

Accepted Manuscript

Monoclonal Antibodies Against IL-13 and IL-31RA in Development for Atopic Dermatitis

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PII: S0190-9622(17)32819-0

DOI: [10.1016/j.jaad.2017.12.018](https://doi.org/10.1016/j.jaad.2017.12.018)

Reference: YMJD 12179

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 8 December 2017

Accepted Date: 9 December 2017

Please cite this article as: Hamann CR, Thyssen JP, Monoclonal Antibodies Against IL-13 and IL-31RA in Development for Atopic Dermatitis, *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2017.12.018.

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1 **Article Type:** Original Article

2 Title: Monoclonal Antibodies Against IL-13 and IL-31RA in Development for Atopic
3 Dermatitis

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14 **Funding Sources:** Bayer, LEO Pharma, Sanofi

15 IRB approval status: N/A

16 Clinicaltrials.gov (or equivalent) listing (if applicable): N/A

17 **Conflicts of Interest:**

18 Jacob P. Thyssen, MD, PhD, DMSc, is supported by an unrestricted grant from the
19 Lundbeck Foundation.

20 Jacob P. Thyssen, MD, PhD, DMSc, has attended advisory boards for Roche and Sanofi-
21 Genzyme and received speaker honorarium from LEO Pharma and Sanofi-Genzyme. He
22 is an investigator for LEO Pharma on their phase 3 tralokinumab study.

23 Carsten R. Hamann, MD, has no relevant conflicts of interest to declare.

24 **Reprint Requests:** Carsten R. Hamann, MD

25 **Manuscript word count:** 2,010

26 **Abstract word count:** 164

27 **Capsule Summary word count:** 49

28 **References:** 30

29 **Figures:** 1

30 Supplementary figures: 0

31 **Tables:** 1

32 Supplementary tables: 0

33 Attachments: 0

34 Keywords: AD atopic dermatitis; DPP-4 dipeptidyl peptidase-4; EASI eczema area and
35 severity index; IL interleukin; IL-31RA IL-31 receptor α ; IGA Investigator's Global
36 Assessment; JAK Janus kinase; JNK c-Jun N-terminal kinase; MAPK mitogen-activated
37 protein kinase; OSMR β oncostatin M receptor β ; STAT signal transducer and activator of
38 transcription; Th T helper; TCS topical corticosteroids; VAS visual analogue

39 Abstract

40 The IL-13 and IL-31 cytokines and inflammatory pathways have been identified as
41 important for atopic dermatitis (AD) pathophysiology. Monoclonal antibodies against IL-13
42 have been studied for the treatment of asthma since 2011. More recently, two phase two
43 trials have been completed with these antibodies in atopic dermatitis treatment. In both
44 trials, significant reductions of Eczema Area and Severity Index (EASI) scores were seen.
45 IL-31 is thought to play a role transmitting itch sensation to the central nervous system,
46 and blocking IL-31 activity reduces itch in atopic dermatitis patients. One phase two trial
47 has been completed for a humanized antibody against IL-31 receptor alpha, one subunit of
48 the IL-31 receptor complex. This study showed significant dose-dependent reductions in

pruritus, EASI scores, and markers of sleep quality. Initial clinical trials for monoclonal antibodies against IL-13 and IL-31 receptor A all show promise, although long term safety and efficacy data are lacking. Nevertheless, these medications will likely play a role in the treatment of moderate-to-severe atopic dermatitis.

Capsule Summary

- IL-13 and IL-31 cytokines and pathways have been identified as important for atopic dermatitis pathobiology.
- Initial clinical trials for tralokinumab, lebrikizumab, and nemolizumab all show promise.
- These medications will likely play a role in the treatment of moderate to severe atopic dermatitis, especially when other more cost-effective treatments fail.

