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Clinical Associate

Professor of Dermatology

Indiana University School of Medicine

Mount Sinai Medical Center, New York, NY

Physicians Skin Care, PLLC

Louisville, KY


HOTTEST AREA
… Atopic Dermatitis


GAP
GAP

I have received funding either as an investigator, consultant, or a speaker from the following pharmaceutical companies:

- Abbott
- Acambis
- Aclaris
- Allergan
- Almirall
- Amgen
- Anacor
- Anaptys
- Astellas
- Asubio
- BMS
- Berlex
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- Biolife
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- Breckenridge Pharma
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- Promius
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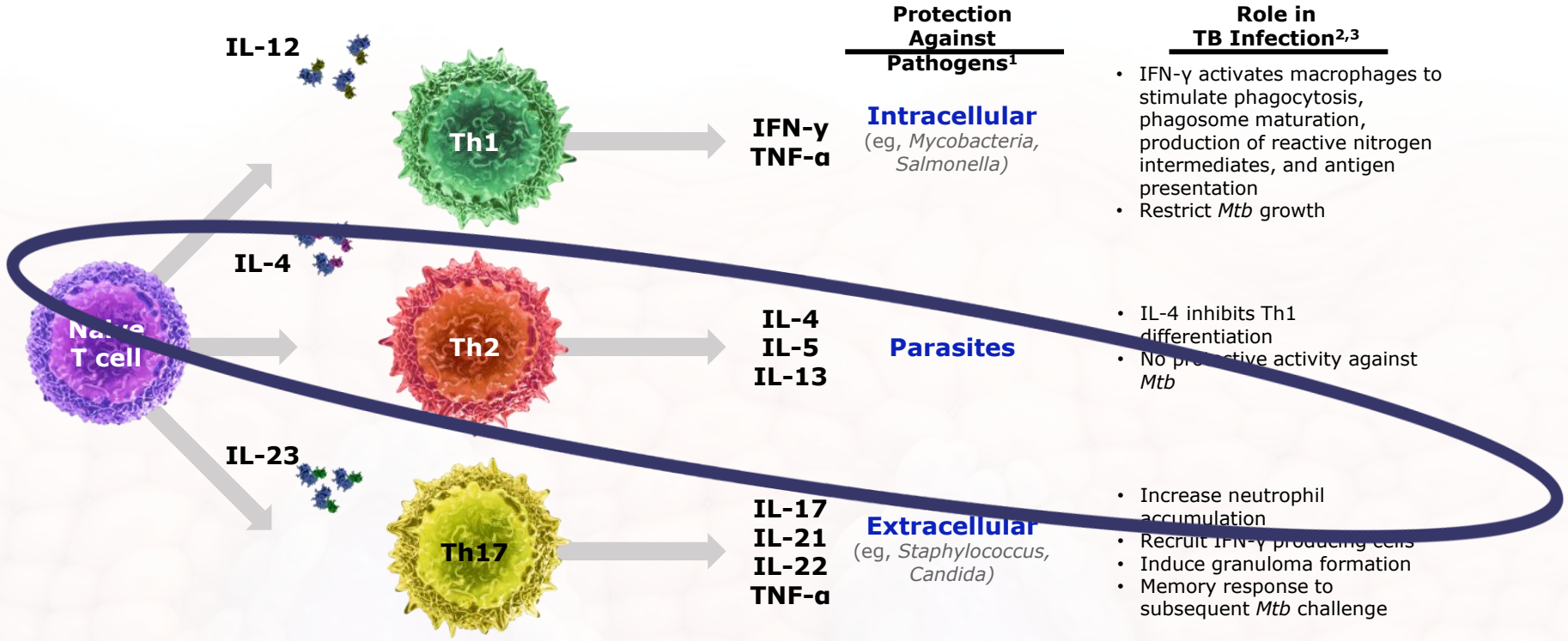
- SkinMedica
- Stiefel
- Sun Pharma
- Taro
- TolerRx
- Triax Pharmaceuticals
- UCB
- Valeant
- Warner & Chilcott
- Xenoport
- ZAGE

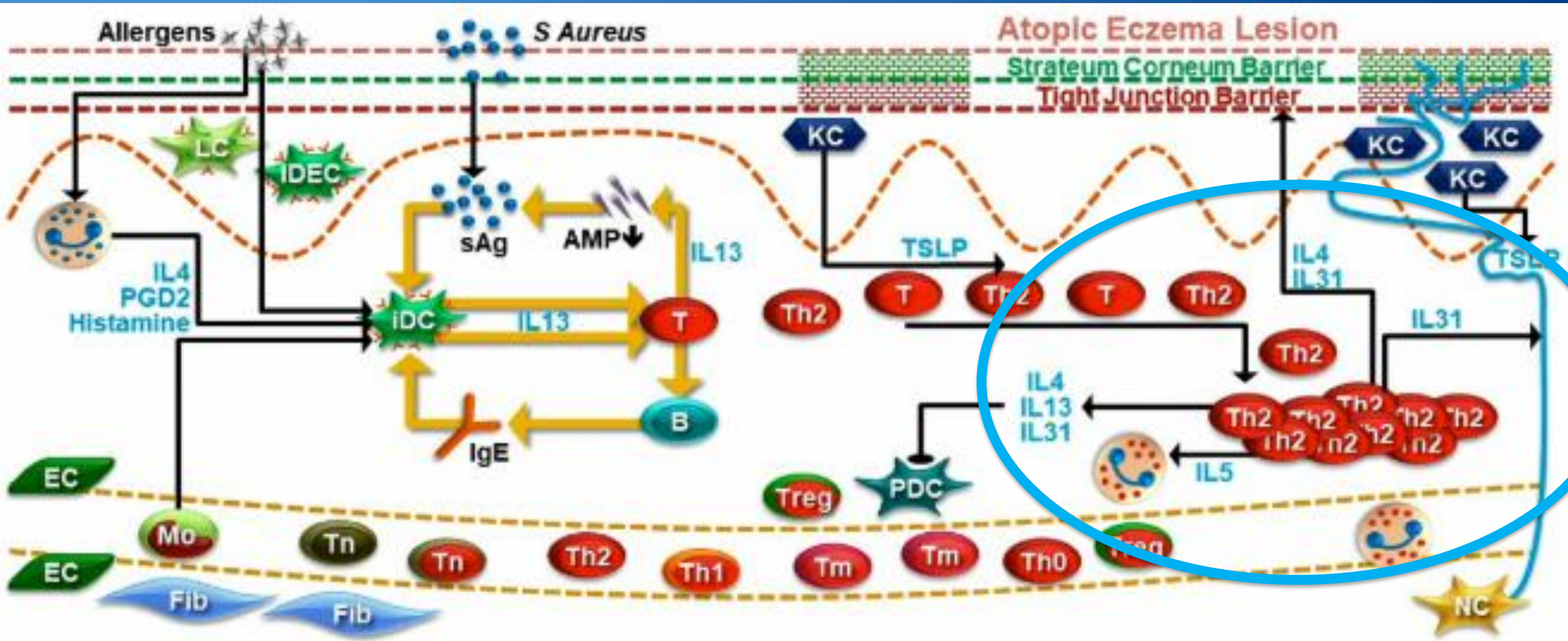
T Helper Cell Subsets



Adapted by permission from Korean Society for Biochemistry and Molecular Biology BMB Reports

Mtb, *Mycobacteria tuberculosis*.

1. van de Veerdonk FL, et al. *BMB Rep*. 2009;42:776-787. 2. da Silva MV, et al. *J Immunol Res*. 2015;639107. 3. Lyadova IV, et al. *Mediators Inflamm*. 2015;854507.


Allergens
S Aureus
Atopic Eczema Lesion
Strateum Corneum Barrier
Tight Junction Barrier
LC
IDEC
KC
KC
KC
KC
sAg
AMP
IL13
TSLP
IL4
IL31
IL4
PGD2
Histamine
iDC
IL13
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IL31
IL4
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IL5
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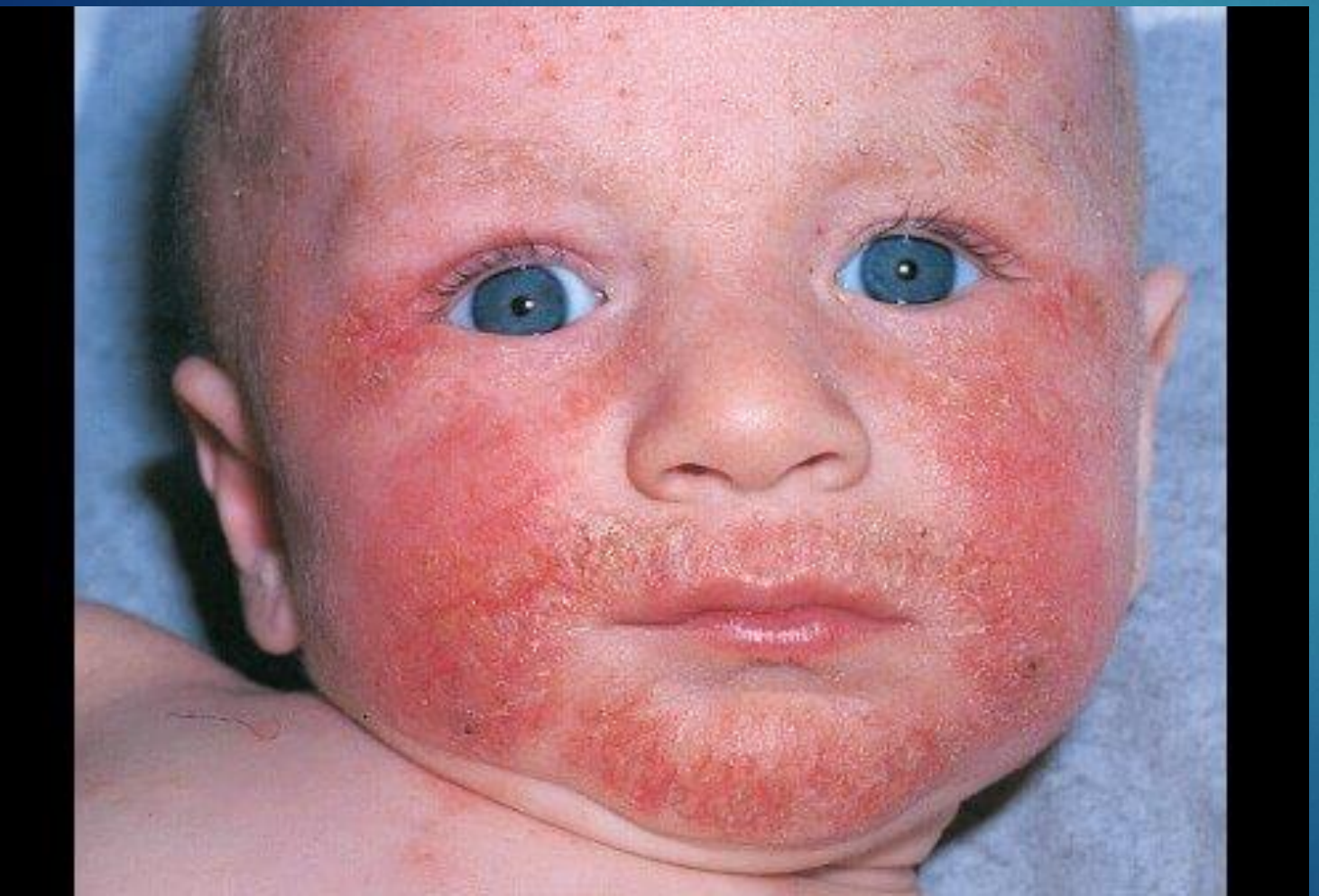
TARGETED TREATMENTS



DUPILUMAB

CONJUNCTIVITIS

Br J Dermatol. 2019 Mar 9. doi: 10.1111/bjd.17869. [Epub ahead of print]

Conjunctivitis in dupilumab clinical trials.

Akinlade B[1], Guttman-Yassky E[2], de Bruin-Weller M[3], Simpson EL[4], Blauvelt A[5], Cork MJ[6], Prens E[7], Asbell P[8], Akpek E[9], Corren J[10], Bachert C[11,12], Hirano I[13], Weyne J[1], Korotzer A[1], Chen Z[1], Hultsch T[14], Zhu X[1], Davis JD[1], Mannent L[15], Hamilton JD[1], Teper A[16], Staudinger H[16], Rizova E[14], Pirozzi G[16], Graham NMH[1], Shumel B[1], Ardeleanu M[1], Wollenberg A[17].

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14 Sanofi Genzyme, Cambridge, MA, U.S.A.
15 Sanofi R&D, Chilly-Mazarin, France.
16 Sanofi, Bridgewater, NJ, U.S.A.
17 Ludwig-Maximilian University, Munich, Germany.

What's already known about this topic?

- Ocular disorders, including allergic conjunctivitis, are common in patients with atopic dermatitis (AD).
- In most dupilumab AD trials, dupilumab-treated patients had higher conjunctivitis incidence than those receiving placebo.
- Most cases were mild to moderate and recovered or were recovering during study treatment; study treatment discontinuation due to conjunctivitis was rare.
- Conjunctivitis incidence was very low and similar for dupilumab and placebo in clinical trials in asthma, chronic rhinosinusitis with nasal polyps and eosinophilic oesophagitis.

