Topical Treatments for Atopic Dermatitis:

Today & Tomorrow

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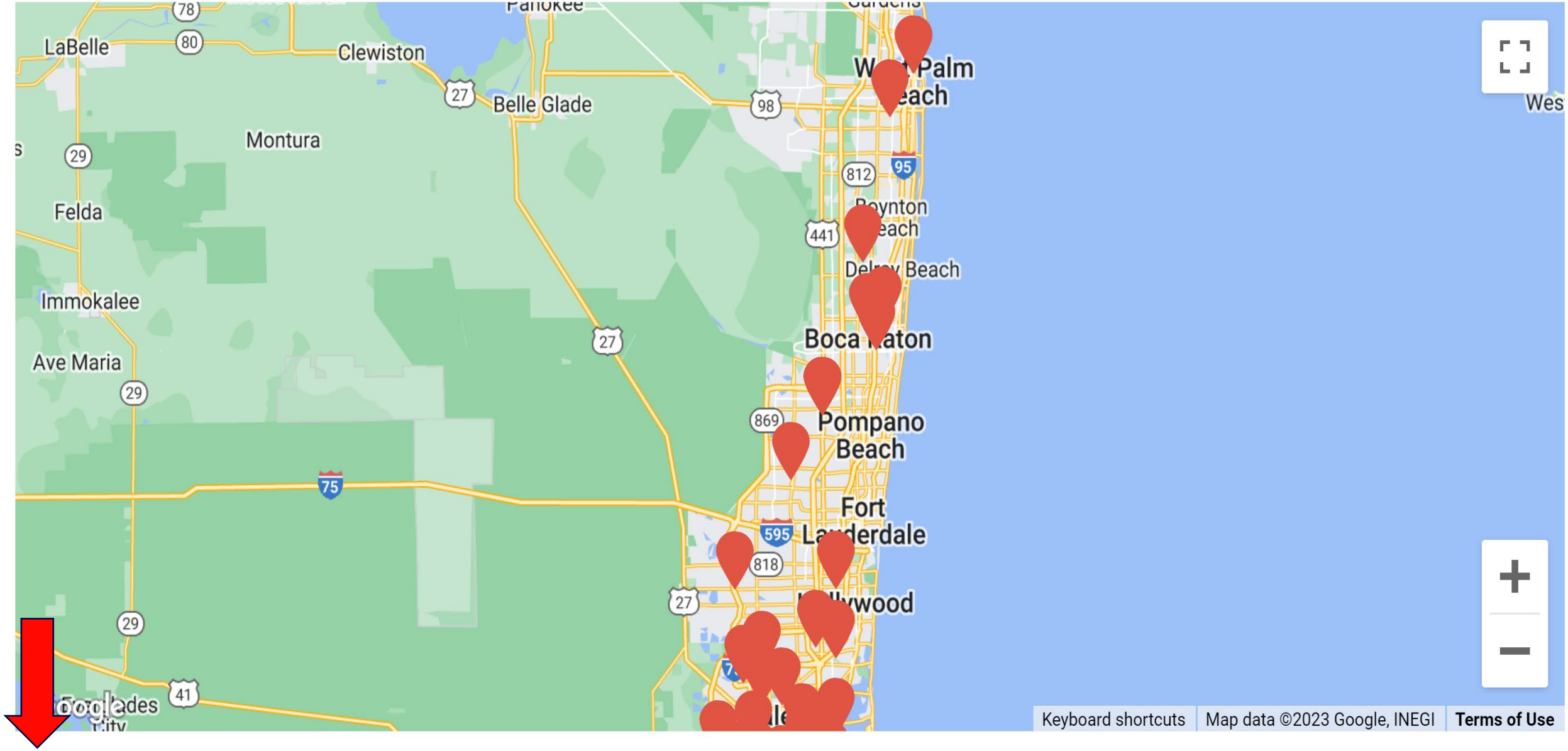
DRS – April 21, 2023, Hollywood Florida



470 clinical trials matching your search

American Academy of Dermatology issues updated guidelines for the management of atopic dermatitis in adults with topical therapies

Both well-established and newer topical treatments addressed

ROSEMONT, Ill. (January 11, 2023) — Often called eczema or atopic eczema, atopic dermatitis is a common skin condition, affecting 1 in 10 Americans. Although atopic dermatitis occurs most frequently in children, it also affects adults and can have a significant impact on patients' quality of life. To help ensure that adult patients with atopic dermatitis receive the best possible treatment, the American Academy of Dermatology (AAD) has published updated guidelines of care for the management of atopic dermatitis in adults with topical therapies in the *Journal of the American Academy of Dermatology*.

This is the second in a series of updated guidelines the AAD is producing on the condition. The updates, which outline best practices for topical treatment of the disease,

"Atopic dermatitis is the most common type of eczema, and it can interfere with a person's daily life without proper treatment," said board-certified dermatologist Robert Sidbury, MD, MPH, FAAD, co-chair of the AAD's Atopic Dermatitis Guideline Workgroup. "The guidelines provide evidence-based recommendations for dermatologists to use in caring for their adult atopic dermatitis patients with topical treatments, which have come a long way since the guidelines were last revised in 2014. This update reflects the latest advances in topical medications that are now available to help adults with atopic dermatitis."

2023 Academy AD GUIDELINES:
GENERAL COMMENTS & RECCOMMENDATIONS (Strong Recommendations)

- **Topical treatments** remain one of the most popular options due to their effective track record and overall safety

- **The Atopic Dermatitis Workgroup** developed **12 recommendations** on how to manage atopic dermatitis in adults with topical therapies. The workgroup provided **new recommendations for non-prescription methods as well as prescription treatments**

- **Moisturizers** help to relieve patients' dry, cracked skin, decrease inflammation, and reduce the severity of and increase the time between flare-ups.

- **Topical corticosteroids** are commonly used as the first-line treatment for patients with atopic dermatitis in all skin regions. They help to relieve itching, decrease inflammation, and can decrease infection

- **Topical calcineurin inhibitors (pimecrolimus 1% cream and tacrolimus 0.03% or 0.1% ointment)** reduce patients' inflammation and itching, as well as decrease their flare-ups.

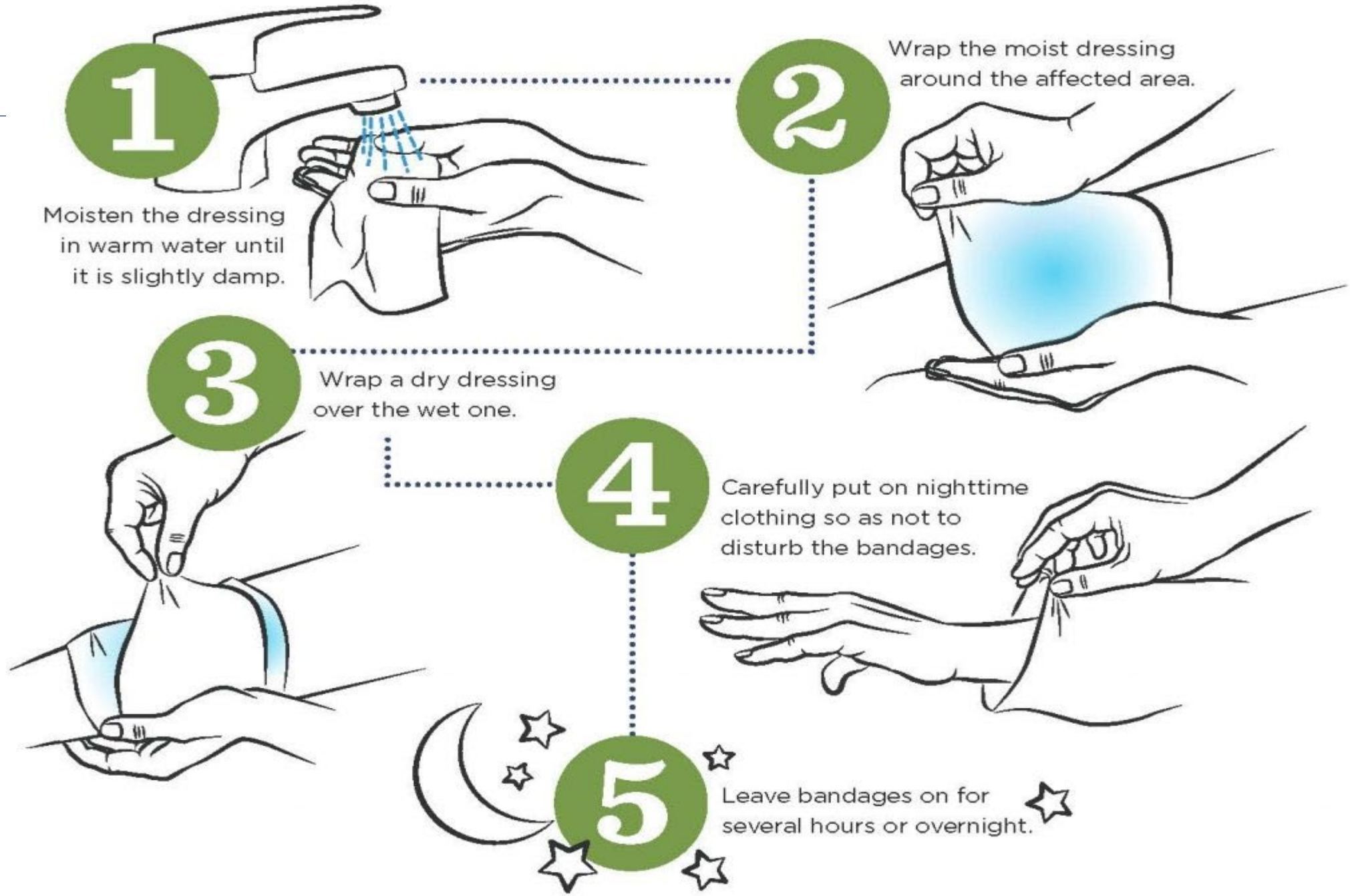
- **Phosphodiesterase-4 inhibitor (crisaborole ointment)** can reduce patients' inflammation, help relieve itching, and decrease infections.

