The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study*

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Conflicts of interest
M.F., H.N., K.K., T.R., J.H. and Y.K. are medical advisors to Chugai Pharmaceutical Co., Ltd. O.N., M.S., R.H. and S.M. were the principal investigators and S.I., M.K., I.H. and K.T. were

Summary

Background The cytokine interleukin-31 (IL-31) is considered to be responsible for the development of pruritus in humans. At present, no available evidence has been provided on the safety and efficacy of blocking the IL-31 signal in humans for the amelioration of pruritus in atopic dermatitis (AD). CIM331 is a humanized antihuman IL-31 receptor A (IL-31RA) monoclonal antibody, which binds to IL-31RA to inhibit subsequent IL-31 signalling.

Objectives To assess the tolerability, safety, pharmacokinetics and preliminary efficacy of CIM331 in healthy Japanese and white volunteers, and Japanese patients with AD.

Methods In this randomized, double-blind, placebo-controlled phase I/Ib study, CIM331 was administered in a single subcutaneous dose. The primary outcomes were safety and tolerability; the exploratory analysis was efficacy.

Results No deaths, serious adverse events (AEs) or discontinuations due to AEs were reported in any part of the study. No dose-dependent increase in the incidence of AEs occurred in any part of the study. In healthy volunteers, all AEs occurred once in the placebo groups, and increased creatine phosphokinase was more common in the CIM331 groups. In patients with AD, CIM331 reduced pruritus visual analogue scale score to about −50% at week 4 with CIM331 compared with −20% with placebo. CIM331 increased sleep efficiency and decreased the use of hydrocortisone butyrate.

Conclusions A single subcutaneous administration of CIM331 was well tolerated in healthy volunteers and patients with AD. It decreased pruritus, sleep disturbance and topical use of hydrocortisone. CIM331 may become a novel therapeutic option for AD by inhibiting IL-31.
Atopic dermatitis (AD) is triggered by an immune response to antigenic substances and by mechanical irritation, with the major symptom being pruritus.1,2 The resulting intense pruritus leads to scratching, which exacerbates the dermatitis and disturbs sleep, thereby reducing patients’ quality of life (QoL). This vicious cycle is known as the itch–scratch cycle.3

The most commonly used treatments for AD are topical corticosteroids and calcineurin inhibitors with emollients. Oral corticosteroids, immunosuppressants such as ciclosporin and/or ultraviolet therapies may be used in patients who do not respond to topical therapy.4,5 The use of systemic corticosteroids is limited by the occurrence of a disease flare (rebound) after withdrawal.6 Systemic ciclosporin is restricted for use in patients with severe and uncontrollable conditions because of the need to monitor renal function and blood pressure.7 Development of a novel, effective treatment for AD is warranted.

Interleukin-31 (IL-31), a cytokine produced mainly by activated T cells, has been implicated in the induction of pruritus in mice and humans. Expression of IL-31 mRNA is increased in the skin of spontaneous AD model mice,8 and transgenic mice overexpressing IL-31 have pronounced scratching behaviour.9 Intradermal injection of IL-31 causes a gradual increase in long-lasting scratching10 which is reduced by anti-IL-31 receptor antibody.11,12 Moreover, IL-31 is also reported to be responsible for the development of pruritus in humans. IL-31 is preferentially produced from T helper 2 (Th2) cells,9,13 and its expression is consistently increased in the skin lesions of patients with AD.13–19 In addition, IL-31 receptor A (IL-31RA) is expressed in epidermal keratinocytes and dermal nerves in the skin lesions of patients with AD, as well as in dorsal root ganglia neurons.16,17 Recently, IL-31-induced itch sensation was investigated by skin prick testing in healthy volunteers and patients with AD. IL-31 challenge evokes late itch responses, without a significant difference in IL-31-induced itch start time, duration or intensity between patients with AD and healthy volunteers.20 IL-31 is involved in Th2-mediated skin inflammation through the release of proinflammatory mediators, such as IL-4 and IL-13.14,15,21 Taken together, the evidence suggests that IL-31 has a pivotal role in the pathogenesis of pruritus and skin inflammation in AD. However, to our knowledge, no human studies have investigated blocking the effects of IL-31 signal on pruritus in patients with AD.

