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ORIGINAL ARTICLE

Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus

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Atopic Dermatitis Pathogenesis

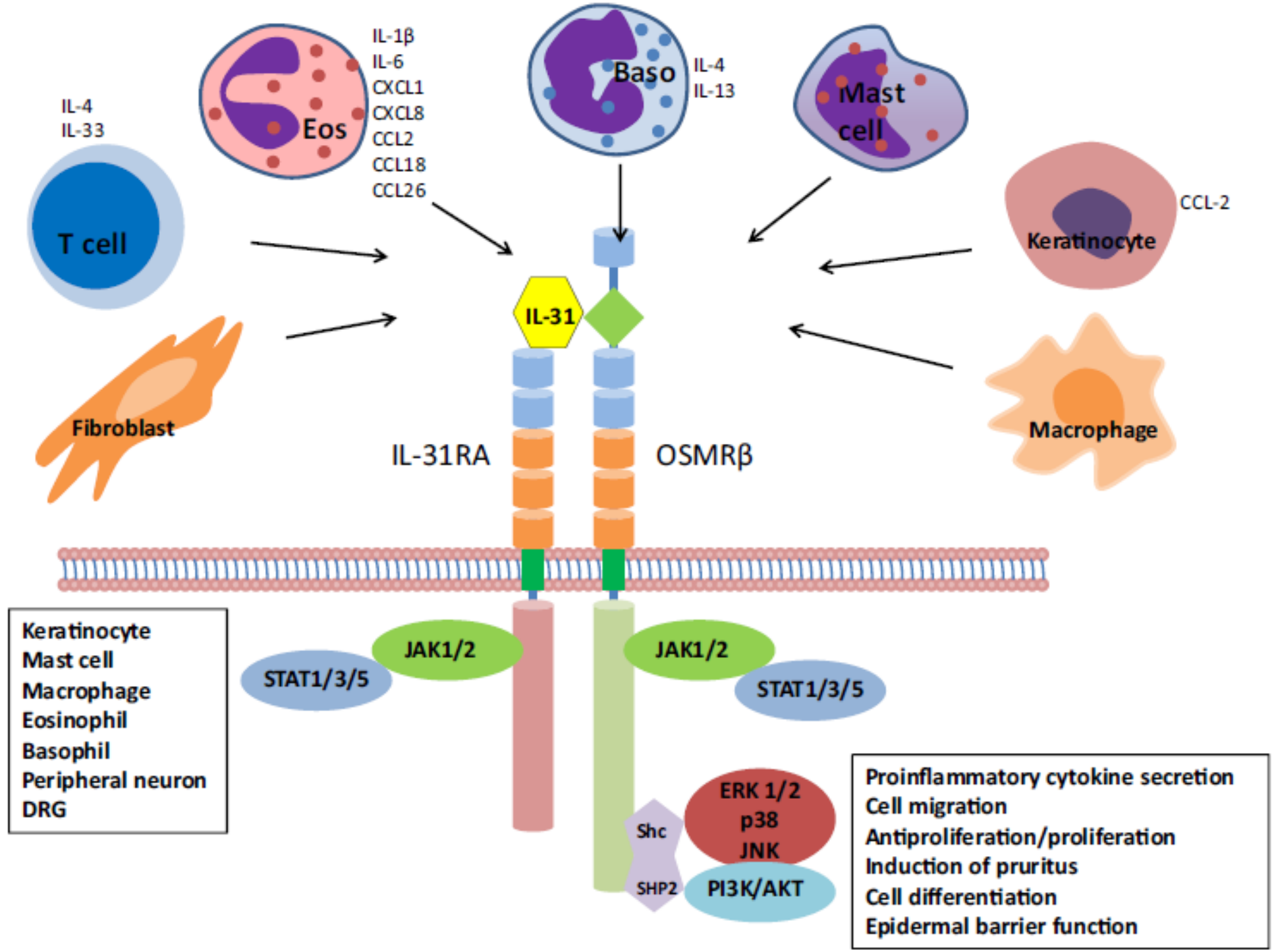
- Disrupted epidermal barrier with dysfunction of epidermal differentiation, keratinocyte junctions, and the lipid barrier in lesions skin – seen across all age groups
- Th2/Th22 cell phenotype
- Th2/Th22 correlates with SCORAD (SCORing Atopic Dermatitis)

