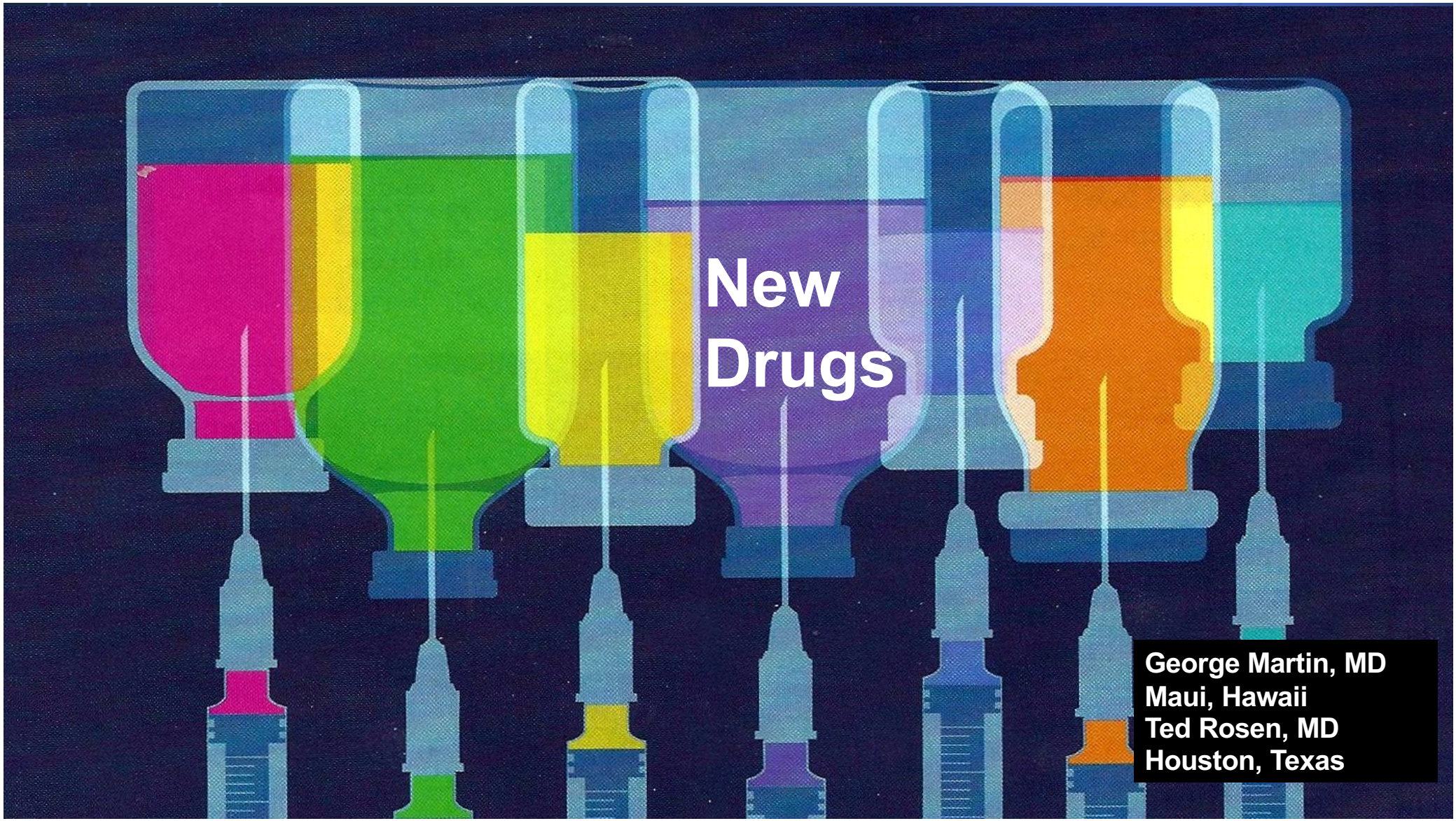

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Dr. Martin's Disclosures:

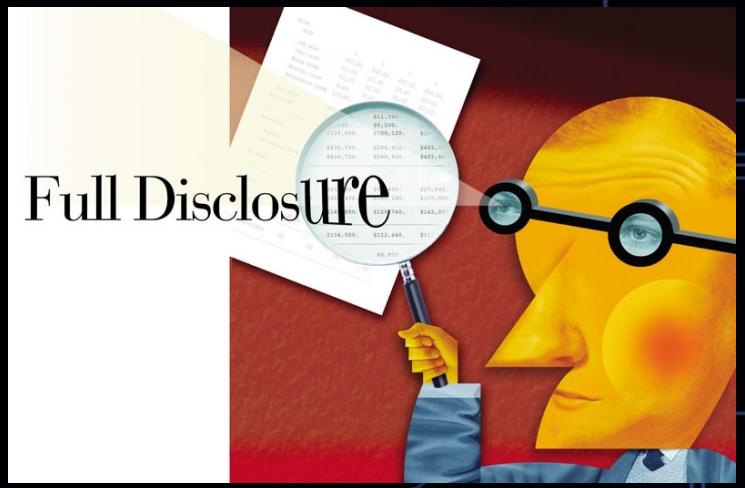
Scientific Advisory Board: Bristol Meyers Squibb, DUSA/SUN, AbbVie, Ortho/Bausch Health, Galderma, Pfizer, LEO, Celgene, Janssen, Horizon, UCB, Trevi, Almirall, Evelo, Organogenesis,, Dermavant, Incyte

Consultant: Bristol Meyers Squibb, DUSA/SUN, AbbVie, Ortho/Bausch Health, Galderma, Pfizer, LEO, Celgene, UCB, Trevi, Almirall, Lilly, Evelo

Speaker: UCB, Almirall, LEO, Incyte, Dermavant

Dr. Rosen's Disclosures:

Advisory Board, with honorarium:
Almirall
Verrica
Consultant
DermTech



Pediculosis capitis

Widespread pyrethroid resistance

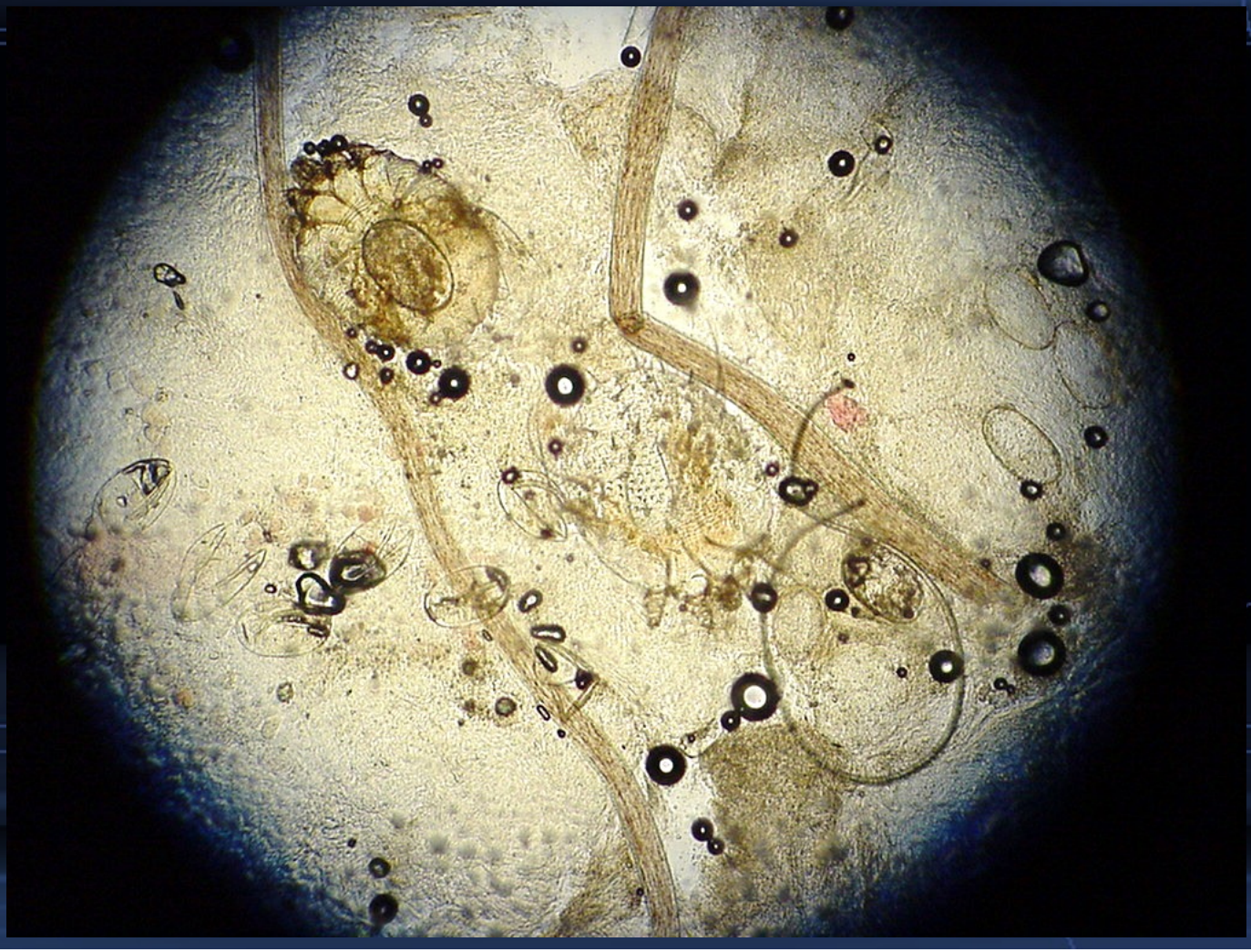
Head Lice: Selfie Craze Makes It Adult Problem


GOOD
NEWS

Good Head Lice News

Ivermectin lotion 0.5%
OTC since 10/2020
Now readily available
No resistance
Approved FOR ≥ 6mo age
Single 10 minute application
75% patients lice-free in 2 weeks
Commercial price $340
But online coupons down to $35

Scabies



> Hautarzt. 2020 Jun;71(6):447-454. doi: 10.1007/s00105-020-04608-0.

[Increase of scabies and therapy resistance among German military personnel : An 8-year follow-up study in the Department of Dermatology of the Armed Forces Hospital Berlin, Germany (2012-2019)]

[Article in German]

E Elsner [1], T Uhlmann [2], S Krause [2], R Hartmann [3]

Resistant *Sarcoptes scabiei*

> Hautarzt. 2020 May;71(5):374-379. doi: 10.1007/s00105-020-04561-y.

[Scabies therapy in Germany : Results of a nationwide survey with a special focus on the efficacy of first-line therapy with permethrin]

[Article in German]

B Hackenberg [1], O N Horváth [2], M Petachti [3], R Schult [4], N Yenigün [5], P Bannenberg [6]

Hautarzt. 2020 May;71(5):374-379
Hautarzt. 2020 May;71(7):447-454

JEADV

Journal of The European Academy of Dermatology and Venereology

EADV

Letter to the Editor

Scabies is becoming less sensitive to permethrin therapy

R. Balestri, M. Magnano ✉, S.D. Infusino, L. Rizzoli, C.R. Girardelli, G. Rech

First published: 26 July 2021 | https://doi.org/10.1111/jdv.17538

Resistant *Sarcoptes scabiei*

J Eur Acad Dermatol Venereol 2021; July 26. doi: 10.1111/jdv.17538

Spinosad for Scabies

- Spinosyns (natural) and spinosoids (synthetic)
- Fermentation products soil actinomycete Saccharopolyspora spinosa
- Most abundant: Spinosyn A and Spinosyn D (Thus: Spinosad)
- Tetracyclic macrolides + two saccharides
- Potent insecticides: disrupt nicotinic acetylcholine receptors
- -Causes hyper-excitation of insect neurologic system
- Selective; no activity against mammals, avian and aquatic animals
- Spinosad 0.9% suspension already approved for head lice
- NEW DATA: USE FOR SCABIES: Single application (6-8hr)
  - Complete cure > vehicle (Vehicle contains benzyl alcohol)
- FDA Approved for scabies: Apr 29, 2021 (Age $\geq$ 4yr)

NCT02485717 (3-23-2020) and NCT02485704 (3-19-2020)

Spinosad: Complete Cure (Day 28) After 1 Application

TRIAL	ACTIVE	VEHICLE
1	69.8%	46.5%
2	83.9%	34.5%

- Application site erythema 3%
- Application site irritation 1%
- Everything else < 1%

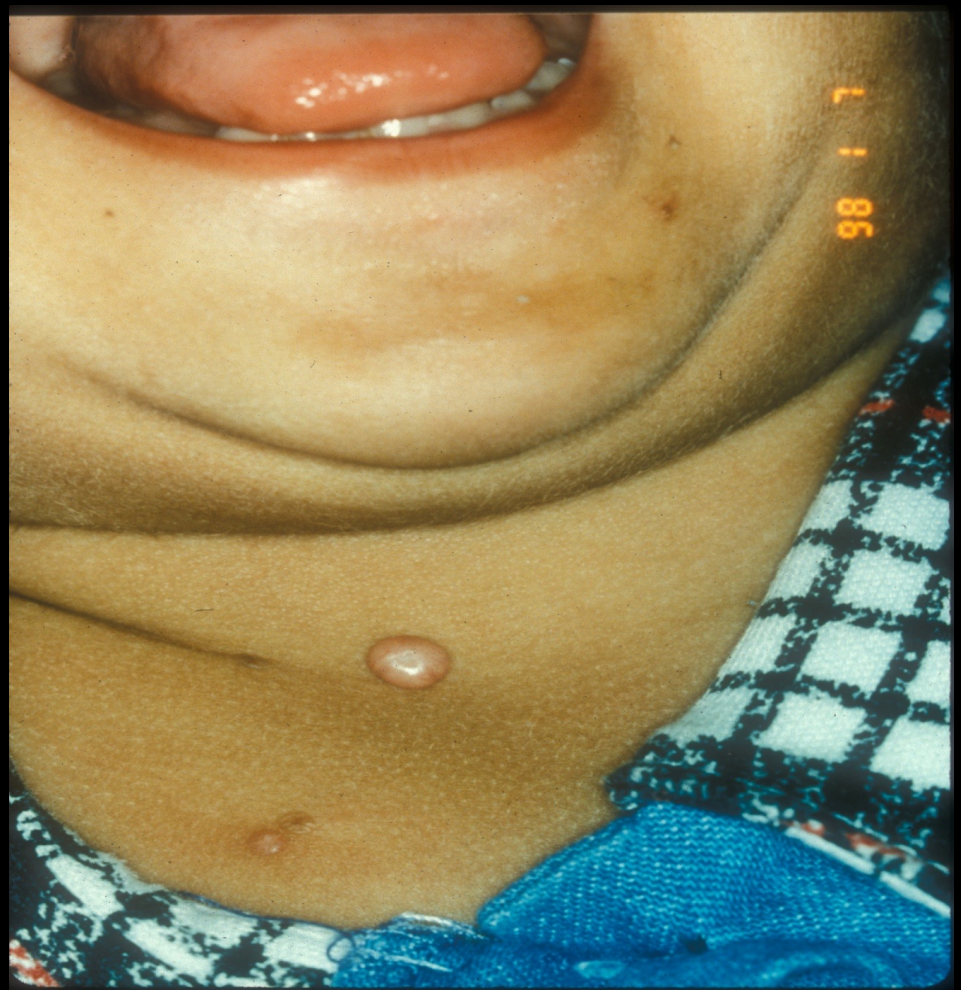
NCT02485717 (3-23-2020) and NCT02485704 (3-19-2020)

Spinosad at 0.9% in the treatment of scabies: Efficacy results from 2 multicenter, randomized, double-blind, vehicle-controlled studies

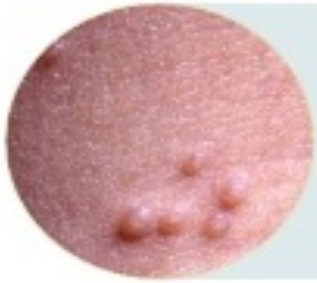
Jeffrey C. Seiler, MD,[a] Richard C. Keech, MD,[b] Julie L. Aker, MT(ASCP),[c] William Miller, MD,[c] Christopher Belcher, MD,[d] and Kerry W. Mettert, MBA, MT(ASCP)[e]
West Palm Beach, Florida; Anaheim, California; Indianapolis and Carmel, Indiana

J Am Acad Dermatol. 2022;86(1):97-103

Molluscum: New Therapy….Coming!