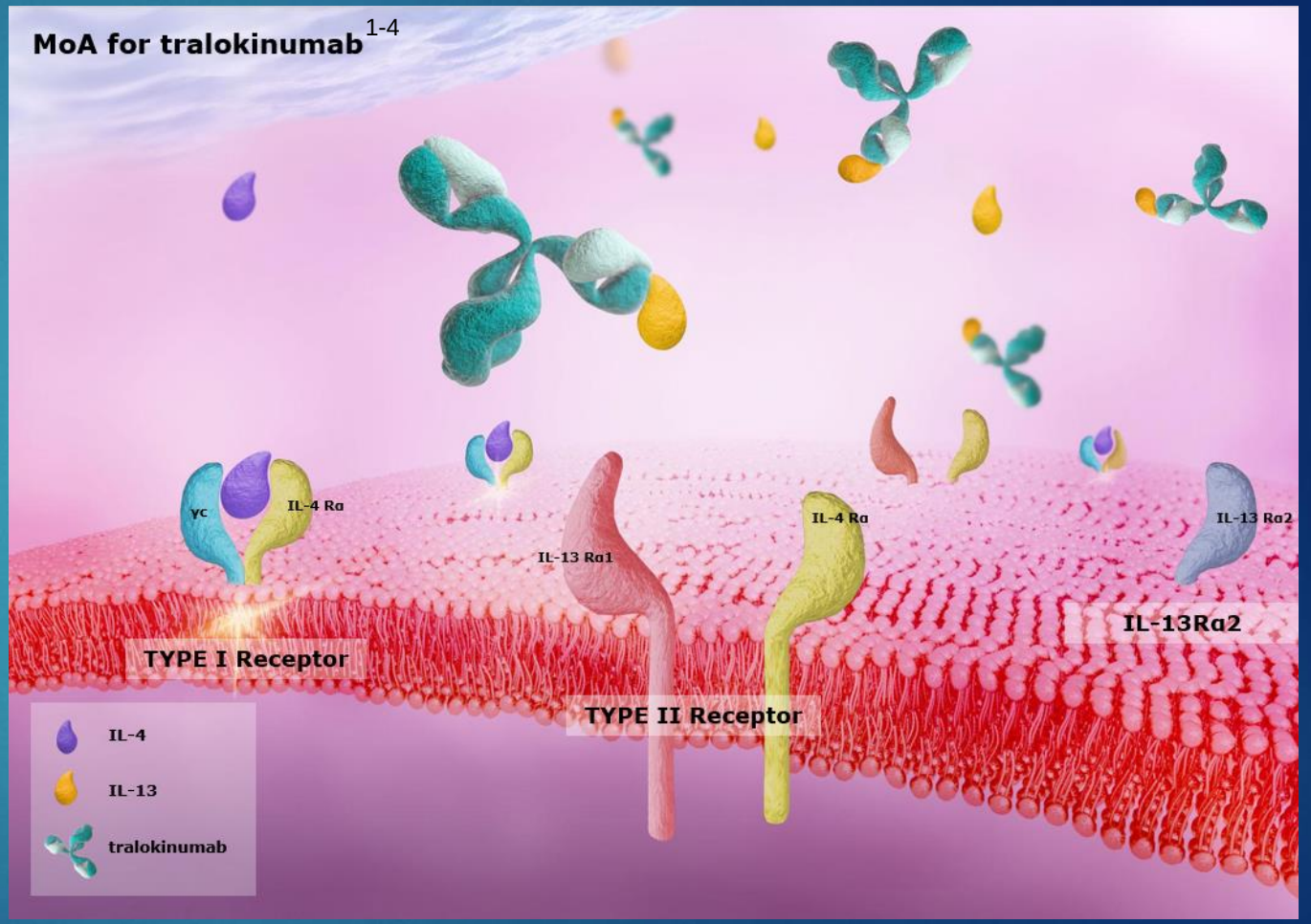
What does this study add?

- This analysis confirms and extends the results of the individual clinical trials.
- Baseline disease-related factors, including AD severity, prior conjunctivitis history and certain biomarkers (thymus and activation-regulated chemokine, IgE, eosinophils), were associated with increased incidence of conjunctivitis.
- Patients who responded well to dupilumab had reduced incidence of conjunctivitis.
- Further study is needed to elucidate the aetiology and treatment of conjunctivitis in dupilumab-treated patients with AD.


CAUTION

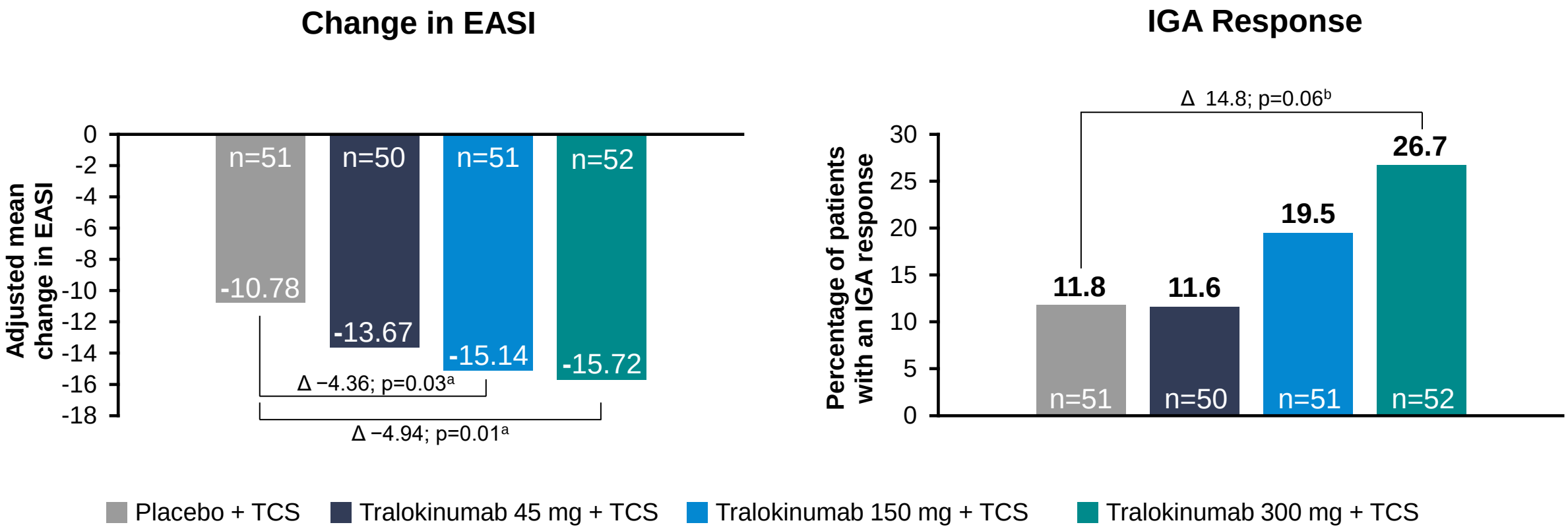
Tralokinumab

- Tralokinumab is a fully human, immunoglobulin (Ig)G4 monoclonal antibody that potently and specifically binds to and neutralizes the effects of IL-13[1]



1. POPOVIC ET AL. J MOL BIOL 2017;429:208–219; 2. MAY ET AL. BR J PHARMACOL 2012;166:177; 3. THOM ET AL. METHODS MOL BIOL 2012;805:393; 4. THOM ET AL. PNAS 2006; 103 (20):7619

Co-primary Endpoint Results



Tralokinumab improved the extent and severity of atopic dermatitis

[a]p-value for the adjusted mean difference compared with placebo; [b]p-value for the adjusted percentage difference compared with placebo

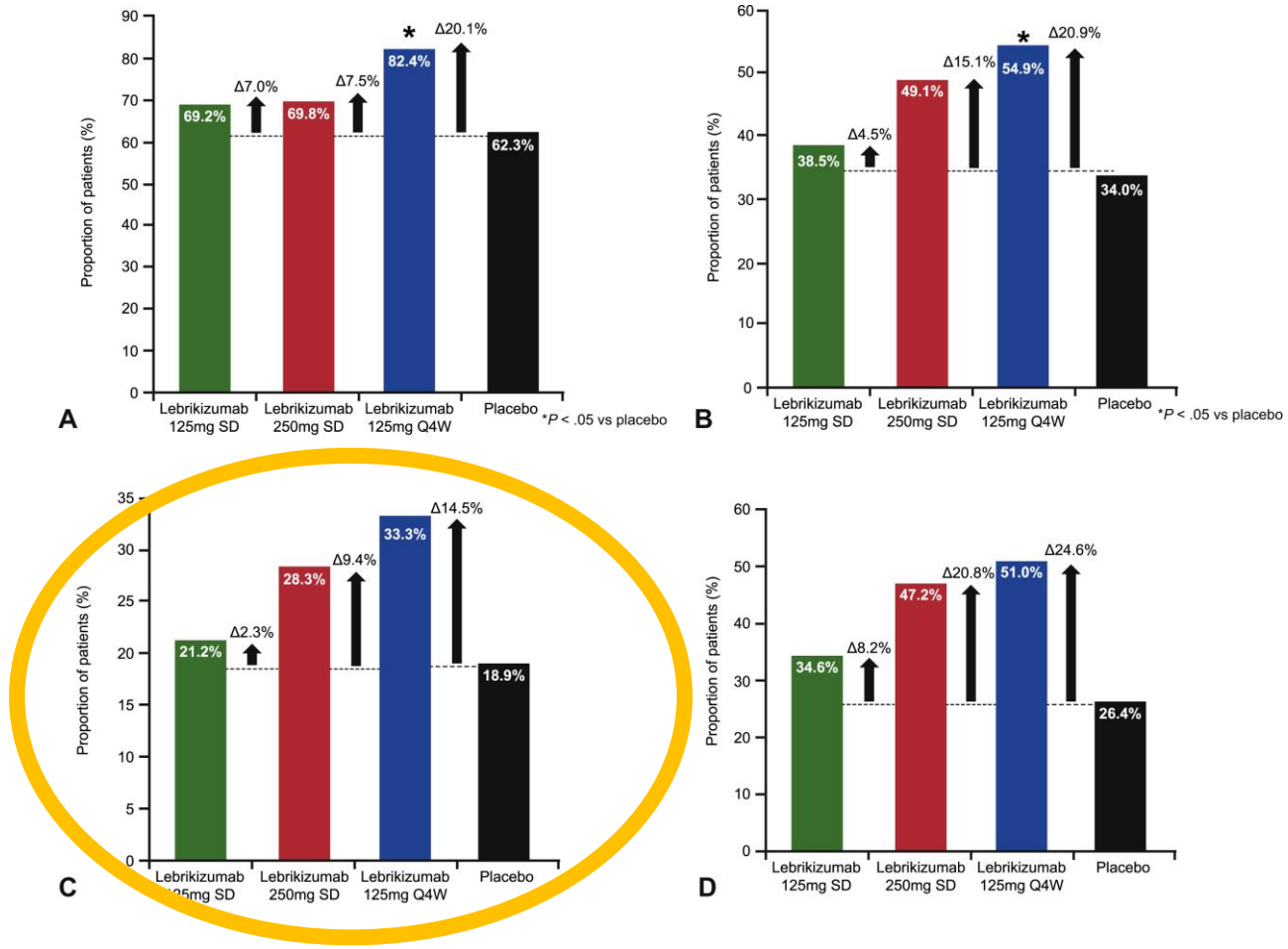
EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; TCS, topical corticosteroid

Adapted from Wollenberg et al. J Allergy Clin Immunol 2018, Article in press. DOI: 10.1016/j.jaci.2018.05.029.

Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE)

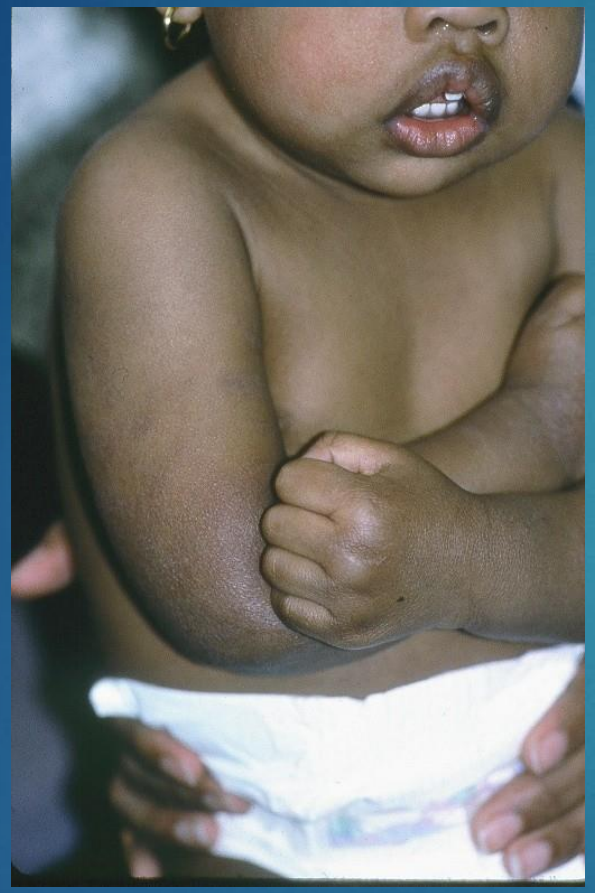
Eric L. Simpson, MD,[a] Carsten Flohr, MD, PhD,[b] Lawrence F. Eichenfield, MD,[c] Thomas Bieber, MD, PhD, MDRA,[d] Howard Sofen, MD,[e] Alain Taïeb, MD,[f] Ryan Owen, PhD,[g] Wendy Putnam, PhD,[g] Marcela Castro, MD,[g] Kendra DeBusk, PhD,[g] Chin-Yu Lin, PhD,[g] Athina Voulgari, PhD,[h] Karl Yen, MD,[i] and Theodore A. Omachi, MD[g]