Interleukin-31

- Pruritogenienic cytokine, perpetuates itch-scratch cycle
- Epidermal terminal differentiation disruption
- Higher expression noted in $CD4^+$ Th2 cells and by skin-homing CD45RO1 (memory) cutaneous lymphocyte–associated antigen-positive T cells
- Lower levels of IL-31 expression seen in Th1 cells
- Binds to IL-31RA and oncostatin M receptor β (OSMRβ) complex
- IL-4 and Il-33 synergize to to produce IL-31 through Th2 dependent signaling
- UVB rays, H_2O_2, and staphylococcal enterotoxin B, and antimicrobial peptides have been shown to increase IL-31 levels

IL-31RA

- Most abundantly expressed in dorsal root ganglia
- OSMRβ expression was demonstrated in a subset of small-sized nociceptive neurons in the dorsal root ganglia colocalized with IL-31RA $\longrightarrow$ project to the inner portion of lamina II in the dorsal horn of the spinal cord and the dermis of the skin
- Signaling occurs through the JAK/STAT pathway


IL-4
IL-33
T cell
Eos
IL-1β
IL-6
CXCL1
CXCL8
CCL2
CCL18
CCL26
Baso
IL-4
IL-13
Mast cell
Keratinocyte
CCL-2
Fibroblast
IL-31
Macrophage
IL-31RA
OSMRβ
Keratinocyte
Mast cell
Macrophage
Eosinophil
Basophil
Peripheral neuron
DRG
JAK1/2
STAT1/3/5
JAK1/2
STAT1/3/5
Shc
SHP2
ERK 1/2
p38
JNK
PI3K/AKT
Proinflammatory cytokine secretion
Cell migration
Antiproliferation/proliferation
Induction of pruritus
Cell differentiation
Epidermal barrier function

Study Design

- Phase 3, randomized, double-blind, parallel group
- Nemolizumab (humanized monoclonal anti-IL-31RA antibody) vs placebo every 4 weeks subcutaneously for 16 weeks
- Optional 52 week open-label study
- Patients recorded the visual analog score (VAS), ranging from 0-100, daily; weekly mean scores were averaged using daily scores
- Primary endpoint: percent change in the weekly mean VAS score for pruritus from baseline to week 16

Statistical Analysis

- Modified intention-to-treat methods were used for the analyses of the primary and secondary end points
- All patients who received at least one dose of nemolizumab or placebo were analyzed
- Two prespecified sensitivity analyses were performed for the primary end point to account for missing data and the use of rescue medication:
  - Tipping-point analysis that used the multiple-imputation method
  - Mixed-effects model was used for repeated measures (MMRM) to calculate the weekly mean VAS score for pruritus