- **Janus kinase inhibitor (ruxolitinib cream)** can be used short term to ease the inflammation and itching of patients with mild to moderate atopic dermatitis.

Conditional recommendations for the use of Bathing and Wet Wrap Therapy

- **Bathing,** followed by moisturization, helps patients hydrate the skin. Bleach baths can help patients prevent infection and get rid of bacteria on their skin.

- **Wet wrap therapy** utilizes wet bandages to help hydrate and soothe patients' skin. This treatment provides a barrier against scratching, helps to decrease redness and inflammation, and can reduce the bacteria on patients' skin.


1
Moisten the dressing in warm water until it is slightly damp.
2
Wrap the moist dressing around the affected area.
3
Wrap a dry dressing over the wet one.
4
Carefully put on nighttime clothing so as not to disturb the bandages.
5
Leave bandages on for several hours or overnight.

The Goals of AD Management

Treat the skin-barrier defect and **inflammation** and to **restore the microbiome** resulting in prolonged patient remission.

Topical therapies are key players in achieving these goals.

Topical agents provide **targeted anti-inflammatory activity** and improve skin pathology with **lower costs and increased safety** compared to systemic treatments.

Atopic dermatitis (eczema) is a chronic inflammatory skin condition affecting nearly the entire skin surface. Lesions, itch, dryness, and other symptoms may occur.

TREATMENT OPTIONS

Basic skin care (emollients, bathing, trigger avoidance)

Topical anti-inflammatory therapies

- Corticosteroids
- Calcineurin inhibitors
- Phosphodiesterase 4 inhibitor
- Janus kinase inhibitor

Advanced therapies may be used if there is no improvement with topical therapies

Advanced systemic therapies

- Immunosuppressants (oral)
- Biologic therapies (injection)
- Janus kinase inhibitor (oral)

Phototherapy (light treatment)

Basic Manage

Trigger avoidance

- Allergy testing wh

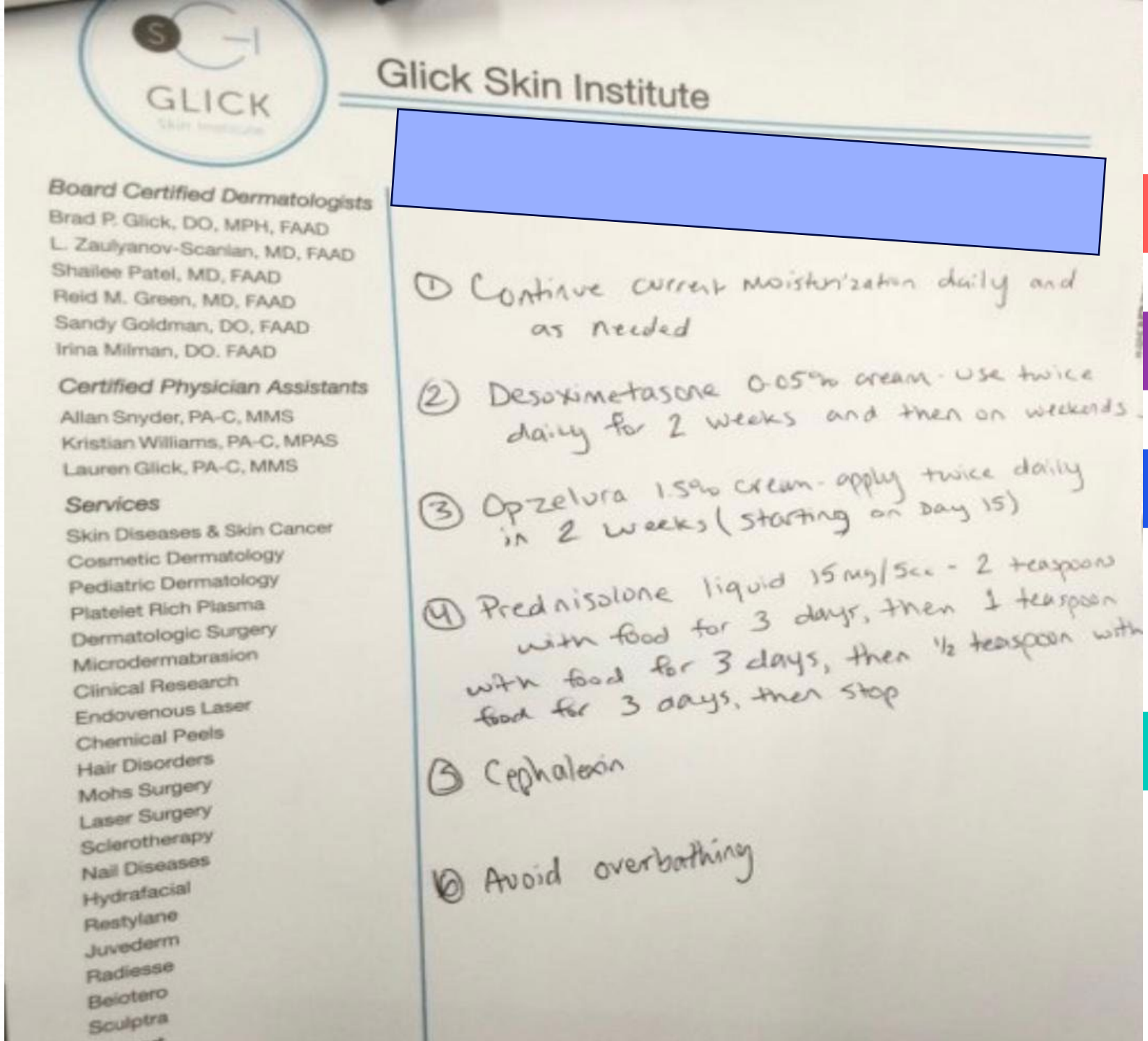
Warm bath or shower

- Nonsoap cleanse

Bleach baths

Moisturizers

- Apply liberally 2-3
- Reapply liberally t
- Use ointments to



1. Eichenfield LF et al. *J Am Acad Dermatol*.
4. Nichol NH. In: Nichol NH, ed. *Dermatologi*
J Allergy Clin Immunol. 2014;134:818-823. 6

Step-Care Management of AD[1]

	Nonlesional	Mild	Moderate	Severe
Maintenance Therapy	**Basic Management** **Skin care** • Moisturizer, liberal and frequent (choice per patient preference) • Warm bath or showers using nonsoap cleansers, usually once daily and followed by moisturizer (even on clear areas) **Trigger avoidance** • Proven allergens, common irritants (eg, soaps, wool, temperature extremes) • Consider comorbidities			
Acute Treatment				

Step-Care Management of AD[1]

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Acute Treatment		**Apply Topical Corticosteroids to Inflamed Skin** Low to medium potency topical corticosteroids 2x daily for 3-7 days beyond clearance (Consider TCI, crisaborole)		

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Acute Treatment	**Apply Topical Corticosteroids to Inflamed Skin** Low to medium potency topical corticosteroids 2x daily for 3-7 days beyond clearance (Consider TCI, crisaborole)		**Apply Topical Corticosteroids to Inflamed Skin** Medium to high potency topical corticosteroids 2x daily for 3-7 days beyond clearance (Consider TCI, crisaborole) If not resolved in 7 days, consider ➡ • Nonadherence • Infection • Misdiagnosis • Contact allergy to medications • Referral	

Step-Care Management of AD[1]

	Nonlesional	Mild	Moderate	Severe
Maintenance Therapy	**Rx TOPICALS** • Moisturizer, liberal and frequent (choice per patient preference) • Warm bath or showers using nonsoap cleansers, usually once daily and followed by moisturizer (even on clear areas) **Trigger avoidance** • Proven allergens, common irritants (eg, soaps, wool, temperature extremes) • Consider comorbidities	**Rx TOPICALS** **Skin care** • Moisturizer, liberal and frequent (choice per patient preference) • Warm baths or showers, nonsoap cleansers, usually once daily and followed by moisturizer (even on clear areas) **Antiseptic measures** • Dilute bleach (or equivalent) ≤2x week according to severity (especially with recurrent infections) • Antibiotics, if needed **Trigger avoidance** • Proven allergens and common irritants (eg, soaps, wool, temperature extremes) • Consider comorbidities	**Rx TOPICALS** Apply on areas of previous or potential symptoms (aka flare) **Maintenance topical corticosteroids** • Low potency 1x-2x daily (including face) • Medium potency 1x-2x weekly (except face) **OR maintenance TCI (pimecrolimus, tacrolimus)** • 1x-2x daily • 2x-3x weekly **OR crisaborole 2%** • 2x daily	**Rx TOPICALS**
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Topical Corticosteroids

Class	Potency	Clinical Considerations	Example(s)
1	Superpotent	Best for thick lichenified/hypertrophic skin; avoid use in children <12 years or infants	Clobetasol lotion/cream/foam/ ointment/solution 0.05%; betamethasone gel/ointment 0.05%
2	Potent	More severe disease; patients outside of infancy; “hot zones” such as wrists, ankles, hands, and feet	Mometasone ointment 0.1%; fluocinonide cream/gel/ointment 0.05%
3	Upper mid-strength		Diflorasone cream 0.05%; fluticasone ointment 0.005%
4	Mid-strength	Short-term treatment of trunk, extremities, and neck in patients who have more moderate disease	Triamcinolone cream/ointment/spray 0.1%; fluocinolone ointment 0.025%
5	Lower mid-strength		Hydrocortisone cream 0.1%; desonide ointment 0.05%
6	Mild	Large treatment areas; facial involvement, folds; use even in young infants	Alclometasone cream/ointment 0.05%; desonide cream 0.05%
7	Least potent		Hydrocortisone; prednisolone

Topical Corticosteroids (Cont'd)

potency

adrenal suppression

telangiectasias, folliculitis,

NO NEED FOR STEROIDOPHOBIA!!!!!