Molluscum Contagiosum (MC)



Molluscum contagiosum is caused by a pox virus and is characterized by small, round, firm, umbilicated, often painless bumps[1-4]

There are **4 known types** of MC virus (MCV1, 2, 3, and 4), with MCV1 and MCV2 being the most common[2,5]

MC can take a long time to resolve, ranging from **13 months to 5 years**[4,6,7]

Absence of an animal or cell culture model for MC poses a **research challenge**[8]

~6 million Americans suffer from MC each year[9,10]

Affects mostly children, yet adults can be impacted, too[7]

Known psychosocial complications of MC include stigma, disfiguring lesions and scars, and bullying[1,6,8]

Up to 73% of children go untreated[11]

Currently, there is **no FDA-approved** medication for MC[12]

FDA, US Food and Drug Administration.

1. Silverberg NB. *Cutis*. 2019;104(5):301-305. 2. Meza-Romero R, et al. *Clin Cosmet Investig Dermatol*. 2019;12:373-381. 3. Bhatia N. *Pract Derm*. 2021;34-35. 4. Butala N, et al. *Pediatrics*. 2013;131(5):e1650-e1653. 5. Coyner T. *J Dermatol Nurs Assoc*. 2020;12(3):115-120. 6. Olsen JR, et al. *Lancet Infect Dis*. 2015;15(2):190-195. 7. Molluscum contagiosum: diagnosis and treatment. American Academy of Dermatology. Accessed July 12, 2022. https://www.aad.org/public/diseases/a-z/molluscum-contagiosum-treatment. 8. Braue A, et al. *Pediatr Dermatol*. 2005;22(4):287-294. 9. About molluscum. Accessed December 3, 2021. https://aboutmolluscum.com/. 10. Global molluscum contagiosum epidemiology forecast to 2028. December 16, 2019. Accessed December 3, 2021. https://www.businesswire.com/news/home/20191216005378/en/Global-Molluscum-Contagiosum-Epidemiology-Forecast-to-2028—ResearchAndMarkets.com. 11. Basdag H, et al. *Pediatr Dermatol*. 2015;32(3):353-357. 12. Ong SK, et al. *Pediatr Dermatol*. 2021;38(5):1400-1403.

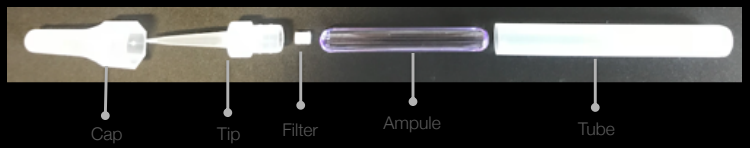
VP-102 (Cantharidin, 0.7% w/v) Drug-Device Combination Product Delivered via a Single-Use Applicator

Topical solution in a single-use applicator

- Active ingredient cantharidin (0.7% w/v) in a unique topical formulation
- Single-use applicator to reduce cross-contamination and facilitate application of the topical solution
- Small opening allows for targeting of affected skin

GMP-controlled, shelf-stable, consistent topical formulation

- Allows for reliable dosing/administration
- Bittering agent to deter oral ingestion
- Visualization agent to identify treated lesions



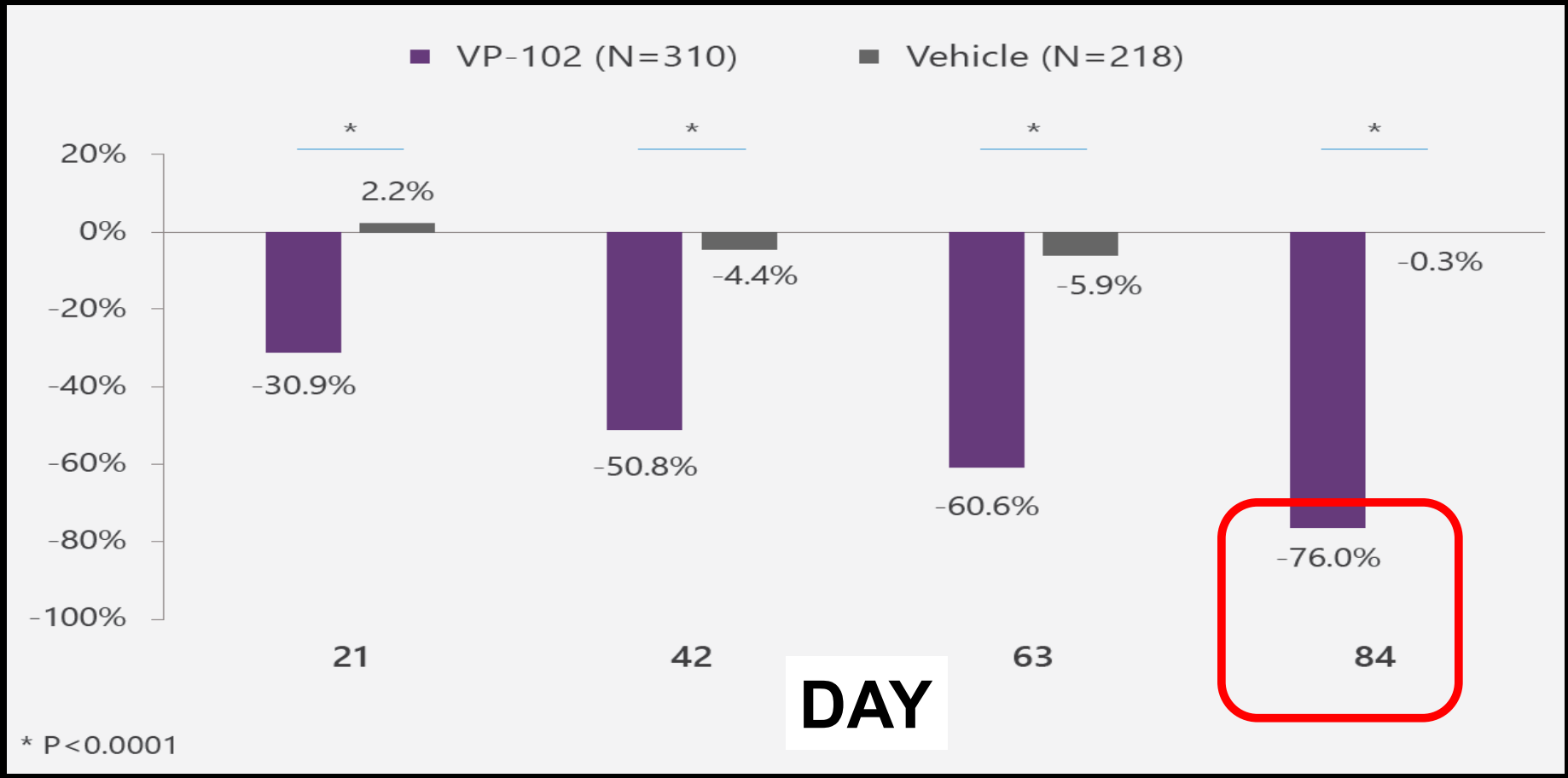
- Note: VP-102 is not FDA-approved, for presentation purposes only

Phase 3 Clinical Trial Results for Safety and Efficacy in Molluscum Contagiosum Published[1]

1. Eichenfield *JAMA Derm* 2020

Pooled Percent Change in Molluscum Contagiosum Lesion Count from Baseline

ITT population[1]



1. Eichenfield *Am J Clin Derm* 2021

Pooled Safety of VP-102: Treatment Emergent AEs by Severity

	VP-102 (N=311)			Vehicle (N=216)		
At Least One Incidence: N (%)	Mild	Moderate	Severe	Mild	Moderate	Severe
Application Site Vesicles	187 (60.1)	100 (32.2)	11 (3.5)	59 (27.3)	4 (1.9)	0
Application Site Pruritus	145 (46.6)	23 (7.4)	1 (0.3)	62 (28.7)	13 (6.0)	0
Application Site Pain	127 (40.8)	59 (19.0)	7 (2.3)	34 (15.7)	2 (0.9)	0
Application Site Scab	120 (38.6)	27 (8.7)	0	44 (20.4)	3 (1.4)	0
Application Site Discoloration	87 (28.0)	12 (3.9)	1 (0.3)	25 (11.6)	2 (0.9)	0
Application Site Erythema	73 (23.5)	65 (20.9)	1 (0.3)	43 (19.9)	15 (6.9)	0
Application Site Dryness	58 (18.6)	5 (1.6)	0	30 (13.9)	1 (0.5)	0
Application Site Edema	21 (6.8)	8 (2.6)	0	7 (3.2)	3 (1.4)	0
Application Site Erosion	20 (6.4)	2 (0.6)	0	2 (0.9)	0	0

1. Eichenfield *Am J Clin Derm* 2021

Phase 3 Results: Nitric Oxide Releasing Berdazimer 10.3% Gel for Molluscum

Efficacy and Safety of Topical Nitric Oxide–Releasing Berdazimer Gel in Patients With Molluscum Contagiosum: Results from B-SIMPLE4, A Phase 3 Randomized Clinical Trial

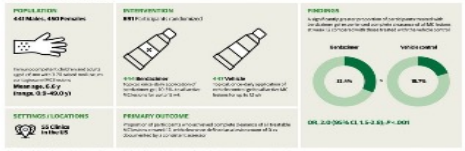
John C. Browning, MD,[1] Carolyn Enloe, MPH,[2] Martina Cartwright, PhD,[2] Adelaide Hebert, MD,[3] Tomoko Maeda-Chubachi, MD, PhD, MBA[2]

[1]Texas Dermatology & Laser Specialists, San Antonio, TX; [2]Novan Inc, Durham, NC; [3]UTHealth McGovern Medical School, Houston, TX

Funding Sources and Disclosures Funded by Novan. Drs. Browning and Hebert were B-SIMPLE4 investigators; Ms. Enloe and Drs. Cartwright and Maeda-Chubachi are Novan employees.

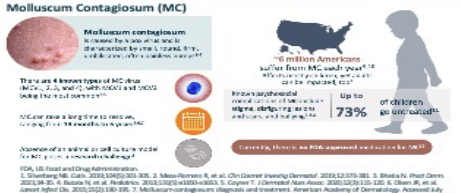
Synopsis

RCT: Efficacy and Safety of Topical Nitric Oxide–Releasing Berdazimer Gel in Patients With Molluscum Contagiosum



Importance

Molluscum Contagiosum (MC)



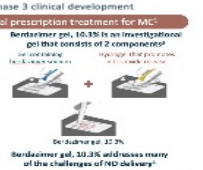
Berdazimer Gel, 10.3%

- A nitric oxide (NO)–releasing medication in phase 3 clinical development

If FDA approved, it could be the first potential prescription treatment for MC

- Berdazimer sodium is a new chemical entity (NCE)
- It is a macromolecule composed of a polyhexamethylene backbone with covalently bonded N-diazeniumdiolate NO donors
- Co-administered with a proton donor promotes NO release from the macromolecule

Berdazimer gel, 10.3% is an investigational gel that consists of 2 components



Berdazimer gel, 10.3% addresses many of the challenges of NO delivery

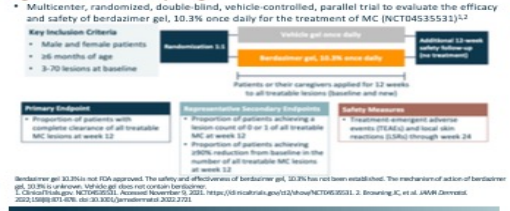
Objective

- To assess the efficacy and safety of berdazimer gel, 10.3%, a novel topical NO–releasing medication, for the treatment of MC

Methods

Figure 1: B-SIMPLE 4 Study Design

- Multicenter, randomized, double-blind, vehicle-controlled, parallel trial to evaluate the efficacy and safety of berdazimer gel, 10.3% once daily for the treatment of MC (NCT04535531)[1,2]

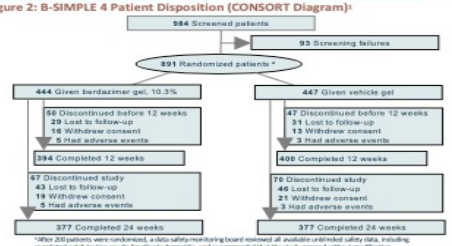


Berdazimer gel 10.3% is not FDA approved. The safety and effectiveness of berdazimer gel, 10.3% has not been established. The mechanism of action of berdazimer gel, 10.3% is unknown. Vehicle gel does not contain berdazimer.

