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Eblasakimab, a novel IL-13 receptor alpha 1 monoclonal antibody, blocks STAT6 phosphorylation with low dose in human volunteers

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ABSTRACT

Eblasakimab is a first-in-class monoclonal antibody under investigation for the treatment of atopic dermatitis (AD), which targets IL-13Rα1, a subunit of the Type 2 receptor complex. IL-13Rα1 stimulates phosphorylation of signal transducer and activator of transcription 6 (STAT6) to drive inflammation. This brief report investigates the mechanistic basis of eblasakimab and its effects on IL-13Rα1 signaling as part of a phase 1a, open-label, single ascending dose study. Single ascending doses of eblasakimab were administered by intravenous or subcutaneous injection to healthy male volunteers. The impact of eblasakimab on IL-13Rα1 receptor occupancy and STAT6 phosphorylation was assessed in participant blood monocytes. No serious treatment emergent adverse events were reported. Eblasakimab effectively blocked the IL-13Rα1 receptor and inhibited STAT6 phosphorylation with single doses of 3 mg/kg intravenously and 300 mg subcutaneously. Results support further clinical development of eblasakimab as a novel biologic for AD, with potential for 2- to 4-week dosing regimens.

1. Introduction

IL-4 and IL-13 are cytokines that play key roles in Th2-driven inflammatory conditions such as atopic dermatitis, allergic rhinitis, and asthma [1–4]. The molecular mechanisms underlying the cellular and systemic effects of these cytokines are attractive therapeutic targets in combating allergic disease [5]. IL-4 binds to the IL-4Rα receptor, forming either the Type 1 receptor complex with the common gamma chain or the Type 2 receptor complex with the IL-13Rα1 receptor [6]. IL-13 binds to IL-13Rα1, which then recruits IL-4Rα to form the Type 2 receptor complex [6]. Biologics currently in use or under investigation for the treatment of Th2-mediated diseases function by either targeting IL-4Rα, thus inhibiting both Type 1 and Type 2 receptors [7,8], or by inhibiting IL-13 signaling through the Type 2 receptor alone [9,10]. Eblasakimab is a first-in-class, fully human monoclonal antibody that blocks Type 2 receptor signaling and is currently under investigation for the treatment of atopic dermatitis [11]. The antibody (previously known as ASLAN004) prevents IL-4 and IL-13 signaling through the Type 2 receptor by binding to the IL-13Rα1 subunit of the Type 2 receptor [12].

The signal transducer and activator of transcription (STAT) family of transcription factors is known to mediate the effects of many pro- and anti-inflammatory cytokines, including IL-4 and IL-13 [13]. Both IL-4 and IL-13 stimulate inflammation through Type 1 and/or Type 2 receptor signaling by inducing phosphorylation of STAT6 [14,15] by Janus tyrosine kinases 1 and 3 [14]. Phosphorylated STAT6 then forms homodimers and translocates to the nucleus to induce transcription of immune-response related genes [14,16] like thymus and activation regulated chemokine (TARC) [17–19] and immunoglobulin E (IgE) [20].

A Phase 1a, open label, single ascending dose study (NCT03721263) of eblasakimab in healthy male volunteers was recently completed. Given that the IL-13Rα1 subunit is a necessary and distinct component of the Type 2 receptor, we tested whether single intravenous (IV) or subcutaneous (SC) dose administration of eblasakimab could block IL-13Rα1 signaling and affect the downstream activation of STAT6 in the immune cells of human volunteers.

2. Methods

2.1. Study design

An open-label, Phase 1a, single ascending dose study (NCT03721263) of eblasakimab was performed in healthy male volunteers. The study protocol, informed consent forms, and other relevant documents were reviewed and approved by an institutional review board. The study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and Council for

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International Organizations of Medical Sciences International Ethical Guidelines, and International Council for Harmonization Good Clinical Practice Guidelines, and informed consent was obtained.

