European Journal of Pharmacology 822 (2018) 138–146

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Endocrine pharmacology

Evaluation of pharmacokinetics/pharmacodynamics and efficacy of one-month depots of TAK-448 and TAK-683, investigational kisspeptin analogs, in male rats and an androgen-dependent prostate cancer model

Akira Tanaka, Daisuke Nakata, Tsuneo Masaki, Masami Kusaka, Tatsuya Watanabe, Hisanori Matsui*

Oncology Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd., 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan

ARTICLE INFO

Keywords:
TAK-448
TAK-683
Kisspeptin
Prostate cancer
Androgen deprivation therapy (ADT)

ABSTRACT

TAK-448 and TAK-683 are kisspeptin agonist analogs with improved in vivo stability and activity. Previous studies showed that continuous subcutaneous administration of TAK-448 or TAK-683 caused rapid and profound reductions in plasma testosterone levels in various species, including male healthy volunteers, suggesting their therapeutic potential as anti-prostate cancer agents. For clinical drug development, one-month sustained-release depots of TAK-448 and TAK-683, TAK-448-SR(1M) and TAK-683-SR(1M), were designed to improve usability in clinical practice. In this study, the pharmacokinetics/pharmacodynamics (PK/PD) profiles of TAK-448-SR(1M) and TAK-683-SR(1M) were initially tested in male rats to ensure their eligibility as one-month depots. The therapeutic advantages of TAK-448-SR(1M) and TAK-683-SR(1M) over TAP-144-SR(1M) were then investigated in a JDCaP xenograft rat model. TAK-448-SR(1M) and TAK-683-SR(1M) maintained certain levels of plasma TAK-448 free form (TAK-448F) and plasma TAK-683 free form (TAK-683F) for at least 4 weeks, before clearance from the circulation. Accompanying their desirable PK profiles, TAK-448-SR(1M) and TAK-683-SR(1M) showed favorable PD responses as one-month depots and demonstrated better testosterone control than TAP-144-SR (1M). Both depots exerted rapid and profound suppression of plasma testosterone levels in male rats. These profound suppressive effects were maintained in dose-dependent manners, before recovery toward normal levels. In the JDCaP xenograft model, TAK-448-SR(1M) and TAK-683-SR(1M) both showed better prostate-specific antigen (PSA) control than TAP-144-SR(1M), although all treatment groups eventually experienced PSA recurrence and tumor regrowth. In conclusion, this study demonstrates that both TAK-448-SR(1M) and TAK-683-SR(1M) have desirable and better PK/PD profiles than TAP-144-SR(1M) in rats, which could potentially provide better clinical outcomes in androgen-dependent prostate cancer.

1. Introduction

Prostate cancer is a globally common cancer in men. Although the cancer death rates in the United States have continued to decline recently, prostate cancer still exhibits high morbidity and mortality in elderly men (Edwards et al., 2014). As prostate cancer primarily grows in an androgen-dependent manner, androgen deprivation therapy (ADT) has been the gold standard for treatment of advanced prostate cancer (Cornford et al., 2017; Mottet et al., 2017; NCCN, 2017). Various ADT regimens have been developed to date, including surgical castration and medical castration with gonadotropin-releasing hormone (GnRH) agonist or antagonist alone or in combination with androgen receptor antagonist.

Kisspeptin (also known as metastin) is the endogenous ligand for the human G-protein-coupled receptor KISS1R (also known as GPR54) (Ohtaki et al., 2001). Kisspeptin plays a key role in reproductive function through stimulation of GnRH release. In general, male reproductive function is centrally regulated through the hypothalamus–pituitary–gonadal axis. GnRH released from the hypothalamus stimulates the pituitary gland to secrete two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH or FSH plays an important role in testicular function, particularly in testosterone synthesis and spermatogenesis. Indeed, acute administration of kisspeptin was shown to activate male reproductive function in a broad range of mammalian species including humans (Gottsch et al., 2004; Thompson et al., 2004; Dhillo et al., 2005; Shahab et al., 2005; Ohkura

* Corresponding author.
E-mail address: hisanori.matsui@takeda.com (H. Matsui).

https://doi.org/10.1016/j.ejphar.2018.01.012
Received 17 October 2017; Received in revised form 5 January 2018; Accepted 15 January 2018

et al., 2009; George et al., 2011). In contrast, chronic administration of kisspeptin was reported to suppress reproductive function in adult male rats (Thompson et al., 2006) and agonadal juvenile male monkeys (Seminara et al., 2006; Ramaswamy et al., 2007).