Other Topical Therapies (Non-Steroidal Therapies)[1-5]

Class/Agent	Recommended Use	Considerations
Calcineurin inhibitors • Tacrolimus ointment • Pimecrolimus cream	Second line, short term, noncontinuous; steroid sparing	• Approved for patients ≥2 years • May cause burning or stinging • Risk of secondary infections and rare cases of malignancy
PDE-4 inhibitor • Crisaborole	Mild to moderate AD in adult and pediatric patients ≥3 months	• Application-site pain/discomfort • Erythema
JAK inhibitor • Ruxolitinib	Mild to moderate AD in adult and pediatric patients ≥12 years who are not immunocompromised	• Boxed warning: serious infections, mortality, malignancy, MACE, and thrombosis

1. Eichenfield LF et al. *J Am Acad Dermatol*. 2014;71:116-132. 2. Eichenfield LF et al. *Pediatr Dermatol*. 2020;37:1030-1037. 3. Schlessinger J et al. *Am J Clin Dermatol*. 2020;21:275-284. 4. Eucrisa (crisaborole) Prescribing Information. https://labeling.pfizer.com/ShowLabeling.aspx?id=5331. 5. Opzelura (ruxolitinib) Prescribing Information. https://www.opzelura.com/prescribing-information.pdf.

Validated Impact Assessment Tool[1-3]

Atopic Dermatitis Control Tool (**ADCT**) is a validated, brief, and easily scored patient self-assessment tool

Six questions to evaluate the different dimensions of AD control identified as relevant by patients and clinicians

ADCT can be **self-administered** by patients or used in routine consultations

ADCT is designed to help facilitate meaningful patient–physician discussion on control of AD in every day clinical practice

Atopic Dermatitis Control Tool (ADCT)[1-3]

ADCT – Atopic Dermatitis Control Tool

Understanding your atopic dermatitis using ADCT

Atopic dermatitis (AD) is a chronic form of eczema. It is a common and treatable disease, but it is not always easy to manage, and it may impact your quality of life in more than one way.

Measuring disease control across all areas of life affected by your AD – including visible skin signs, symptoms such as itch and pain, or overall quality of life – can help your doctor monitor treatment response, guide conversations about optimal care that is right for you, and set achievable treatment goals.

Atopic Dermatitis Control Tool (ADCT) is a tool developed to assist patients and their doctors in comprehensively and efficiently understanding their disease. To self-assess how well controlled your AD is, please answer the following questions. Your responses to ADCT will help your doctor or nurse better understand your treatment needs.

Step 1: Complete six brief questions about your AD

Please complete the questions below. To use ADCT correctly, you must answer all six questions.

Atopic Dermatitis Control Tool

Please answer the following questions thinking about your experiences with eczema, sometimes called "atopic dermatitis"

1. Over the last week, how would you rate your eczema-related symptoms (for example, itching, dry skin, skin rash)?
   ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe
2. Over the last week, how many days did you have **intense episodes of itching** because of your eczema?
   ☐ Not at all ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ Every day
3. Over the last week, how **bothered** have you been by your eczema?
   ☐ Not at all ☐ A little ☐ Moderately ☐ Very ☐ Extremely
4. Over the last week, how many nights did you have **trouble falling or staying asleep** because of your eczema?
   ☐ No nights ☐ 1-2 nights ☐ 3-4 nights ☐ 5-6 nights ☐ Every night
5. Over the last week, how much did your eczema **affect your daily activities**?
   ☐ Not at all ☐ A little ☐ Moderately ☐ A lot ☐ Extremely
6. Over the last week, how much did your eczema **affect your mood or emotions?**.
   ☐ Not at all ☐ A little ☐ Moderately ☐ A lot ☐ Extremely

© Atopic Dermatitis Control Tool_Version 1, 27 Nov 2018 Sanofi Group and Regeneron Pharmaceuticals Inc. All Rights Reserved.
ADCT – US/English

To learn how to calculate your ADCT total score, please turn over to reverse side.

SAGLB.AD.19.10.1557c | February 2020

The Atopic Dermatitis Control Tool (ADCT) was developed to facilitate patient-physician discussion on control of atopic dermatitis. The ADCT is not intended to replace the physician's medical judgment in diagnosing and treating the patient.

ADCT – Atopic Dermatitis Control Tool

Step 2: Calculate your ADCT total score

After you have answered all six questions, use the ADCT table below to calculate your ADCT total score.

- **For each question, your answer is scored between 0 points and 4 points.** Fill in the grey boxes in the right-hand column of the ADCT table below with the points you scored for each question.
- **The sum of points for your answers to the six ADCT questions is your ADCT total score.** Calculate the sum of your points in the grey boxes and write it into the **purple** box at the bottom. Your ADCT total score will be between 0 and 24.
- Note down today's date in the box on the top left. You might want to refer back to the time you recorded your ADCT total score when you speak to your doctor about your AD.

Today's date:

						Note your points for each question in the grey boxes
1. Over the last week, how would you rate your eczema-related symptoms?	(None) **0 points**	(Mild) **1 point**	(Moderate) **2 points**	(Severe) **3 points**	(Very Severe) **4 points**	
2. Over the last week, how many days did you have intense episodes of itching because of your eczema?	(Not at all) **0 points**	(1-2 days) **1 point**	(3-4 days) **2 points**	(5-6 days) **3 points**	(Every day) **4 points**	
3. Over the last week, how bothered have you been by your eczema?	(Not at all) **0 points**	(A little) **1 point**	(Moderately) **2 points**	(Very) **3 points**	(Extremely) **4 points**	
4. Over the last week, how many nights did you have trouble falling or staying asleep because of your eczema?	(No nights) **0 points**	(1-2 nights) **1 point**	(3-4 nights) **2 points**	(5-6 nights) **3 points**	(Every night) **4 points**	
5. Over the last week, how much did your eczema affect your daily activities?	(Not at all) **0 points**	(A little) **1 point**	(Moderately) **2 points**	(A lot) **3 points**	(Extremely) **4 points**	
6. Over the last week, how much did your eczema affect your mood or emotions?	(Not at all) **0 points**	(A little) **1 point**	(Moderately) **2 points**	(A lot) **3 points**	(Extremely) **4 points**	
					Sum of your points = **Your ADCT total score:**	

Step 3: Speak to your doctor about how your AD affects your day-to-day life

Your AD may not be well controlled if:

- **Your ADCT total score is at least 7 points**
  OR
- **One of your answers falls in a blue coloured box of the ADCT table above**
  OR
- **Your ADCT total score has increased by 5 points or more since you last used ADCT**

✓ If you are concerned that your AD may not be well controlled, you should seek medical advice
✓ Bring your completed ADCT with you for your next scheduled consultation
✓ Speak to your doctor about your responses to the ADCT questions and how your AD is affecting you