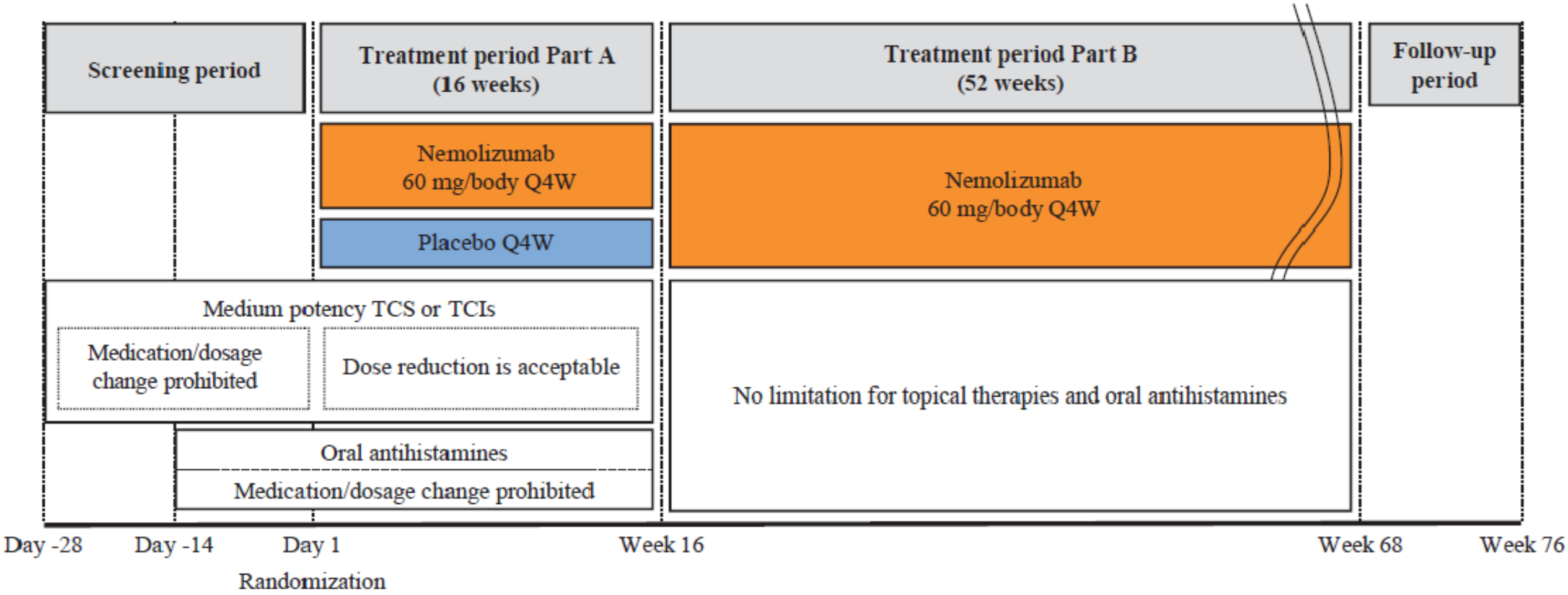
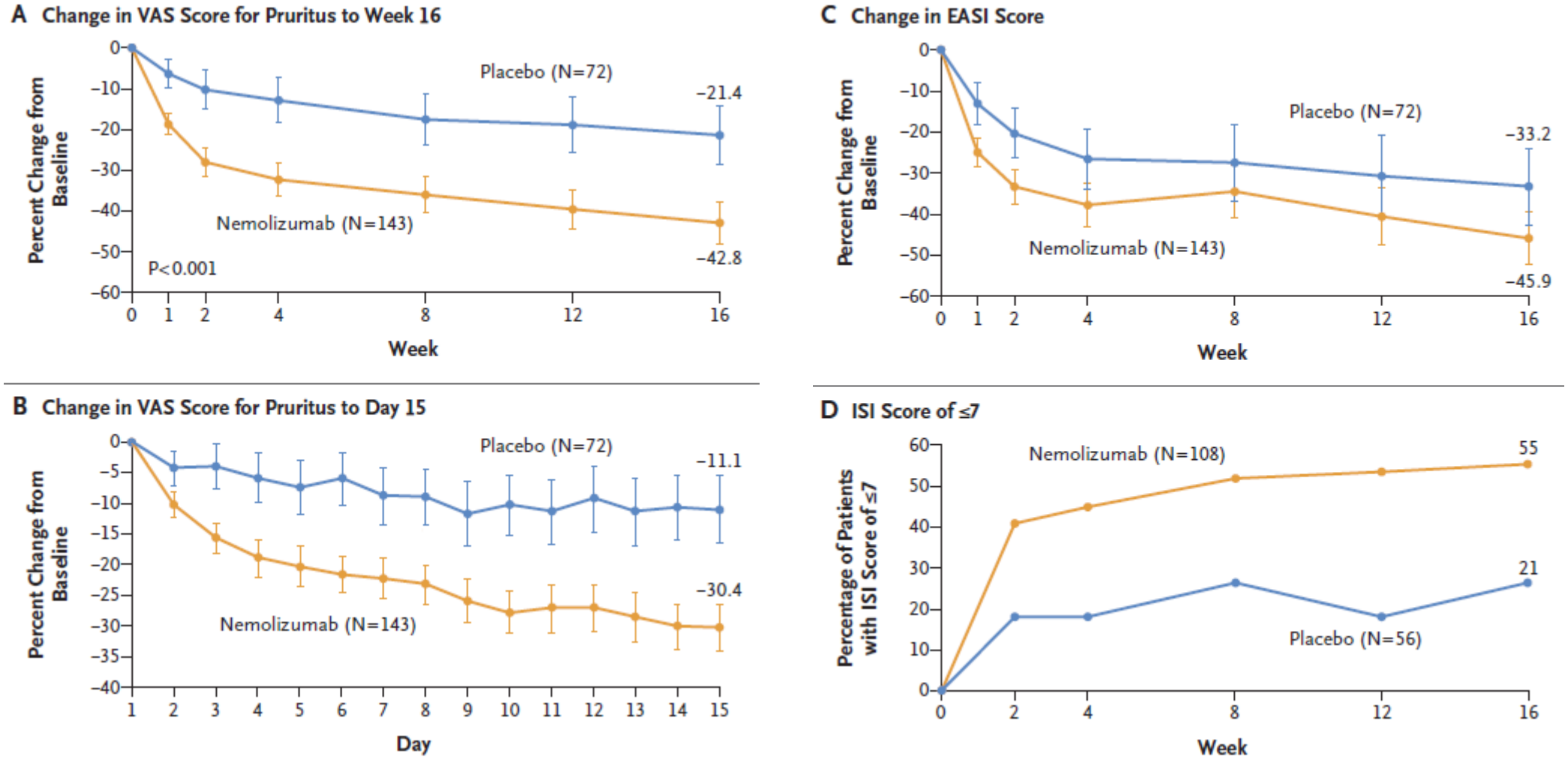