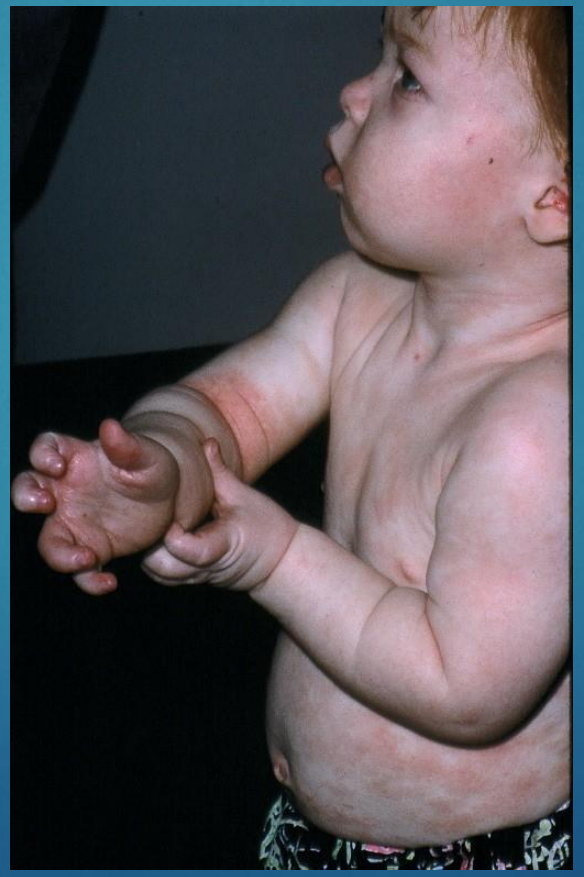
Portland, Oregon; London and Welwyn Garden City, United Kingdom; San Diego, Los Angeles, and South San Francisco, California; Bonn, Germany; Bordeaux, France; and Basel, Switzerland

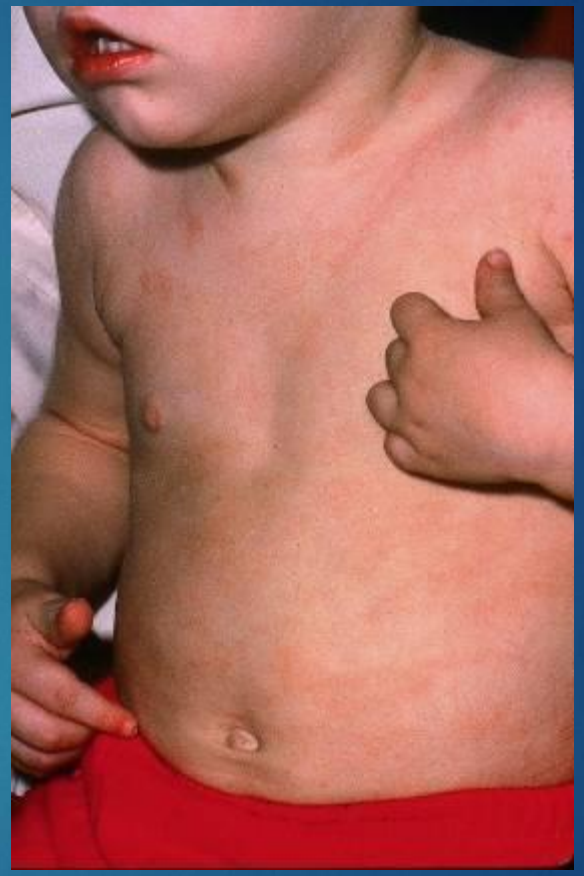


Proportion of atopic dermatitis patients achieving (A) a 50% reduction of Eczema Area and Severity Index, (B) a 75% reduction of Eczema Area and Severity Index, (C) an Investigator Global Assessment of 0 or 1, and (D) a 50% reduction of SCORing Atopic Dermatitis at week 12 of lebrikizumab treatment. Q4W, Every 4 weeks; SD, single dose.

Atopic Dermatitis
"an itch that gets a rash"








IF I DON'T SLEEP,
NOBODY SLEEPS!

NEMOLIZUMAB

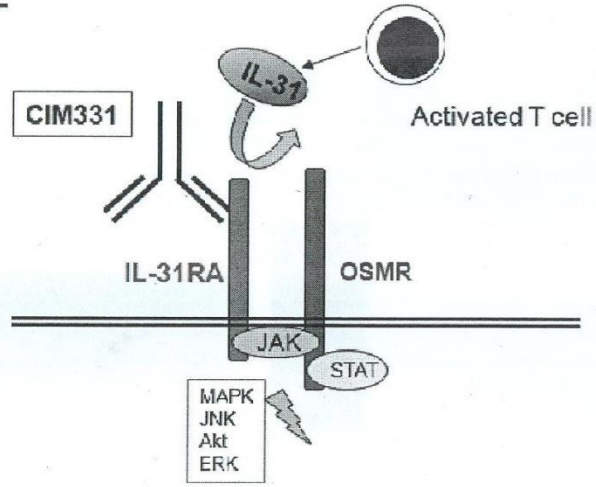
Mechanism of action of study drug

(extract from the IB) **CIM331**

- Interleukin 31 (IL-31) has been identified as a cytokine that induces pruritus, involved in the induction of pruritus in atopic dermatitis.
- CIM331, blocking the IL-31 pathway, is anticipated to become a drug that will be added to the treatment options to achieve adequate control of pruritus.

Administration route

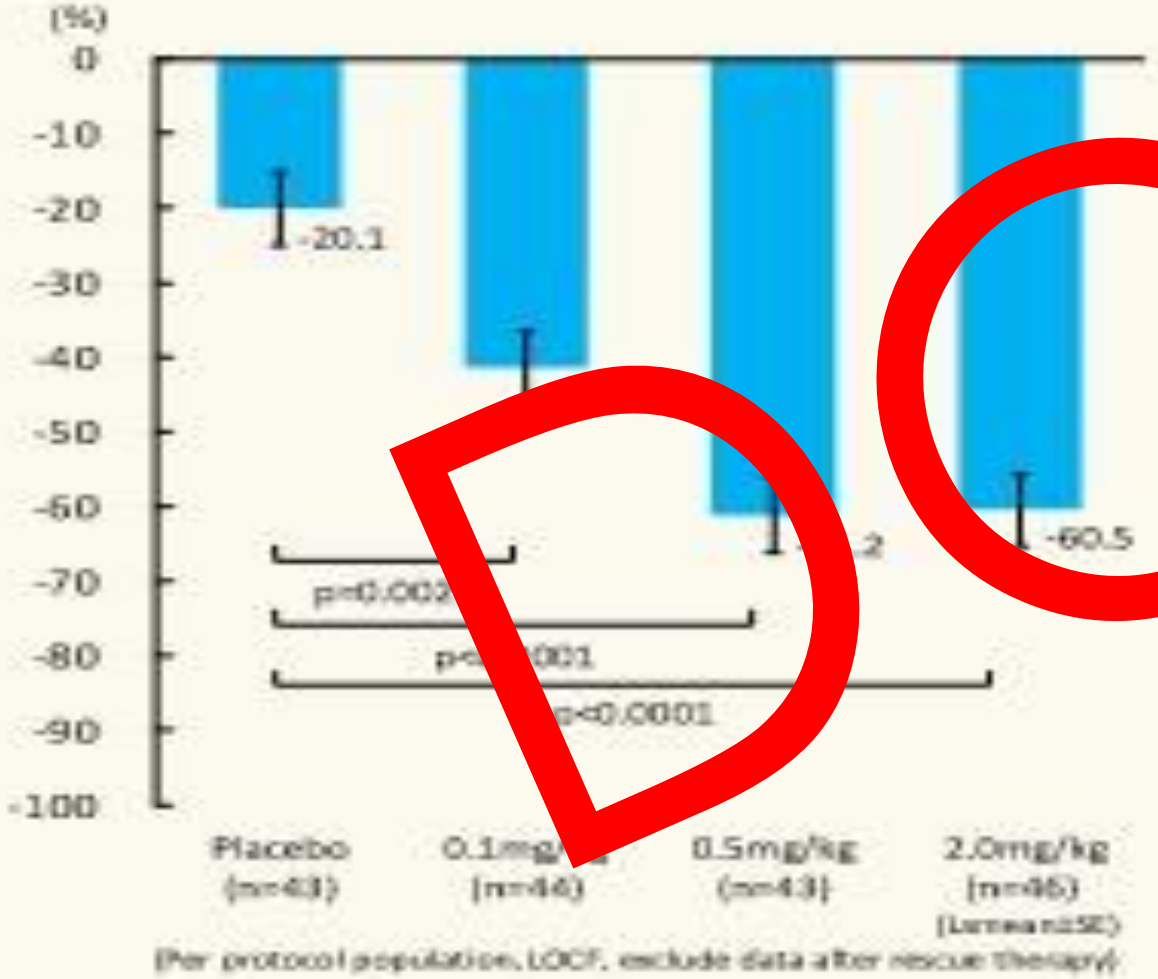
Subcutaneous



Akt – serine–threonine kinase
ERK – extracellular-signal-regulated kinases
JAK – Janus kinase
JNK – c-Jun N-terminal kinases
MAPK – mitogen activated protein kinase
OSMR – oncostatin M receptor
STAT – signal transducer and activator of transcription

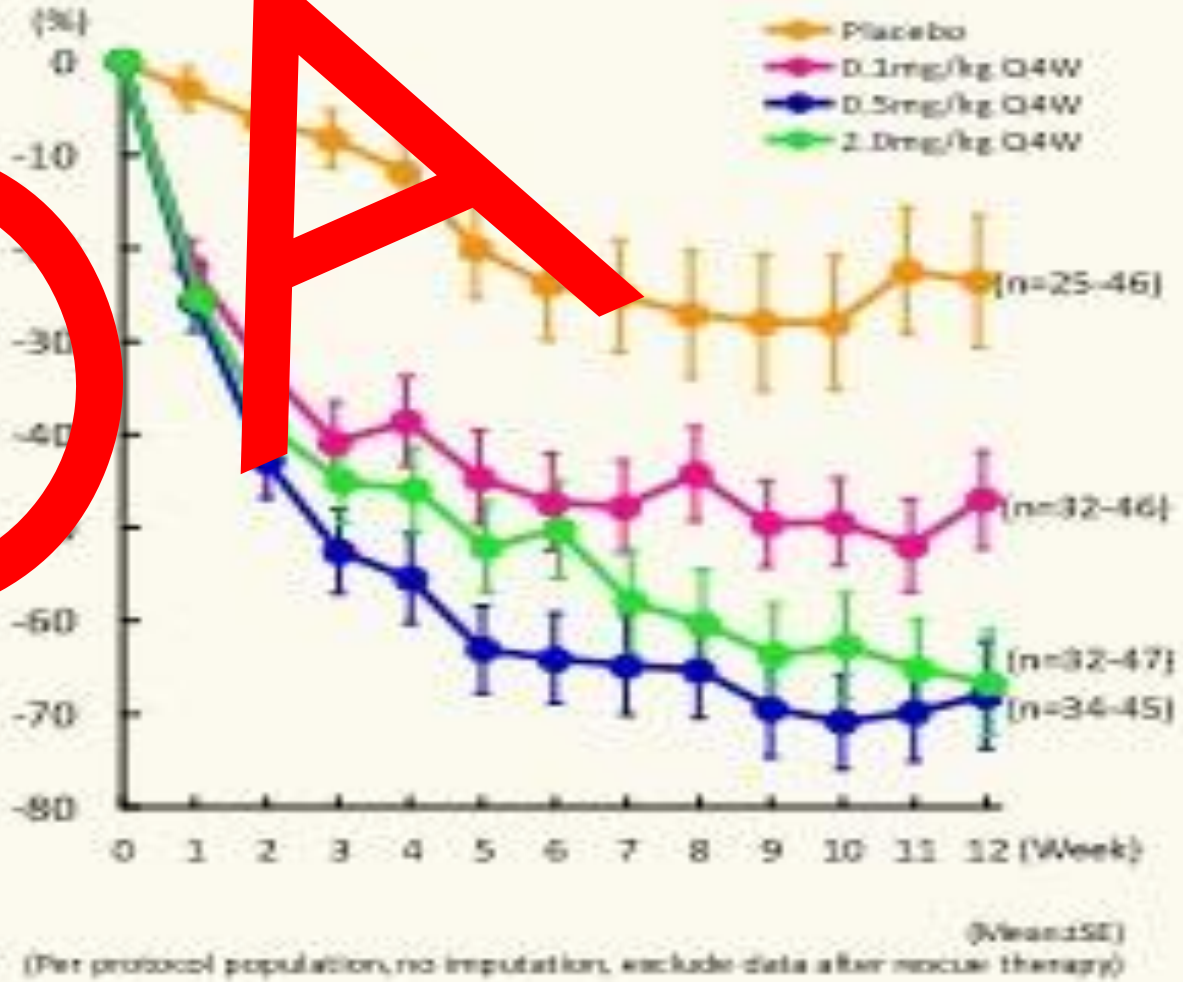
Nemolizumab reduced pruritus VAS

% Change of Pruritus VAS at Week 12



(Per protocol population, LOCF, exclude data after rescue therapy)

Time Course of % Change of Pruritus VAS



(Per protocol population, no imputation, exclude data after rescue therapy)

ANB-020 ETOKIMAB

Selective inhibitor of IL-33 which is highly expressed in the lesions of atopic dermatitis