CIM331, a humanized anti-human IL-31 receptor A monoclonal antibody, was well tolerated in healthy volunteers and patients with AD. CIM331 markedly improved pruritus in patients with AD.

What’s already known about this topic?
- Interleukin-31 (IL-31) has been implicated in the induction of pruritus, the major symptom of atopic dermatitis (AD).

What does this study add?
- This is the first human trial to investigate whether inhibition of IL-31 signalling ameliorates pruritus in AD.
- Single subcutaneous administration of CIM331, a humanized anti-human IL-31 receptor A monoclonal antibody, was well tolerated in healthy volunteers and patients with AD.
- CIM331 markedly improved pruritus in patients with AD.

Materials and methods

Study design
This placebo-controlled, randomized, double-blind, interindividual, dose-escalation study was divided into three parts (A–C). In part A (n = 56), CIM331 or placebo (physiological saline solution) was given as a single subcutaneous injection to healthy Japanese male volunteers at doses of 0·003, 0·01, 0·03, 0·1, 0·3, 1·0 or 3·0 mg kg−1. Each group comprised eight volunteers (six for CIM331 and two for placebo). In part B (n = 24), healthy white male volunteers received CIM331 (0·3, 1·0 and 3·0 mg kg−1) or placebo. Each group consisted of eight volunteers (six for CIM331 and two for placebo). In part C (n = 36), Japanese patients with AD received CIM331 (0·3, 1·0 and 3·0 mg kg−1) or placebo. Each group consisted of 12 patients (nine for CIM331 and three for placebo) (Fig. 1). Because this is the first study to evaluate CIM331 in humans, an interindividual dose-escalation study method was used, in which the tolerability and safety of lower doses were assessed for 168 h (day 8) before escalation to higher doses.

The randomization manager of the investigational product randomly assigned eligible participants. Following eligibility screening, the manager allocated CIM331 and placebo at 3 : 1, then provided the randomization tables prior to starting the study. To ensure blinding, filled syringes were
indistinguishable from each other, and the investigator who administered the study drug was different from the one who evaluated the safety in the same dose group. No participant was allowed to participate in more than one dose group.

The study was conducted at four clinics in Japan between August 2011 and December 2012, in accordance with the Declaration of Helsinki, the Pharmaceutical Affairs Law and Good Clinical Practice. The study protocol was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from each participant.

**Study population**

Participants in parts A (Japanese) and B (white) were healthy volunteers aged 20–49 years. Body mass index was ≥18.5 and < 25.0 (Japanese) or < 30.0 (white). Part C enrolled Japanese patients aged 20–49 years, who had been diagnosed with AD of moderate or greater severity, with marked inflammatory cutaneous lesions covering ≥5% of their body surface area, despite continued treatment with topical corticosteroids for ≥12 weeks; a visual analogue scale (VAS) score for pruritus of ≥50 mm; and who were receiving topical treatment with hydrocortisone butyrate (Locoid®; Torii Pharmaceutical Co., Ltd, Tokyo, Japan) and/or moisturizers during the run-in period (day −7 to −1).

Exclusion criteria were a skin disease other than AD, ocular symptoms, eczema herpeticum, molluscum contagiosum, impetigo, an allergic disease requiring treatment with corticosteroids or antihistamines, new topical therapy or changes to the dosage regimen of a topical therapy, and use of inhaled or intranasal corticosteroids other than topical hydrocortisone butyrate within 2 weeks of the start of or during the run-in period. Patients were not allowed to use concomitant drugs for AD other than hydrocortisone butyrate and moisturizers during the run-in period.

**Outcomes and assessments**

The observation period was decided based on the dosage. Safety and tolerability were the primary outcome measures of the study, and were evaluated for a maximum of 127 days by assessment of adverse events (AEs), laboratory test values (haematology, blood chemistry, blood coagulation and urinalysis), clinical symptoms, vital signs and 12-lead electrocardiograms. Pharmacokinetics was a secondary outcome measure. Serum concentrations of CIM331 capable of binding to IL-31RA and of inhibiting IL-31 signal transduction were measured by enzyme-linked immunosorbent assay. Anti-CIM331 antibody was also measured.