TAK-448 and TAK-683 are investigational kisspeptin analogs that have improved metabolic stability with maintained potent agonistic activity for KISS1R compared with the natural peptide (Asami et al., 2013). It was previously reported that continuous subcutaneous administration of TAK-448 or TAK-683 induced transient increases in plasma testosterone, followed by more rapid and profound plasma testosterone reductions compared with TAP-144 (leuprolide) in male rats (Matsui et al., 2014). Similar profound testosterone-lowering effects were observed in dogs, monkeys, and human male healthy volunteers (Tanaka et al., 2010; Scott et al., 2013; MacLean et al., 2014). Furthermore, chronic TAK-448 and TAK-683 administration showed good therapeutic responses with prostate-specific antigen (PSA) reductions in the human androgen-dependent prostate cancer (ADPC) JDCaP xenograft rat model (Matsui et al., 2014) and prostate cancer patients (MacLean et al., 2014). These findings suggest that chronic administration of TAK-448 or TAK-683 may hold promise as novel therapeutic agents for the treatment of prostate cancer.

TAK-448-SR(1M) and TAK-683-SR(1M) were recently developed as one-month sustained-release depots of TAK-448 and TAK-683, by applying the drug delivery technology for TAP-144-SR(1M) (Toguchi et al., 1991). In this study, we determined the pharmacodynamics (PD) and pharmacokinetics (PK) of TAK-448-SR(1M) and TAK-683-SR(1M) in intact male Sprague-Dawley rats, and then investigated their therapeutic advantages over TAP-144-SR(1M) in the JDCaP xenograft rat model.

2. Materials and methods

2.1. Materials

Once-a-month injectable sustained-release depots of TAK-448, TAK-683, and leuprolide acetate, designated TAK-683-SR(1M), TAK-448-SR (1M), and TAP-144-SR(1M), and their vehicle solution (Lupron vehicle 2ML) were manufactured at Takeda Pharmaceutical Company Ltd. (Osaka, Japan). TAK-448 and TAK-683 used for the depots were also manufactured by Takeda pharmaceutical company Ltd with good laboratory practice standard. Aprotinin (Bayer Health Care Pharmaceuticals, Leverkusen, Germany) and EDTA-2Na (Dojindo Laboratories, Kumamoto, Japan) were used for plasma sampling.

2.2. Animals

Adult male Sprague-Dawley Crl:CD(SD) rats (Sprague-Dawley rats; 8 weeks of age) were purchased from Charles River Laboratories Japan (Kanagawa, Japan). Male F344/N Jcl-rnu/rnu rats (nude rats; 5 weeks of age) were purchased from CLEA Japan (Tokyo, Japan). All animals were housed in a room with controlled temperature and humidity on a 12-h/12-h light/dark cycle, and had free access to food and water. All animal experiments were approved by our Experimental Animal Care and Use Committee.

2.3. PK/PD profiles of TAK-448-SR(1M) and TAK-683-SR(1M) in male Sprague-Dawley rats

Two separate experiments were conducted to determine the PK/PD profiles of TAK-448-SR(1M) or TAK-683-SR(1M) in male Sprague-Dawley rats, and then each PD profile was compared with that of TAP-144-SR(1M). In both experiments, male Sprague-Dawley rats were evenly divided into 10 groups (n = 14 per group) based on body weight after habituation for 1 week or more. TAK-448-SR(1M), TAK-683-SR (1M), or TAP-144-SR(1M) was suspended in the Lupron vehicle 2ML on the day of dosing (day 0). The doses tested in this study were