1. ClinicalTrials.gov. NCT04535531. Accessed November 9, 2021. https://clinicaltrials.gov/ct2/show/NCT04535531. 2. Browning JC, et al. *JAMA Dermatol*. 2022;158(8):871-876. doi:10.1001/jamadermatol.2022.2721

Results

Figure 2: B-SIMPLE 4 Patient Disposition (CONSORT Diagram)[1]

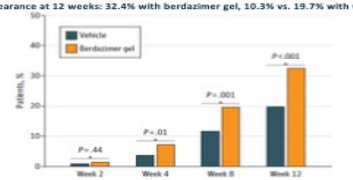


*After 200 patients were randomized, a data safety monitoring board reviewed all available unblinded safety data, including completed patch testing results for allergic dermatitis, and recommended that the study proceed without modification.

Primary Endpoint

Figure 3A: Berdazimer Gel, 10.3% Demonstrated Statistically Significant Efficacy in the Primary Endpoint of Complete Clearance of All Lesions By Week 12[1]

Clearance at 12 weeks: 32.4% with berdazimer gel, 10.3% vs. 19.7% with vehicle



Encore (B-SIMPLE4 efficacy and safety results published in *JAMA Dermatology*[1]).

Secondary Endpoints

- Berdazimer gel, 10.3% demonstrated statistically significant efficacy in **secondary endpoints** of 0 or 1 remaining lesion and ≥90% clearance at week 12[1]

Figures 3B, 3C: A Higher Proportion of Patients Treated with Berdazimer Gel Compared with Vehicle Gel Had 0 Or 1 Lesion at Week 12 and ≥90% Complete Clearance at Week 12

Figure 3B: ≤1 lesion at week 12

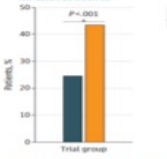


Figure 3C: ≥90% clearance at week 12

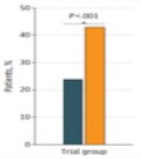
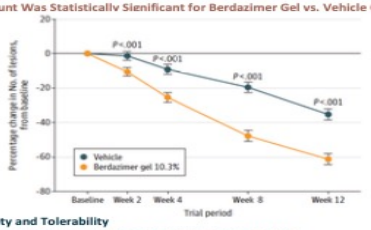


Figure 4: In B-SIMPLE 4 the Mean Percent Change from Baseline Lesion Count Was Statistically Significant for Berdazimer Gel vs. Vehicle Gel[1]



Safety and Tolerability

Table 1: Treatment-emergent Adverse Events (TEAEs)

- TEAEs were mostly mild if they occurred, with few TEAEs leading to study drug discontinuation[1]

TEAE	Berdazimer gel, 10.3% (n=444) n (%)	Vehicle gel (n=447) n (%)
Patients with ≥1 TEAE	181 (40.8)	108 (24.2)
Patients with ≥1 serious TEAE	0	1 (0.2)[a]
Patients with ≥1 TEAE leading to study drug discontinuation	18 (4.1)	3 (0.7)
Patients with a TEAE leading to death	0	0
Maximum severity		
Mild	108 (24.3)	75 (16.8)
Moderate	7 (17.8)	26 (5.8)
Severe	5 (1.1)	2 (0.4)
Patients with TEAE leading to study drug discontinuation	18 (4.1)	3 (0.7)
Application-site pain	10 (2.3)	3 (0.7)
Application-site dermatitis	4 (0.9)	0

[a] Herpes zoster (moved not treatment related).

Table 2: TEAEs At Application Site Affecting ≥5% of Patients in Either Group, By Severity n (%)

	Berdazimer gel, 10.3% (n=444)			Vehicle gel (n=447)		
Application-site TEAE	Mild	Moderate	Severe	Mild	Moderate	Severe
Patients with ≥1 TEAE	108 (24.3)	78 (17.6)	5 (1.1)	75 (16.8)	26 (5.8)	2 (0.4)
Application-site pain [a]	64 (14.4)	18 (4.1)	1 (0.2)	21 (4.7)	2 (0.4)	0
Application-site erythema	25 (5.6)	26 (5.9)	1 (0.2)	5 (1.1)	1 (0.2)	0
Application-site pruritus	25 (5.6)	8 (1.8)	0	4 (0.9)	1 (0.2)	0
Application-site exfoliation	11 (2.5)	16 (3.6)	0	0	0	0
Application-site dermatitis	8 (1.8)	16 (3.6)	2 (0.5)	1 (0.2)	2 (0.4)	0
Application-site scar [b]	20 (4.5)	1 (0.2)	0	28 (6.3)	0	0

[a] **Transient pain** is discussed in the text, not the table.
[b] **Application-site scar**: The US Food and Drug Administration required that temporary epidermal atrophy from the resolution of a space occupying lesion be captured as a scar. All scars, including pitted scars (indentations), were considered AEs.

Summary of Local Skin Reactions (LSRs)[1]

- LSRs were evaluated based on a 0, 1, 2, 3, 4 scoring system
- Flaking/scaling, crusting, and swelling were not present in >90% of patients at week 12
- Most patients (≥92%) in both groups had an absence of vesiculation/pustulation and erosion/ulceration at week 12

Table 3: Erythema Was Most Frequently Observed LSR Throughout Study[1]

LSR–Erythema (events) by week, n (n/N) [a]	Berdazimer gel, 10.3% (n=444)	Vehicle gel (n=447)
Week 2	206 (50)	100 (24)
Week 4	195 (47)	89 (21)
Week 8	166 (42)	81 (20)
Week 12	110 (28)	82 (21)
Erythema severity at week 12, %		
0 (not present)	71.8%	79.3%
1 (slightly pink)	16.9%	14.1%
2 (pink or light red)	7.9%	5.5%
3 (red, restricted to treatment area)	2.6%	0.5%
4 (red extending outside treatment area)	0.8%	0.5%

[a] Percentages for LSRs over time are based on observed data at each timepoint and represent the sum of all patients with a score of 1, 2, 3, or 4.

Table 4: Summary of LSRs by Composite Score and Other Local AEs[1]

Mean LSR composite score by week (LSR scores were summed, range, 0-24)*	Berdazimer gel, 10.3% (n=444)	Vehicle gel (n=447)
Week 2	2.3	0.6
Week 4	2.4	0.5
Week 8	1.8	0.6
Week 12	1.0	0.5
Other local AEs, n (%)		
Scar [b]		
Week 12	13 (2.9)	10 (2.2)
Week 24	12 (2.7)	18 (4.0)
Hypo- and hyperpigmentation		
Through week 12	6 (1.4)	0
Through week 24	3 (0.7)	0

*Sum of 6 LSR component scores (range, 0-4 for each component).
[b] Scar assessment was performed at each visit independent of AE assessment. Clinically significant scars were reported as AEs. No patients in either group had keloidal or hypertrophic scars during the 24-week study period.

Conclusion

- Once-daily application of berdazimer gel, 10.3%, a novel topical NO–releasing medication, appears to demonstrate efficacy and favorable safety in patients 6 months and older with molluscum[1]

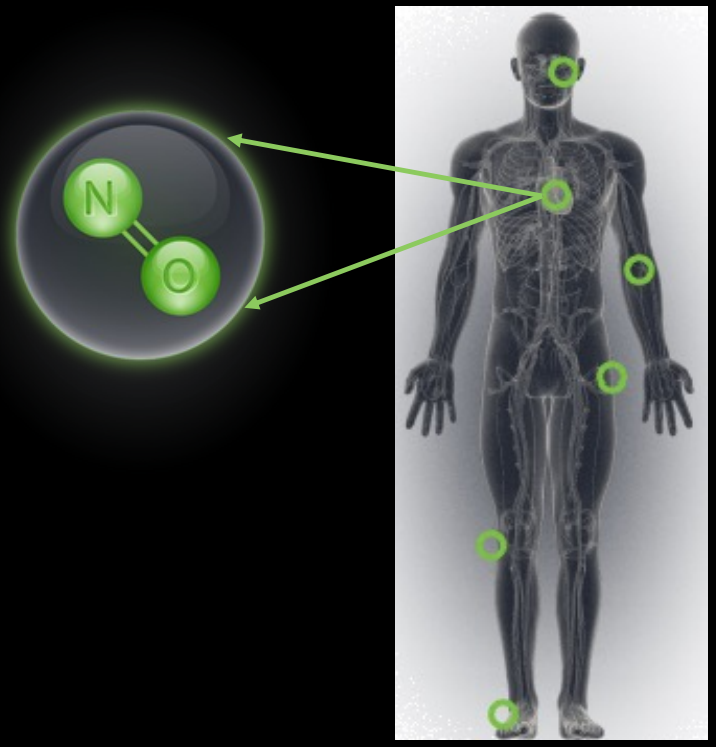
References

1. Browning JC, Enloe C, Cartwright M, et al. Efficacy and Safety of Topical Nitric Oxide–Releasing Berdazimer Gel in Patients With Molluscum Contagiosum: A Phase 3 Randomized Clinical Trial. *JAMA Dermatol*. 2022;158(8):871-878. doi:10.1001/jamadermatol.2022.2721 (OPEN ACCESS)

NOVAN

Nitric Oxide Mechanisms of Action

- *Science* – Breakthrough of the Year (1992)
- Nobel Prize in Medicine (1998)
- >100,000 peer-reviewed manuscripts
- Broad-spectrum antimicrobial
  - Antibacterial
  - Antiviral
  - Antifungal
- Immunomodulatory agent
  - Decreases key biomarkers for inflammation
  - Inhibits T-cell proliferation
  - Results in NO-derived regulatory T cells

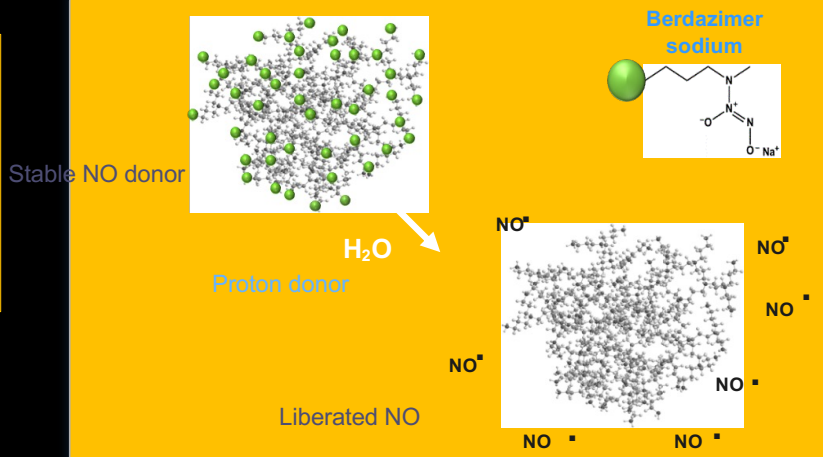


Nitric oxide plays a vital role in the natural immune system response against microbial pathogens and is a critical regulator of inflammation.

Berdazimer 10.3% For The Treatment of Molluscum Contagiosum

Berdazimer 10.3% gel is in Phase 3 development and poised to be a first-in-class, topical, controlled-NO-release medication for the treatment of molluscum contagiosum. NDA to be filed second half of 2022

- Nitric oxide (NO) is an endogenous small molecule
  - Short-lived immune modulator
  - Direct broad-spectrum antimicrobial agent
- Berdazimer sodium is a new chemical entity (NCE)
  - Macromolecule covalently bound to *N*-diazeniumdiolate NO donors
- Co-administration with a proton donor (hydrogel)
  - Promotes NO release from the macromolecule
  - Stable delivery of NO to site of application



- **Stable**
- **Engineered macromolecule**
- **Tunable delivery at the site of application**

Berdazimer Gel 10.3%: Nitric Oxide Releasing Medication

Berdazimer Gel, 10.3%

- A nitric oxide (NO)–releasing medication in phase 3 clinical development

If FDA approved, it could be the first potential prescription treatment for MC[1]

- **Berdazimer sodium is a new chemical entity (NCE)[2]**
- It is a macromolecule composed of a polysiloxane backbone with covalently bound *N*-diazeniumdiolate NO donors[3]
- Co-administration with a proton donor promotes NO release from the macromolecule[3]

Berdazimer gel, 10.3% is an investigational gel that consists of 2 components[3]

Berdazimer gel, 10.3% addresses many of the challenges of NO delivery[4]

Berdazimer gel 10.3% is not FDA approved. The safety and effectiveness of berdazimer gel, 10.3% has not been established. The mechanism of action of berdazimer gel, 10.3% is unknown.

1. Browning JC, et al. *JAMA Dermatol.* 2022;158(8):871-878. doi:10.1001/jamadermatol.2022.2721 2. Data on File. FDA communication. Novan Inc 2022. 3. Maeda-Chubachi T, et al. *JID Innov.* 2021;1(3):100019. 4. Del Rosso JQ, Kircik LH. *J Drugs Dermatol.* 2017;16(1):s4-s10.