In part C, efficacy was evaluated as an exploratory pharmacodynamic end point, using measurements of pruritus VAS score, hydrocortisone butyrate use and sleep efficiency. The amount of hydrocortisone used was monitored at each visit by measuring actual usage. A validated method (actigraphy) was used to evaluate sleep efficiency, the total sleeping time divided by the total time in bed. To obtain these data, patients wore an Actiwatch® (Philips Respironics, Bend, OR, U.S.A.) on their non-dominant wrist, which could monitor whole-body movement but not the patient’s scratching behaviour with the dominant wrist, to determine sleep and wake while they were in bed.

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**Fig 1.** Study design. AD, atopic dermatitis. *A patient discontinued after refusing treatment after administration, but was included in the analysis because of evaluation before discontinuation.*
Statistical analysis

No statistical sample size calculations were conducted. However, a sample size of nine patients per group gave post hoc powers of 43%, 40% and 31% to detect differences in mean of 30%, 29% and 25%, respectively, for pruritus VAS score at week 4, assuming a common SD of 33%, using a two-group t-test with a two-sided significance level of \( P < 0.05 \) for percentage change from baseline between placebo and each active group.

The number of participants permitted adequate assessment of safety and tolerability at each dose while minimizing the number exposed to CIM331. All study data were listed, summarized and/or plotted. The onset of increased blood creatine phosphokinase (CK), increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT) and exacerbation of AD were evaluated every 28 days.

For some efficacy measurements, although statistical tests to explore efficacy were not planned in advance, \( P \)-values were calculated for reference. To calculate \( P \)-values, analysis of covariance with treatment as a fixed factor and an efficacy measurement at baseline as a covariate was done on the efficacy measurement at weeks 4 or 8. \( P \)-values were presented without adjusting for multiple comparisons, in an exploratory manner. For the analyses, all observations recorded after any additional medication for AD were excluded and missing values were imputed using the last observation carried forward method.

Noncompartmental analysis was conducted using Phoenix WinNonlin v6.2 (Certara L.P., St Louis, MO, U.S.A.). Maximum serum concentration (\( C_{\text{max}} \)), time to reach maximum serum concentration (\( T_{\text{max}} \)), elimination half-life (\( T_{1/2} \)) and area under the serum concentration–time curve (AUC) were calculated from CIM331 serum concentration.

Adverse events were recorded using Medical Dictionary for Regulatory Activities version 14.1 (http://www.meddra.org), and the number of participants with AEs and the number of AEs were tabulated by event.

Results

Baseline participant characteristics

Figure 1 shows the distribution of patients across the placebo and CIM331 groups in study parts A–C. Mean pruritus VAS score in part C at baseline was 60–4–65–6. In all parts, no difference was found in baseline characteristics between the placebo and CIM331 groups (Table 1).

Safety

No deaths, serious AEs or discontinuations occurred as a result of AEs. All AEs were mild or moderate, and most AEs resolved. No dose-dependent increase in the incidence of AEs occurred in any study part.

In part A, two AEs were reported in two of 14 participants in the placebo group, whereas 16 AEs were reported in 11 of 42 participants in the CIM331 groups (0.003–3.000 mg kg\(^{-1} \)). AEs in the placebo group were infectious enteritis (\( n = 1 \)) and contact dermatitis (\( n = 1 \)). Common AEs in the CIM331 groups were infectious enteritis (\( n = 3 \)), increased C-reactive protein (\( n = 3 \)) and nasopharyngitis (\( n = 2 \)).

In part B, six AEs were reported in three of six participants in the placebo group, whereas 22 AEs were reported in 11 of 18 participants in the CIM331 groups. AEs in the placebo group were increased blood glucose, pharyngitis, upper respiratory tract infection, back pain, allergic rhinitis and contusion (all \( n = 1 \)). Common AEs in the CIM331 groups were increased blood CK (\( n = 6 \)), increased ALT (\( n = 3 \)), increased AST (\( n = 2 \)), pharyngitis (\( n = 2 \)) and myalgia (\( n = 2 \)). Across all parts of our study, seven participants with increased blood CK [within six times the upper limit of normal (ULN)] had clinical signs of myalgia, resulting from several hours of excessive exercise (e.g. walking and cycling) prior to the observation visits. Asymptomatic CK increases not due to myalgia have been reported; however, no clear dose-dependent changes were observed in time of onset or magnitude.