The first volunteer enrolled on October 15, 2018, and the last volunteer completed on June 20, 2019. Eblasakimab was administered either by IV or SC injection to male adults under the age of 65 at a single research site in Singapore. All cohorts had sentinel dosing, with the first volunteer of each cohort observed for 24–48 h prior to dosing the remaining volunteers in the cohort. Volunteers in the IV group (administered for 60 min with a syringe pump) were separated into 5 ascending dose cohorts: 0.1 mg/kg ($N = 2$); 0.3 mg/kg ($N = 3$); 1 mg/kg (N = 3); 3 mg/kg ($N = 6$); 10 mg/kg (N = 6). Those in the SC group were divided into 4 cohorts: 75 mg (N = 6); 150 mg (N = 6); 300 mg (N = 6); and 600 mg (N = 6). Safety data reviews were conducted before escalation to each sequential dosing cohort, with IV cohorts initiated before SC cohorts. The first SC cohort (75 mg) began after completion of the 1 mg/kg IV cohort; subsequently, IV and SC cohorts were escalated independently.

2.2. Safety measures

A safety follow-up period for adverse event assessments was carried out for up to 85 days from the last dose. Safety assessments included vital signs, adverse events, ECGs, clinical laboratory results, and physical exams. Immunogenicity was evaluated by measuring anti-drug antibodies present in serum.

2.3. Evaluation of signal transduction effects

Whole blood samples were collected at pre-dose, 1, 2, 4, and 8 h, and 2, 4, 8, 15, 22, 26, 29, 43, 57, and 86 days post-dosing. Flow cytometry was used to assess IL-13Rα1 receptor occupancy and pSTAT6 inhibition in monocytes. Monocytes defined as $CD45^{+}/CD14^{+}/CD49d^{+}$. Flow cytometry results were acquired using a BD LSR II Fortessa (Beckman Coulter, Brea, CA) and analyzed using FlowJo software (version 10.5). Samples were performed in triplicates for both assays; means and standard deviations were calculated based on triplicate readings.

2.3.1. IL-13Rα1 receptor occupancy (RO)

Whole blood samples were stained using a monocyte-staining antibody cocktail and incubated accordingly with 0.5 μg/mL biotin labelled eblasakimab and 2 μg/mL streptavidin-phycoerythrin (PE) with and without 100 μg/mL molar excess unlabeled eblasakimab for 60 min. The PE median fluorescence intensity (MFI) values were used to calculate percentage of free unbound IL-13Rα1 receptor in monocytes. Unlabeled eblasakimab was used as a negative control.

2.3.2. STAT6 phosphorylation inhibition

In the pSTAT6 inhibition assay, whole blood samples were stained using a monocyte-staining antibody cocktail for 20 min and stimulated with 2 ng/mL IL-13 (R&D Systems Cat 213-ILB-025) for 30 min. The samples were then permeabilized and incubated with pSTAT6 (tyr641)-PE antibody (BD Biosciences Cat.562078) to determine pSTAT6 levels.

3. Results

3.1. Baseline characteristics

Eblasakimab was administered to 44 healthy volunteers. All volunteers were male and Asian; those in the IV cohorts were a mean (SD) age of 38.6 (7.2) years, had a mean (SD) body weight of 72.0 kg (9.1 kg), and had a mean (SD) BMI of 23.9 kg/m^2 (2.7 kg/m^2). Volunteers in the SC cohorts were a mean (SD) age of 39.3 (8.5) years, had a mean (SD) body weight of 73.5 kg (10.1 kg), and had a mean (SD) BMI of 24.5 kg/m^2 (2.8 kg/m^2). Demographic and baseline characteristics were similar across cohorts.

3.2. Safety

Of the 44 study volunteers, 18 (40.9%) experienced at least one treatment-emergent adverse event (TEAE). In the IV cohorts, upper respiratory tract infection (20% [4/20]), decreased appetite (15%) [3/20]), headache (15% [3/20]), oropharyngeal pain (15% [3/20]), and pyrexia (15% [3/20]) were the most frequent TEAEs (>10%). In the SC cohorts, all TEAEs occurred at a rate of <10%, the most frequent of which were headache (8.3% [2/24]) and elevated C-reactive protein (8.3% [2/24]). One volunteer in the SC cohorts experienced pruritus at the injection site that resolved within 24 h.