IL-13 Antagonists

Mechanism of Action

Interleukin (IL)-13 is a pleiotropic T helper (Th) 2 cytokine that has been implicated in the pathogenesis of atopic dermatitis (AD), asthma, and pulmonary fibrosis.¹ IL-13 is predominately released from Th2 cells, but may also be secreted from granulocytes and monocytes/macrophages. Free IL-13 binds to the receptor unit IL-13R α 1 on all human cells, but in particular on monocytes and B-cells.^{2,3} This results in recruitment of IL-4R α , and together the two receptors form a signal transducer,³ which activates Janus kinase (JAK)1, JAK2, signal transducer and activator of transcription (STAT)-1, STAT 3, STAT6 and STAT dimerization, and in turn gene transcription (Figure 1).¹ IL-13 binds with a relatively reduced affinity to IL-14R α compared to IL-4, and these two cytokines seem to compete for receptor binding.¹ Secreted IL-13, but not IL-4, also binds with very high affinity to IL-13R α 2. This receptor has been proposed to represent a decoy as it has no

cytoplasmic tail. However, in vivo studies have suggested that IL-13R α 2 is pro-inflammatory, whereas in vitro observations have suggested that it could have inhibitory activities, e.g. through attenuating IL-4 activities.¹ More research is clearly needed to clarify the exact role of IL-13R α 2. Moreover, IL-13 can down-regulate skin barrier proteins including filaggrin, and therefore further impair the skin barrier in AD.^{4,5} Notably, serum periostin and dipeptidyl peptidase-4 (DPP-4) represent promising biomarkers for IL-13 activation in epithelia.⁶

Efficacy data

Specific monoclonal antibodies that bind and neutralize secreted IL-13 have been studied for AD treatment. A randomized, placebo-controlled, double-blind, clinical phase 2b dose-ranging study was performed with subcutaneous injections of tralokinumab in 204 adult patients with moderate-to-severe AD (Table 1).⁷ Included patients had an Eczema Area and Severity Index (EASI) score ≥ 12 , SCORing Atopic Dermatitis (SCORAD) ≥ 25 , Investigator's Global Assessment (IGA) ≥ 3 and affected body surface area $\geq 10\%$. The primary outcomes were change from baseline in total EASI at week 12, percentage of patients achieving an IGA score of 0 or 1 (clear or almost clear), and at least a 2-grade reduction from baseline at week 12. The mean EASI scores at baseline in the treatment groups were 24.8-27.3. After a 2 week run-in period with topical corticosteroids (TCS), a dose of 300 mg tralokinumab every other week resulted in a significant improvement in AD compared to placebo. Thus, the adjusted mean changes in EASI scores from baseline were -15.7 and -10.8, in the tralokinumab and placebo groups, respectively ($P=0.011$).⁷ Moreover, 26% of patients in the tralokinumab group achieved an IGA of 0-1 compared to 12% in the placebo group, but the difference was non-significant. Compared with placebo, tralokinumab therapy significantly decreased the pruritus numeric rating scale ($P=0.002$),

97 EASI75 ($P = 0.003$) and EASI50 ($P = 0.025$) scores, the number of staphylococcus aureus
98 colonized patients ($P = 0.015$), as well as the levels of periostin, TARC/CCL17 and serum
99 IgE (all $P = 0.001$).⁷ Patients with elevated DPP-4 at baseline, indicating increased IL-13
100 levels, showed a better response to tralokinumab. Importantly, and as opposed to the
101 dupilumab trials,⁸ AD patients in the tralokinumab study applied mid-strength TCS
102 throughout the trial, which could limit insight in the true effect size of tralokinumab. Side-
103 effects in both treatment and placebo groups included nasopharyngitis (16.7%), upper
104 respiratory tract infection (9.3%), headache (6.4%) and exacerbation of AD (6.4%).⁷
105 Nasopharyngitis and headache appeared to occur more frequently in tralokinumab treated
106 patients, whereas upper respiratory tract infections occurred equally frequent.
107
108 A phase 2 randomized, double-blind, prospective, placebo-controlled, multicenter study
109 has also been performed for lebrikizumab in 18-75 year olds with moderate-to-severe AD
110 with inadequate response to TCS (Table 1).^{9,10} Inclusion criteria included EASI ≥ 14 , IGA $\geq$
111 3, AD affecting $\geq 10\%$ of the body surface area, and pruritus visual analogue scale (VAS)
112 ≥ 3 . The primary outcome was the proportion of patients that achieved a 50% reduction of
113 their AD severity (EASI 50) at week 12. A 2-week TCS run-in period was performed in all
114 patients, and a mid-potency TCS (triamcinolone acetonide 0.1% or hydrocortisone 2.5%
115 cream [only for lesions affecting the face and intertriginous areas]) was used twice daily on
116 lesional skin during the entire trial period. A total of 209 patients were randomized to
117 placebo + TCS ($n=53$), single dose 125 mg lebrikizumab + TCS ($n=52$), single dose 250
118 mg lebrikizumab + TCS ($n=53$), or 125 mg lebrikizumab every 4 weeks + TCS ($n=51$). The
119 EASI50 in the four groups were, respectively, 62.3, 69.2, 69.8, and 82.4. The difference
120 was significant when comparing the placebo group and the 125 mg lebrikizumab injected