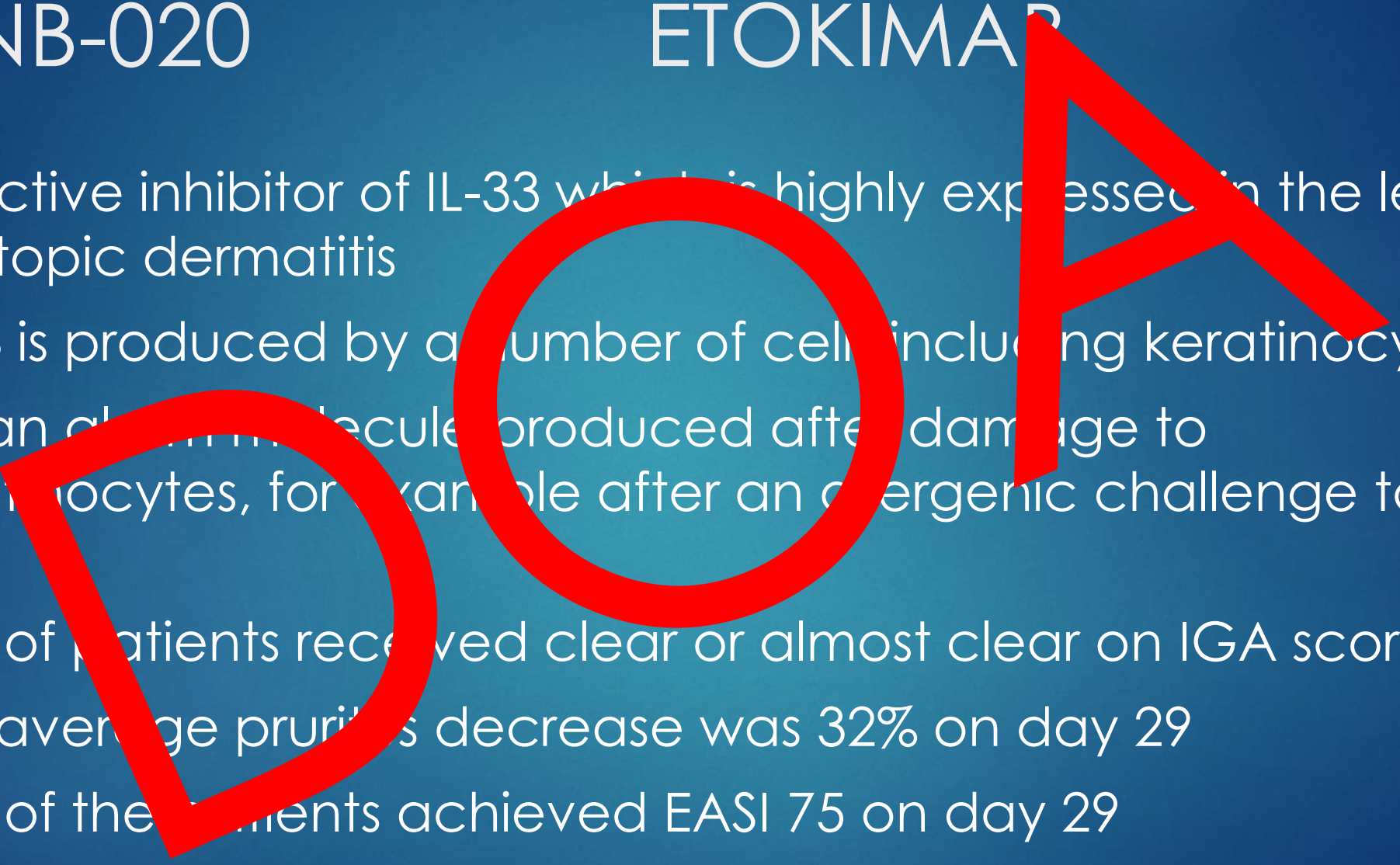
IL-33 is produced by a number of cells including keratinocytes

It is an alarmin molecule produced after damage to keratinocytes, for example after an allergenic challenge to the skin

25% of patients received clear or almost clear on IGA score

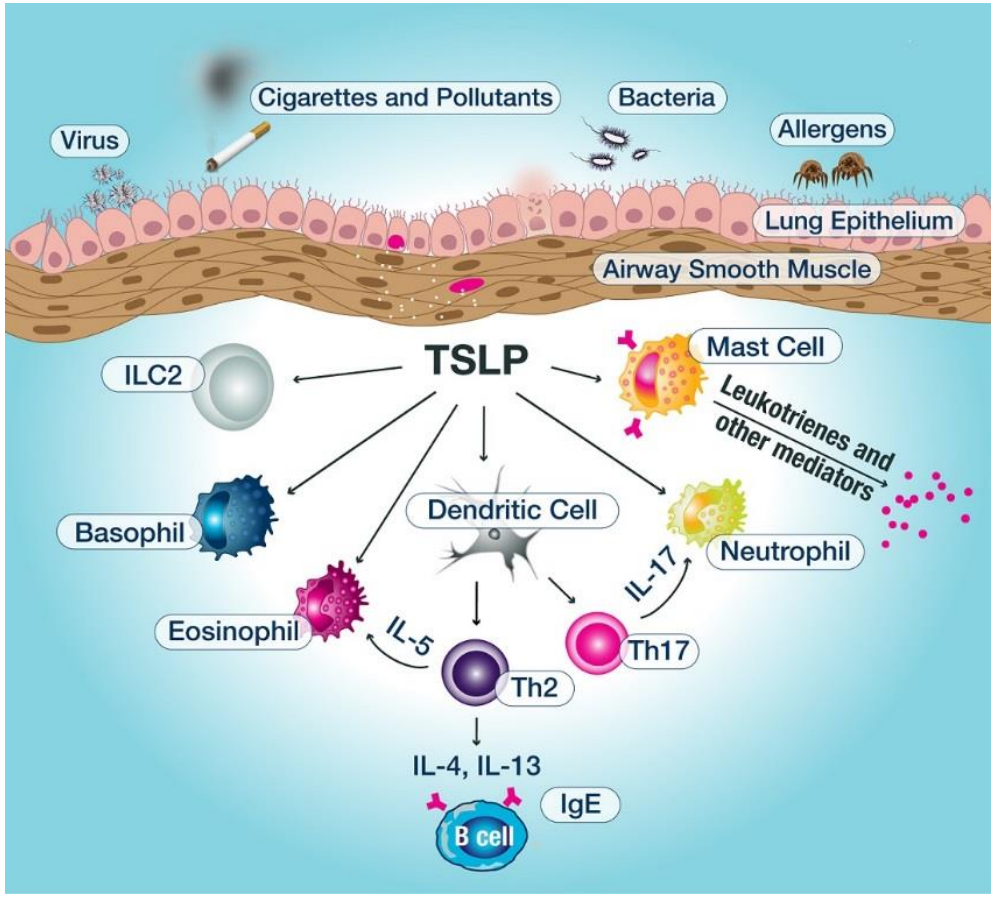
The average pruritus decrease was 32% on day 29

33% of the patients achieved EASI 75 on day 29



Thymic Stromal Lymphopoietin
TSLP: Role and Function in Allergic Inflammation

- TSLP is an epithelial-derived cytokine central to the regulation of type 2 immunity[1-4]
- TSLP expression is produced in response to proinflammatory stimuli and is increased in the airways of patients with asthma and locally in patients with atopic dermatitis, and correlates with Th2 cytokine and chemokine expression, and disease severity[1,5-7]



IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; Th, T-helper cell; TSLP, thymic stromal lymphopoietin.

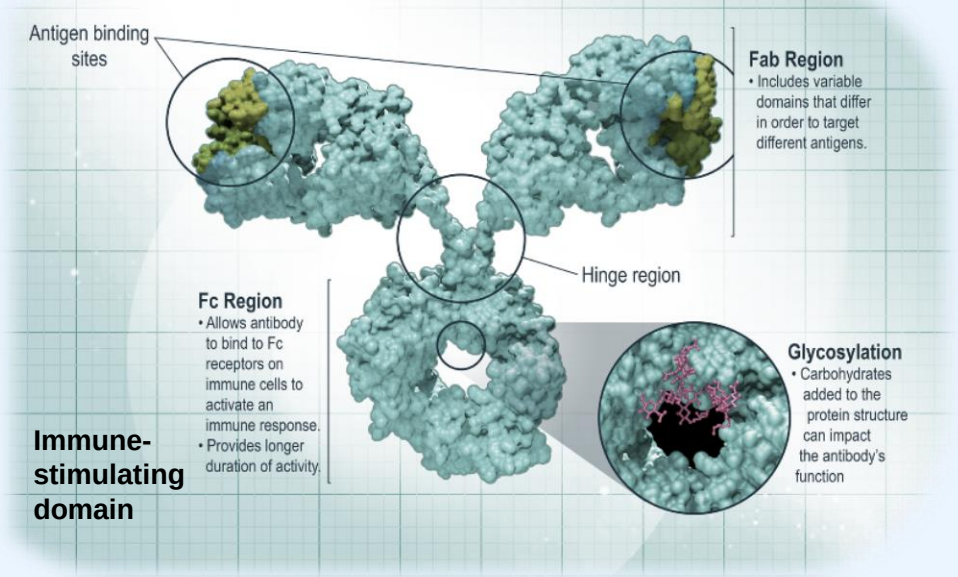
1. Ziegler SF, et al. *Nat Immunol.* 2010;11:289-293. 2. Soumelis V, et al. *Nat Immunol.* 2002;3:673-680. 3. Allakhverdi Z, et al. *J Exp Med.* 2007;204:253-258. 4. Ziegler SF, et al. *Adv Pharmacol.* 2013;66:129-155. 5. Shikotra A, et al. *J Allergy Clin Immunol.* 2012;129:104-111.e1-9. 6. Ying S, et al. *J Immunol.* 2005;174:8183-8190. 7. Ying S, et al. *J Immunol.* 2008;181:2790-2798.

Tezepelumab* (AMG 157): A Human Monoclonal Antibody That Inhibits the Action of TSLP[1]

RATIONALE & MOA

- Tezepelumab (AMG 157) is a potential first-in-class human monoclonal antibody that inhibits the action of TSLP, critical in the initiation and persistence of allergic inflammation[1]
- Blocking TSLP may prevent the release of pro-inflammatory cytokines by immune cells, resulting in the prevention of asthma exacerbations and improved asthma control[2-8]
- Due to its activity early in the inflammation cascade, tezepelumab (AMG 157) may be suitable for a broad population of asthma patients irrespective of patient phenotype or T2 biomarker status[2-8]

MODALITY



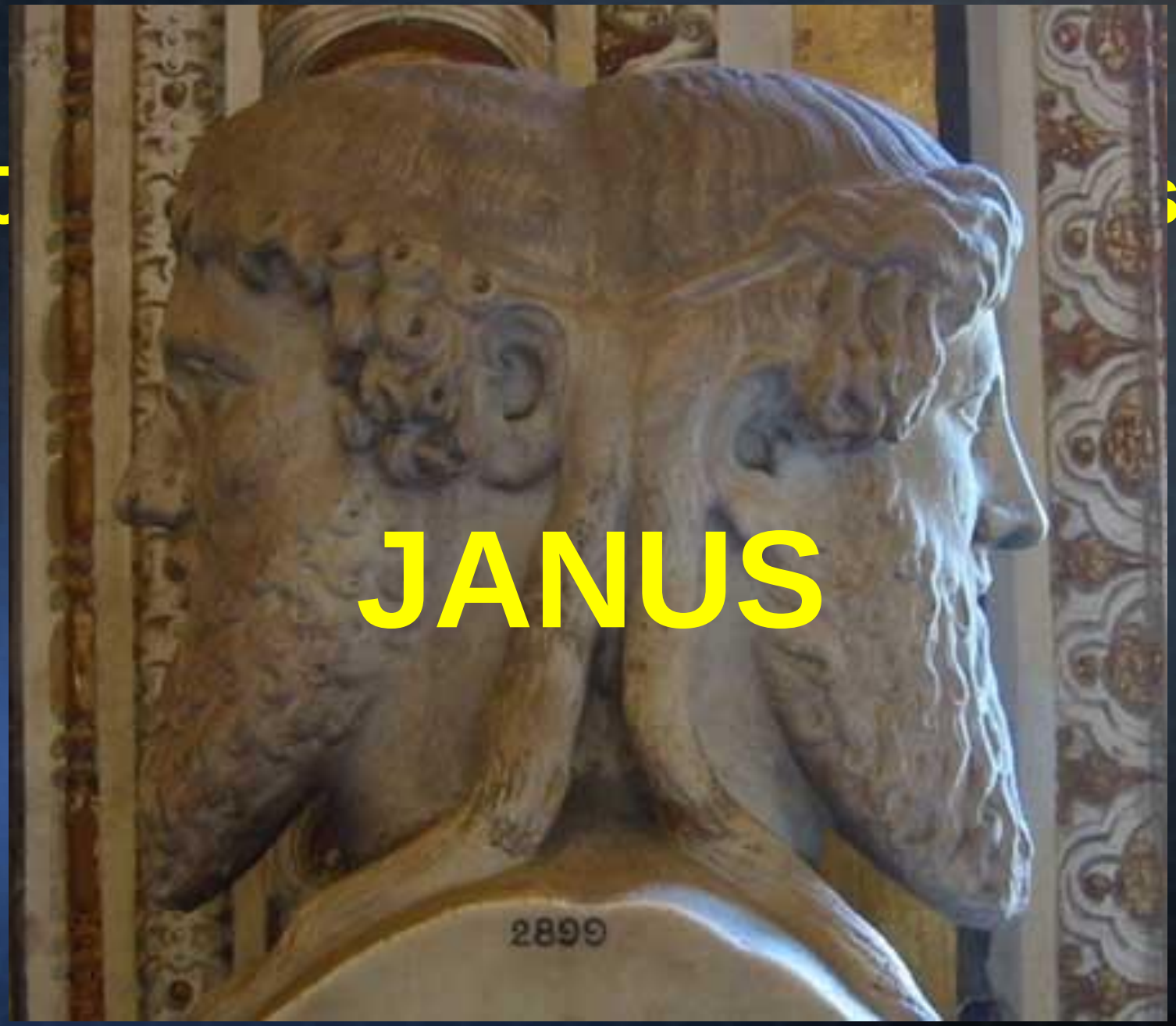
Monoclonal antibodies are potent and highly selective bioengineered molecules that are designed to target specific proteins involved in disease[9]

MOA, mechanism of action; T2, type 2; TSLP, thymic stromal lymphopoietin.