In the overall population, five (11.4%) volunteers experienced at least one TEAE that was determined to be likely related to the study drug. Five volunteers (11.4%) experienced severe TEAEs, including gastroenteritis, cough, lethargy, and upper respiratory tract infection, none of which were considered to be related to the study drug. There were no serious adverse events related to study drug or fatalities, and no volunteers withdrew from the study due to an adverse event. TEAE frequency did not demonstrate a dose response, and no safety signals were observed. No anti-drug antibodies to eblasakimab were detected in study volunteers.

3.3. IL-13Rα1 signal transduction

3.3.1. IL-13a1 receptor occupancy

RO assays were conducted to determine the level of IL-13Rα1 receptors occupied by eblasakimab as well as the timing and duration of full receptor occupancy, if it was reached. The percentage of free IL-13Rα1 receptors in monocytes was 100% at baseline and notably dropped to 0% within 1 h after IV eblasakimab administration (Fig. 1A). The duration of this effect increased in a dose-dependent manner, lasting for 15 days in the 3.0 mg/kg cohort and for at least 29 days in the 10 mg/kg cohort. Of note, doses as low as 1 mg/kg at day 8 post dose resulted in complete receptor occupancy in 2 out of 3 participants. Two outliers account for the high variability observed at day 84 in the 10 mg/kg IV cohort (Fig. 1A).

When administered subcutaneously, a slower decrease in free IL-13Rα1 receptors was observed, but full RO was reached by 24 h post administration (Fig. 1B). A dose-dependent occupancy effect was also observed in the SC cohorts and lasted between 15 and 29 days at the highest 600 mg dose. There was more variability between volunteers in the SC cohorts compared with the IV cohorts in the RO assay (Fig. 1B), which is a common observation between the two administration routes [21].

3.3.2. pSTAT6 inhibition

IL-4- and IL-13-induced pSTAT6 signaling is a crucial pathway mediating cellular downstream effects. Inhibition of pSTAT6 in monocytes was measured to assess the inhibitory potency of eblasakimab. Complete inhibition of IL-13-induced phosphorylation of STAT6 was observed within 1 h after IV eblasakimab administration in the 3.0 mg/kg and 10 mg/kg cohorts and maintained for 15 and 29 days, respectively (Fig. 1C). Inhibition of pSTAT6 was not observed in the 0.1 mg/kg or 0.3 mg/kg cohorts at 1 h post IV administration (Fig. 1C). Partial inhibition was observed in the 1 mg/kg cohort, though it should be noted that one volunteer subject had an infection and increased monocyte counts, deemed unrelated to eblasakimab administration, which may have impacted these results (Fig. 1C).

In the SC cohorts, complete pSTAT6 inhibition was observed by 24 h post-dose in the 300 mg and 600 mg cohorts. Inhibition of STAT6 phosphorylation was still observed at 15 days at the highest 600 mg SC dose, but this effect was lost between 15 and 29 days (Fig. 1D).