every 4 weeks. Moreover, when comparing patients receiving 125 mg lebrikizumab every 4 weeks + TCS with the placebo + TCS group, significantly more patients achieved EASI75 and EASI90 in the lebrikizumab group. No detailed written information on side effects has yet been published, but an oral presentation at the 2016 European Academy of Dermatology and Venereology Congress showed slightly higher rates of injection site reactions and herpes infections in the lebrikizumab-treated patients compared to placebo-treated patients.¹¹ The occurrence of conjunctivitis was 8% in the placebo group, and 13% in the 125 mg lebrikizumab single dose group, 10% in the 250 mg lebrikizumab single dose group and, finally, 6% in the 125 mg lebrikizumab every 4 week group.¹¹

Besides AD, monoclonal antibodies against IL-13 have been examined in pulmonary fibrosis and trialed for Hodgkins lymphoma, ulcerative colitis, and asthma. In the pivotal 52-week lebrikizumab phase 3 studies (LAVOTA I and II) in patients with asthma, only LAVOLTA I met its primary endpoint and reduced asthma exacerbation rates.¹² In this study, increased periostin levels did not predict treatment success. Lebrikizumab therapy caused an increase in blood eosinophil counts, most likely due to reduced migration into tissue. While there was no difference in the frequency of serious adverse events between the study groups, five events in the lebrikizumab groups were related to eosinophilia (Churg-Strauss, eosinophilic pneumonia and otitis media).¹²

The incidence of herpes zoster was also higher among lebrikizumab treated patients. Tralokinumab also failed to meet its primary endpoint in a phase 2b trial in patients with asthma,⁶ i.e. reduction of asthma exacerbations in patients with severe uncontrolled disease. No relevant difference in the frequency of serious adverse events between treatment and placebo groups was observed. However, increased eosinophilia was noted

in the tralokinumab groups. Finally, the first of two pivotal phase 3 trials (STRATOS 1) examining the effect of tralokinumab in reducing annual asthma exacerbation rate in severe, uncontrolled asthma patients failed to meet its endpoint.¹³

IL-31RA Antagonist

Mechanism of Action

There is increasing evidence that the inflammatory cytokine IL-31, a member of the gp130/IL-6 cytokine family, plays a key role in AD pathogenesis and disease propagation.^{14,15} In particular IL-31 is thought to mediate itch in AD patients.¹⁵ Like IL-13, IL-31 is released primarily by Th2 cells, and in particular CD4⁺ Th2 cells, but also to a lesser extent from eosinophils, dendritic cells, and macrophages.^{14,16} Notably, IL-31 is also released by skin-homing CD45RO⁺ cutaneous lymphocyte-associated antigen-positive T cells in individuals with AD.¹⁷ IL-31 signaling is accomplished when IL-31 binds to a heterodimeric receptor complex composed of oncostatin M receptor β (OSMR β) and IL-31 receptor α (IL-31RA)(Figure 1).^{14,16} Activation of IL-31RA drives signaling through multiple pathways, most notably through JAK, STAT3 and mitogen-activated protein kinase (MAPK) in epithelial cells, but also to a lesser extent STAT1, STAT5, c-Jun N-terminal kinase (JNK), and protein kinase-B (AKT).^{16,18,19} IL-31 activation of this complex also drives signaling through the OSMR β receptor, including additional JAK/STAT activity, as well as the ERK1/ERK2, JNK, and phosphatidylinositol-3-kinase (PI3K)/AKT pathways.^{18,19} Several studies have shown that both lesional and non-lesional skin in AD patients has increased expression of IL-31 and IL-31RA compared to skin of healthy volunteers.^{17,20-22} Similarly, there is increased serum IL-31 in patients with AD and increased levels of IL-31 producing lymphocytes.^{22,23} Both serum and skin IL-31 levels have been shown to correlate with AD severity.¹⁴