Adverse events reported by \( \geq 5\% \) of patients in part C are summarized in Table 2. In the placebo group, 14 AEs were reported in six of nine patients, including exacerbation of AD (\( n = 5 \)), folliculitis (\( n = 5 \)) and cellulitis (\( n = 2 \)). In the CIM331 groups, 44 AEs were reported in 17 of 27 patients, with common AEs being exacerbation of AD (\( n = 14 \)), folliculitis (\( n = 4 \)) and nasopharyngitis (\( n = 3 \)).

Pharmacokinetics

In part A, the serum concentration of CIM331 at doses of 0.003 and 0.010 mg kg\(^{-1} \) was below the lower limit of quantification (0.1 \( \mu g \) mL\(^{-1} \)) in all observation periods.

Through study parts A–C, median serum CIM331 concentration after a single administration of CIM331 reached a maximum 4–10 days later; mean \( T_{1/2} \) was 12.6–16.5 days (Fig. 2). Overall, dose-dependent increases in AUC and \( C_{\text{max}} \) were confirmed after a single subcutaneous administration of CIM331 (Table 3).

Anti-CIM331 antibody was detected in one participant in part A. However, he had previously had a positive result before the injection of CIM331 and experienced no AEs.

Efficacy (part C)

Pruritus VAS was markedly decreased at week 1 after administration of CIM331 in all groups (\(-24\%\), \(-24\%\) and \(-33\%) in the 0.3, 1.0 and 3.0 mg kg\(^{-1} \) CIM331 groups, respectively, vs. \(-9\%\) in the placebo group). Change in pruritus VAS score at week 4 from baseline was \(-50\%\), \(-44\%\) and \(-48\%) in the 0.3, 1.0 and 3.0 mg kg\(^{-1} \) CIM331 groups, respectively, compared with \(-20\%\) in the placebo group (\( P = 0.05 \), \( P = 0.17 \) and \( P = 0.10 \), respectively). At week 8, it was \(-47\%\), \(-34\%\) and \(-46\%) in the 0.3, 1.0 and 3.0 mg kg\(^{-1} \) CIM331 groups,
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Table 1 Baseline characteristics

| Study part A: healthy Japanese volunteers | CIM331 0.003 mg kg⁻¹ (n = 6) | CIM331 0.01 mg kg⁻¹ (n = 6) | CIM331 0.03 mg kg⁻¹ (n = 6) |
|------------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Age (years)                              | 25.5 ± 4.4                    | 22.8 ± 4.3                    | 24.8 ± 4.2                    |
| Body weight (kg)                         | 63.5 ± 7.5                    | 64.4 ± 5.5                    | 60.1 ± 6.3                    |
| BMI (kg m⁻²)                             | 21.9 ± 1.9                    | 20.9 ± 1.7                    | 20.8 ± 0.6                    |
| Study part B: healthy white volunteers   | CIM331 0.01 mg kg⁻¹ (n = 6)   | CIM331 0.03 mg kg⁻¹ (n = 6)   | CIM331 1.0 mg kg⁻¹ (n = 6)    |
| Age (years)                              | 31.0 ± 6.6                    | 30.5 ± 6.7                    | 29.3 ± 6.3                    |
| Body weight (kg)                         | 69.7 ± 4.4                    | 74.0 ± 8.1                    | 78.5 ± 8.7                    |
| BMI (kg m⁻²)                             | 21.4 ± 1.7                    | 23.2 ± 2.1                    | 23.8 ± 1.6                    |
| Study part C: Japanese patients with AD  | Placebo (n = 9)               | CIM331 0.3 mg kg⁻¹ (n = 9)    | CIM331 1.0 mg kg⁻¹ (n = 9)    |
| Sex                                       | Male                          | 8                             | 6                             |
|                                          | Female                        | 1                             | 3                             |
| Age (years)                              | 26.7 ± 4.9                    | 26.2 ± 7.2                    | 31.6 ± 10.6                   |
| Body weight (kg)                         | 62.4 ± 11.9                   | 61.8 ± 7.2                    | 58.4 ± 6.6                    |
| BMI (kg m⁻²)                             | 22.1 ± 3.4                    | 21.8 ± 3.3                    | 21.3 ± 1.7                    |
| Duration of AD (years)                   | 24.3 ± 5.4                    | 20.7 ± 10.0                   | 21.1 ± 11.0                   |
| Pruritus VAS score (mm)                  | 60.4 ± 6.2                    | 62.9 ± 7.4                    | 65.6 ± 7.5                    |
| Hydrocortisone butyrate use (g per week) | 21.6 ± 21.3                   | 16.9 ± 17.7                   | 18.6 ± 14.7                   |