1. Gauvreau GM, et al. *N Engl J Med*. 2014;370:2102-2110. 2. Ziegler SF, et al. *Nat Immunol.* 2010;11:289-293. 3. Soumelis V, et al. *Nat Immunol.* 2002;3:673-680.
4. Allakhverdi Z, et al. *J Exp Med.* 2007;204:253-258. 5. Ziegler SF, et al. *Adv Pharmacol.* 2013;66:129-155. 6. Shikotra A, et al. *J Allergy Clin Immunol.* 2012;129:104-111.e1-9.
7. Ying S, et al. *J Immunol.* 2005;174:8183-8190. 8. Ying S, et al. *J Immunol.* 2008;181:2790-2798. 9. Amgen Science website. https://www.amgenscience.com/items/monoclonal-antibodies/. Accessed October 26, 2018.

Disclaimer: This product is investigational and is not currently licensed anywhere in the world.

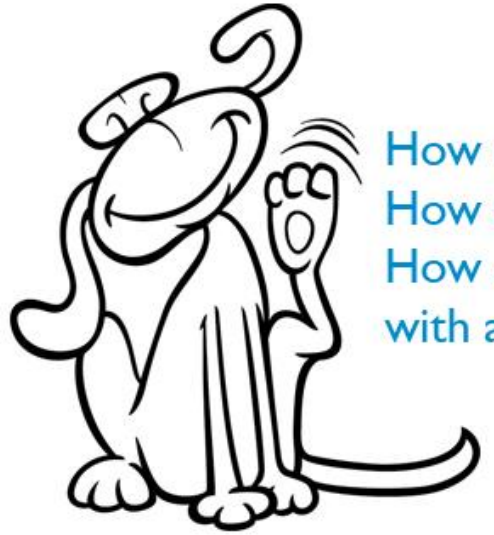
JAK/STAT Signaling Pathways


JANUS

$2.76

1-800-PetMeds

Oclacitinib for itchy dogs



How effective is it?
How safe is it?
How does it compare
with alternative treatments?

VETRx
VETERINARY PRESCRIBER

BARICITINIB

Lilly Announces Top-Line Phase 3 Results for Oral JAK Inhibitor Baricitinib, in Combination with Topical Corticosteroids in Adult Patients with Moderate to Severe Atopic Dermatitis

August 23, 2019

INDIANAPOLIS, Aug. 23, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE:LLY) and Incyte Corporation (NASDAQ:INCY) announced today tha baricitinib met the primary endpoint in BREEZE-AD7, the third pivotal Phase 3 trial in the BREEZE-AD program to be completed in 2019.

BREEZE-AD7, an investigational study evaluating the efficacy and safety of baricitinib, an oral JAK inhibitor, to treat moderate to severe atopic dermatitis (AD) in adults met its primary endpoint. Adding baricitinib to standard-of-care topical corticosteroids significantly improved disease seve measured by the validated Investigator's Global Assessment for AD (vIGA) score of "clear or almost clear" skin (vIGA 0, 1), the primary endpoint o study at 16 weeks.

	Placebo (N=109)	Baricitinib 2-mg (N=109)	Baricitinib 4-mg (N=111)
vIGA of 0 or 1 at Week 16, n (%)	16 (14.7)	26 (23.9)*	34 (30.6)*
EASI75 at Week 16, n (%)	25 (22.9)	47 (43.1)**	53 (47.7)***
4-point improvement in Itch NRS at Week 16, n (%)	21 (20.2)	37 (38.1)**	44 (44.0)***

*NS, ** P≤0.01, and *** P≤0.001 for baricitinib compared to placebo by analysis unadjusted for multiplicity.

BREEZE-AD7, conducted outside of the United States, is the third of five placebo-controlled trials in the Phase 3 program and recruited patients fr Asia, Europe, South America and Australia.

Safety data were consistent with the known safety profile of baricitinib. The most common treatment-emergent adverse events observed were nasopharyngitis, upper respiratory tract infection and folliculitis. One pulmonary embolism was reported in the baricitinib group. One opportunistic infection was reported in the placebo group. No malignancies, major adverse cardiovascular events (MACE), or deaths were reported in the study

UPADICITINIB

Effects of Upadacitinib on Atopic Dermatitis Signs, Symptoms and Patient-Reported Outcomes from a Phase 2b Randomized, Placebo-Controlled Trial

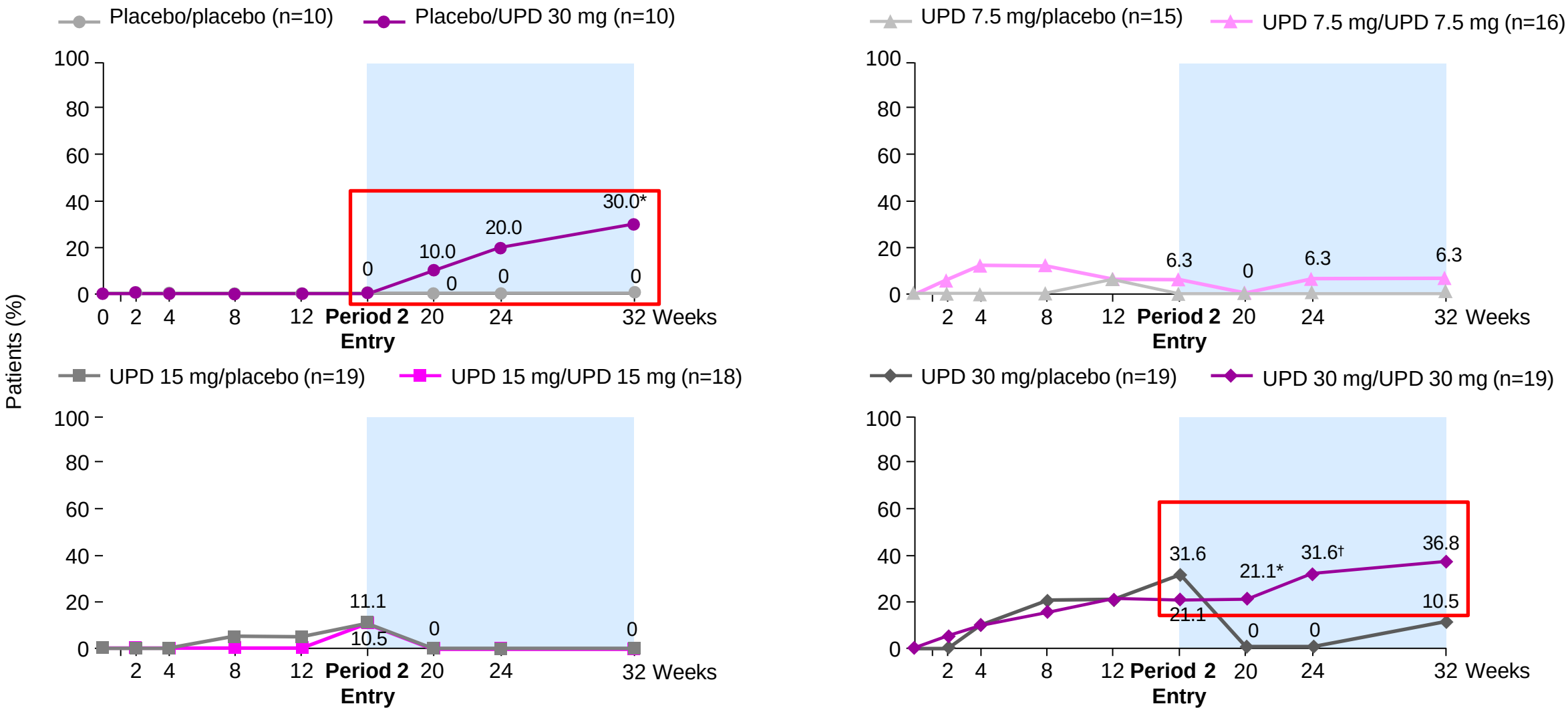
Marjolein S de Bruin-Weller, MD, PhD[1]

Emma Guttman-Yassky, MD, PhD[2]; Seth B Forman, MD[3]; Amit Bodhani, MS, MPH[4]; Su Chen, PhD[4]; Aileen L Pangan, MD[4]; Henrique D Teixeira, PhD[4]

1 University Medical Center Utrecht, The Netherlands
2 Icahn School of Medicine at the Mount Sinai Medical Center, New York, USA
3 Forward Clinical Trials, Inc, Tampa, FL, USA
4 AbbVie Inc, North Chicago, IL, USA

Presented at the 10th Georg Rajka International Symposium on Atopic Dermatitis

Phase 2b trial of upadacitinib in patients with AD: EASI 100 response through 32 weeks



*P<0.05; †P<0.01; ‡P<0.001; LOCF imputation for continuous variables; NRI for categorical variables

Guttman-Yassky E, et al. EADV 2018, P0236. Sponsored by AbbVie Inc

Treatment-emergent AEs of special interest

Patients, n (%)	Placebo, N=40	Upadacitinib (UPA) QD		
		7.5 mg, N=42	15 mg, N=42	30 mg, N=42
Infection	8 (20.0)	22 (52.4)	18 (42.9)	17 (40.5)
Serious infection	0	2 (4.8)	1 (2.4)	0
Hepatic disorder	1 (2.5)	0	2 (4.8)	0
Neutropenia	0	1 (2.4)	1 (2.4)	2 (4.8)
Lymphopenia	0	0	1 (2.4)	0
CPK elevation	1 (2.5)	0	3 (7.1)	4 (9.5)
Cardiac arrhythmia	1 (2.5)	0	0	0

There were no AEs of:

- Opportunistic infection
- Malignancy
- Gastrointestinal perforation
- Anemia
- Adjudicated CV events
- Deep vein thrombosis/pulmonary embolism
- Herpes zoster
- Renal dysfunction
- Tuberculosis
- Death

Adapted from Marjolein S de Bruin-Weller presentation the 2018 International Symposium on Atopic Dermatitis

ABROCITINIB

- The Janus Kinase 1 (JAK1) Inhibitor PF-04965842 Reduces Signs and Symptoms of Moderate to Severe Atopic Dermatitis (AD)

Melinda Gooderham,[1] Seth Forman,[2] Robert Bissonnette,[3] Jean S. Beebe,[4] Weidong Zhang,[4] Christopher Banfield,[4] Linda Zhu,[4] Jocelyne Papacharalambous,[4] Michael Vincent,[4] Elena Peeva[4]

[1]SKiN Centre for Dermatology, Peterborough, ON, Canada; [2]Forward Clinical Trials, Tampa, FL, USA; [3]Innovaderm Research, Montreal, QC, Canada, [4]Pfizer Inc., New York, NY, USA

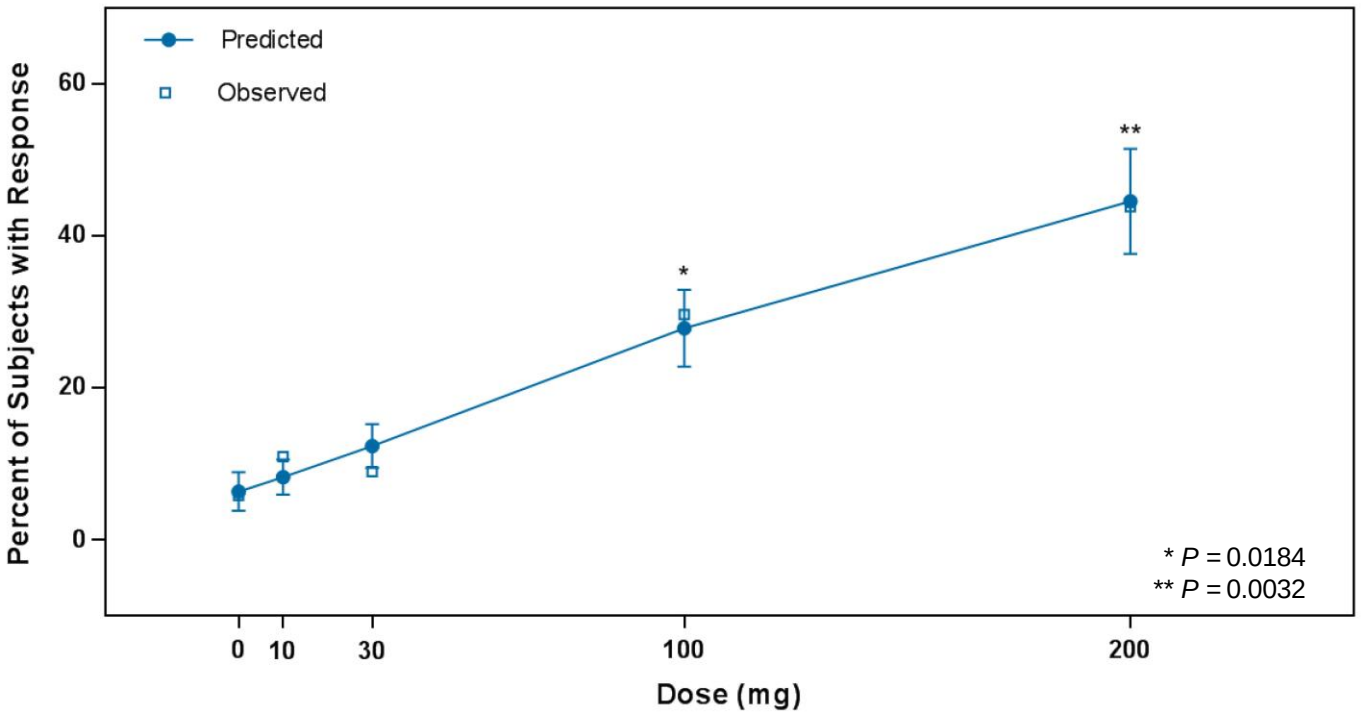
Presented at the 7th IID Meeting

May 16-19, 2018

Orlando, Florida

A Greater Proportion of Patients Achieved a Response at Week 12 With the 100-mg and 200-mg Doses

Primary End Point: IGA Response[a] at Week 12



	Placebo	10 mg	30 mg	100 mg	200 mg
Response	6.3%	8.2%	12.3%	27.8%	44.5%
95% CI	-0.2-12.9	2.2-14.1	4.9-19.7	14.8-40.9	26.7-62.3
***P* value**	—	0.1210	0.1065	**0.0184**	**0.0032**

CI, confidence interval; E_{max}, the difference between maximum achievable response (at infinite dose) and baseline; FAS, full analysis set; IGA, Investigator's Global Assessment; NRI, nonresponder imputation; SE, standard error.