4. Discussion

Here, a phase 1a study evaluated safety and receptor signaling and

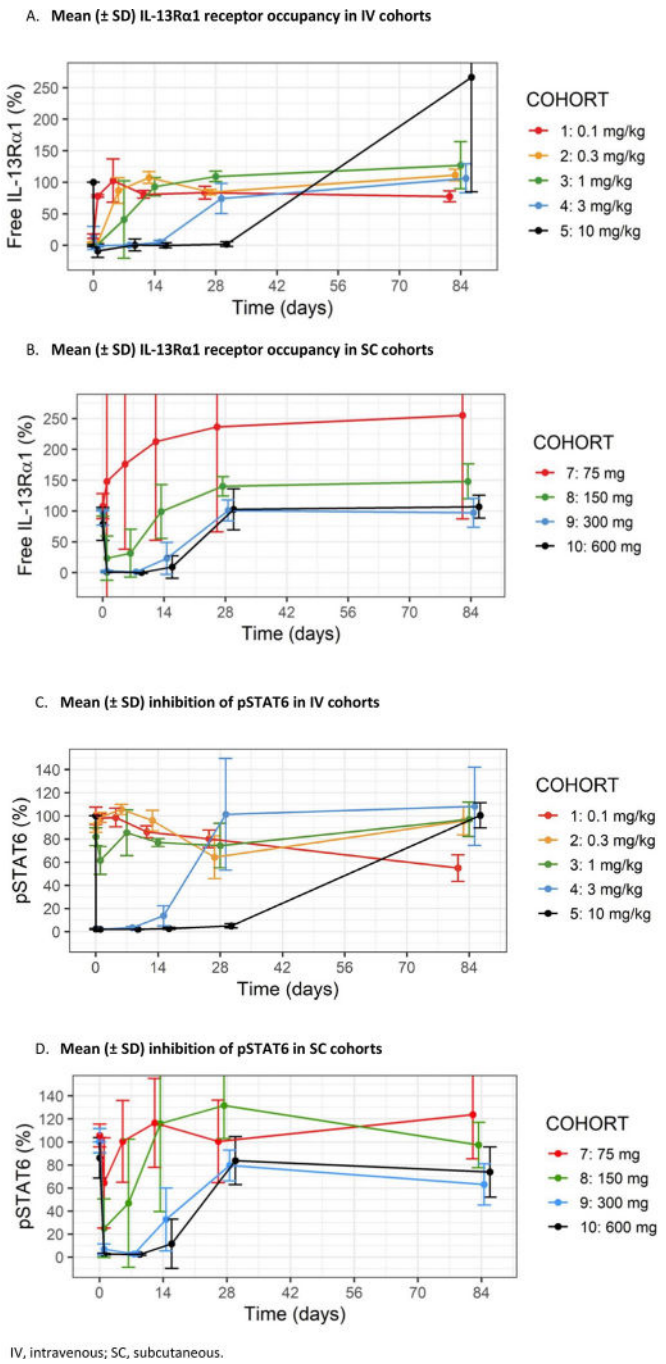

Fig. 1. IL-13α1 receptor occupancy and pSTAT6 Inhibition via Eblasakimab.
A. Mean (± SD) IL-13Rα1 receptor occupancy in IV cohorts.
B. Mean (± SD) IL-13Rα1 receptor occupancy in SC cohorts.
C. Mean (± SD) inhibition of pSTAT6 in IV cohorts.
D. Mean (± SD) inhibition of pSTAT6 in SC cohorts.
IV, intravenous; SC, subcutaneous.

occupancy effects in immune cells of healthy volunteers after a single dose of eblasakimab, a human monoclonal IL-13Rα1 antibody. Eblasakimab is currently being developed for the treatment of moderate-to-severe atopic dermatitis. Overall, results of this single ascending dose study showed that eblasakimab was well tolerated when administered both intravenously and subcutaneously across a range of doses up to 10 mg/kg and 600 mg, respectively. No serious adverse events related to the drug occurred during the study and no volunteers withdrew due to an adverse event. Receptor occupancy and phosphorylation assay results demonstrated that eblasakimab completely occupies the IL-13Rα1 receptor and inhibits STAT6 phosphorylation for at least 15 days with single doses as low as 3 mg/kg when administered intravenously and 300 mg when administered subcutaneously. These effects lasted for at least 29 days at the 10 mg/kg IV dose. Since STAT6 is responsible for driving expression of many Th2 effector molecules [14], these results suggest that 2- to 4-week dosing of eblasakimab may be effective treatment regimens for Th2-mediated diseases. In a multiple ascending dose, phase 1b proof-of-concept study [22], serum biomarkers associated with atopic dermatitis severity remained suppressed in the eblasakimab treatment groups for 4–6 weeks following the last subcutaneous dose, indicating the potential for a 4-week dosing regimen. A phase 2b dose-finding clinical trial is currently underway to further investigate the full pharmacokinetic and pharmacodynamic parameters of different SC doses of eblasakimab and define a dosing regimen for efficient treatment of moderate-to-severe atopic dermatitis.