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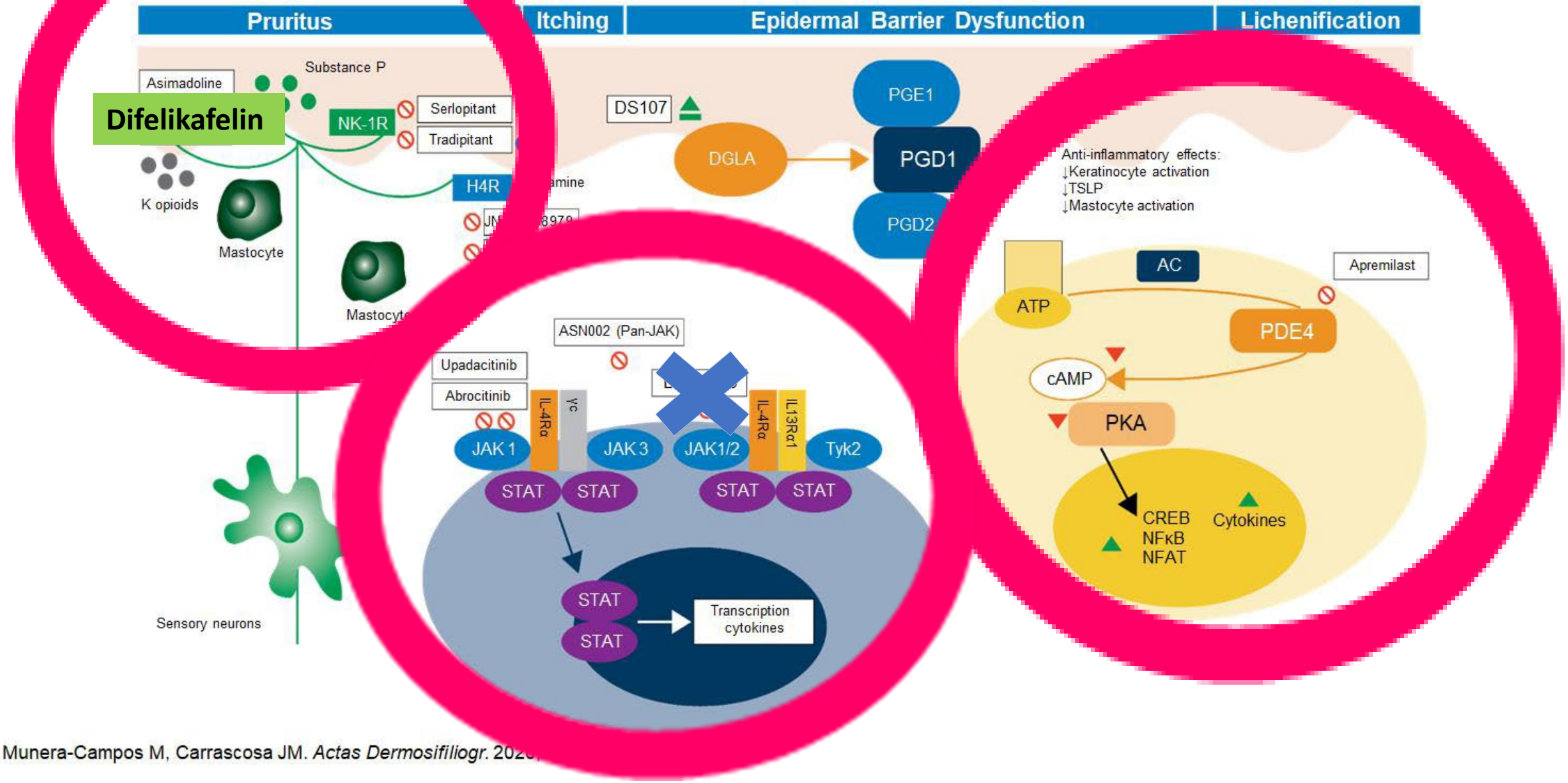
Small Molecules and Specific Targets in the Pathogenesis of AD[1]



1. Munera-Campos M, Carrascosa JM. *Actas Dermosifiliogr.* 202

Therapeutics for Mild-to-Severe AD

Approved:

Ruxolitinib 1.5 % Cm, Pimecrolimus 1% Cm, crisaborole 2% ointment (mild-to-moderate)
Tacrolimus 0.1% ointment (moderate-to-severe)

TOPICAL

Oral systemics: Abrocitinib, Upadacitinib
Injectibles: (sc) Dupilumab,Tralokinumab

Therapeutics for Moderate-to-Severe AD

In development:

Injectables (22 total): Lebrikizumab, Nemolizumab, Bermekimab, Amlitelimab, Astegolimab, Tozorakimab

Oral (17 total): Baricitinib, Tradipitant, Difelikefalin, Estrasimod, Gusacitinib, Asimadoline

Topical (40 total): Tapinarof, Roflumilast, Orsimilast, Delgocitinib, Brepocitinib, Cerdulatinib

Other (2 total): Fecal microbial transplantation, super protein multifunction (SPM)

The Janus Kinase (JAK) Signal Transduction - Activator Pathways of Transcription (STAT)

Janus kinase inhibitors in dermatology: Part I. A comprehensive review

Stephanie Chapman, MS, MD, Michael Kwa, MD, Linda Stein Gold, MD, and Henry W. Lim, MD
Detroit, Michigan

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) intracellular signaling pathway is utilized by many proinflammatory molecules to mediate downstream effects and activate gene transcription. Activation of the JAK-STAT pathway contributes to a number of inflammatory dermatoses. Clinical trials and smaller studies have demonstrated the efficacy of JAK inhibitors in the treatment of a variety of dermatologic conditions. Here, we review the use of JAK inhibitors for the treatment of a wide range of dermatologic diseases in a two-part review series. (J Am Acad Dermatol 2022;86:406-13.)

Key words: dermatology; immunodermatology; immunology; JAK inhibitor; JAK-STAT pathway; Janus kinase inhibitor; Janus kinase-signal transducer and activator of transcription pathway; review.

What about JAK?

- The **JAK family of intracellular enzymes** associated with **cytokine receptors on the surface of cells (JAK 1,2,3, TYK-2)**
- Part of the Signal Transducer and Activation of Transcription **(STAT)** pathway - **involved in inflammatory and immune processes such as immunity, cell division & death, and tumorigenesis**
- **The pathway communicates info from extracelluar chemical signals to the nucleus resulting in gene transcription**
- An abnormality along this pathway may cause abnormal proliferation of cells. Outcomes include **polycythemia vera, leukemia and lymphoma.**
- **Inhibiting JAK** can reduce immune responses in autoimmune conditions such as **RA, PsA, AD, AA, vitiligo, IBD, & HS**
- **Ruxolitinib & baricitinib** mainly inhibit **JAK1 and 2**. Tofacitinib inhibits Janus kinase 1 and 3. **Abrocitinib & upadacitnib** appear to be more selective for **JAK 1. Deucravacitinib is highly selective for TYK 2 via allosteric inhibition**
- As JAKnibs alter immune responses they may increase the risk of infections. There is a possibility that they may also increase the risk of cancer.

J Am Acad Dermatol
Volume 86, Number 2

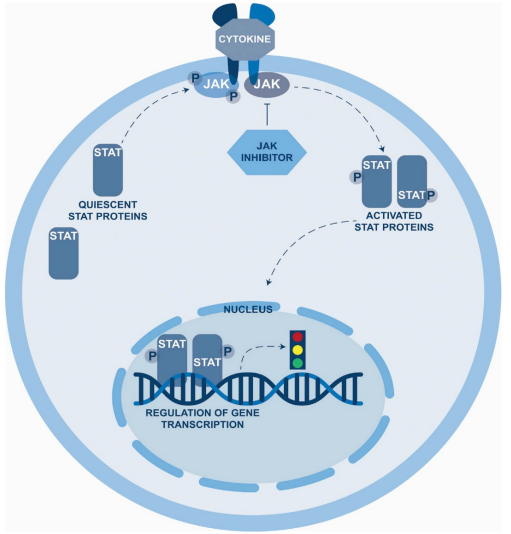
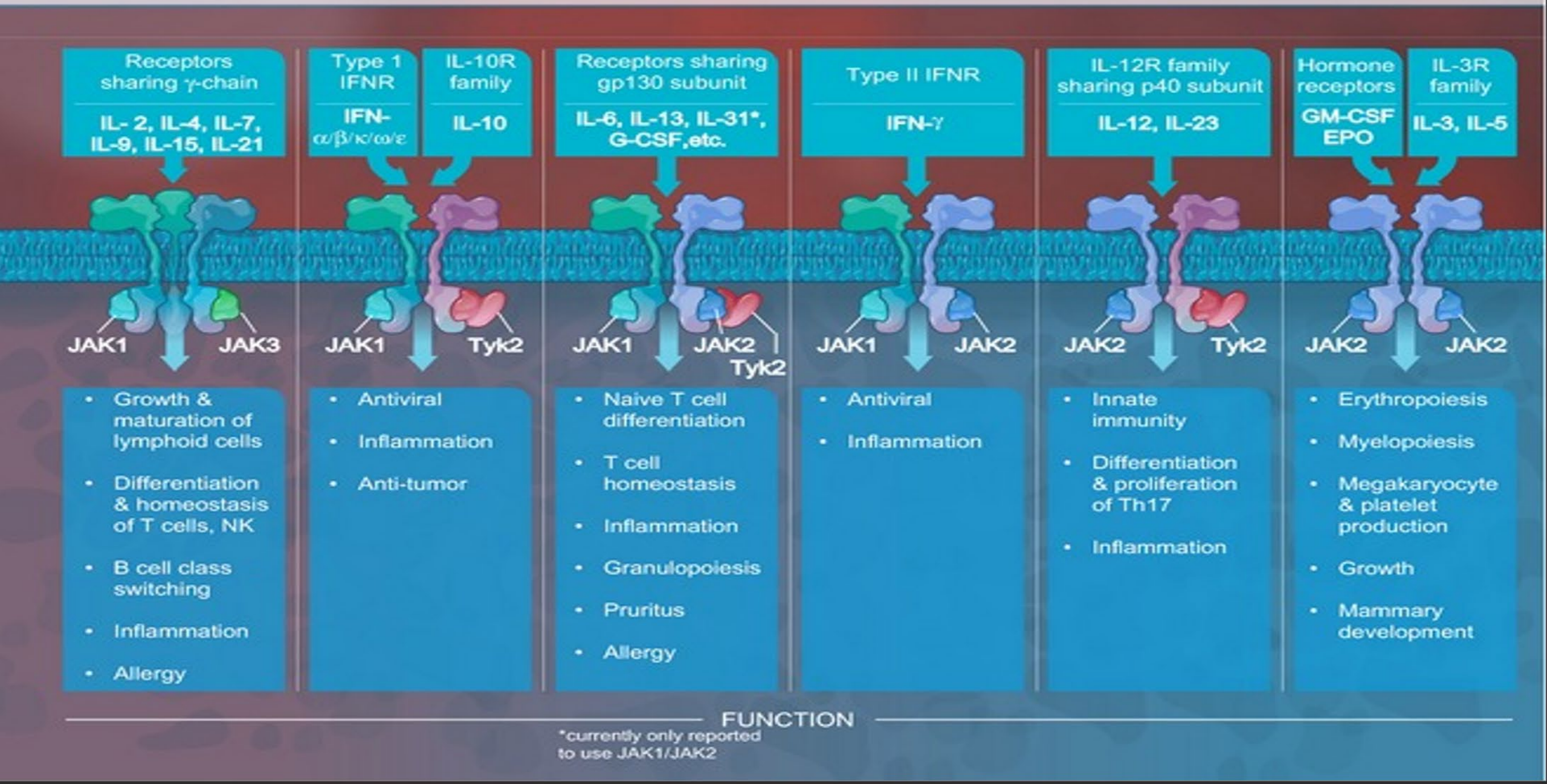


Fig 1. Janus kinase (JAK)-signal transducer and activator of transcription (JAK-STAT) pathway. *P*, Phosphorylation.