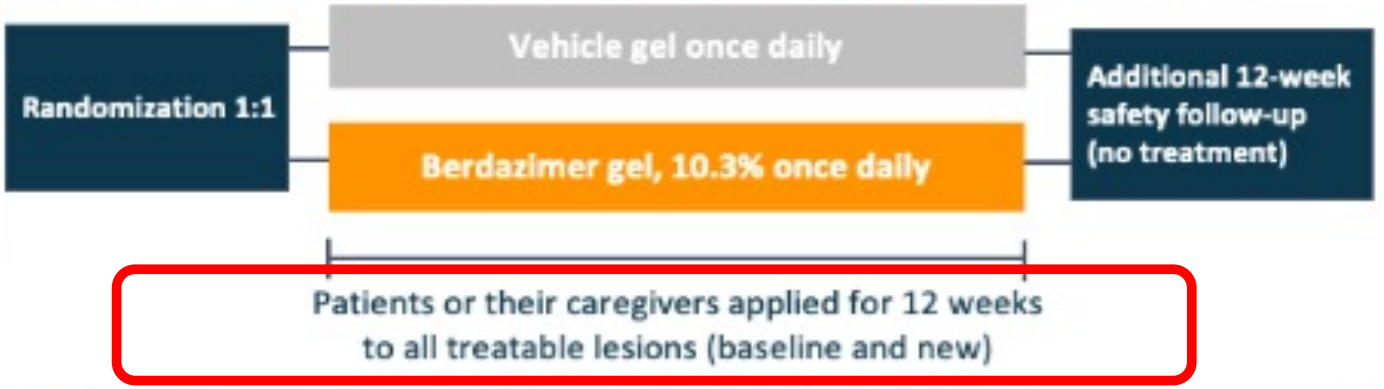
Trial Design

Figure 1: B-SIMPLE 4 Study Design

- Multicenter, randomized, double-blind, vehicle-controlled, parallel trial to evaluate the efficacy and safety of berdazimer gel, 10.3% once daily for the treatment of MC (NCT04535531)[1,2]

Key Inclusion Criteria

- Male and female patients
- ≥6 months of age
- 3-70 lesions at baseline



Primary Endpoint

- Proportion of patients with complete clearance of all treatable MC lesions at week 12

Representative Secondary Endpoints

- Proportion of patients achieving a lesion count of 0 or 1 of all treatable MC at week 12
- Proportion of patients achieving ≥90% reduction from baseline in the number of all treatable MC lesions at week 12

Safety Measures

- Treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs) through week 24

Efficacy Results of B-SIMPLE4

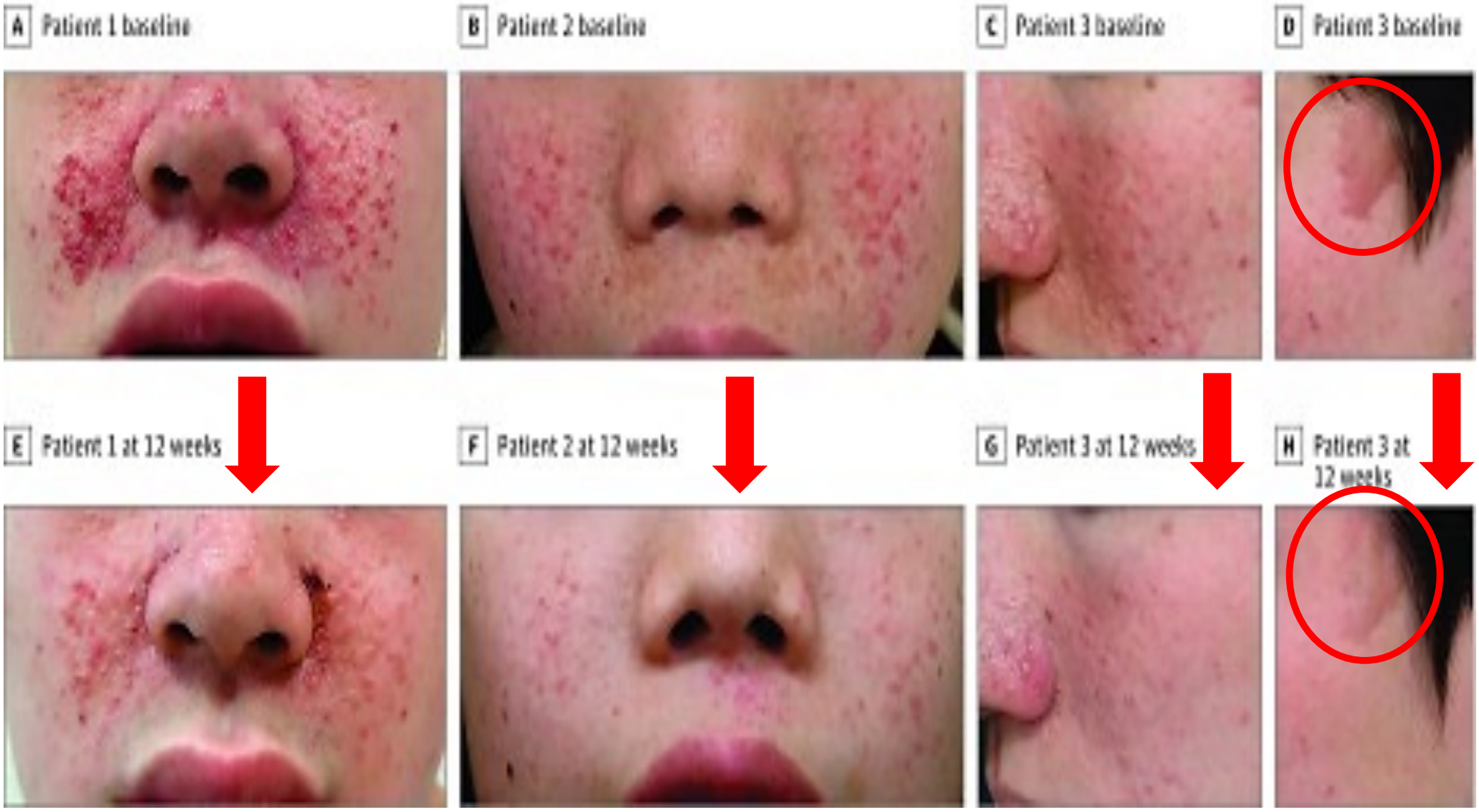
	B-SIMPLE4 SB206 (N=444)	Vehicle (N=447)	p-value
Primary Endpoint: Complete Clearance of All Lesions at Week 12	32.4%	19.7%	p<0.0001
Secondary Endpoint: Proportion Achieving a Lesion Count of 0 or 1 at Week 12	43.5%	24.6%	p<0.0001
Secondary Endpoint: Proportion Achieving ≥90% Clearance of Lesions at Week 12	43.0%	23.9%	p<0.0001
Secondary Endpoint: Complete Clearance of All Lesions at Week 8	19.6%	11.6%	p=0.0014

2% Sirolimus Gel (HYFTOR™)
Treatment of Angiofibromas Associated with Tuberous Sclerosis

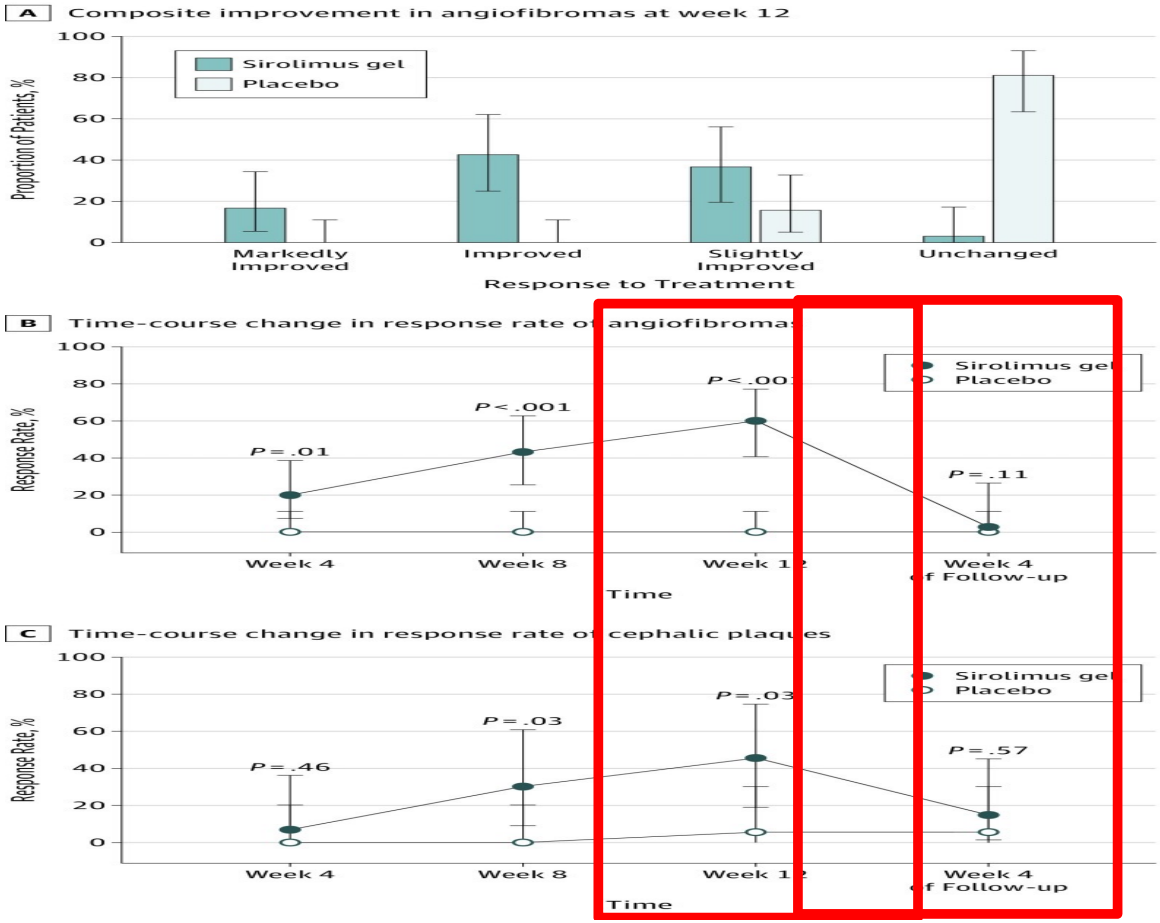
Phase 3 Trial

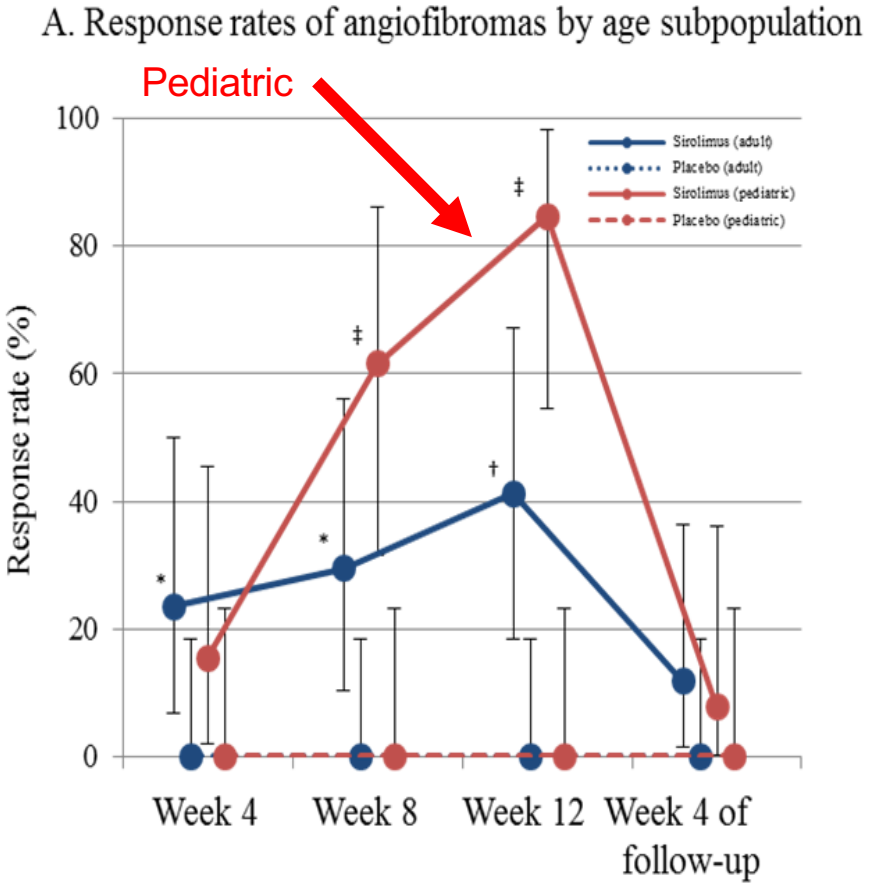
- **Tuberous sclerosis complex (TSC),** an autosomal-dominant disorder caused by the constitutive activation of **m**ammalian **t**arget **o**f **r**apamycin (mTOR), gives rise to **hamartomas in multiple organs.**
  - Angiofibromas are the most predominant skin lesions observed in patients with TSC older than 5 year
- **Phase 3,** multicenter, randomized, double-blind, 1:1 (drug: placebo) placebo-controlled trial conducted at 9 sites in Japan
- **Eligibility:** ≥3 years definitive diagnosis of TSC displayed 3 or more reddish papules of facial angiofibromas (≥2 mm in diameter), and had difficulty or did not desire to undergo laser therapy and/or surgery.
- **Criteria:** size and color evaluated 6 categories: “markedly improved,” “improved,” “slightly improved,” “unchanged,” “slightly aggravated,” and “aggravated” by an independent review committee (IRC) comprising 3 blinded dermatologists.

Wataya-Kaneda M, et al Sirolimus Gel Treatment vs Placebo for Facial Angiofibromas in Patients With Tuberous Sclerosis Complex: A Randomized Clinical Trial. JAMA Dermatol. 2018 Jul 1;154(7):781-788. doi: 10.1001/jamadermatol.2018.1408. PMID: 29800026; PMCID: PMC6128500.


A Patient 1 baseline
B Patient 2 baseline
C Patient 3 baseline
D Patient 3 baseline
E Patient 1 at 12 weeks
F Patient 2 at 12 weeks
G Patient 3 at 12 weeks
H Patient 3 at 12 weeks

Composite Improvement and Age at Week 12 and at 4 Week Follow-Up OFF Medication





Efficacy

- **Response rate:**
  - **Higher in pediatric (n = 13/ 85%) than in adult (n = 17/ 41%) subpopulations concerning the size but not color (46% vs 35%) of angiofibromas**
  - **Decreased at week 4 of follow-up reflecting the transient efficacy of mTOR inhibition by topical sirolimus.**
    - **Angiomyolipomas[1] in patients with TSC and lymphangioleiomyomatosis[2] recurred after discontinuation of their oral sirolimus treatment.**

1 Bissler JJ, McCormack FX, Young LR, et al.. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. 2008;358(2):140-151. [PMC free article] [PubMed] [Google Scholar]
2. McCormack FX, Inoue Y, Moss J, et al.; National Institutes of Health Rare Lung Diseases Consortium; MILES Trial Group . Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364(17):1595-1606.

Warnings: DO NO USE IF…

- You have a skin infection at the treatment site
- You have high cholesterol or high triglycerides in your blood
- You are scheduled to receive an immunization (vaccine). You should avoid receiving live vaccines during treatment with HYFTOR. Vaccines may be less effective during treatment with HYFTOR.
- You are pregnant or plan to become pregnant. HYFTOR may harm your unborn baby. You should not become pregnant during HYFTOR treatment
  - Females who are able to become pregnant should use effective birth control (contraception) before starting treatment with HYFTOR, during treatment, and for 12 weeks after your final dose of HYFTOR. Talk to your healthcare provider about types of birth control that you can use during this time.
- You are breastfeeding or plan to breastfeed. It is not known if HYFTOR passes into breast milk. You should not breastfeed during treatment with HYFTOR.