169 Efficacy Data

170 There are currently two medications in development for the treatment of AD that utilize this
171 IL-31 pathway. The first, nemolizumab, is a humanized antibody against IL-31RA that has
172 now gone through phase one and two clinical trials with significant success (Table 1).^{24,25}
173 From December 2013 through April 2015 a randomized, double-blind, placebo-controlled,
174 12-week, dose-ranging study was performed with subcutaneous injections of nemolizumab
175 in 264 patients with moderate-to-severe AD, not adequately controlled by topical therapies.
176 Included patients had EASI scores of at least 10 and IGA of at least 3.²⁵ Mean EASI
177 scores at baseline in the treatment groups were 28.2-32.4.²⁵ In contrast to clinical trials on
178 IL-13 antagonists, the primary end point for this study was percentage improvement of
179 pruritus based on a visual analogue scale. From baseline to week 12, significant
180 reductions in pruritus were seen in all three primary treatment arms (those receiving 0.1,
181 0.5 or 2.0 mg/kg nemolizumab every four weeks). Percent reductions were -43.7% ($P =$
182 0.002) in the 0.1 mg/kg group, -59.8% ($P < 0.001$) in the 0.5 mg/kg group, and -63.1%
183 ($P < 0.001$) in the 2.0 mg/kg group, compared with -20.9% in the placebo group.²⁵
184 Significant dose-dependent reductions in pruritus score based on a verbal rating scale,
185 improvements in four measures of sleep quality, improvement in Dermatology Life Quality
186 Index and dose-dependent reduction in EASI score were also found. In particular, EASI
187 score reduction from baseline was $-23.0 \pm 7.5\%$ in the 0.1 mg/kg group, $-42.3 \pm 7.3\%$ in the
188 0.5 mg/kg group and $-40.9 \pm 7.5\%$ in the 2.0 mg/kg group, compared with 26.6% in the
189 placebo group.²⁵ Patients who did not have any improvement in the pruritus VAS or in
190 eczematous skin changes at 4 weeks were allowed use of potent TCS as rescue therapy
191 which may have artificially improved the study's results.²⁶ A two-part phase one trial (BMS-

981164) with a monoclonal antibody against IL-31 itself, as opposed to IL-31RA was completed in 2015 but no data have yet been published (NCT01614756).²⁷

The safety and side-effects profile for nemolizumab were evaluated in both the phase one and two trials.^{24,25} In the initial phase one trial, no severe adverse events were noted in either the placebo or treatment groups. Common side effects in the treatment groups included elevated aspartate transaminase, alanine transaminase, creatinine kinase or C-reactive protein levels, myalgia, folliculitis, exacerbation of AD and pharyngitis or nasopharyngitis.²⁴ Across all nemolizumab treatment groups 39/87 (44.8%) of participants reported at least one adverse event compared with 11/29 (37.9%) of those in placebo groups. However, no dose-dependent increase in the incidence of any of the adverse events was noted.²⁴ Adverse events were slightly more common in the phase two trial, with 36/53(68%) of patients receiving placebo reporting adverse events compared with 151/211 (71.6%) of patients in the treatment groups, but like in the phase one trial, no clear dose-dependent relationship was seen. In contrast to the phase one trial, there were 2 severe adverse events reported in the placebo arm and 1, 3, and 2 events in the 0.1 mg/kg every 4 weeks, 2.0 mg/kg every 4 weeks and 2.0 mg/kg every 8 weeks arms, respectively.²⁵ Like in the phase one trial, adverse events included AD exacerbation, nasopharyngitis, and increased creatinine kinase levels, but also upper respiratory tract infection and peripheral edema. However, only AD exacerbation and peripheral edema were more common in the nemolizumab treatment groups.²⁵