[a]Emax fitted curve with SE. Baseline was defined as last measurement before first dosing. IGA response was defined as a score of clear (0) or almost clear (1) with a ≥2-point improvement from baseline at week 12 (FAS, NRI). For discontinued subjects, any missing value for all subsequent visits until week 12 was imputed using the NRI approach. Bars indicated SE.

Summary of Adverse Events

n (%)	Placebo N=77	Abrocitinib 100 mg N=156	Abrocitinib 200 mg N=154
TEAEs	44 (57.1)	108 (69.2)	120 (77.9)
Serious AEs	3 (1.9)	5 (3.2)	5 (3.2)
Discontinuations because of AEs	7 (9.1)	9 (5.8)	9 (5.8)
Deaths	0	0	0
Venous thromboembolism[1]	0	0	0
Herpes zoster	0	1 (0.6)	2 (1.3)
Eczema herpeticum	1 (1.3)	2 (1.3)	0
TEAEs in ≥5.0% of patients in any group			
Nausea[a]	2 (1.6)	14 (9.0)	31 (20.1)
Nasopharyngitis	8 (10.4)	23 (14.7)	18 (11.7)
Headache[b]	2 (2.6)	12 (7.7)	15 (9.7)
Upper respiratory tract infection	5 (6.5)	11 (7.1)	11 (7.1)
Dermatitis atopic	13 (16.9)	22 (14.1)	8 (5.2)

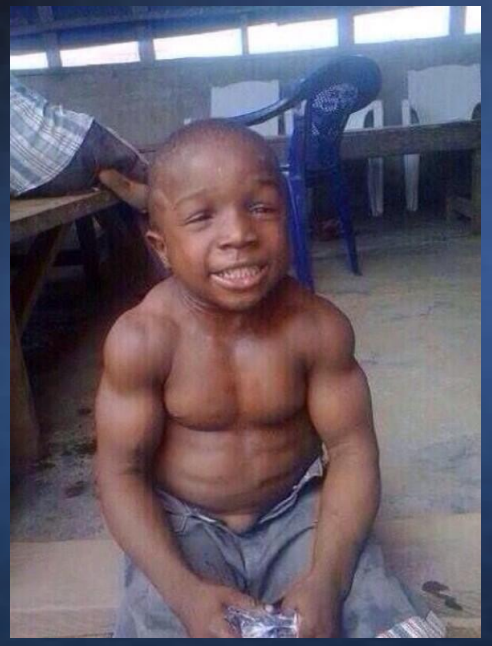
- There were no cases of malignancy or major adverse cardiovascular events

AE, adverse event; CI, confidence interval; NE, not evaluable; TEAE, treatment-emergent adverse event. [1]Study not designed to assess people at higher risk of venous thromboembolism [a]The median duration of nausea (95% CI) was 39.0 days (12.0–NE) in the 200-mg group and 13.0 days (4.0–NE) in the 100-mg group. [b]The median duration of headache (95% CI) was 3.0 days (1.0–4.0) in the 200-mg group and 4.0 days (1.0–37.0) in the 100-mg group. [c]The incidence of individual herpes viral infections was <3.0% in all treatment arms.

ATOPIC DERMATITIS TREATMENT OPTIONS

Topical corticosteroids

I DON'T WANT MY KID ON STEROIDS



Presented at the 24th World Congress of Dermatology
June 10–15, 2019; Milan, Italy

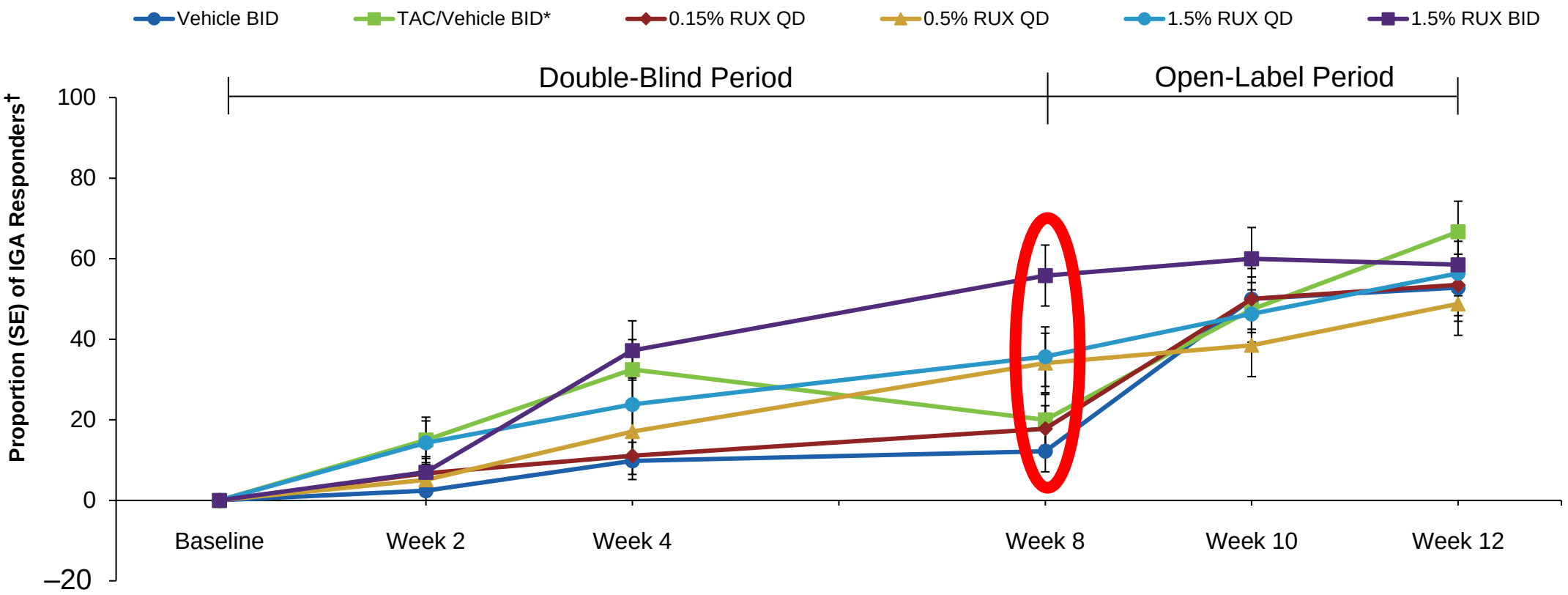
12-Week Efficacy and Safety Data of Ruxolitinib Cream in Adult Patients With Atopic Dermatitis: Results From a Phase 2 Study

Tooraj Raoof, MD,[1] Leon Kircik, MD,[2] Michael E. Kuligowski, MD, PhD, MBA,[3]
May Venturanza, MD,[3] Kang Sun, PhD,[3] Jerry Tan, MD[4]

[1]Encino Research Center, Encino, CA, USA; [2]Derm Research, Louisville, KY, USA;
[3]Incyte Corporation, Wilmington, DE, USA; [4]Windsor Clinical Research, Windsor, ON, Canada

Proportion of Patients With IGA Response

- Switching to 1.5% RUX BID was associated with substantial improvement

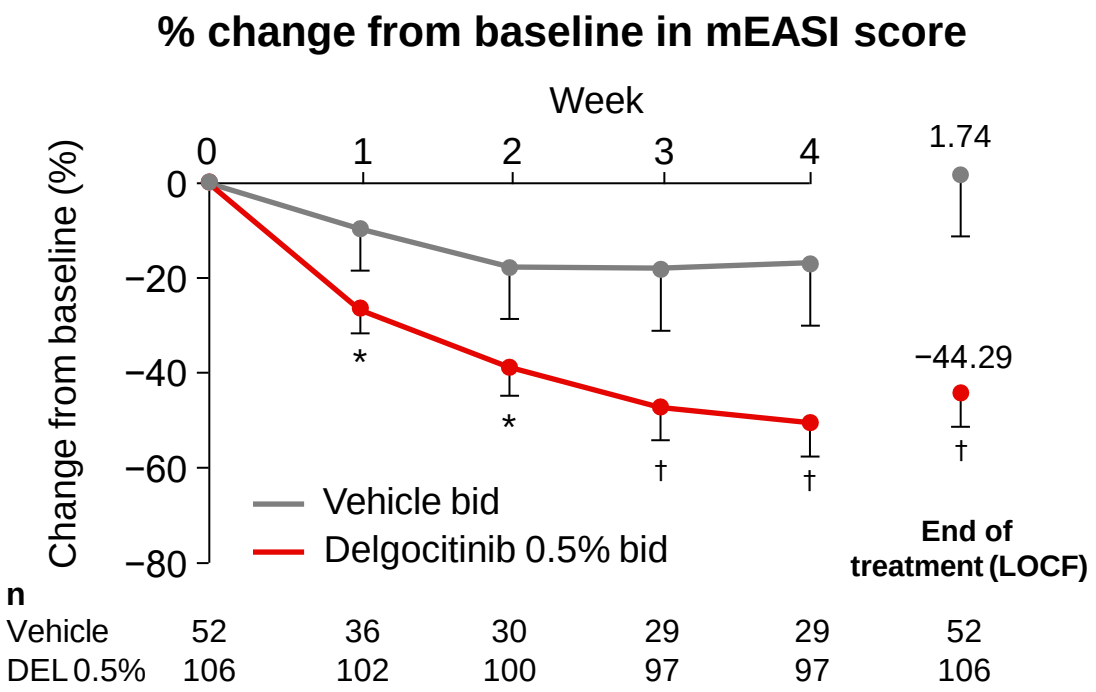


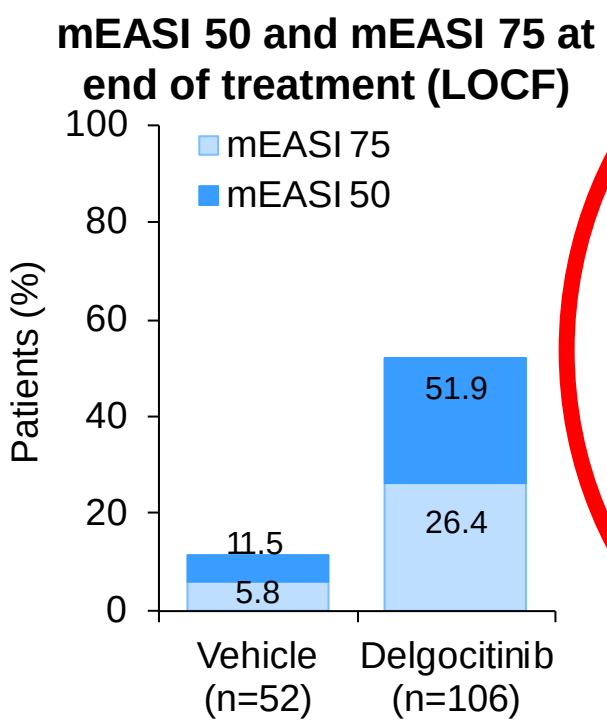
* TAC arm received 0.1% TAC cream through Week 4 and vehicle through Week 8.
† Defined as a patient achieving an IGA score of 0–1 with an improvement of ≥2 points from baseline.