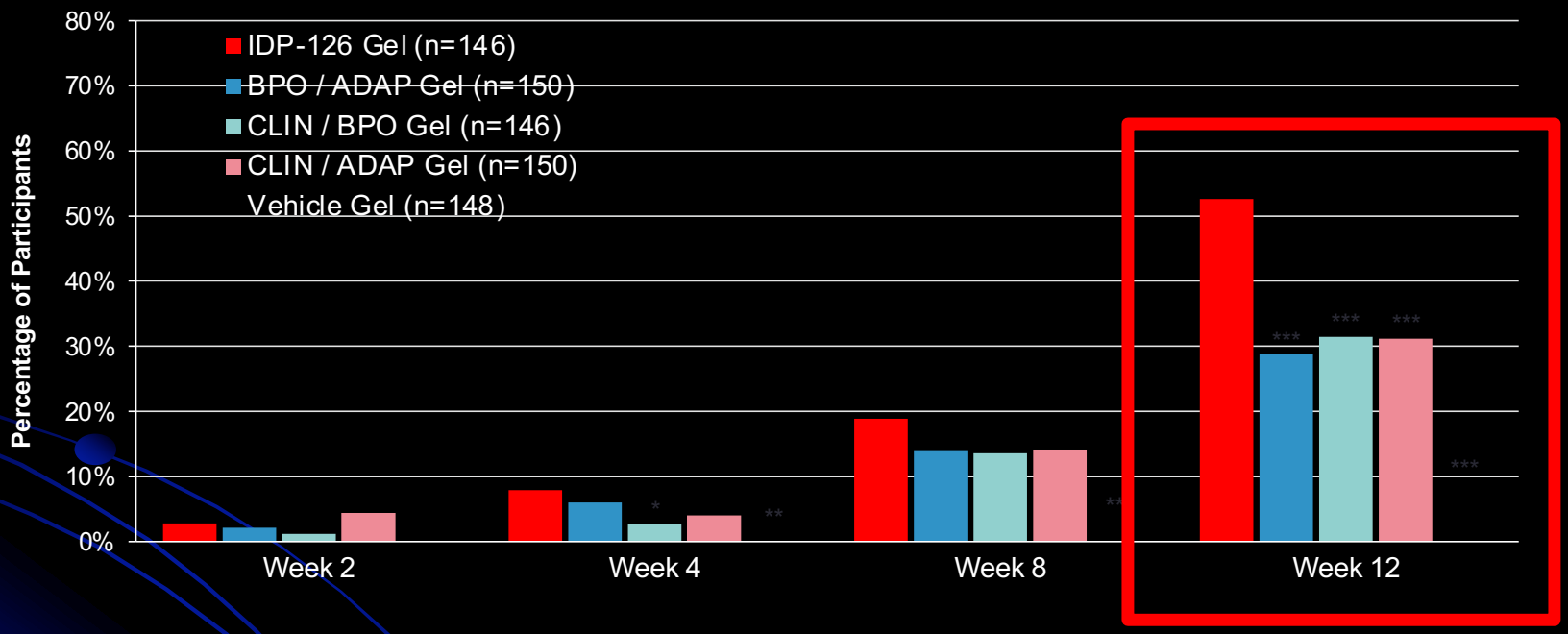
Does a Triple Combo Acne Medication Work Better Than A Two Drug Combo Treating Acne?

IDP-126: 1.2% clindamycin phosphate + 3.1% benzoyl peroxide + 0.15% adapalene

VS

BPO/Adapalene Gel AND Clinda/Adapalene Gel AND Clinda/BPO Gel

Phase 2: Treatment Success Through Week 12

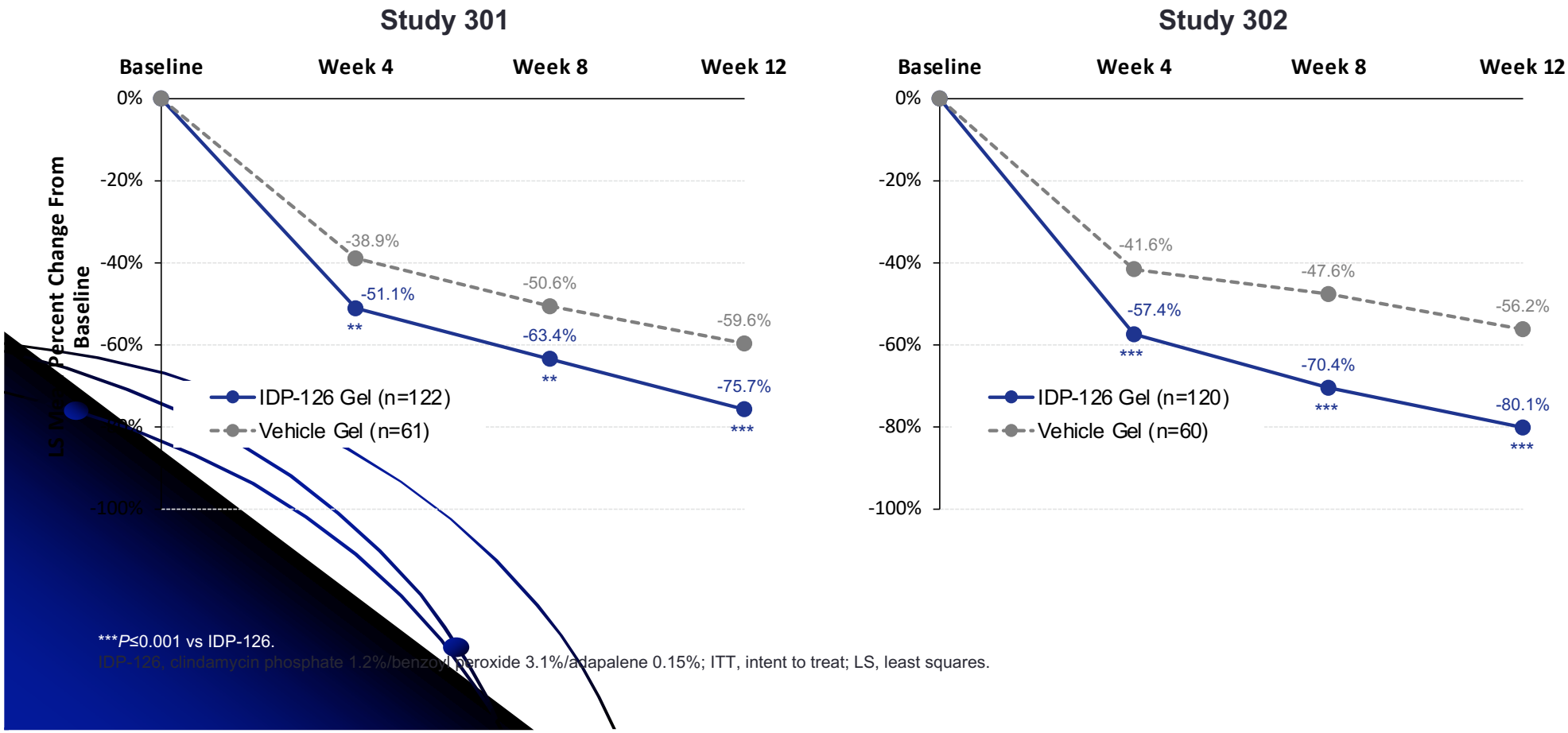


*P<0.05; **P<0.01; ***P≤0.001 vs IDP-126.
Treatment success defined as at least a 2-grade reduction from baseline in EGSS and a score of 0 (clear) or 1 (almost clear).
ADAP, adapalene 0.15%; BPO, benzoyl peroxide 3.1%; CLIN, clindamycin phosphate 1.2%; EGSS, Evaluator's Global Severity Score; IDP-126, clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%.

Phase 3 Efficacy: % Reductions in Inflammatory Lesion Counts

ITT Population

PHASE 3

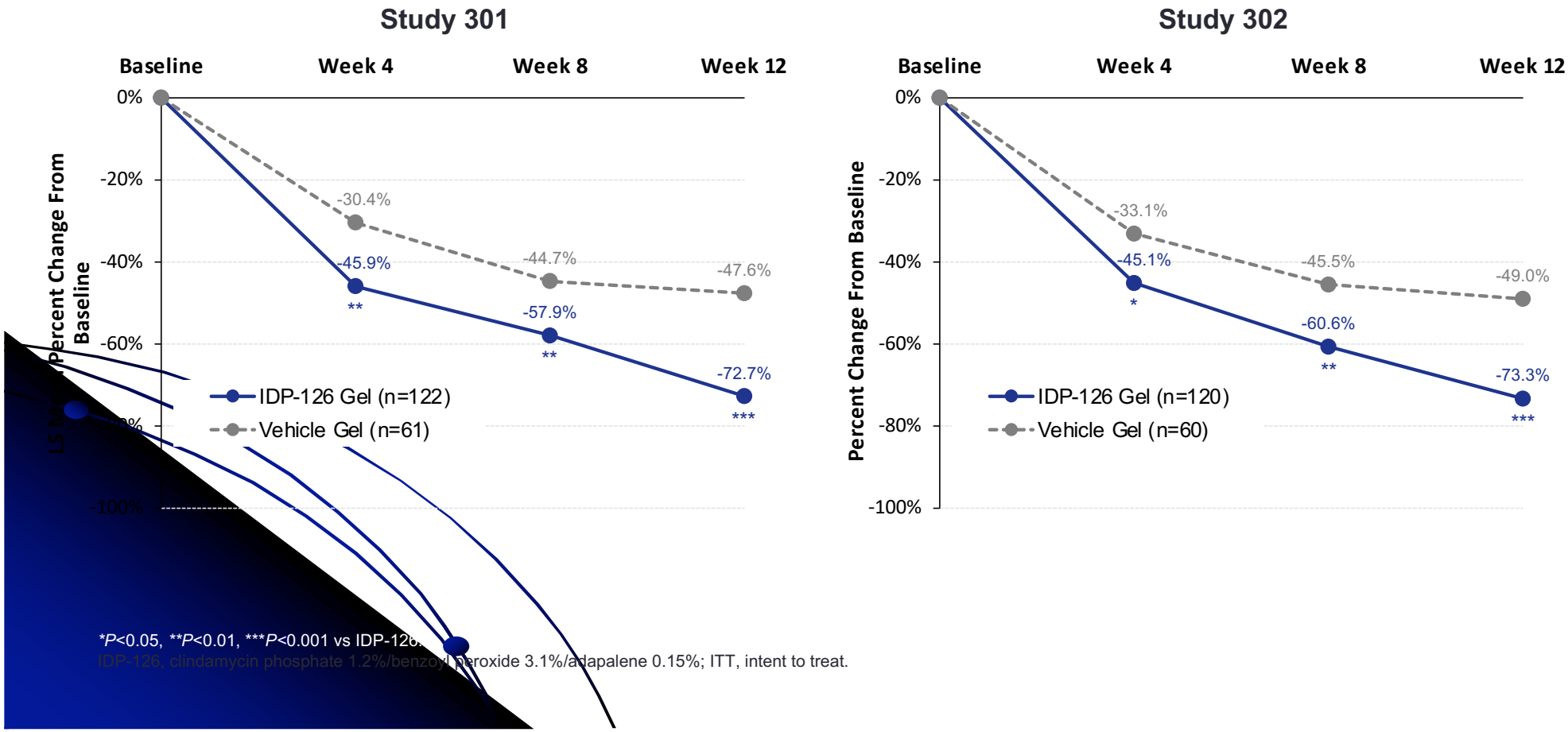


***$P \leq 0.001$ vs IDP-126.

IDP-126, clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%; ITT, intent to treat; LS, least squares.

Phase 3 Efficacy: % Reductions in Noninflammatory Lesion Counts

ITT Population



*P<0.05, **P<0.01, ***P<0.001 vs IDP-126.

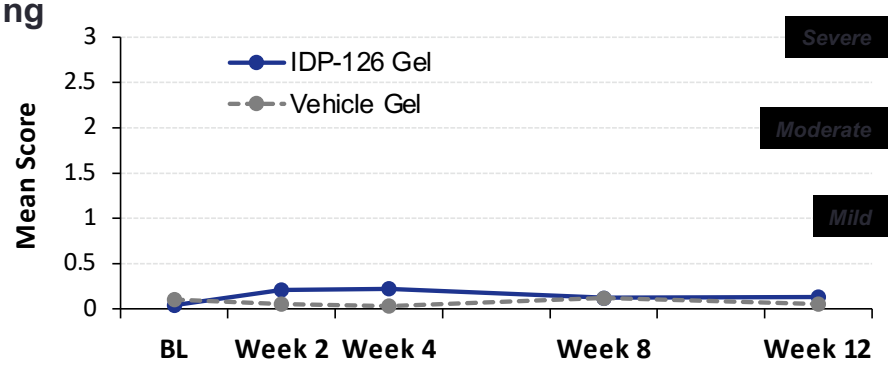
IDP-126, clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%; ITT, intent to treat.