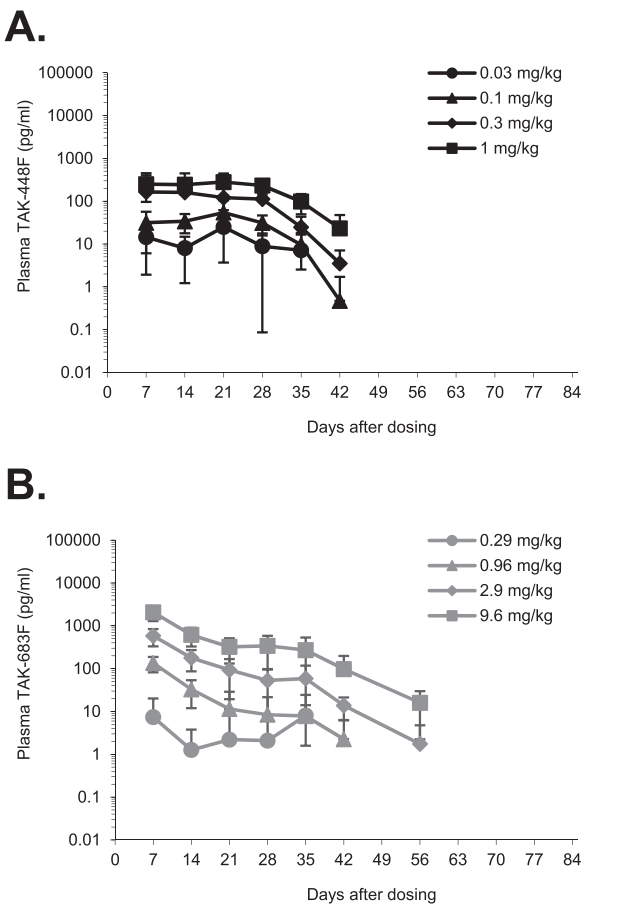

Fig. 1. Plasma TAK-448F or TAK-683F levels after single dosing of TAK-448-SR(1M) or TAK-683-SR (1M) in male rats. (A) Concentrations of TAK-448F after TAK-448-SR(1M) administration. (B) Concentrations of TAK-683F after TAK-683-SR(1M) administration. Data represent means ± S.D. (n = 14, days 7–28; n = 7, days 35–84).

determined based on the results in preliminary studies for formulation optimization. The doses of each suspended formulation were calculated as the free form of each active pharmaceutical ingredient (TAK-448F, TAK-683F, and leuprolide): Experiment 1, TAK-448-SR(1M) 0.03, 0.1, 0.3, and 1.0 mg/kg versus TAP-144-SR(1M) 0.3, 1, 3, and 10 mg/kg; Experiment 2, TAK-683-SR(1M) 0.29, 0.96, 2.9, and 9.6 mg/kg versus TAP-144-SR(1M) 0.29, 0.95, 2.9, and 9.5 mg/kg. In one of the groups in each experiment, all rats underwent a bilateral orchiectomy (ORX) performed on day 0 as a positive control. Blood samples were obtained via the tail vein, mixed with aprotinin solution containing 10% (wt/vol) EDTA-2Na, and centrifuged to obtain plasma samples for measurement of plasma testosterone and test compound levels. Half of the animals in each group were euthanized on day 28 to measure the weights of the prostate, seminal vesicles, and testes to assess the impact of TAK-448-SR(1M), TAK-683-SR(1M), or TAP-144-SR(1M) on reproductive organs. The weights of the prostate, seminal vesicles, and testes were expressed as relative weights compared to each animal's body weight (percent body weight).

2.4. Efficacy study in the JDCaP subrenal capsule xenograft rat model

The JDCaP xenograft model was maintained in nude mice as previously described (Kimura et al., 2009). At the beginning of the study, a small piece of JDCaP xenograft was transplanted under the subrenal capsule of each male nude rat, and its growth was monitored by measuring serum PSA levels. Rats who showed a sufficient PSA increase were selected and assigned to the following 10 groups based on their PSA levels: control, ORX, TAK-448-SR(1M) 0.1, 0.3, and 1 mg/kg, TAK-