Data are presented as mean ± SD. AD, atopic dermatitis; BMI, body mass index; VAS, visual analogue scale.

Table 2 Adverse events (AEs) reported by ≥ 5% Japanese patients with atopic dermatitis (study part C)

| AEa                        | Placebo (n = 9) | CIM331 0.3 mg kg⁻¹ (n = 9) | CIM331 1.0 mg kg⁻¹ (n = 9) | CIM331 3.0 mg kg⁻¹ (n = 9) |
|----------------------------|-----------------|----------------------------|----------------------------|----------------------------|
| Infections and infestations|                 |                            |                            |                            |
| Folliculitis               | 3               | 2                          | 1                          | 1                          |
| Nasopharyngitis            | 1               | 1                          | 2                          |                            |
| Herpes simplex             | 1               | 1                          | 1                          |                            |
| Paronychia                 | 1               |                            |                            |                            |
| Pharyngitis                | 1               |                            |                            |                            |
| Cellulitis                 | 2               |                            |                            |                            |
| Skin and subcutaneous tissue disorders | 5       | 3                            | 6                          | 5                          |
| Dermatitis atopicb         |                 |                            |                            |                            |
| Dyshidrosis                |                 |                            |                            |                            |

aAdverse event terms were converted to the corresponding preferred term and classified according to the corresponding system organ class based on Medical Dictionary for Regulatory Activities version 14.1 (http://www.meddra.org). bExacerbation of atopic dermatitis.

respectively, compared with −21% in the placebo group (Fig. 3).

Sleep efficiency, assessed as a QoL measurement, improved from week 1 in the CIM331 groups compared with the placebo group, which was in agreement with the reduced pruritus VAS score. At week 4, sleep efficiency was further improved in the CIM331 groups (mean 76%, 79% and 78% in the 0.3, 1.0 and 3.0 mg kg⁻¹ CIM331 groups, respectively) compared with a mean of 53% in the placebo group (P < 0.01 in all groups) (Fig. 4).

At baseline, mean weekly topical hydrocortisone butyrate use was similar between the placebo and CIM331 groups. It
increased at week 1 in the placebo group, whereas it decreased at week 1 in all CIM331 groups. At week 4, it was 33.6 g per week in the placebo group compared with 9.4, 11.3 and 7.2 g per week in the 0.3, 1.0 and 3.0 mg kg⁻¹ CIM331 groups, respectively (P < 0.01, P = 0.02 and P < 0.01, respectively) (Fig. 5). Mean cumulative amounts of topical hydrocortisone butyrate at weeks 4 and 8 were 138.8 and 272.5 g in the placebo group, 39.0 and 84.9 g in the 0.3 mg kg⁻¹ CIM331 group, 46.9 and 103.7 g in the 1.0 mg kg⁻¹ CIM331 group, and 32.1 and 87.8 g in the 3.0 mg kg⁻¹ CIM331 group.
Discussion

Earlier evidence from both murine and human studies suggests a pivotal role for the IL-31 signal in itch sensation.\(^8\)\(^–\)\(^19\) We investigated the tolerability, safety, pharmacokinetics and preliminary efficacy of CIM331. This is the first clinical study of CIM331 in humans. A single subcutaneous administration of CIM331 was well tolerated in healthy volunteers and patients with AD. CIM331 has no apparent difference in pharmacokinetic profile between healthy Japanese and white participants. CIM331 improved pruritus, sleep disturbance and topical use of hydrocortisone.