Phase 3 Cutaneous Safety

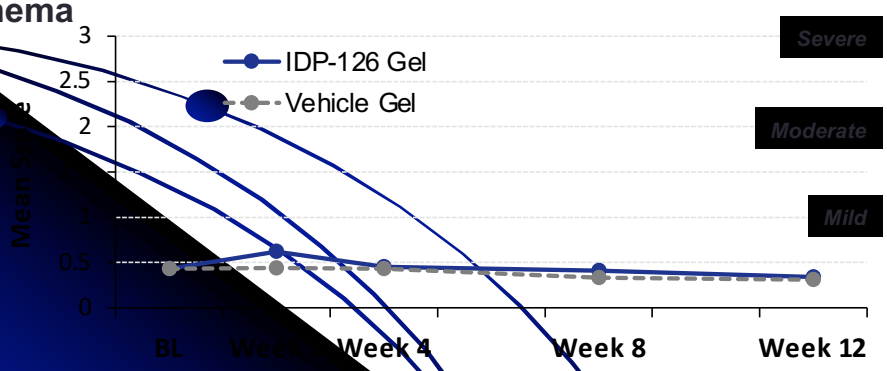
Safety Population

Study 301

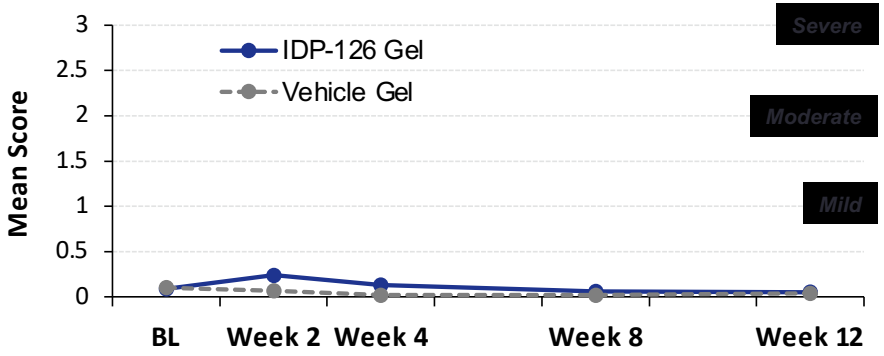
Scaling

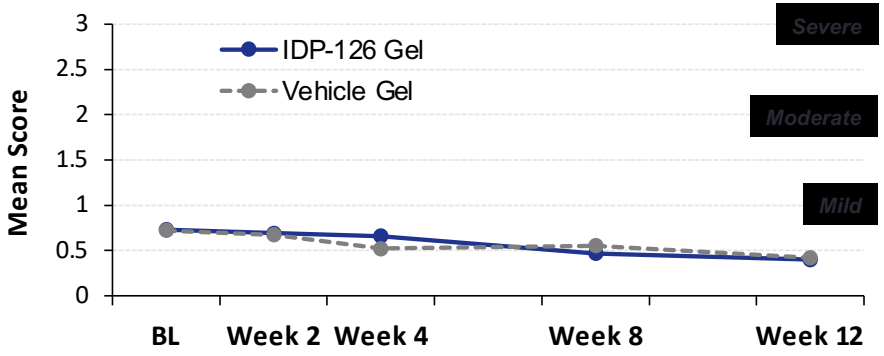


Erythema



Study 302



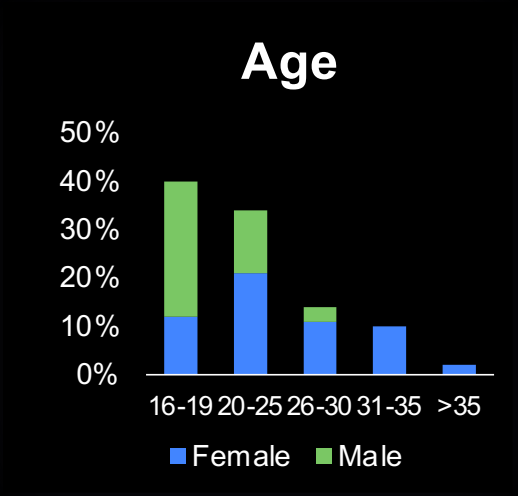


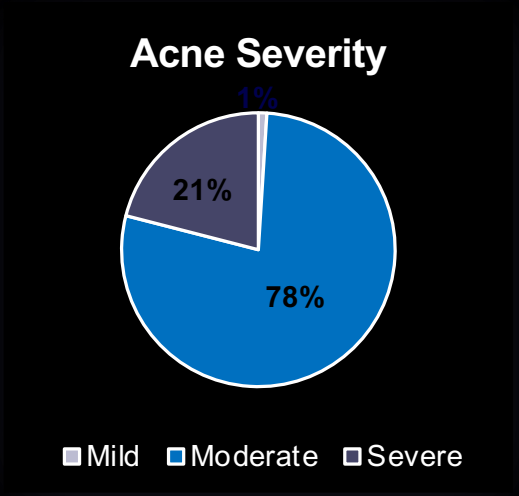
N values: Study 301 BL: IDP-126 n=122, vehicle n=61; Week 12: IDP-126 n=107, vehicle n=55; Study 302 BL: IDP-126 n=120, vehicle n=60; Week 12: IDP-126 n=107, vehicle n=55.
BL, baseline; IDP-126, clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%.

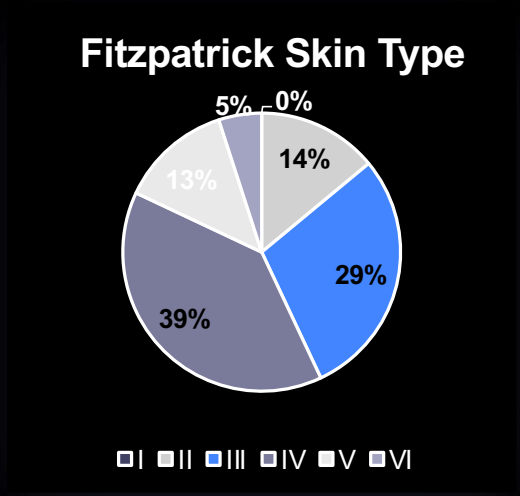
Treatment of Mild, Moderate and Severe Acne with a 1726 nm Laser

Pivotal Clinical Study[3]

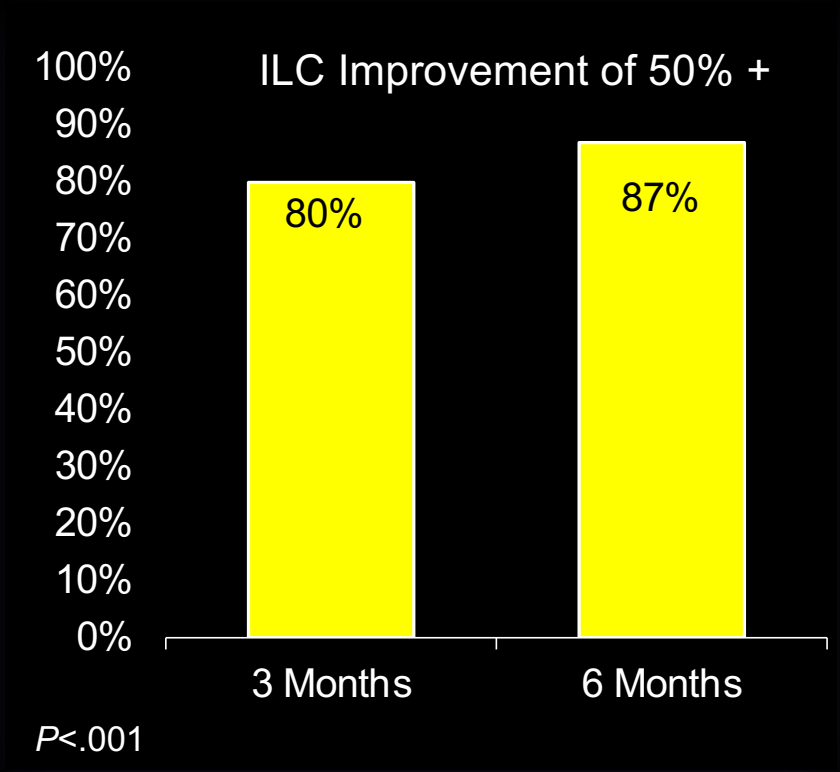
- Non-randomized open label study
- 104 subjects, ≥16 years, with mild to severe acne vulgaris
- Three, 30-minute laser treatments spaced 1 month apart
- Primary endpoint was patients who achieved a 50% reduction in lesion count by 3 months after final treatment.
- Post-treatment follow-ups at 1, 3, 6, 12 months after final treatment session



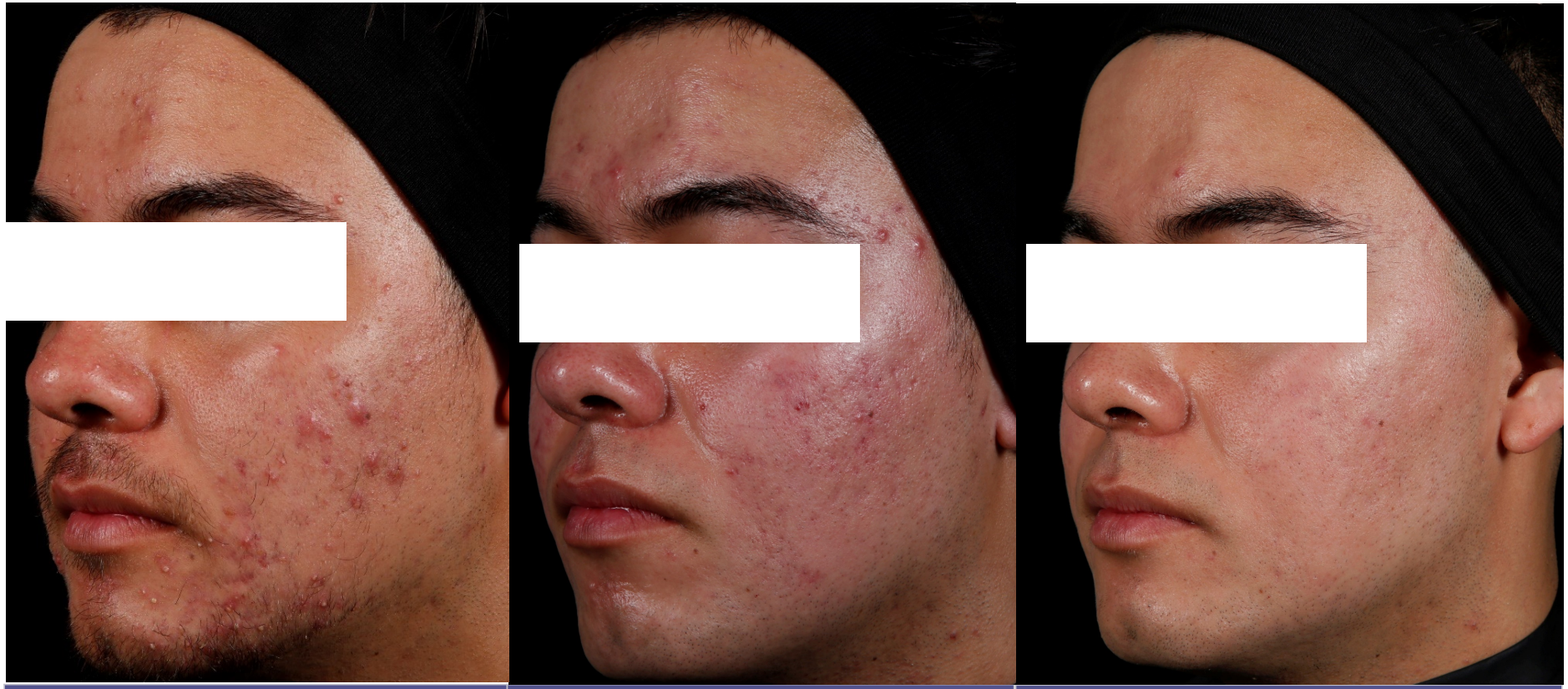




Primary Endpoint and Inflammatory Lesion Reduction[3]

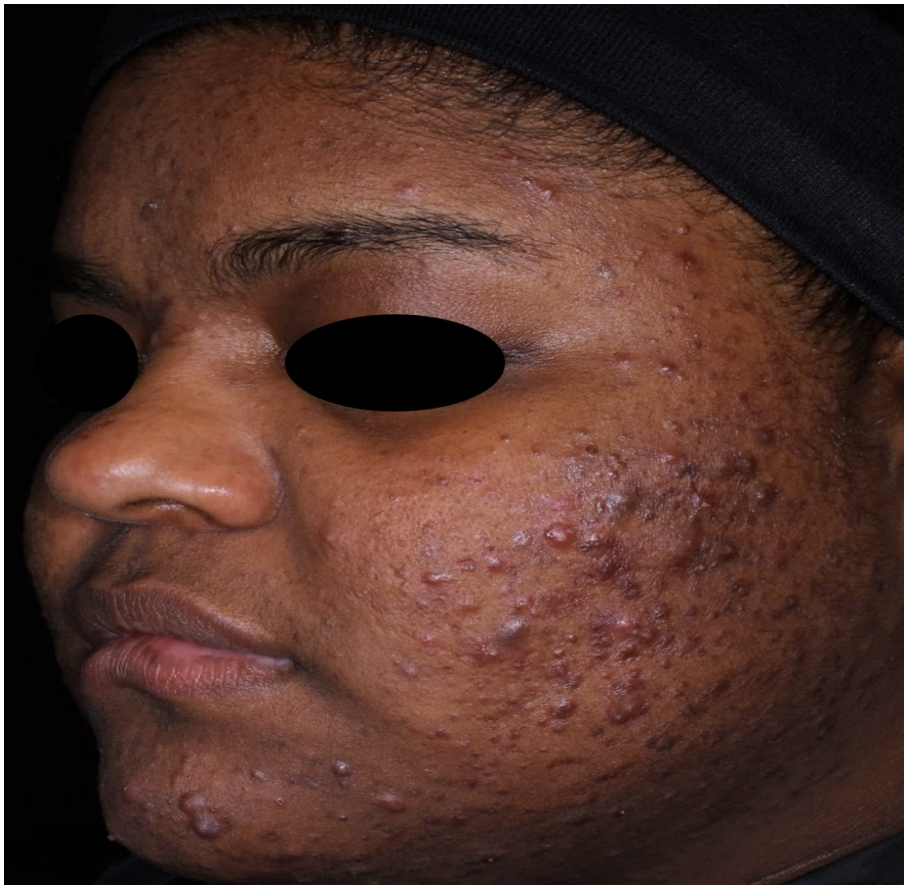


Patient Photos[3]

