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A randomized, placebo-controlled, single ascending-dose study to assess the safety, tolerability, pharmacokinetics, and immunogenicity of subcutaneous tralokinumab in Japanese healthy volunteers

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ABSTRACT

Tralokinumab is a human monoclonal antibody in clinical development for asthma and atopic dermatitis that specifically neutralizes interleukin-13. This phase I, single-blind, randomized, placebo-controlled, single ascending-dose study assessed the safety, tolerability, pharmacokinetics (PK), and immunogenicity of subcutaneous tralokinumab (150, 300, or 600 mg) in thirty healthy Japanese adults. The most frequent treatment-emergent adverse event (TEAE) in all treatment groups was injection-site pain. The frequency and severity of TEAEs was similar across tralokinumab doses. C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ increased in a dose-proportional manner, and mean $t_{1/2}$ ranged from 20 to 25 days. No anti-drug antibodies were detected. A *post-hoc* pooled population PK modeling analysis, incorporating PK data from this study, demonstrated that Japanese individuals had greater systemic exposure to tralokinumab than non-Japanese individuals. This difference was not clinically relevant and was primarily due to differences in body weight, with lower body weight associated with greater PK exposure. Japanese ethnicity was not a significant predictor of tralokinumab PK. This study indicates that single-dose subcutaneous administration of tralokinumab 150–600 mg was well tolerated in Japanese healthy volunteers, and supports the 300 mg dose selection for Japanese patients with asthma in ongoing clinical trials.

1. Introduction

A number of monoclonal antibodies (mAbs) have been approved as therapeutic drugs for people of Japanese and non-Japanese ethnicity for various diseases such as rheumatoid arthritis, Crohn's disease, and breast cancer, with more mAbs currently under investigation [1,2]. The pharmacokinetic (PK) properties of mAbs are well-documented [3,4]. Due to their large molecular size (~150 kDa) and polarity, the typical route of administration is parenteral [3,5]. When administered subcutaneously, mAbs are slowly absorbed from the injection site, most likely via the lymphatic system [3]. Distribution into peripheral tissue is relatively limited and is primarily mediated by convective extravasation [6] with a putative additional role of neonatal Fc receptor (FcRn)-mediated transcytosis [4,7]. Elimination of mAbs is governed by two processes: a target-specific saturable elimination pathway; and a non-specific proteolytic degradation process. In the latter, FcRn-mediated cellular mechanisms play a protective role by salvaging mAbs from lysosomal degradation. This process explains the relatively long terminal half-life of mAbs, prolonging their retention time in the body [3,8,9].

Although body weight and/or body surface area are generally related to the clearance of mAbs, their clinical relevance is often low. Unlike small molecules, mAbs show limited ethnicity-related effects on PK parameters, and observed differences have largely been attributed to differences in body weight [1] and/or antigen

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concentrations [2]. Ishii-Watabe and colleagues demonstrated ethnic differences in polymorphisms of the gene encoding FcRn between Japanese individuals [10] and non-Japanese participants of a previous study [11], but concluded that it was unlikely these variants contributed to the inter-individual variations observed in PK of mAbs [10]. However, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan requires at least one single-dose phase I study to be conducted to confirm the safety and PK of an investigational product in Japanese healthy volunteers (HVs) [12]. Results should be compared with those obtained in similar studies with non-Japanese individuals, and the possible ethnic differences should be assessed prior to Japanese people joining a global clinical trial [12].

Tralokinumab is a human immunoglobulin G_4 mAb currently in development for asthma [13–15] and atopic dermatitis [16] that potently and specifically neutralizes interleukin-13 (IL-13), preventing its interaction with the IL-13 receptor α1 and α2 subunits [17]. IL-13 is thought to be a central mediator in some types of asthma [18], and tralokinumab has demonstrated positive effects on asthma control in people with severe, uncontrolled asthma, particularly in those with increased IL-13 activity [14]. Severe asthma is classified by the Japanese Asthma Guidelines and by the Global Initiative for Asthma (GINA) guidelines as asthma requiring high-dose inhaled corticosteroids (ICS) and additional controller therapies, or disease that remains uncontrolled despite these therapies [19,20]. The proportion of Japanese people with asthma has been increasing in recent years, with the mean prevalence estimated to have increased from approximately 6%–10% in adults since the 1960s [19]. The prevalence of asthma classified as severe is reportedly 5.7–7% among people with asthma in Japan [21,22], which is similar to the 5–10% reported in the USA [23]. Therefore, there is a large medical need in Japan for new treatments for severe asthma.