Screening period
Treatment period Part A
(16 weeks)
Treatment period Part B
(52 weeks)
Follow-up
period
Nemolizumab
60 mg/body Q4W
Placebo Q4W
Nemolizumab
60 mg/body Q4W
Medium potency TCS or TCIs
Medication/dosage
change prohibited
Dose reduction is acceptable
No limitation for topical therapies and oral antihistamines
Oral antihistamines
Medication/dosage change prohibited
Day -28
Day -14
Day 1
Randomization
Week 16
Week 68
Week 76

Table 1. Baseline Demographic and Clinical Characteristics (Modified Intention-to-Treat Population).*

Characteristic	Nemolizumab (N=143)	Placebo (N=72)
Male sex — no. (%)	93 (65)	48 (67)
Median age (range) — yr	39.0 (13–73)	40.5 (13–80)
Median duration of disease (range) — yr	30.3 (1.1–61.3)	28.9 (1.3–59.9)
Median VAS score for pruritus (range)†	75.7 (49.7–100.0)	75.1 (53.3–100.0)
Median score on five-level itch scale (range)‡	3.0 (2–4)	3.0 (2–4)
Median EASI score (range)§	24.2 (10–65)	22.7 (10–58)
sIGA score — no. (%)¶		
0–3	82 (57)	45 (62)
≥4	61 (43)	27 (38)
DLQI score‖		
No. of patients with available data	136	69
Median (range)	12.0 (2–26)	12.0 (2–30)
ISI score**		
No. of patients with available data	142	72
Median (range)	12.0 (2–28)	12.0 (1–28)
POEM score††		
No. of patients with available data	142	72
Median (range)	22.0 (5–28)	20.5 (8–28)
Median no. of pruriginous lesions and papules (range)‡‡	8.0 (0–270)	11.0 (0–400)
Baseline treatment — no. (%)		
Topical therapy§§	143 (100)	72 (100)
Medium-potency topical glucocorticoid	139 (97)	70 (97)
Topical calcineurin inhibitor	59 (41)	29 (40)
Oral antihistamines§§	127 (89)	63 (88)
Nonsedating	126 (88)	61 (85)
Sedating	17 (12)	11 (15)

Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Nemolizumab (N=143)	Placebo (N=72)	Difference (95% CI)
			percentage points
Primary end point: percent change in pruritus VAS score from baseline to wk 16	−42.8±2.6	−21.4±3.6	−21.5 (−30.2 to −12.7)†
Secondary end points‡			
Percent change in pruritus VAS score from baseline to day 29	−34.4±2.2	−15.3±3.0	−19.3 (−26.6 to −11.9)
Percent change in EASI score from baseline to wk 16	−45.9±3.3	−33.2±4.7	−12.6 (−24.0 to −1.3)
Percentage of patients with a DLQI score of ≤4 at wk 16 (no./total no.)§	40 (51/129)	22 (15/67)	17 (2 to 31)
Percentage of patients with a decrease of ≥4 points in the DLQI score from baseline to wk 16 (no./total no.)¶	67 (89/133)	50 (34/68)	17 (3 to 31)
Percentage of patients with an ISI score of ≤7 at wk 16 (no./total no.)‖	55 (59/108)	21 (12/56)	33 (17 to 48)


A Change in VAS Score for Pruritus to Week 16
Percent Change from Baseline
0
−10
−20
−30
−40
−50
−60
Placebo (N=72)
−21.4
Nemolizumab (N=143)
−42.8
P<0.001
0 1 2 4 8 12 16
Week
B Change in VAS Score for Pruritus to Day 15
Percent Change from Baseline
0
−5
−10
−15
−20
−25
−30
−35
−40
Placebo (N=72)
−11.1
Nemolizumab (N=143)
−30.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Day
C Change in EASI Score
Percent Change from Baseline
0
−10
−20
−30
−40
−50
−60
Placebo (N=72)
−33.2
Nemolizumab (N=143)
−45.9
0 1 2 4 8 12 16
Week
D ISI Score of ≤7
Percentage of Patients with ISI Score of ≤7
60
50
40
30
20
10
0
Nemolizumab (N=108)
55
21
Placebo (N=56)
0 2 4 8 12 16
Week

Safety

- 71% of patients reported adverse events
- Most common adverse event was worsening AD
- Elevate thymus and activation-regulated chemokine (TARC) seen only in nemolizumab group and was seen in 10 patients
- Three patients reported 4 treatment-related adverse events which included AD, alopecia, peripheral edema, and Meniere's disease
- No deaths were reported

Table 3. Adverse Events (Safety Analysis Set).*

Adverse Event	Nemolizumab (N=143)	Placebo (N=72)
	no. of patients (%)	
Any adverse event	101 (71)	51 (71)
Severe	3 (2)†	0
Moderate	32 (22)	14 (19)
Mild	90 (63)	45 (62)
Serious adverse event	3 (2)	2 (3)
Treatment modification		
Discontinuation	3 (2)	0
Dose interruption	3 (2)	2 (3)
Dose reduction	0	0
Adverse events of special interest		
Injection-related reaction	12 (8)	2 (3)
Asthma	0	0
Worsening of atopic dermatitis‡	34 (24)	15 (21)
Skin infection	10 (7)	7 (10)
Elevated creatine kinase	4 (3)	1 (1)
Musculoskeletal and connective-tissue symptoms	7 (5)	6 (8)
Death	0	0
Adverse events reported by ≥3% of patients in either group§		
Dermatitis atopic‡	33 (23)	15 (21)
Nasopharyngitis	18 (13)	11 (15)
Cytokine abnormal	10 (7)	0
Blood creatine kinase increased	5 (3)	1 (1)
Acne	2 (1)	3 (4)

Conclusions

- Nemolizumab resulted in a greater reduction in pruritus than placebo over a period of 16 weeks in patients who were not adequately controlled with oral antihistamines or topical agents
- Secondary outcomes including sleep, QoL, and eczema outcomes all trended toward improvement
- The most common adverse events were injections site reactions, worsening AD, and increased TARC

References

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- Kabashima K., Matsumura T., Komakazi H., et al. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. *NEJM*. 2020;383(2):141-50.
- Renert-Yuval Y., Del Duca E., Pavel A., et al. The molecular features of normal and atopic dermatitis skin in infants, children, adolescents, and adults. *J Allergy Clin Immunol*. 2021;148(1):148-63.