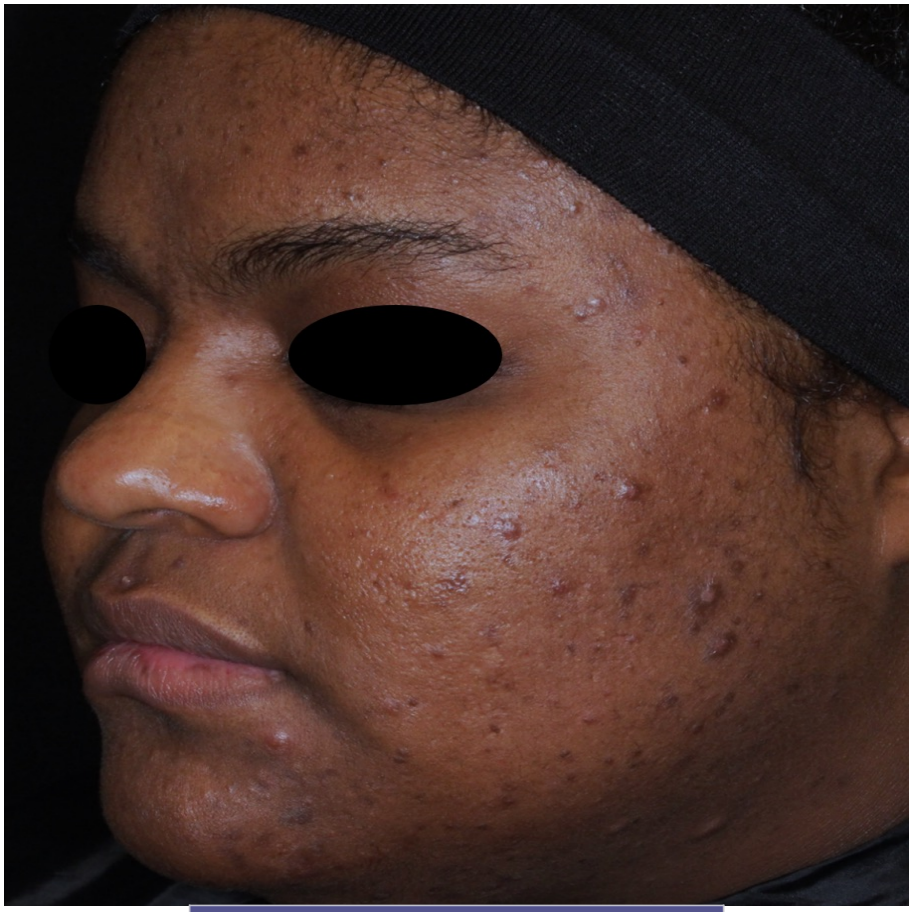


Baseline,	6 Months After Final Treatment Session	12 Months After Final Treatment Session

Patient Photos



Baseline, Severe



6 Months After Final Treatment Session, Moderate

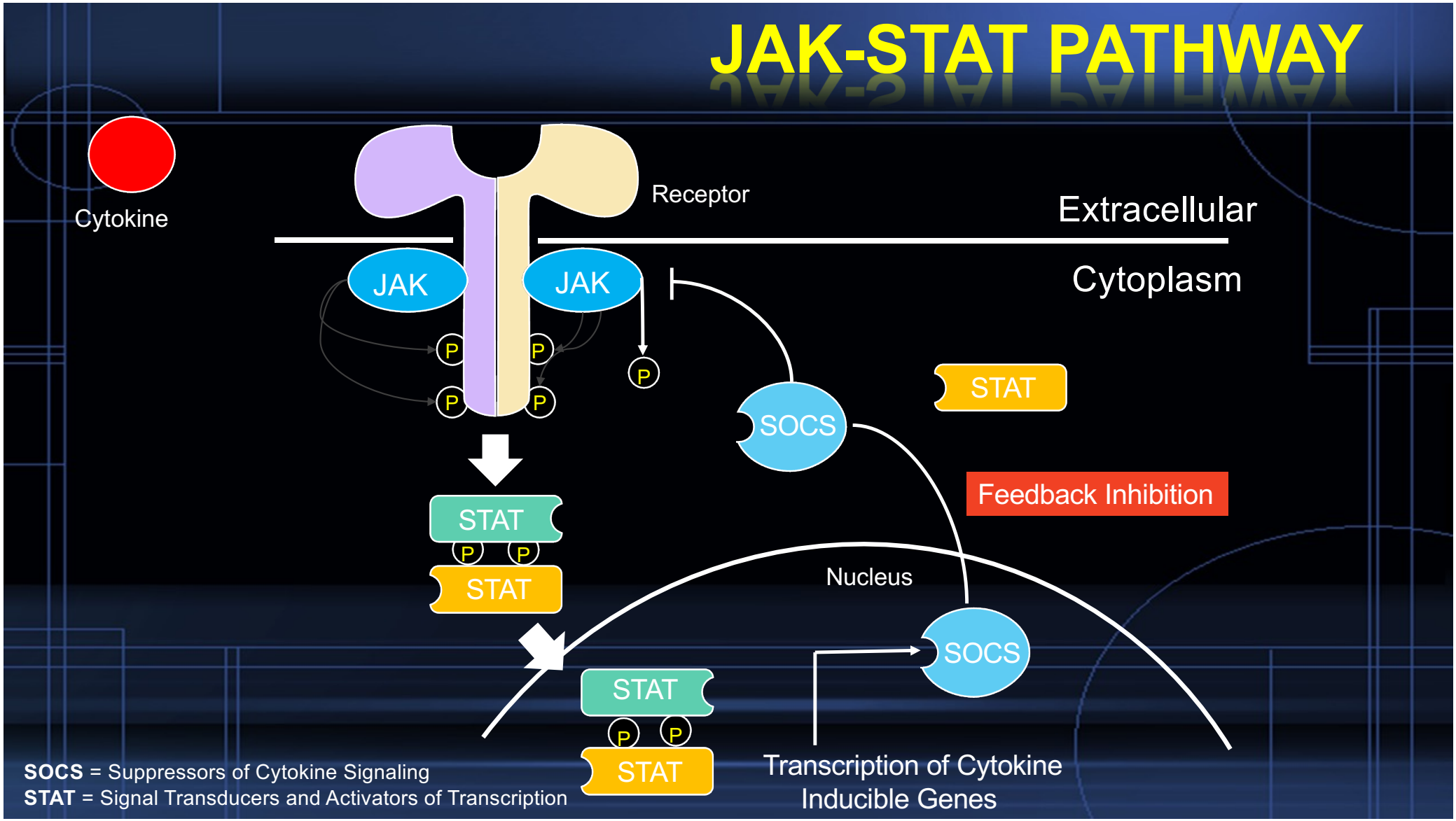
JAK INVASION

NOT ALL JAK inhibitors are the same!

4 JAKs: JAK 1, 2, 3 & TYK2

Tokarski J, Zupa-Fernandez A, Tredup JA, et al. Tyrosine kinase 2-mediated signal transduction in T lymphocytes is blocked by pharmacological stabilization of its pseudokinase domain. *J Biol Chem*. 2015;290:11061-11074.

JAK-STAT PATHWAY



SOCS = Suppressors of Cytokine Signaling
STAT = Signal Transducers and Activators of Transcription

Over 50 Cytokines Signal Through The JAK-STAT Pathway

This group is perhaps the largest cytokine pathway

Comprises:

- **Hematopoietic growth factors** such as **EPO**
- **Immunomodulatory cytokines** such as **IL-2**
- **Inflammatory cytokines** such as **IFN-γ**

Table I. *List of Cytokines that Signal through the JAK/STAT Pathway*

Abbreviation	Name	Major Functions
Class I cytokines		
IL-2 family		
IL-2	Interleukin-2	Immune response, T-cell differentiation
IL-4	Interleukin-4	T_H2 differentiation
IL-7	Interleukin-7	T-, B-cell growth factor
IL-9	Interleukin-9	Pleiotropic, Stimulates, T-, B- and NK cells
IL-15	Interleukin-15	Stimulates T- and NK-cells
IL-21	Interleukin-21	Stimulates, T-, B- and NK cells
IL-3 family		
IL-3	Interleukin-3	Multi-lineage haematopoietic growth factor
IL-5	Interleukin-5	B-cell development, eosinophils
GM-CSF	Granulocyte/Macrophage Colony Stimulating Factor	Multi-lineage haematopoietic growth factor, especially monocytes, neutrophils, eosinophils and basophils
IL-6 family		
IL-6	Interleukin-6	Pleiotropic, haematopoiesis, acute phase response, lymphoid differentiation
LIF	Leukemia Inhibitory Factor	Pleiotropic, blastocyst implantation, bone remodeling, CNS
CNTF	Ciliary NeuroTrophic growth Factor	Neuronal growth factor
CT1	Cardiotrophin 1	Cardiac myocytes growth factor
CLC	Cardiotrophin-like cytokine	Neurological growth factor
OSM	Oncostatin M	Pleiotropic, bone formation
IL-31	Interleukin-31	Inflammatory, cell-mediated immunty
NP	Neuropoietin	Neural growth factor
Homodimeric		
G-CSF	Granulocyte Colony Stimulating Factor	Stimulates granulocyte production, mobilises stem cells
EPO	Erythropoietin	Stimulates formation of erthrocytes
TPO	Thrombopoietin	Stimulates formation of megakaryocytes/platelets
GH	Growth Hormone	Growth
PRL	Prolactin	Milk production
LEP	Leptin	Regulates appetite
Others		
IL-12	Interleukin-12	Stimulates T- and NK-cells
IL-13	Interleukin-13	Pleiotropic, airway epithelia, allergic response
IL-23	Interleukin-23	Inflammation
TSLP	Thymic Stromal LymphoPoietin	Inflammatory, stimulates T- and B-cells
Class II cytokines		
Type I interferon		
IFNα	Interferon alpha (23 subtypes)	Anti-viral, secreted by lymphocytes, fibroblasts and monocytes
IFNβ	Interferon beta	Anti-viral, ubiquitously expressed
IFNε	Interferon epsilon	Anti-viral, expressed in female reproductive tract
IFNκ	Interferon kappa	Anti-viral, expressed by keratinocytes
IFNω	Interferon omega	Anti-viral, secreted by leukocytes
Type II interferon		
IFNγ	Interferon gamma	Pro-inflammatory, secreted by T- and NK-cells, activates macrophages/monocytes
Type III interferon		
IFNλ1	Interferon lambda1	Anti-viral, similar to type I but acts on fewer cell-types
IFNλ2	Interferon lambda2	Anti-viral, similar to type I but acts on fewer cell-types
IFNλ3	Interferon lambda3	Anti-viral, similar to type I but acts on fewer cell-types
IL-10 family		
IL-10	Interleukin-10	Anti-inflammatory, inhibits macrophage activation
IL-19	Interleukin-19	Inflammatory, acts on dermal cells
IL-20	Interleukin-20	Inflammatory, acts on dermal cells
IL-22	Interleukin-22	Inflammatory, secreted by Th1 cells, acts on dermal cells
IL-24	Interleukin-24	Inflammatory, acts on dermal cells
IL-26	Interleukin-26	Antimicrobial, T_H17 cytokine

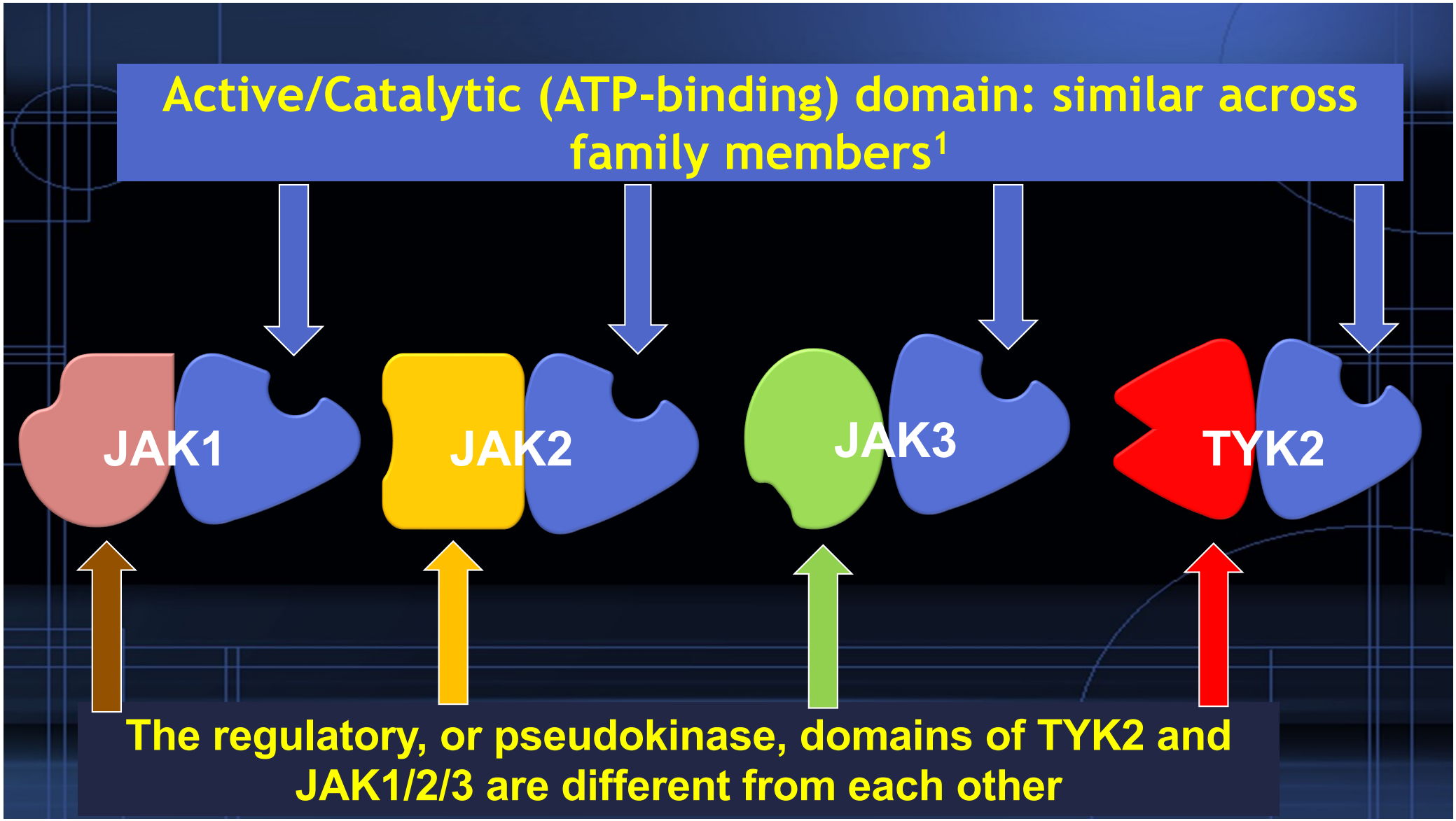
JAK STRUCTURE

Regulatory (pseudokinase) domain: different across family members[1]

Active/Catalytic (ATP-binding) domain:
Similar across family members[1];

Binding site for most JAKinibs

Tokarski J, Zupa-Fernandez A, Tredup JA, et al. Tyrosine kinase 2-mediated signal transduction in T lymphocytes is blocked by pharmacological stabilization of its pseudokinase domain. *J Biol Chem*. 2015;290:11061-11074.