Multiple Functions of Janus Kinase Proteins



What About JAKs in Dermatologic Disease?

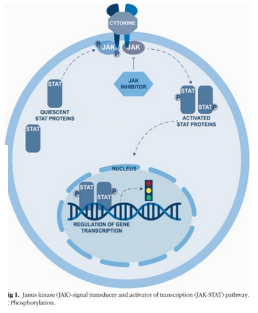


Table I. JAK proteins and associated cytokines that signal through each protein[3]

JAK protein	Cytokines	
JAK1	IFN-alpha, IFN-beta, IFN-gamma, IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-13, IL-15, IL-19, IL-21, IL-22, IL-27, IL-28, IL-29, and IL-35	AD, AA, V
JAK2	IL-3, IL-5, IL-6, IL-10, IL-11, IL-13, IL-12, IL-19, IL-22, IL-23, IL-27, IL-35, IFN-gamma, GM-CSF, G-CSF, EPO, GH, TPO, and leptin	AD, PD, HS, IBD, V
JAK3	IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, and IL-21	AD, AA, V
Tyk2	IFN-alpha, IFN-beta, IL-6, IL-10, IL-11, IL-12, IL-19, IL-22, IL23, IL-27, IL-28, and IL-29	PD, AD, AA, HS

EPO, Erythropoietin; *G-CSF*, granulocyte colony-stimulating factor; *GH*, growth hormone; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IFN*, interferon; *IL*, interleukin; *JAK*, Janus kinase; *TPO*, thrombopoietin; *Tyk2*, tyrosine kinase 2.

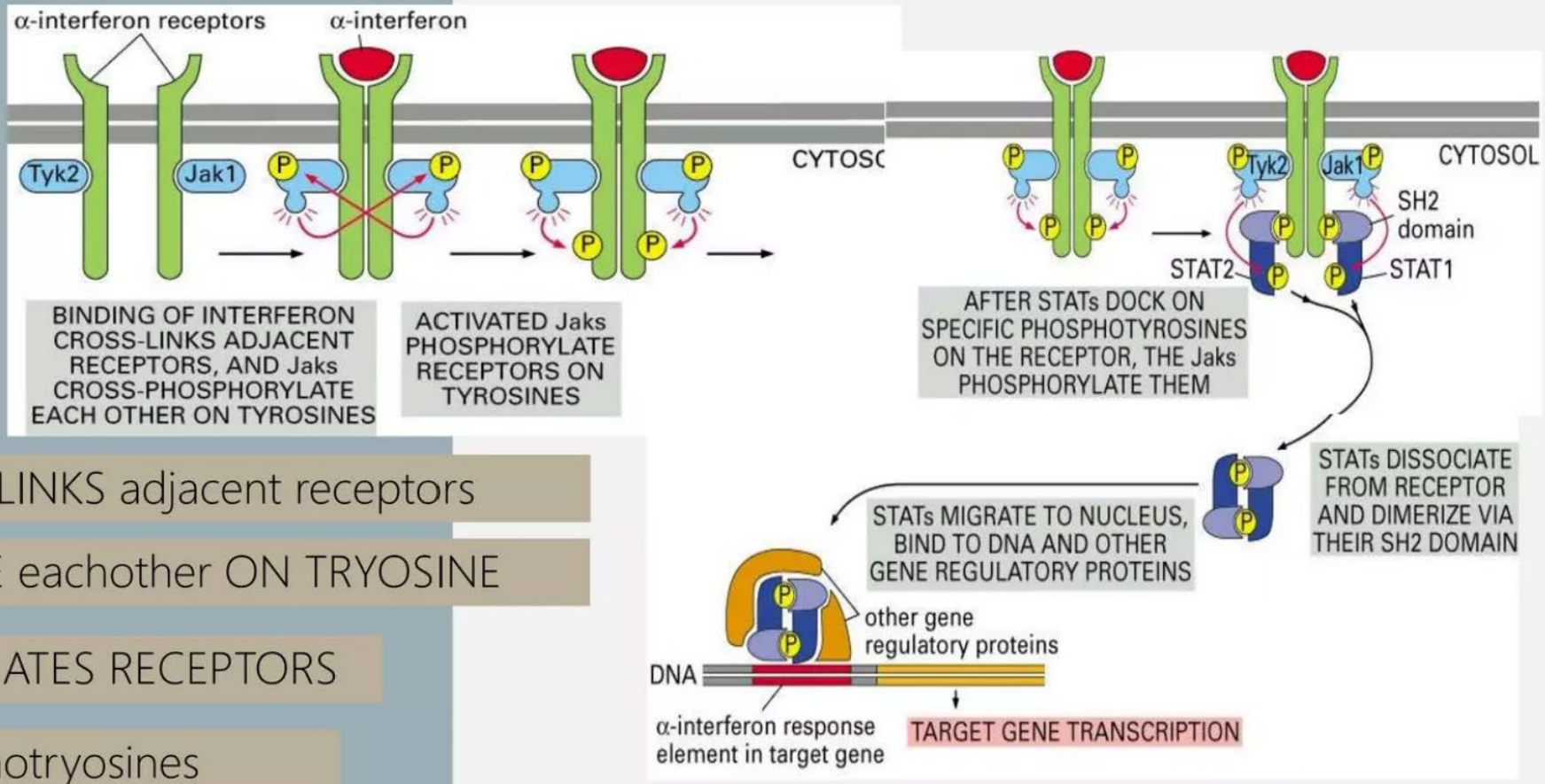
MECHANISM

SIGNALLING MOLECULE- alpha interferon

RECEPTOR- TYK2 & JAK2

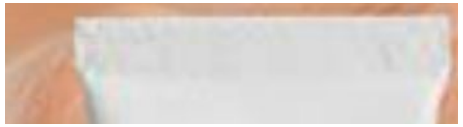
STAT ACTIVATED- STAT1 & STAT2

RESPONSE- increase cell response to viral infection



1. BINDING of interferon CROSS LINKS adjacent receptors
2. JAKs CROSS PHOSPHORYLATE eachother ON TRYOSINE
3. ACTIVATED JAKs PHOSPHORYLATES RECEPTORS
4. STATs DOCK on specific phosphotryosines
5. JAKs phosphorylates them
6. STATs DISSOCIATES from RECEPTORS
7. DIMERISES by SH2 domain
8. STATs migrates to NUCLEUS
9. BIND to DNA & other gene regulation proteins
10. TARGET GENE TRANSCRIPTION

JAK Inhibitors for AD: Topical Agents



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WARNING: RISK

See full prescribing infor

Tuberculosis (TB), invasive fun
some fatal, have occurred in pa
for latent TB; if positive, start t
[redacted] Monitor all patients
initial latent TB test is negative