Unlike some of the other biologics undergoing trials for efficacy in AD treatment such as ustekinumab and secukinumab, neither nemolizumab nor any other biologic targeting the IL-31 pathway has been studied in other diseases. While IL-31 has been implicated in the pathogenesis of inflammatory bowel disease, cutaneous T-cell lymphoma, asthma and

216 airway hypersensitivity, no clinical trials and limited in-vivo studies have been performed.²⁸⁻

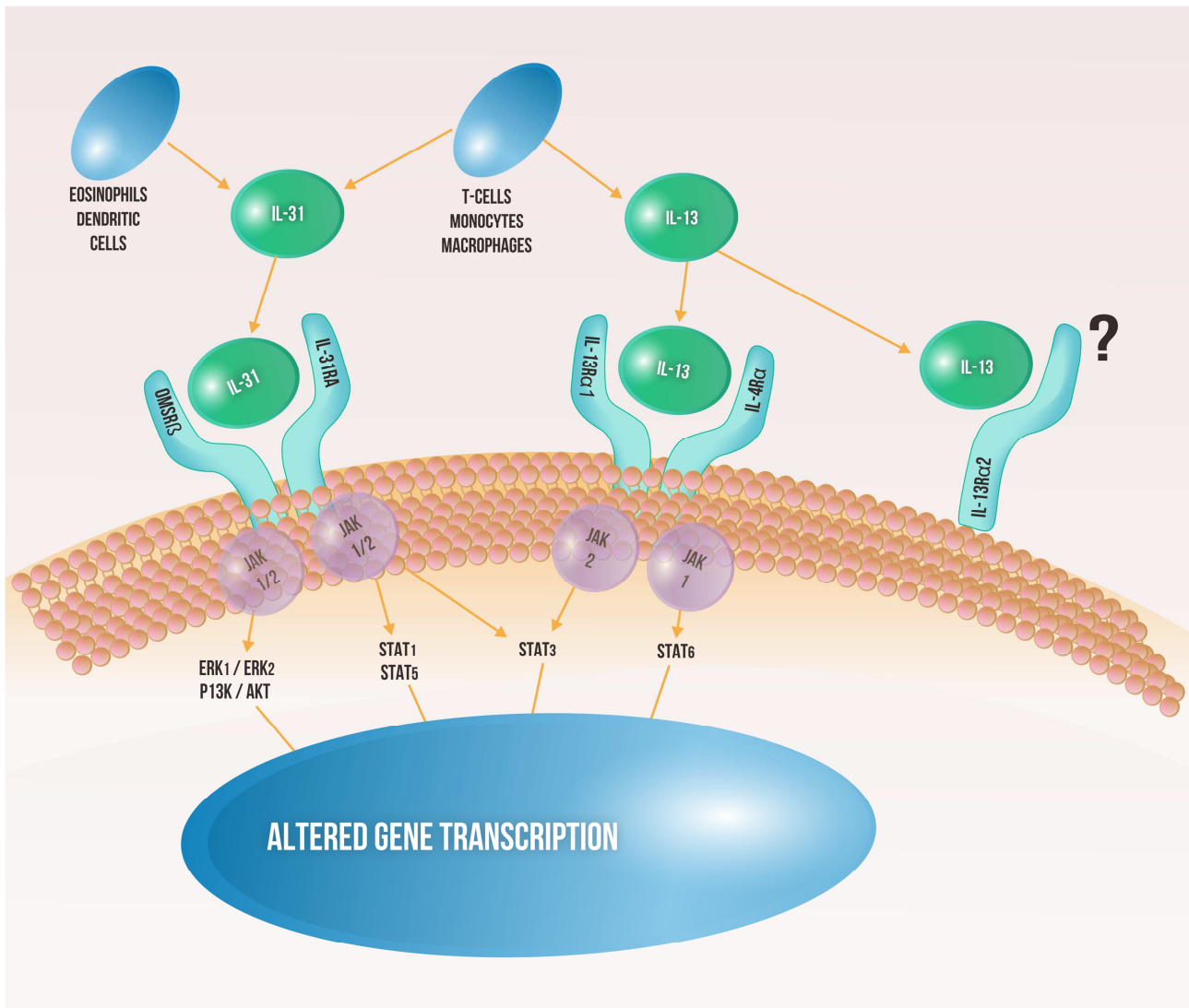
217 ³⁰

218 Conclusions

219 The IL-13 and IL-31 cytokines and pathways have been identified as important for AD
220 pathobiology. Initial clinical trials for tralokinumab , lebrikizumab, and nemolizumab all
221 show promise and in the future these medications will likely play a role in the treatment of
222 moderate to severe AD, especially when other more cost-effective treatments fail. Exactly
223 where they will fit in in the growing AD armamentarium is unclear. More research is
224 needed both into these medications' safety and efficacy but also how they differ from other
225 new biologics in development for AD patients.

226 Figure Legend:

227 Figure 1: IL-31 and IL-13 signaling pathways



228

229

230

231 Table 1: Monoclonal antibodies against IL-13 and IL-31RA in development