Research has shown the importance of IL-13Rα1 in atopic dermatitis [23], eosinophilic esophagitis [24] and asthma [25]. Several monoclonal antibodies have been approved or are under investigation for the treatment of Th2-mediated diseases through various mechanisms, including blocking IL-4 and IL-13 signaling through both the Type 1 and Type 2 receptors [7,8] or preventing IL-13 signaling by binding the IL-13 ligand (which allows IL-4 signaling through the Type 2 receptor to continue) [9,10]. However, some patients experience inadequate responses to these treatments, necessitating the development of new biologics.

By binding the IL-13 receptor, eblasakimab provides complete and specific blockade of Type 2 receptor-mediated signaling. This unique mechanism may provide certain advantages in the treatment of Th2-mediated inflammatory disease such as moderate-to-severe atopic dermatitis. First, eblasakimab can bind to IL-13Rα1 with about 60-fold higher affinity than the ligand itself [5,12], enabling low doses of eblasakimab to compete with the binding of IL-13 to IL-13Rα1. In atopic dermatitis, IL-4 has been implicated in the initiation of inflammation, whereas IL-13 has been shown to be the key cytokine maintaining the inflammation driving disease pathology [1,26]. Eblasakimab's direct blockade of IL-13 signaling may be more effective than other monoclonal antibodies that block IL-13 signaling indirectly [10,27]. Second, by binding the receptor complex, eblasakimab has also been shown to block IL-4 signaling as well as IL-13 signaling [12], which may be important in addressing IL-4-driven allergic co-morbidities.

Additionally, eblasakimab offers the potential to differentially block Type 2 receptor-mediated signaling while sparing Type 1 receptor signaling, as the target IL-13Rα1 is a component of the Type 2 receptor but not the Type 1 receptor. In contrast, IL-4Rα is a shared component of both the Type 1 and Type 2 receptor complexes. Blockade of Type 1 receptor signaling has been put forward as a possible explanation for certain side effects, such as conjunctivitis, which are observed with drugs targeting IL-4Rα [9,28].

In summary, by binding IL-13Rα1, the distinct (unshared) receptor subunit of the Type 2 receptor, eblasakimab specifically hinders allergic and inflammatory signaling of IL-4 and IL-13 in chronic Th2-driven inflammatory diseases. Data from the present study are an encouraging first step in exploring eblasakimab's potential as a novel therapeutic agent with flexible dosing options for the treatment of atopic dermatitis, asthma, and diseases of IL-13-related etiology and provide a strong foundation to advance to the next phase of the clinical trial program. By design, this study was limited to single doses of eblasakimab in healthy male adults. While pharmacokinetic data were collected in the present study, the focus of this report is the mechanism underlying the potential of eblasakimab to reduce Th2-mediated inflammation. Ongoing and future studies will further evaluate the pharmacokinetic characteristics of multiple doses of eblasakimab in patients with moderate-to-severe atopic dermatitis. These studies will also investigate the potential suppressing effects of eblasakimab treatment on biomarkers for atopic dermatitis and their relationship with clinical efficacy.

5. Conclusion

Data from this open-label, phase 1a, single ascending dose study show that the human IL-13Rα1 specific monoclonal antibody eblasakimab was well tolerated when administered both intravenously and subcutaneously. Eblasakimab appears to completely block IL-13Rα1 and inhibit IL-13 induced activation of STAT6, a key transcription factor for the expression of Th2 effector cytokines. These results are an important first step in developing eblasakimab as a novel biologic agent for treating inflammatory diseases. Eblasakimab has the potential to be differentiated from other monoclonal antibodies that act on the Th2 pathway by its distinct blocking of Type 2 receptor signaling via IL-13Rα1 specific binding on inflammatory immune and non-immune cells, without impairing Type 1 receptor signaling.

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Declaration of Competing Interest

F. Cevikbas, C. Firth, and K.A. Veverka are employees of ASLAN Pharmaceuticals; A. Ward is a former employee of ASLAN Pharmaceuticals.

Data availability

Data supporting the findings of this study are available from the corresponding author upon request.

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