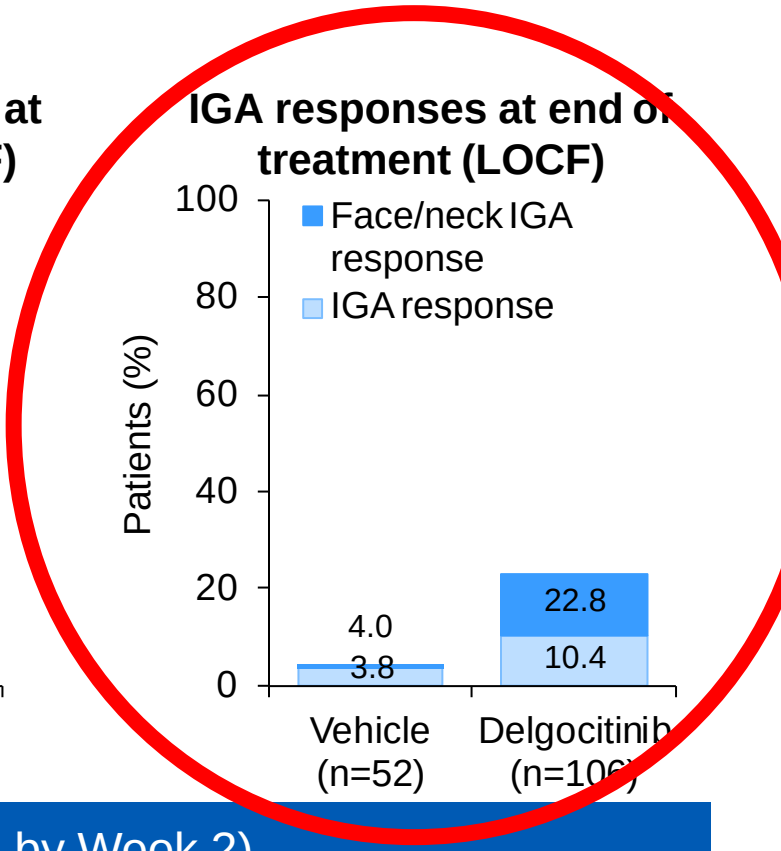
Delgocitinib (JTE-052)

Pan-JAK inhibition

Phase 3 trial: mEASI and IGA responses with topical delgocitinib among patients with moderate to severe AD







- Unusually low vehicle response in LOCF analysis (vehicle arm lost 22 patients by Week 2)
- Significant improvements compared with vehicle at end of treatment, and it seems even higher responses were achieved for the face
- This is a severe disease population to treat with topicals, which perhaps explains the low IGA 0/1 response

*P<0.01; †P<0.001 versus vehicle; end of treatment value defined as the value at Week 4 or study discontinuation; error bars represent 95% CI;
IGA response was defined as IGA 0/1 and ≥2-point improvement from baseline
Nakagawa H, et al. AAD 2019, P8214 Sponsored by Japan Tobacco, Inc

Topical Tapinarof

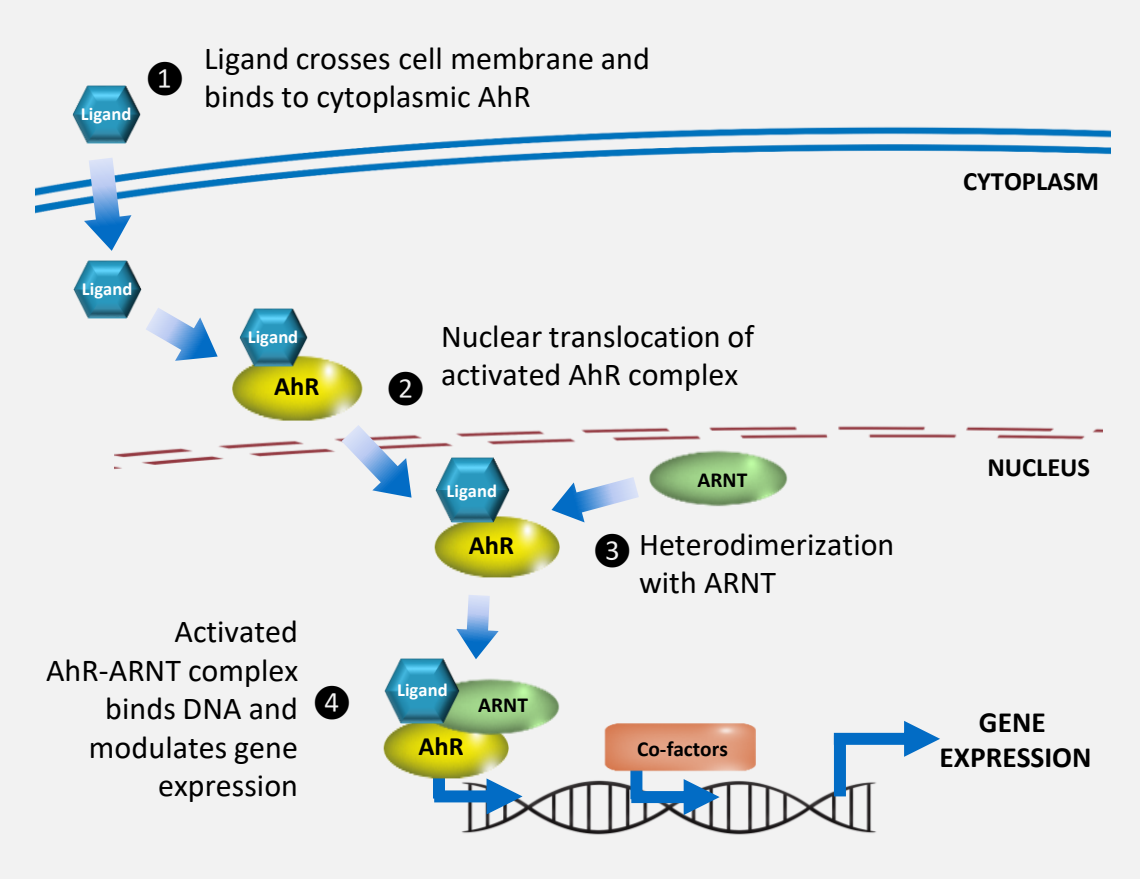
Therapeutic Aryl Hydrocarbon Receptor Modulating Agent

DMVT-505

Tapinarof: Therapeutic AhR Modulating Agent (TAMA)

- Tapinarof is a topical, small molecule TAMA that directly binds to and activates AhR transcription factor[1]
- AhR activation via tapinarof *in vitro* and animal models leads to:
  - Reduction of Th17 cytokine expression[1]
  - Reduction of Th2 cytokine expression[1,2]
  - Decreased oxidative stress[1]
  - Increased skin barrier proteins[1]

AhR pathway[3]

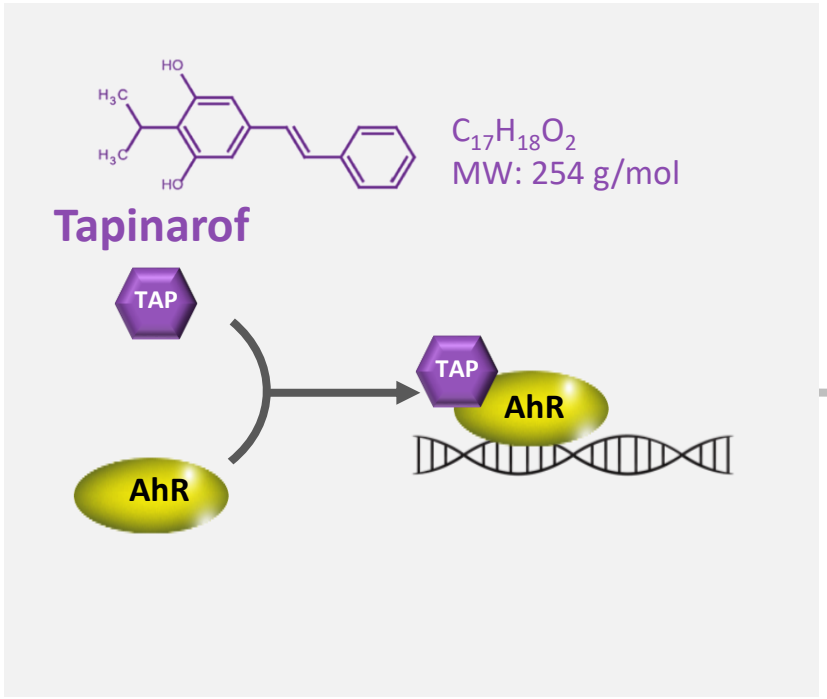


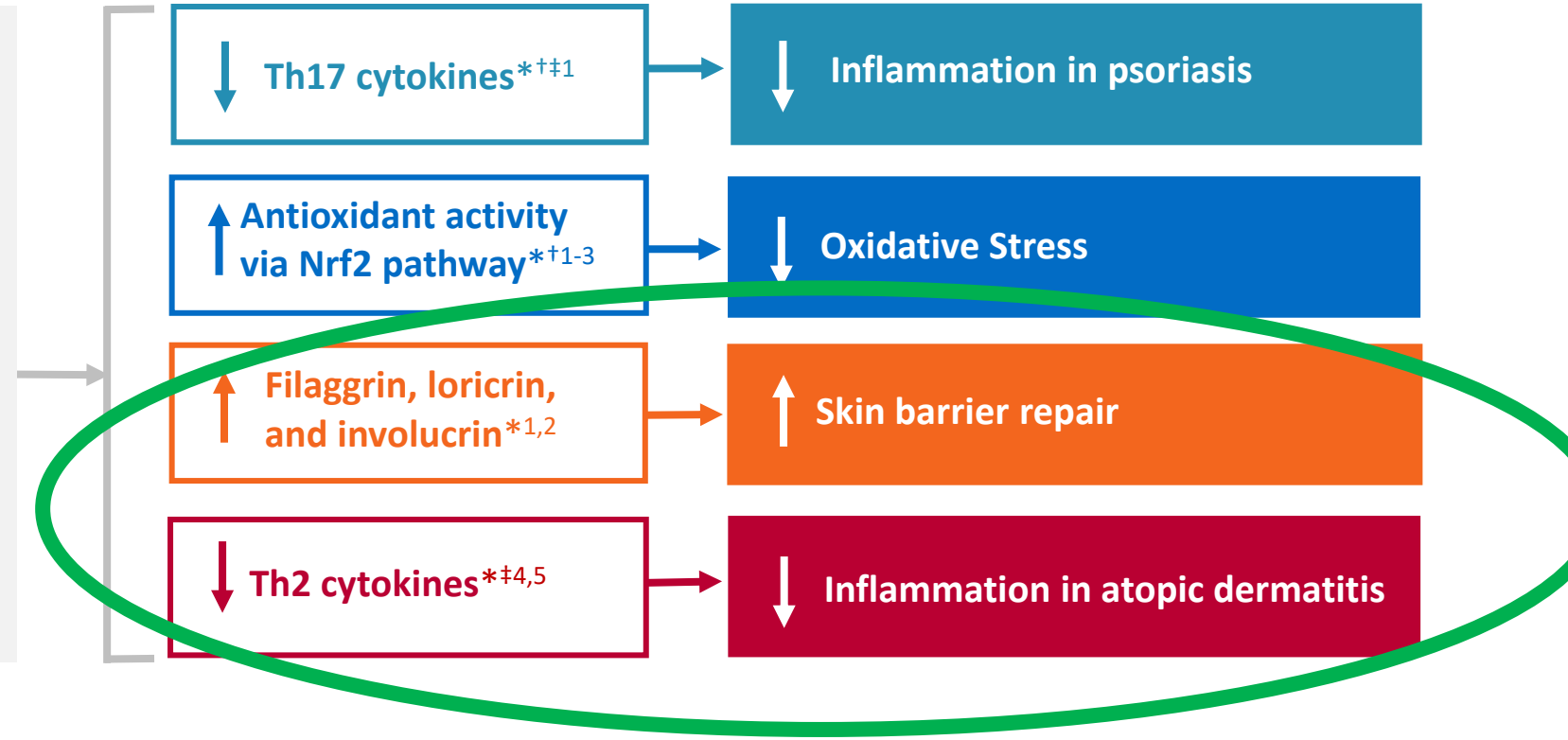
AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; TAMA, therapeutic aryl hydrocarbon receptor modulating agent; Th, T helper cell.

1. Smith SH et al. *J Inv Dermatol* 2017;137:2110–2119; 2. Negishi T et al. *J Immunol.*2005;175;7348–7356; 3. Furue M et al. *J Dermatological Sci*. 2015;80:83–88.

Biologic Effects of Tapinarof

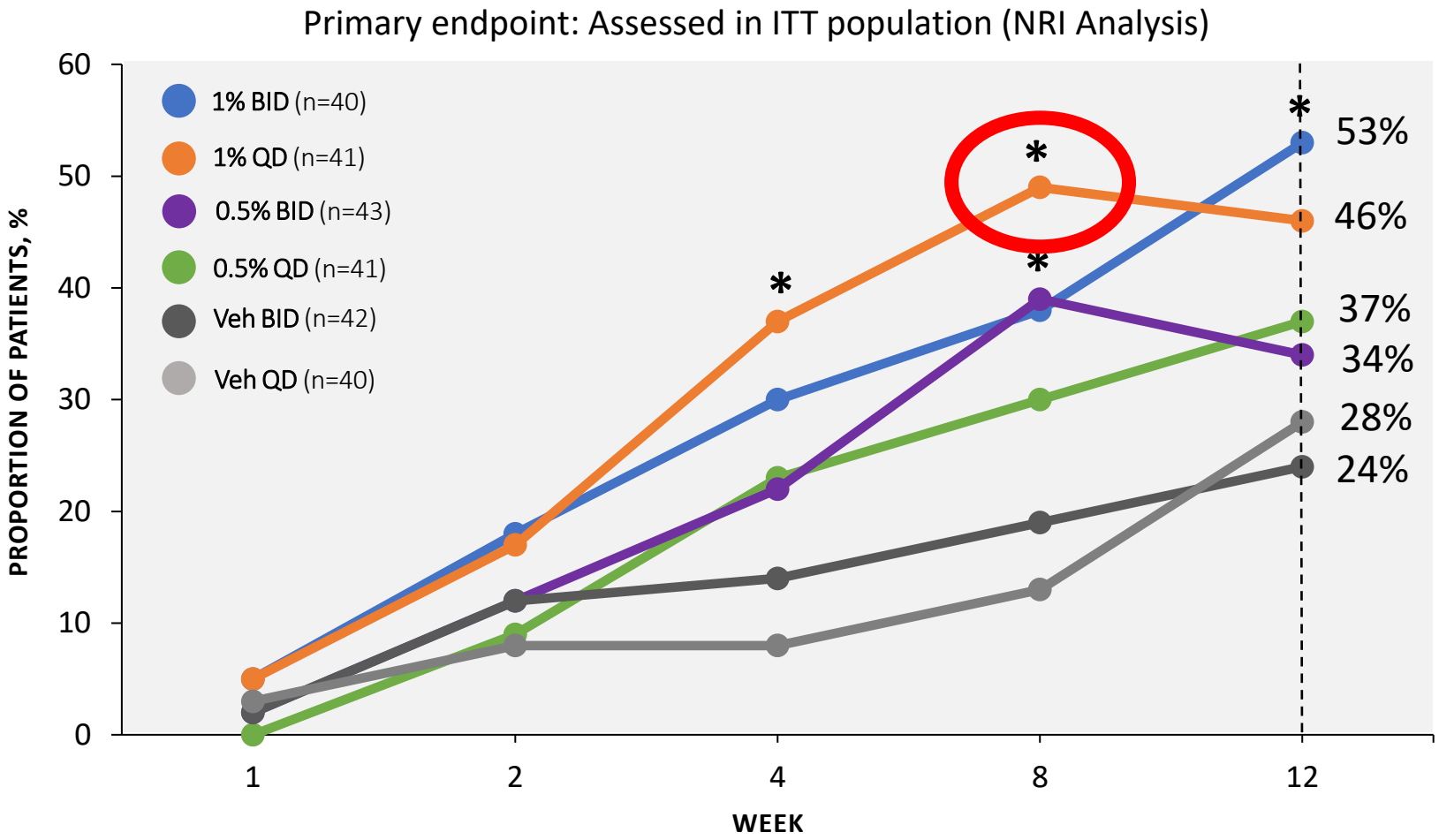
- Tapinarof is a small molecule therapeutic AhR modulating agent (TAMA) that uniquely activates the AhR pathway to decrease pro-inflammatory cytokines, decrease oxidative stress, increase skin barrier proteins and re-establish skin homeostasis[1]





*Demonstrated *in vitro*. †Demonstrated *ex vivo*. ‡Demonstrated in mice models. AhR, aryl hydrocarbon receptor; Nrf2, nuclear factor erythroid 2-related factor 2; TAMA, therapeutic AhR modulating agent; Th, T helper cell. **1**. Smith SH et al. *J Inv Dermatol* 2017;137:2110–2119. **2**. Furue M et al. *J Dermatological Sci.* 2015;80:83–88. **3**. Tsuji G et al. *J Invest Dermatol.* 2012;132:59–68. **4**. Dermavant DOF [DMVT-505 Th2 Polarization; Apr 2015]. **5**. Dermavant DOF [DMVT-505 AD Mouse Model; Oct 2016].