Thrombosis

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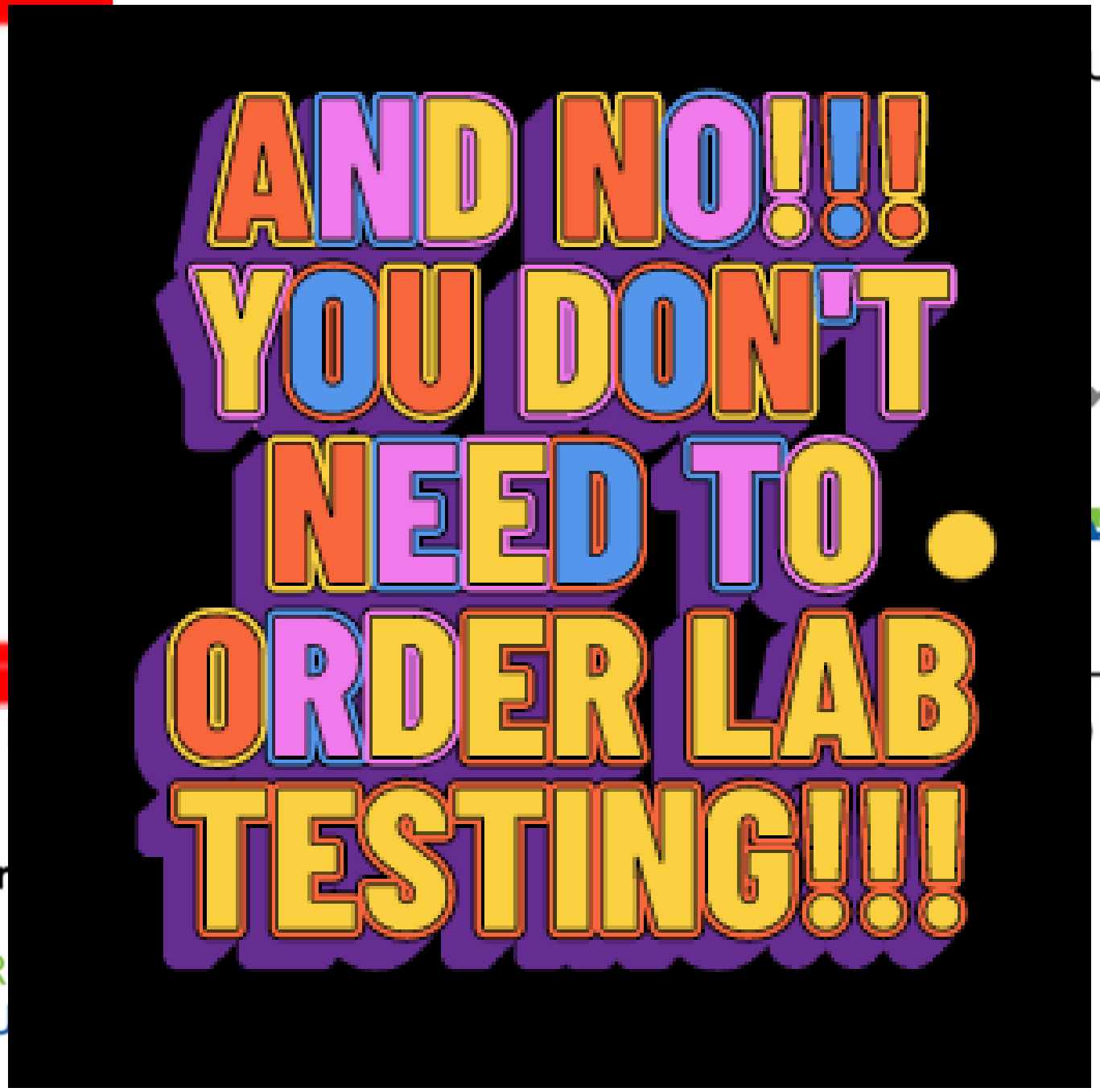
Kim BS et al. *J Allergy Clin Immunol* 2020;145(2):572-82.



UX cream

Mean Daily Worst Itch NRS Score

7
6
5
4
3
2
1

3.5
2.0
1.8

56

Number

Day 56

Vehicle 131

0.75% R 289

1.5% RU 314

ABSTRACT

Dermatologists treating atopic dermatitis are interested in the safety profile of the recently available JAK inhibitors, upadacitinib and abrocitinib, especially after they received boxed safety warnings. Long-term clinical trial data using these JAK inhibitors for the treatment of atopic dermatitis suggest that they are associated with very low incidence rates of malignancy, major adverse cardiac events, and thromboembolic events. However, a knowledge gap exists regarding the incidence of adverse events for JAK inhibitors compared to traditional systemic therapies used to treat poorly controlled atopic dermatitis as well as baseline rates in both atopic dermatitis and reference control populations. To address this gap, we analyzed data regarding adverse events of special interest for methotrexate, cyclosporine, and systemic corticosteroids and calculated the incidence of adverse events per 100 patient-years for these drugs. We also examined data regarding baseline incidence of adverse events in atopic dermatitis and control patients. We found that compared to upadacitinib and abrocitinib, traditional systemic therapies for atopic dermatitis demonstrated equal or higher incidence rates for malignancy (excluding non-melanoma skin cancer), non-melanoma skin cancer, major adverse cardiac events, and venous thromboembolism. Moreover, the use of upadacitinib and abrocitinib also exhibited either comparable or lower incidence of malignancy (excluding non-melanoma skin cancer), major adverse cardiac events, and venous thromboembolism, but higher rates of non-melanoma skin cancer, in comparison to baseline rates in atopic dermatitis or control patients. These findings indicate that JAK inhibitors should be positioned, at least based on safety, ahead of traditional systemic therapies for atopic dermatitis treatment.

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What's In The Pipeline?

Review

New and Upcoming Topical Treatments for Atopic Dermatitis: A Review of the Literature

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Abstract: Atopic dermatitis (AD) is a chronic inflammatory dermatosis with periods of exacerbation and remissions. AD is characterized by intense, persistent pruritus and heterogeneity in clinical symptomatology and severity. Therapeutic goals include the amelioration of cutaneous eruptions, diminishing relapses and eventually the disease burden. To date, topical corticosteroids (TCS) and calcineurin inhibitors (TCI) have yet been deemed the mainstay of topical treatments in AD management. Nevertheless, despite their indisputable efficiency, TCS and TCI are not indicated for continuous long-term use given their safety profile. While research in AD has concentrated predominantly on systemic therapies, more than 30 novel topical compounds are under development. The existing data appear encouraging, with some regimens that are already FDA-approved (ruxolitinib was the most recent in September 2021) and several pharmaceutical pipeline products for mild-to-moderate AD that are in an advanced stage of development, such as tapinarof, difamilast and roflumilast. Larger, long-term studies are still required to evaluate the efficacy and safety of these novel compounds in the long run and weigh their advantages over present treatments. In this review, we aim to provide an overview of the latest knowledge about AD topical treatments, echoing upcoming research trends.

check for updates

Citation: Sideris, N.; Paschou, E.; Bakirtzi, K.; Kiritsi, D.; Papadimitriou, I.; Tsentemeidou, A.; Sotiriou, E.;

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Table 1. JAK inhibitors for the topical treatment of AD.

Name	Selectivity	Phase	Age/Severity	Regimens
Delgocitinib	pan-JAK	approved (Japan)	approved for children 2–15, adults >16, moderate-to-severe	0.25% children 0.5% adults, b.i.d
Ruxolitinib	JAK1, 2	approved (USA)	approved for >12, on trial for 2–12, mild-to-moderate	1.5% b.i.d
Tofacitinib	JAK1, 3	II	18–60, mild-to-moderate	2% b.i.d for 4 weeks
Brepocitinib	JAK1, TYK2	II	12–75, mild-to-moderate	0.1%, 0.3%, 1%, 3% q.d, 0.3%, 1% b.i.d for 6 weeks
ATI-1777	JAK1, 3	II	18–65, moderate-to-severe	2% b.i.d for 4 weeks
Ifidancitinib	JAK1, 3	II	>18, moderate-to-severe	0.46% b.i.d for 4 weeks
Jaktinib	pan-JAK	II	18–65, mild-to-moderate	0.5%, 1.5%, 2.5% b.i.d, 2.5% q.d
Ivarmacitinib	JAK1	III	>12, mild-to-moderate	0.5%, 1%, 2% b.i.d

Deglocitinib

JapicCTI-173554:
Mean percent change in mEASI at week 4: –44.3% in the drug group vs. 1.7% for vehicle. (p < 0.001).

JapicCTI-173555: Safety: AEs in 69% of patients. 15.4% considered treatment-related. 1.4% considered serious (eczema herpeticum)

group was maintained, while that of the TCS group worsened.

Topical tofacitinib

JAK 1/3 inhibitor, was evaluated in a 4-week, phase 2a, randomized study (NCT02001181)

Sixty-nine **adults with mild-to-moderate AD** were randomized 1:1 to 2% tofacitinib or vehicle ointment b.i.d.

Percentage change from baseline in EASI score at week 4 was the primary endpoint.

Safety, local tolerability and pharmacokinetics were monitored.

The mean percentage change from baseline at week 4 in EASI score was −81.7% for tofacitinib and −29.9% for vehicle ($p < 0.001$).

Similarly, all other efficacy endpoints were significantly improved with tofacitinib compared to vehicle ($p < 0.001$). Safety was comparable between regimens

Brepoctinib

IGA score of 0/1 at week 6: 27.8–44.4% of patients on q.d drug vs. 10.8% for q.d vehicle.

EASI 90 at week 6: 27.8–41.7% of patients on 0.3%, 1%, and 3% q.d cream, vs. 10.8% for q.d vehicle, 27% of patients on 1% b.i.d cream, vs. 8.3% b.i.d vehicle.

Improvement of at least 4 points on the **PP-NRS at week 6**: 45.2% of patients on 1% cream q.d, **50% on 3% q.d**, and 40.7% on 1% b.i.d, vs. 17% for vehicle.

ATI-1777 - “soft” JAK1/JAK3 inhibitor

“Soft” JAK inhibitors are designed to provide JAK inhibition at the site of application and be rapidly metabolized in the systemic circulation.

A phase 2 randomized study (NCT04598269) has been completed, but results have not been published yet.

The developer has reported positive results in a press release [25], namely a 74.4% reduction in mEASI score from baseline at week 4 in the drug arm, compared to a 41.4% reduction in patients applying vehicle.

NO serious adverse events were reported

Ifidancitinib (ATI-502)

JAK1/JAK3 inhibitor evaluated in a phase 2, open-label safety study (NCT03585296).

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PGA of near clear with ≥2 grade improvement:

10.5%, 23.5%, 41.2% of patients at weeks 1, 2, and 4.

PDE- 4 Inhibitors

Table 2. PDE-4 inhibitors for the topical treatment of AD.