Trade name	Target	Trial	Patient population	Results	Reported adverse events	Studied for use in other diseases
Tralokinumab	IL-13	Placebo-controlled 12-week phase 2B trial ⁷	204 patients with moderate-to-severe AD	Significant reductions in EASI scores, increased % of patients achieving a IGA of 0-1, decreased pruritus	Nasopharyngitis, upper respiratory tract infection, headache, exacerbation of AD	Asthma, idiopathic pulmonary fibrosis, ulcerative colitis, alopecia areata
Lebrikizumab	IL-13	Placebo-controlled 12-week phase 2B trial (TREBLE) ¹⁰	209 patients with moderate-to-severe AD	Significant reductions in EASI and SCORAD scores	Injection site reactions, herpes zoster infections, conjunctivitis	Asthma, nasal polyposis, idiopathic pulmonary fibrosis, Chronic obstructive pulmonary disease
Nemolizumab	IL-31RA	Placebo controlled 12-week phase 2 trial ²⁵	264 patients with moderate-to-severe AD	Significant reductions in pruritus and EASI scores, improvement in DLQI and sleep quality	AD exacerbation, nasopharyngitis, increased creatinine kinase levels, upper respiratory tract infection, peripheral edema	None
BMS-981164	IL-31	Placebo controlled, 16 week phase 1 trial ²⁷	Healthy subjects and patients with moderate-to-severe AD	Not published	Not published	None