The objectives of this single ascending-dose trial were to explore the safety, tolerability, PK, and immunogenicity of tralokinumab 150 mg, 300 mg, and 600 mg administered subcutaneously (SC) in Japanese HVs. We also performed a cross-study comparison with SC PK data from a previous study (NCT00638989 [24]) of tralokinumab in non-Japanese male HVs. Finally, a *post-hoc* population PK analysis that pooled PK data from eight studies of tralokinumab (including the two aforementioned studies) in both Japanese (n = 65) and non-Japanese (n = 513) participants was conducted. The purpose of this population PK analysis was to quantify the potential impact of baseline demographic and physiological covariates on the PK of tralokinumab, and evaluate the need for dose adjustment in Japanese patients in global clinical trials.

2. Materials and methods

2.1. Clinical study

2.1.1. Study design and eligibility

This was a phase I, single-blind, randomized, placebo-controlled, single ascending-dose trial of tralokinumab in Japanese healthy male and female adults (NCT01093040). Volunteers were required to be aged between 20 and 55 years, with a body mass index (BMI) between 18 and 27 kg/m^2, and no significant irregularities on clinical examination, medical history, electrocardiogram (ECG), clinical chemistry, hematology, or urinalysis results. The study was conducted at a single center in the USA between March 2010 and July 2010. For a volunteer to be considered ethnically Japanese, both parents and both sets of grandparents were required to be Japanese. Volunteers must have been born in Japan, hold a valid Japanese passport, and must not have lived outside Japan for more than 5 years. Key exclusion criteria included: previous treatment with a mAb or a similar related protein, which might sensitize volunteers to tralokinumab; a history of an active infection within 4 weeks prior to screening; any acute illness in the 14 days before dosing on Day 1; use of any medication excluding hormonal contraception within 14 days of Day 1; blood donation or significant loss of blood within 56 days (or plasma donation within 7 days) of study initiation; and positive test, or a history of treatment, for hepatitis B, hepatitis C, HIV, and/or other immunodeficiency disorders.

Following confirmation of eligibility, volunteers were assigned sequentially to three cohorts. Volunteers within each cohort were randomized using a computer-generated randomization code to receive a single, SC dose of either placebo or tralokinumab in a ratio of 2:8 (placebo [n = 2], tralokinumab [n = 8]). Cohort 1 received tralokinumab 150 mg (single SC injection), Cohort 2 received tralokinumab 300 mg (two SC injections of 150 mg), and Cohort 3 received tralokinumab 600 mg (four SC injections of 150 mg) (Fig. 1). These doses were chosen to match those tested in a phase IIa study of tralokinumab in non-Japanese patients with asthma, and were selected based on PK modeling and simulations [13], so that Japanese patients could be enrolled into a subsequent phase IIb study [14] once the optimal dosage(s) were identified. At each dose level the volunteer, but not the investigator, was blinded to treatment allocation. This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation's Guidance for Good Clinical Practice, and ethics approval was obtained from the Institutional Review Board before initiation of the study. All volunteers provided written informed consent.

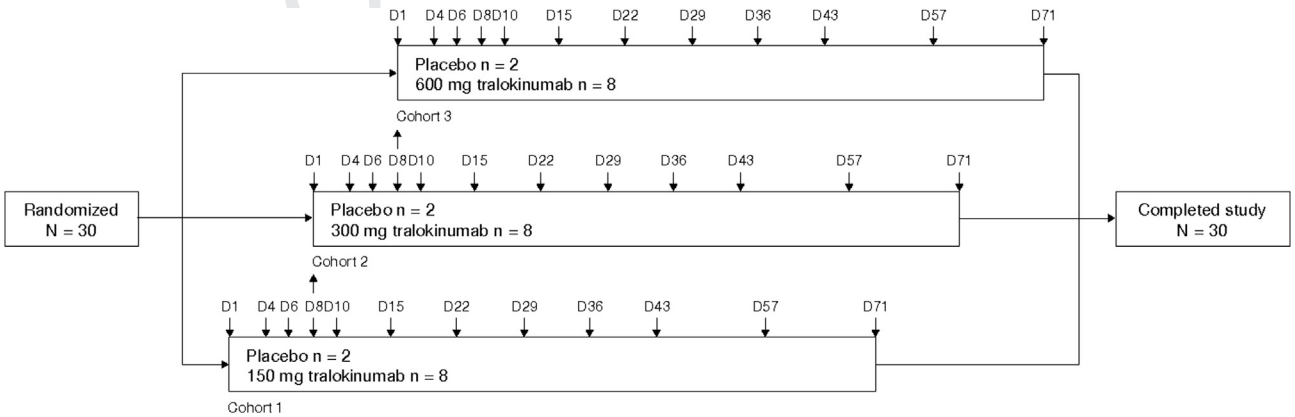

Fig. 1. Flowchart of volunteer assignment and treatment. Subjects were dosed on Day 1. A safety review was performed by the Safety Review Committee after all subjects in a cohort had completed the Day 8 assessment, before escalation to the next cohort.

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