Name	Phase	Age/Severity	Regimens
Crisaborole	approved	>3 months, mild-to-moderate	2% b.i.d
Difamilast (OPA-15406)	III	15–70, mild-to-moderate	1% b.i.d for 4 weeks
Lotamilast (E6005, RVT-501)	II	20–64, all	0.2% b.i.d for 12 weeks
Roflumilast	II	18–65, moderate. 3 months—17 years currently on trial	0.5% b.i.d for 15 days, 0.05% and 0.15% for 4 weeks currently on trial
DRM02	II	18–70	0.25% b.i.d for 6 weeks
Hemay808	II	18–65, mild-to-moderate	1%, 3%, 7% for 29 days
PF-07038124	II	18–70, mild-to-moderate	0.01% q.d for 6 weeks
LEO-39652	I	>18, mild-to-moderate	3 weeks
Orismilast (LEO-32731)	I	>18, mild-to-moderate	3 weeks

Roflumilast

Roflumilast is a highly potent PDE4 inhibitor with ~25- to >300-fold higher potency than PDE4 inhibitors currently approved for dermatologic indications, crisaborole and

The Safety and Efficacy of Roflumilast Cream 0.15% and 0.05% in Patients With Atopic Dermatitis: Randomized, Double-Blind, Phase 2 Proof of Concept Study

FIGURE 3. Exploratory efficacy endpoint vIGA-AD. Data presented for intent-to-treat population. Error bars represent 95% confidence intervals. LS, least square; vIGA-AD, Validated Investigator Global Assessment–Atopic Dermatitis.

The "**IN**terventional **T**rial **E**valuatin**G** rofl**UM**ilast cream for the treatm**EN**t of a**T**opic dermatitis" (INTEGUMENT-1 and INTEGUMENT-2) are two identical Phase 3, parallel group, double blind, vehicle-controlled trials in which roflumilast cream 0.15% or vehicle was applied once daily for four weeks to individuals 6 years of age and older with mild to moderate AD involving ≥3% body surface area.

A total of 1,337 individuals were randomized across both studies. The primary endpoint was IGA Success, defined as vIGA-AD score of 'clear' or 'almost clear' plus a 2-grade improvement from baseline at Week 4. Multiple secondary endpoints were also evaluated, including itch as measured by WI-NRS as well as the proportion of subjects who attained an EASI-75 at Week 4.

After completing INTEGUMENT-1 and INTEGUMENT-2, individuals were eligible to enroll in an open-label extension study (INTEGUMENT-OLE) evaluating treatment with once-daily roflumilast cream 0.15% for up to 12 months.

Application site pain	0	1 (2.2)	1 (2.2)
Atopic dermatitis worsening	0	0	1 (2.2)
Skin laceration	0	1 (2.2)	0

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Roflumilast 0.05%: mild rash (n=1) and moderate application site pain (n=1); vehicle: mild application site pain (n=1) and moderate worsening of AD (n=1).
[b]Mild traumatic spinal cord compression is considered unrelated to study drug.

J Drugs Dermatol. 2023;22(2):139-147. doi:10.36849/JDD.7295

PDE-4 Inhibitors

The role of PDE4 activity in the circulating leukocytes in AD pathology = the degradation of cyclic adenosine monop

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ISGA score 0/1 with ≥2 grade improvement at day 29:

32.8% (AD-301) and 31.4% (AD-302) reduction vs. 25.4% (p = 0.038) and 18% (p < 0.001) for vehicle.

Rapid improvement in pruritus (as early as 24 h after the first application) and the normalization of epidermal pathology toward nonlesional skin

Difamilast

OPA-15406 is a novel topical treatment for AD with high selectivity for phosphodiesterase-4-B.

IGA 0–1 with ≥2 grade improvement at week 4:

38.46% of patients in the ointment group vs. 12.64% for vehicle ($p < 0.0001$)

Primary endpoint of IGA 0,1 with ≥2-grade improvement at week 4 was achieved by 38.46% of patients in the ointment group, compared to 12.64% in the vehicle.

No serious adverse events were reported.

Lotamilast

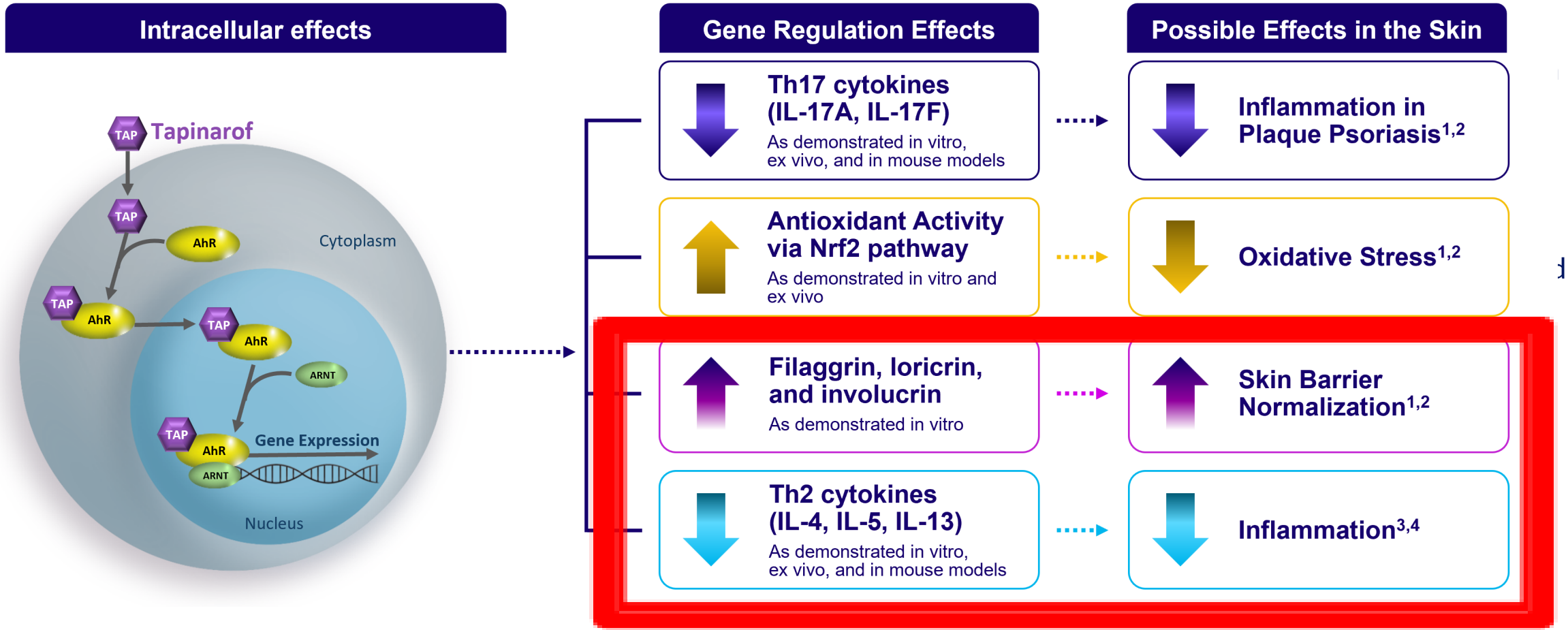
Long-term safety and tolerance: Neither death nor serious TEAEs were encountered in the entire study period.

In the randomization phase, the incidence of TEAEs was 50.0% in the drug group vs. 38.5% for vehicle group.

The incidence of TEAEs leading to study withdrawal was 9.6% in the drug group and 15.4% for vehicle group.

Tapinarof Has Multiple Effects on AhR-Mediated Gene Expression[1-3]

Tapinarof is a novel, first-in-class, small-molecule topical aryl hydrocarbon receptor (AhR) agonist.
The specific mechanisms by which tapinarof exerts its therapeutic action in psoriasis patients are unknown.



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Dermavant Reports Positive Topline Results from ADORING 2 Atopic Dermatitis Phase 3 Trial of VTAMA® (tapinarof) Cream, 1% Once Daily in Adults and Children as Young as 2 Years Old

Published: Mar 15, 2023

Tapinarof Phase 3 Data (8 weeks – ADORING 2)

Endpoint	VTAMA 1% QD	Vehicle QD	P value
vIGA-AD success[1]	46.4 %	18.0 %	<0.0001
EASI75[2]	59.1 %	21.2 %	<0.0001
≥4-point reduction in PP-NRS[3]	52.8 %	24.1 %	0.0015

Emerging therapies

AD Skin Microbiome Therapies

S.aureus toxins induce **mast cell degranulation**, promoting innate and adaptive immune responses, and **induce IL-1b production from monocytes**. In the dermis, through the defective skin barrier, **S.aureus interacts with immune cells and triggers cytokine production including IL-4, IL-13, IL-22 and TSLP**:

Roseomonas mucosa (R.mucosa) is a commensal Gram-negative bacteria used in an open-label trial with topical application twice-weekly for 6 weeks in both adults and children (9–14 years old) with AD was associated with improvements in SCORAD, pruritus and a reduction in TCS use. There were no significant AEs

Staphylococcus hominis A9 (ShA9) is another healthy human skin microbiome bacterium trialed as a topical therapy for AD. ShA9 killed S.aureus on the skin of mice and inhibited the expression of the toxin psmα that promotes inflammation. Phase 1, randomized, 1-week trial topical ShA9 or vehicle was applied on the forearm skin of 54 adults with S. aureus-positive AD. The primary endpoint of safety was met, and a small improvement of AD lesions was also induced, rendering ShA9 a safe and potentially beneficial future treatment

Nitrosomonas eutropha is an ammonia-oxidizing Gram-negative bacterium able to produce nitric oxide, which is an important mediator with beneficial metabolic and potential anti-inflammatory properties. Results of three phase 1 and 2 trials are pending, although prelimary data show pruritus and AD appearance were significantly improved in adults and children

AD Skin Microbiome Therapies

R.mucosa	50% improvement in SCORAD: 66.7% of patients	75% improvement in SCORAD: 40% of patients. Subjective pruritus: significantly decreased.
FB-401	EASI50: 58% in drug arm vs. 60% in placebo arm	-
ShA9	Safety through day 8 compared to vehicle: Significantly fewer AEs in participants treated with ShA9 ($p = 0.044$)	EASI and SCORAD: no significant difference Decrease in S. aureus and increased ShA9 DNA: endpoints met
Nitrosomonas eutropha	Not yet available, positive results in pruritus and AD appearance reported in press release	-
Omiganan gel	*S.aureus* reduction at day 28: Statistically significant in the omiganan 1% ($p = 0.03$) and 2.5% ($p = 0.01$) vs. vehicle.	Clinical improvement evaluated by EASI, SCORAD, IGA, POEM, DLQI and NRS: no improvement
ATx201	Safety: safe and well tolerated	Expression of biomarkers related to skin-barrier function: Significantly increased ($p < 0.05$). Histological responders: 51.7% of those receiving 2% cream vs. 31.0% for vehicle.