Reference List

1. McCormick SM, Heller NM. Commentary: IL-4 and IL-13 receptors and signaling. *Cytokine*. 2015;75(1):38-50.
2. Matsunaga MC, Yamauchi PS. IL-4 and IL-13 Inhibition in Atopic Dermatitis. *J Drugs Dermatol*. 2016;15(8):925-929.
3. Popovic B, Breed J, Rees DG, et al. Structural Characterisation Reveals Mechanism of IL-13-Neutralising Monoclonal Antibody Tralokinumab as Inhibition of Binding to IL-13Ralpha1 and IL-13Ralpha2. *Journal of molecular biology*. 2017;429(2):208-219.
4. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol*. 2009;124(3 Suppl 2):R7-r12.
5. Kim BE, Leung DY, Boguniewicz M, Howell MD. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin Immunol*. 2008;126(3):332-337.
6. Brightling CE, Chanez P, Leigh R, et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *The Lancet. Respiratory medicine*. 2015;3(9):692-701.
7. Wollenberg A, Howell MD, Guttman-Yassky E, et al. A phase 2b dose-ranging efficacy and safety study of tralokinumab in adult patients with moderate to severe atopic dermatitis (AD). *Journal of the American Academy of Dermatology*. 2017;76(6, Supplement 1):AB20.
8. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med*. 2016;375(24):2335-2348.
9. Silverberg JI, Kantor R. The Role of Interleukins 4 and/or 13 in the Pathophysiology and Treatment of Atopic Dermatitis. *Dermatol Clin*. 2017;35(3):327-334.
10. Simpson E, Flohr C, Eichenfield L. Efficacy and safety of lebrikizumab in patients with atopic dermatitis: a Phase II randomized, controlled trial (TREBLE). Paper presented at: 25th European Academy of Dermatology and Venerology Congress 2016.
11. Simpson EL. Abstract D3T01.1F. Paper presented at: European Academy of Dermatology and Venereology; September 27, 2017, 2016; Vienna.
12. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *The Lancet. Respiratory medicine*. 2016;4(10):781-796.
13. AstraZeneca provides update on STRATOS 1 Phase III trial of tralokinumab in severe, uncontrolled asthma [press release]. 2017.
14. Zhang Q, Putheti P, Zhou Q, Liu Q, Gao W. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine & growth factor reviews*. 2008;19(5-6):347-356.
15. Saleem MD, Oussedik E, D'Amber V, Feldman SR. Interleukin-31 pathway and its role in atopic dermatitis: a systematic review. *J Dermatolog Treat*. 2017:1-9.
16. Dillon SR, Sprecher C, Hammond A, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol*. 2004;5(7):752-760.
17. Bilsborough J, Leung DY, Maurer M, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2006;117(2):418-425.
18. Chattopadhyay S, Tracy E, Liang P, Robledo O, Rose-John S, Baumann H. Interleukin-31 and oncostatin-M mediate distinct signaling reactions and response patterns in lung epithelial cells. *J Biol Chem*. 2007;282(5):3014-3026.

19. Hermanns HM. Oncostatin M and interleukin-31: Cytokines, receptors, signal transduction and physiology. *Cytokine Growth Factor Rev.* 2015;26(5):545-558.
20. Raap U, Weissmantel S, Gehring M, Eisenberg AM, Kapp A, Folster-Holst R. IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis. *Pediatr Allergy Immunol.* 2012;23(3):285-288.
21. Neis MM, Peters B, Dreuw A, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. *J Allergy Clin Immunol.* 2006;118(4):930-937.
22. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol.* 2006;117(2):411-417.
23. Szegeedi K, Kremer AE, Kezic S, et al. Increased frequencies of IL-31-producing T cells are found in chronic atopic dermatitis skin. *Exp Dermatol.* 2012;21(6):431-436.
24. Nemoto O, Furue M, Nakagawa H, et al. 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. *Br J Dermatol.* 2016;174(2):296-304.
25. Ruzicka T, Hanifin JM, Furue M, et al. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. *N Engl J Med.* 2017;376(9):826-835.
26. Egeberg A, Thyssen JP, Wu JJ. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. *N Engl J Med.* 2017;376(21):2092-2093.
27. A Two-Part, Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose-Escalation Study of Subcutaneous and Intravenous Administration of IL-31 mAb (Anti-Interleukin 31 Monoclonal Antibody; BMS-981164) in Healthy Subjects and Adult Subjects With Atopic Dermatitis. Bristol-Myers Squibb; 2015.
28. Dambacher J, Beigel F, Seiderer J, et al. Interleukin 31 mediates MAP kinase and STAT1/3 activation in intestinal epithelial cells and its expression is upregulated in inflammatory bowel disease. *Gut.* 2007;56(9):1257-1265.
29. Lei Z, Liu G, Huang Q, et al. SCF and IL-31 rather than IL-17 and BAFF are potential indicators in patients with allergic asthma. *Allergy.* 2008;63(3):327-332.
30. Ferretti E, Corcione A, Pistoia V. The IL-31/IL-31 receptor axis: general features and role in tumor microenvironment. *Journal of leukocyte biology.* 2017;102(3):711-717.