Adverse events associated with CIM331 were mild and transient, and recovered without treatment; they included increased blood CK and increased hepatic enzyme activity (AST, ALT) in healthy participants. In part, strenuous exercise could explain the increases in the liver function parameters, as well as in CK levels.\(^24\) Across all parts of our study, most of the increased blood CK (within six times the ULN) and of myalgia were observed in participants who had been performing several hours of excessive exercise (e.g. walking and cycling) prior to the observation visits, despite the fact that participants should not perform strenuous exercise when taking part in a clinical trial. Increased AST and increased ALT were associated with increased blood CK, suggesting that previous strenuous exercise causes muscle damage, resulting in simultaneous release of CK, AST and ALT into the bloodstream.\(^24\) These enzymatic level AEs might not have a causal relationship with CIM331 but might be associated, in part, with exercise or other potentially hepatotoxic concomitant medications. Because the number of volunteers was small, the present study could not conclude the real cause of these enzymatic fluctuations. Future clinical studies with a larger number of patients should examine whether these events may be related to the use of CIM331. Exacerbation of AD and folliculitis were the most common AEs in patients with AD receiving placebo or CIM331. These characteristics of AEs are comparable with the other systemic antibody treatments; most AEs of dupilumab for AD (\(n = 207\)) were transient and mild-to-moderate in severity.\(^25\) The most common AEs were nasopharyngitis, headache and injection site reactions.

In patients with AD, exacerbation of AD was the most common AE; exacerbation of AD began just after treatment in the placebo group but approximately 1 month after treatment in the CIM331 group. However, the frequency of AEs was similar in both groups. At present, the precise mechanism of the

![Fig 3. Percentage change (mean ± SE) in pruritus visual analogue scale (VAS) from baseline. AD, atopic dermatitis.](image1)

![Fig 4. Transitional change (mean ± SE) in sleep efficiency. Sleep efficiency was calculated as total sleeping time divided by total time in bed. AD, atopic dermatitis.](image2)
delayed exacerbations of AD in CIM331 is not clear. It may be related to the decrease in serum concentration of CIM331 and the consequent decrease in its antipruritic effects, as the present study evaluated the safety of single administration of CIM331. Further study will be needed to uncover the detailed safety profile of CIM331.

No AEs dose dependently increased in occurrence or severity at doses of \( \leq 3 \) mg kg\(^{-1} \) CIM331. This suggests that a single administration of CIM331 is well tolerated at doses up to 3 mg kg\(^{-1} \).

No differences in the pharmacokinetics of CIM331 were observed between healthy Japanese and white participants. Previous ethnic sensitivity studies suggest that there are no inter-racial differences in therapeutic antibodies between healthy Japanese and non-Japanese participants.\(^{26,27} \)

Regarding the efficacy of CIM331 in patients with AD, their VAS score for pruritus had reduced sharply by week 1 after CIM331 administration, which was associated with \( T_{\text{max}} \) (4–5 days). In parallel with the decrease in pruritus, sleep efficiency in patients with AD (approximately 60% at baseline) was restored by CIM331 treatment to normal levels (approximately 80%) at week 4.\(^{28} \)

AD is managed and treated by topical corticosteroids as a first-line therapy,\(^{4} \) although these can cause cutaneous AEs such as skin atrophy. A single injection of CIM331 decreased the amount of topical corticosteroids used in this study by 70%. The steroid-sparing effect of CIM331 will be beneficial for patients with AD as it may reduce the AEs of topical corticosteroids. It could ameliorate the daily burden of topical application for patients or caregivers, and improve QoL and adherence.\(^{29,30} \)

The limitation of the present study is that it was a single-dose phase I study. The safety profile for repeated doses of CIM331 remains unknown.

In conclusion, a single subcutaneous administration of CIM331 was well tolerated in healthy volunteers and patients with AD. It decreased pruritus and sleep disturbance. CIM331 may become a novel therapeutic option for AD via the inhibition of IL-31.

Fig 5. Transitional change (mean ± SE) in weekly use of hydrocortisone butyrate. AD, atopic dermatitis.

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