ISI: Itch Severity Item, PP-NRS: Peak Pruritus Numerical Rating Scale, SPA: Subject's Pruritus Assessment, DLQI: Dermatology Life Quality Index, VRS: verbal rating scale, PAP: Participants' Assessment of Pruritus.

New Generation Emollients

Non-medicated emollients containing active ingredients termed “emollient plus” or AD therapeutic moisturizers that improve skin barrier with antipruritic, anti-inflammatory and antioxidant effects.

Active ingredients are, for example, ceramides, saponins, colloidal oatmeal and nonpathogenic bacterial lysates from Aquaphilus dolomiae or Vitreoscilla filiformis with possible molecular targets as it emerges from in vitro and clinical research data

A prospective, doubleblind, placebo-controlled clinical study demonstrated that patients with mild AD who received cream with 5% Vitreoscilla filiformis decreased SCORAD levels and pruritus significantly compared with those who received placebo

These lysates might **influence the skin microbiome due to the reduction in Staphylococcus aureus colonization** and display immunomodulatory effects locally on the skin.

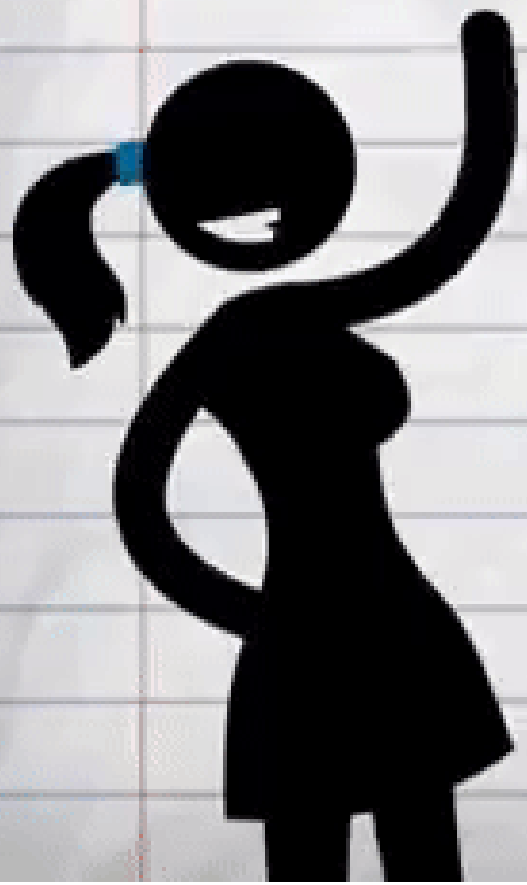
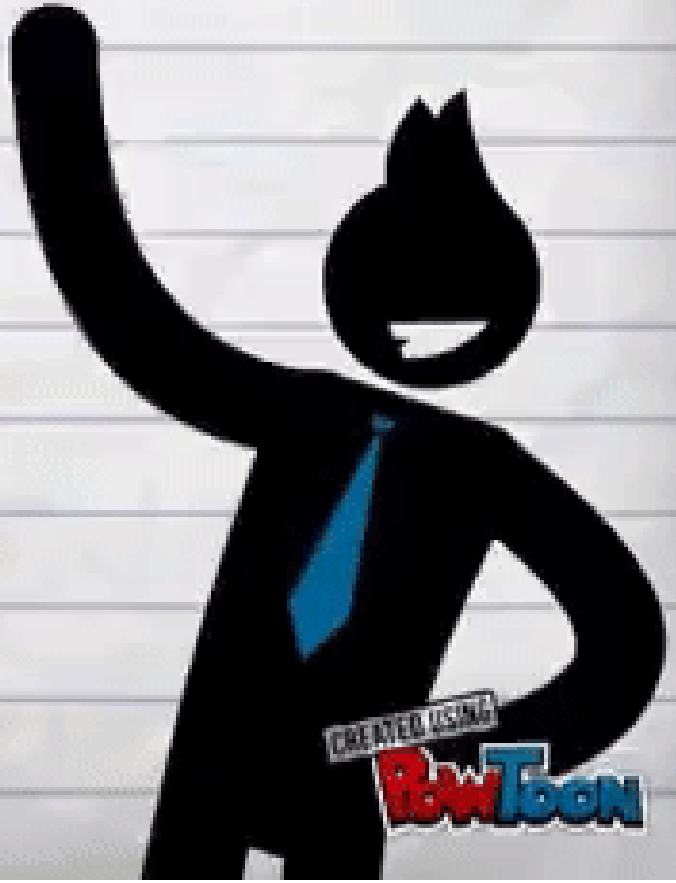
Therapeutic approach targeting prevention of relapses and stabilization of AD skin

Emerging therapies

Agent	Mechanicm of Action	NCT ID
ALX-101 Gel 1.5% (Rovazolac)	LXR agonists	NCT03175354
AM1030-CREAM	5-HT2BR antagonist	NCT02379910
AMTX-100 CF	Nuclear transport modifier (NTM)	NCT04313400
ASN008 (*1)	Targets small afferent sodium channels/Antipruritic	NCT03798561
Atuzabrutinib (SAR 444727 or PRN 473)	BTK inhibitor	NCT04992546
Aurstat Hydrogel	Emolient/Antipruritic	NCT01905631
BEN2293	TRK inhibitor	NCT04737304
BioLexa	Antibacterial	NCT04544943
BMX-010	Antioxidant	NCT03381625
BPR 277	Kallikrein-related peptidase	NCT01428297
BX005-A (*2)	Phage cocktail targeting S.aureus	NCT05240300
CD 5024/Ivermectin (Soolantra)	Chloride channel agonists	NCT03250624
CYCLATOP(Cyclosporine 5% solution) (*3)	Calcineurin inhibitor	NCT02865356
DBI-001 (*4)	Antibacterial	NCT05253755
DMT210 Topical Gel	G protein-coupled receptor agonist	NCT02949960
DS 107/DGLA (*5)	Bioactive lipid (dihomo-γ-linolenic acid) inhibiting the expression of CD40	NCT02925793 NCT03676036 NCT03676933
Ectoin Dermatitis Cream 7% (EHK02)	Emolient	NCT04097327
FMX114 (tofacitinib and fingolimod) (*6)	Jak inhibitor and sphingosine-1-phosphate receptor modulator	NCT04927572
GM-XANTHO	Botanical drug balm	NCT04369846
HAT01	Botanical complex	NCT03089229
HL-009 Liposomal Gel(Cobamamide)	Vitamin B12 analogues, Nitric oxide inhibitor.	NCT01568489
HY209 Gel/Taurodeoxycholic acid	G Protein Coupled Receptor 19(GPCR19) agonist	NCT04530643
IDP-124	Undefined mechanism	NCT03058783 NCT03002571
Isopentenyltheophylline 0.44% + Glycerin 4.56%	Undefined mechanism	NCT05057351
Jaungo (Shiunko in Chinese) (*7)	Herbal ointment	NCT02900131
Lactibiane Topic AD	Emolient/Cosmetic product	NCT04728269
Lactobacillus reuteri (ADreuteri)	Probiotic	NCT04265716

Emerging Therapies

Table 4. *Cont.*

Agent	Mechanicm of Action	NCT ID
Levagen+/ Palmitoylethanolamide (PEA)	Endocannabinoid-like lipid mediator	NCT05003453
Menthoxypropanediol	Anti-TRPM8/Antipruritic	NCT03610386
MH004	Unknown	NCT04815148
NLAC (Natural Lactic Acid-enriched Cream)	Emolient	NCT05092464
PR022 (Hypochlorous acid)	Antiseptic	NCT03351777
Q301(Zileuton) (*8)	leukotriene inhibitor	NCT03571620 NCT02426359
RelizemaTM cream	Antioxidant/ Antipruritus	NCT05259774
SB414 (Berdazimer sodium) (*9)	Nitric oxide donors	NCT03431610
SB011	GATA3 transcription factor inhibitor	NCT02079688
SNG100	Unknown	NCT04615962
TER-101	Unknown	NCT04753034
Topialyse Baume Barrière (TOPIA)	Emolient	NCT05006300
ZEP-3Na	synthetic analogue of a compound of rattle snake venom	NCT04307862
ZK245186 (Mapracorat)	Selective glucocorticoid receptor agonists (SEGRAs).	NCT01228513 NCT00944632 NCT01359787
0.5% Cannabidiol and 1% Hemp Oil (Celosia)	Emolient	NCT04045314
2.5% and 5% Cis-urocanic Acid	Emolient	NCT01320579

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