of 10% (one-sided). This study design with 440 patients in total was based on the assumption that a clear mechanistic proof for the effect of AZD1386 is established in the tooth extraction study.

3.2. Option 2 (programme with a smaller Phase IIa study followed by a Phase IIb dose-finding study)

The outcomes from the tooth extraction study mentioned before were on one hand encouraging due to the clear pain reducing effect but on the other hand raised concerns. The implications for osteoarthritis of the just short lasting effect