Tapinarof Phase 2b Study in Atopic Dermatitis
IGA 0 or 1 and ≥2-grade Improvement†



- Tapinarof resulted in higher IGA response† at all timepoints beyond Week 2 compared with vehicle

*Difference vs vehicle is statistically significant at α=0.05 level (the 95% confidence interval excludes 0). †IGA response: IGA score of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline.
BID, twice daily; IGA, Investigator Global Assessment; ITT, intention to treat; NRI, non-responder imputation; QD, once daily; Veh, vehicle.
Peppers J, et al. *J Am Acad Dermatol.* 2019;80:89-98.

GAME CHANGER IN PSORIASIS AND ATOPIC DERMATITIS TREATMENT

Human Microbiome Project[1]

1. The NIH HMP Working Group et al. Genome Res. 2009;19:2317-2323

BOTANICALS

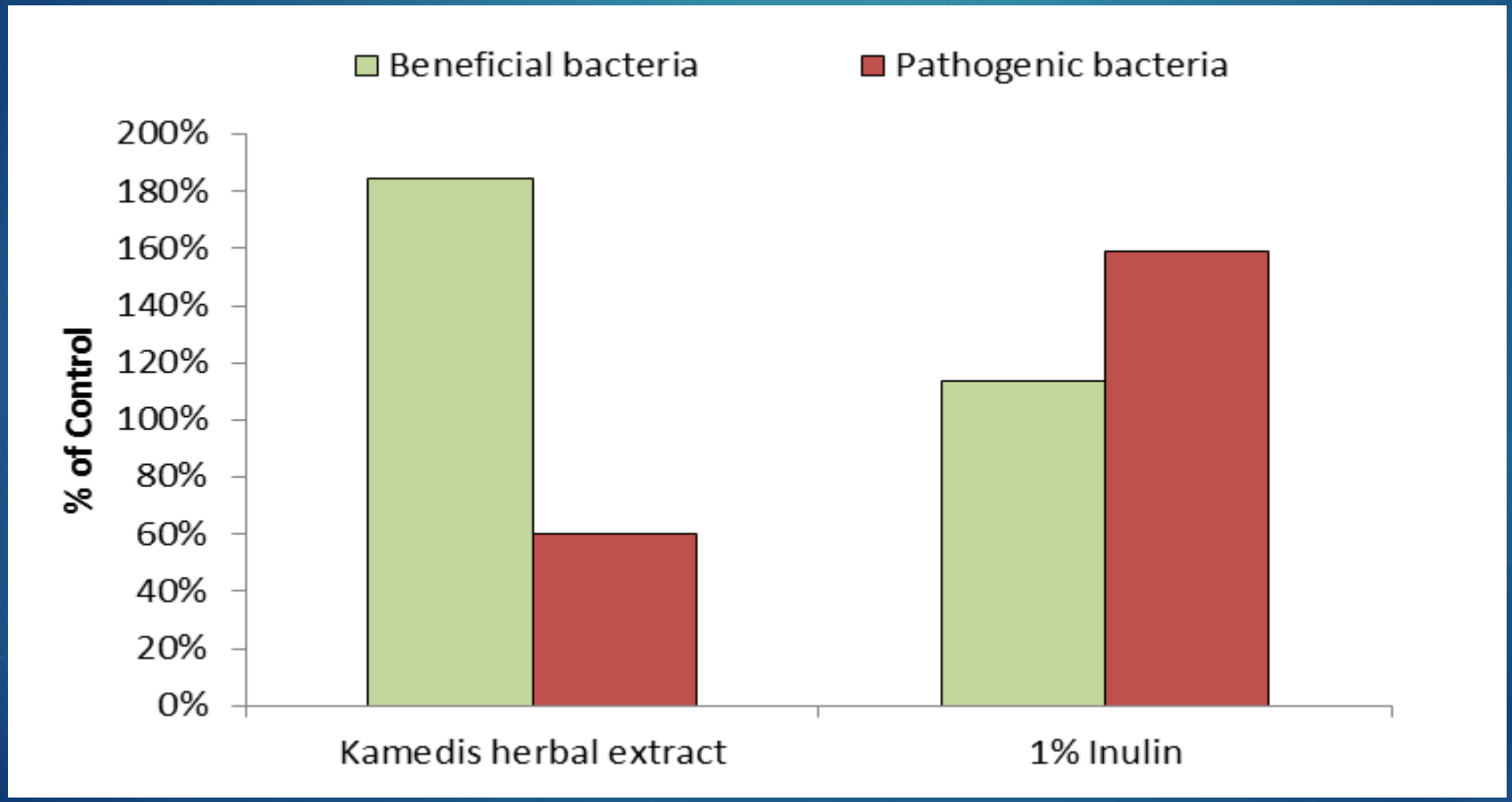
BOTANICAL Eczema Therapy Cream - List of ingredients

- **Active Ingredient**
- Sulphur 12X HPUS

- Inactive Ingredients
- Acetylated Lanolin Alcohol, Baikal Skulcap (Scutellaria Baicalensis) Root Extract, Benzyl Alcohol, Caprylic/Capric Triglyceride, Carbomer, Ceramide AP, Ceramide EOP, Ceramide NP, Cetearyl Alcohol, Cetearyl Ethylhexanoate, Cetearyl Glucoside, Cetyl Acetate, Cetyl Alcohol, Chinese Rhubarb (Rheum Palmatum) Root Extract, Cholesterol, Dehydroacetic Acid, Dimethicone, Glycerin, Glyceryl Stearate, Great Burnet (Sanguisorba Officinalis) Root Extract,Hyaluronic Acid, Lactic Acid, Licorice (Glycyrrhiza Glabra) Root Extract, Magnesium Aspartate, Monnier's Snowparsley (Cnidium Monnieri) Fruit Extract, Mineral Oil, Oleyl Acetate, PEG-100 Stearate, Petrolatum, Phytosphingosine, Potassium Aspartate, Potassium Sorbate, Propylene Glycol, Sarcosine, Shea Butter (Butyrospermum Parkii), Sodium Cocoyl Amino Acids, Sodium Lauroyl Lactylate, Stearyl Acetate, Sucrose Stearate, Tree of Heaven (Ailanthus Altissima) Bark Extract, Vitamin E (Tocopheryl Acetate), Water, Xanthan Gum.

BOTANICALS

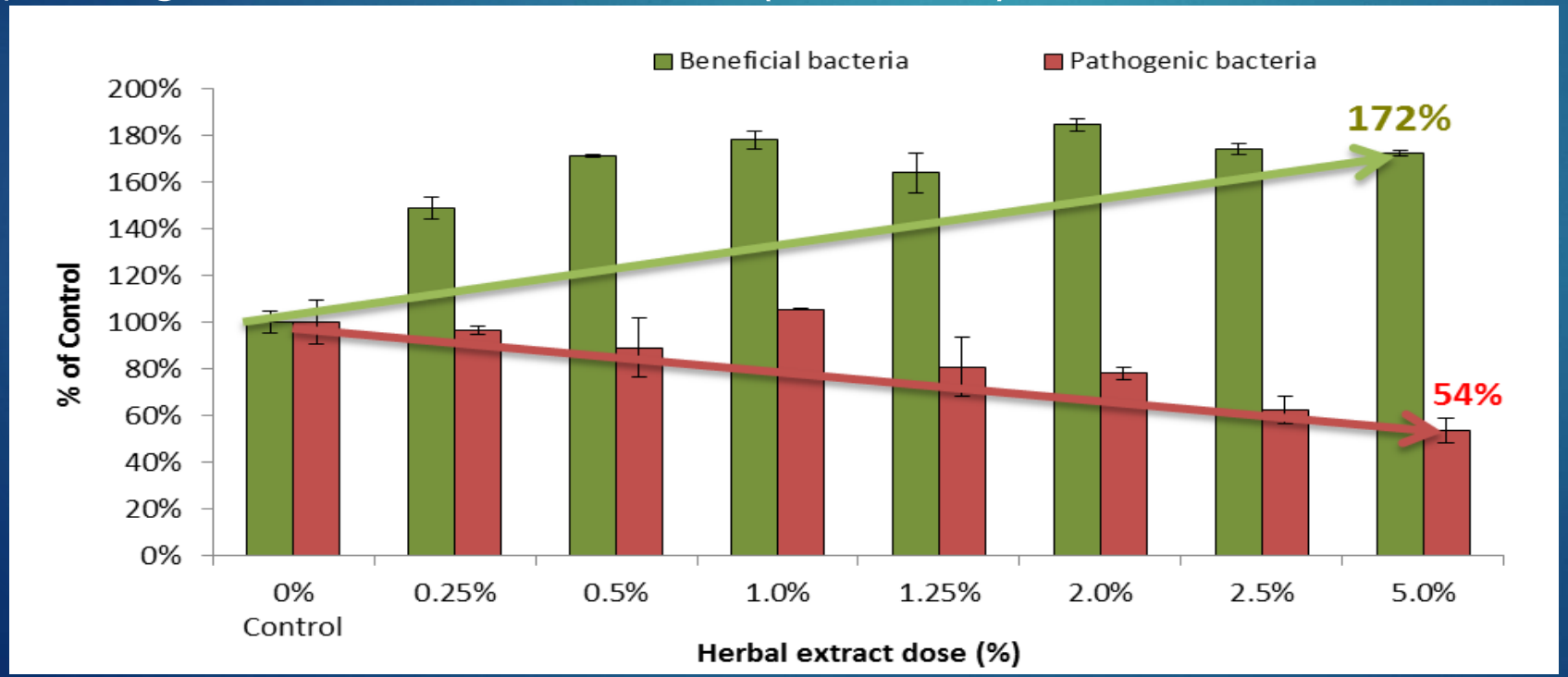
prebiotic action of herbal extracts and of Inulin – commercially available prebiotic product



Dual prebiotic and antibiotic action of herbal extracts in all products

Example:

Effect of herbal extract on growth of beneficial S. epidermidis and pathogenic S. aureus bacteria. (Mean±SE)



ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy of Topical Botanical Treatment of Children With Mild to Moderate Atopic Dermatitis

Zoe Diana Draelos MD,[a] Michael Traub ND FABNO,[b] Michael H. Gold MD,[c] Lawrence J. Green MD,[d] Mark Amster MD,[e] Deganit Barak-Shinar PhD,[f] Leon H. Kircik MD[g]

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[c]Tennessee Clinical Research Center, Nashville, TN

[d]George Washington University School of Medicine, Washington, DC

[e]Metro Boston Clinical Partners, LLC, Boston, MA

[f]Kamedis Ltd. Tel-Aviv, Israel

[g]Icahn School of Medicine at Mount Sinai, NY;

Indiana Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC,; DermResearch, PLLC, Louisville, KY

IGA 'Clear' SCORE

Product	# of 'Clear Subjects (IGA=0) following 4 weeks of treatment	Total # of Subjects who concluded the study	Percentage of 'Clear' out of Total (%) Per examined product
Eczema Therapy Cream	11	32	34%
Vehicle	6	32	19%
Comparator	12	35	34%

The IGA of the Eczema Therapy Cream test product is higher by more than 80% comparing to the vehicle, from 19% of clear subjects with the vehicle to 34% with Eczema Therapy Cream

Draelos, ZD, Traub, M, Gold M.H. et. Al Validation of Botanical Treatment Efficacy for Adults and Children Suffering from Mild to Moderate Atopic Dermatitis *J Drugs Dermatol.* 2019;18(6):557-561.

STUDY RESULTS

- **IGA Analysis:**
  - Botanical test product as well as the comparator reached exactly the same percentage, 34%, of 'clear' IGA subjects out of the enrolled subjects, presenting a clear advantage over the vehicle that showed 19%.
- **BSA Analysis:**
  - The BSA improvement comparison analysis of the botanical test product vs. the vehicle yielded P value of 0.0369, which is statistically significant.

Study Subset Results - IGA

- **Children 3-18 analysis:** 60% achieved Clear or Almost Clear vs. 38% for the vehicle and 48% for the comparator at 4 weeks.
- **Skin type analysis: the botanical test product is more effective in treating patients with skin of color.**
  - 40% of study participants with skin type V-VI achieved a "Clear" score at 4 weeks vs. 25% for all other skin types.

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