Active/Catalytic (ATP-binding) domain: similar across family members[1]
JAK1
JAK2
JAK3
TYK2
The regulatory, or pseudokinase, domains of TYK2 and JAK1/2/3 are different from each other

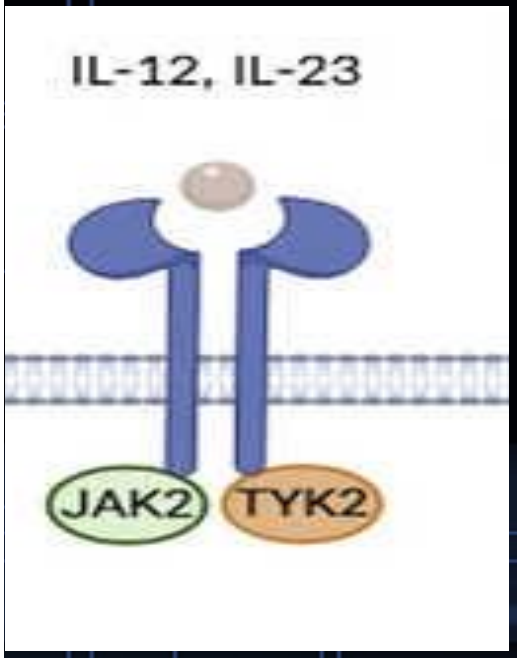
Broad Overview: Systems Affected By Cytokines Signaling Through JAK1, 2, 3,TYK2

SYSTEMS IMPACTED BY JAKinibs *	JAK1 	JAK2 	JAK3 	TYK2 
Immune system	✓	✓	✓	✓
Hematopoietic		✓		
Metabolic activity	✓	✓	✓	
Bone development & lipid metabolism	✓	✓		

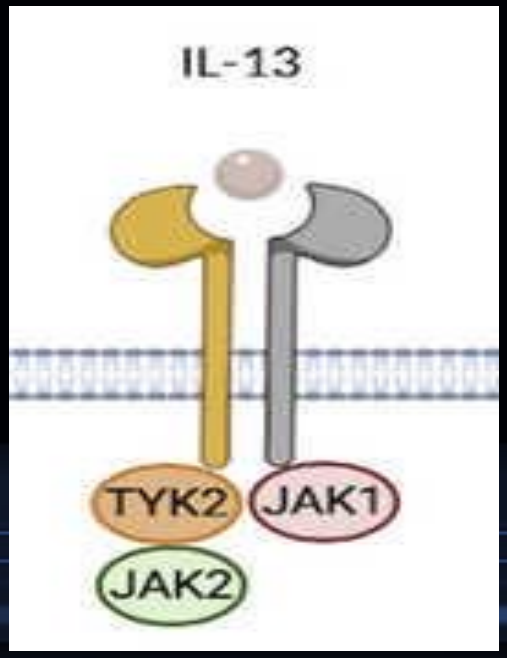
* Adapted with permission from a BMS slide; Above list is incomplete but representative of some of the systems impacted by JAK inhibition
JAK=Janus kinase; TYK2=tyrosine kinase 2.

Key Cytokine Drivers in Skin Diseases Mediated by JAK Signaling

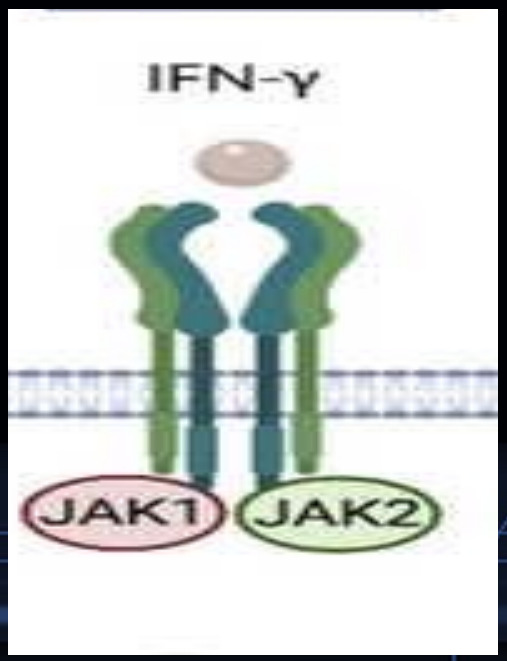
PSORIASIS



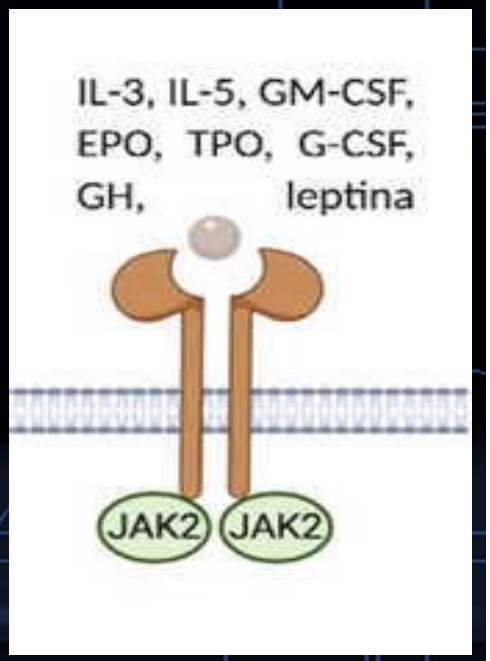
ATOPIC DERMATITIS



ALOPECIA AREATA
VITILIGO



Issues with JAK2 Inhibition

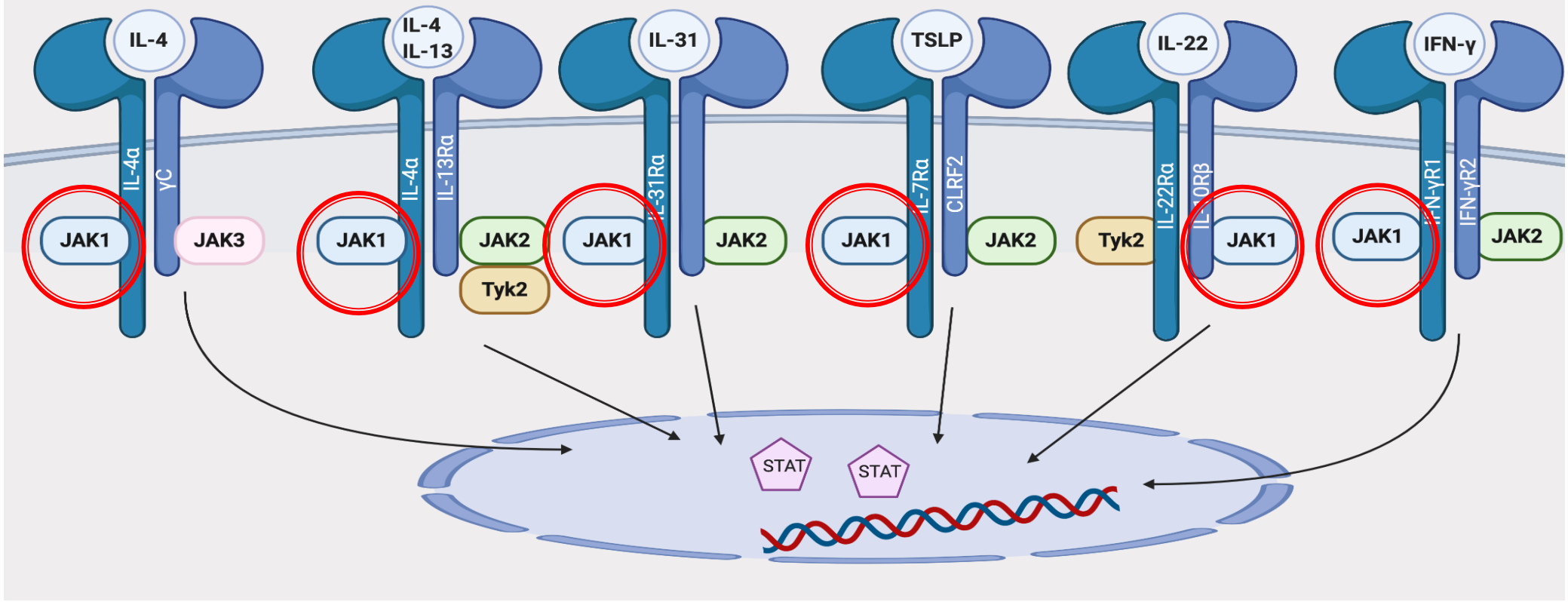


Actas Dermosfiliogr. 2021; 112:503-515

ATOPIC DERMATITIS

Key Cytokines in AD Mediated By The JAK1 Pathway

Note: All are mediated in part by JAK1



DRUG	MOA	FDA Approved (Under investigation)
Ruxolitinib cream 1.5% QD Opzelura® Short-term, Non-continuous use	JAK1/2 inhibitor	Approved: Mild-moderate AD: Up to 20% BSA (9/21) Non-segmental Vitiligo ≥ 12 yo (7/22) (Mild-moderate PsO: phase 2 completed) (Alopecia Areata) (Hidradenitis Suppurativa)
Topical Tapinarof 1% Cream QD VTAMA® Continuous Use	Aryl hydrocarbon receptor modulating agent	Plaque PsO in adults Approved 5/22 ⇒ (Mid-moderate AD) (Alopecia Areata) (Vitiligo)
Topical Roflumilast Cream (& Foam) 0.3% QD Continuous Use	High potency PDE4 inhibitor	Plaque PsO ≥ 12 yo Approved 7/22 ⇒ (Mild-moderate AD) (Seborrheic dermatitis) (Scalp PsO)

1.5% Ruxolitinib Cream: Opzelura® (JAK 1,2)

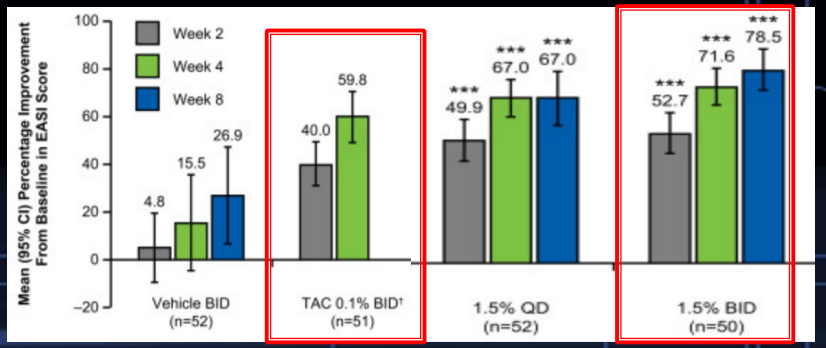
- Approved Sept 22, 2021
- **Short term, noncontinuous treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients ≥12 yo, not adequately controlled by topical Rx or if other Rx not advisable**
- **First topical JAK inhibitor: JAK 1 and JAK 2 inhibition**
- **BID application to ≤ 20% BSA, no more than 60g/week**

8 Week Phase 3 Studies	RUXOLITINIB Cr.	VEHICLE
IGA Success (0-1, 2 grade improvement)	51.3-53.8%	7.6-15.1%
ITCH NRS (≥4 point improvement)	50.7-52.2%	15.4-16.3%

1.5% Ruxolitinib Cream: It Doesn't Burn or Sting; Works BETTER Than Triamcinolone

n (%)	Vehicle (n=250)	RUX 0.75% (n=500)	RUX 1.5% (n=499)
Any AE	84 (34)	147 (29)	131 (26)
Application site reactions Burning Pruritus	 10 (4) 6 (2)	 2 (0.4) 4 (1)	 4 (1) 0
Discontinuation due to AE	8 (3)	4 (1)	3 (1)
Serious AEs[a]	2 (1)	4 (1)	3 (1)
[a]No serious AEs were related to ruxolitinib treatment			

Mean % Improvement From Baseline in EASI Score



Kim BS et al. J Allergy Clin Immunol. 2020 Feb;145(2):572-582

Adverse Events

Adverse Reaction	1.5% Ruxolitinib (N=499) n (%)	Vehicle (N=250) n (%)
*Subjects with any TEAE**	*132 (27)*	*83 (33)*
Nasopharyngitis	13 (3)	2 (1)
Bronchitis	4 (1)	0 (0)
Ear infection	4 (1)	0 (0)
Eosinophil count increased	4 (1)	0 (0)
Urticaria	4 (1)	0 (0)
Diarrhea	3 (1)	1 (< 1)
Folliculitis	3 (1)	0 (0)
Tonsillitis	3 (1)	0 (0)
Rhinorrhea	3 (1)	1 (< 1)

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions (5.1)]*.

MORTALITY

Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions (5.2)]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions (5.3)]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions (5.4)]*.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated *[see Warnings and Precautions (5.5)]*.

BLACK BOX WARNINGS!
Serious infection, All Cause Mortality, Malignancy, MACE, Thrombosis
INCLUDED EVEN IN TOPICALS

A CLINICIAN'S PERSPECTIVE

Special editorial: When prescribing Janus kinase inhibitors for dermatologic conditions, be mindful of the Food and Drug Administration's September 1, 2021, data safety communication

Morgan Murphrey, MD,[a] Reid Alexander Waldman, MD,[b] Timothy Durso, MD,[c] and Jane M. Grant-Kels, MD[d]
Davis, California; Glastonbury and Farmington, Connecticut; and Joint Base Andrews, Maryland

Much of the expanded Black Box warning came from ORAL study, exclusively studying older RA patients, with underlying CV risk factors; Is this generalizable to ALL JAKiibs?

J Am Acad Dermatol. 2022;86(1):42-43

ORAL JAKinibs For Atopic Dermatitis

- **Abrocitinib (Cibinqo®) JAK1:** FDA approved January, 2022 for AD
- **Upadacitinib (Rinvoq®) JAK1:** FDA-approved January, 2022 for AD
- **Baricitinib (Olumiant®) JAK1/2:** AD phase 3 completed; ***approval status?***

Oral JAKinibs Approved in Atopic Dermatitis

- **Upadacitinib (Rinvoq®) : JAK1 inhibitor**
  - Treatment of refractory moderate to severe atopic dermatitis in non-immunocompromised patients **>12 yo, >40kg,** who are not adequately controlled by systemic Rx or if other Rx not advisable
  - 15 mg/day; can increase to 30 mg/day
- **Abrocitinib (Cibinqo®): JAK1 inhibitor**
  - Treatment of refractory moderate to severe atopic dermatitis in non-immunocompromised adult **(age 12 and older)** not adequately controlled by systemic Rx or if other Rx not advisable
  - 100 mg/day; can increase to 200mg/day

Upadacitinib vs. Dupilumab

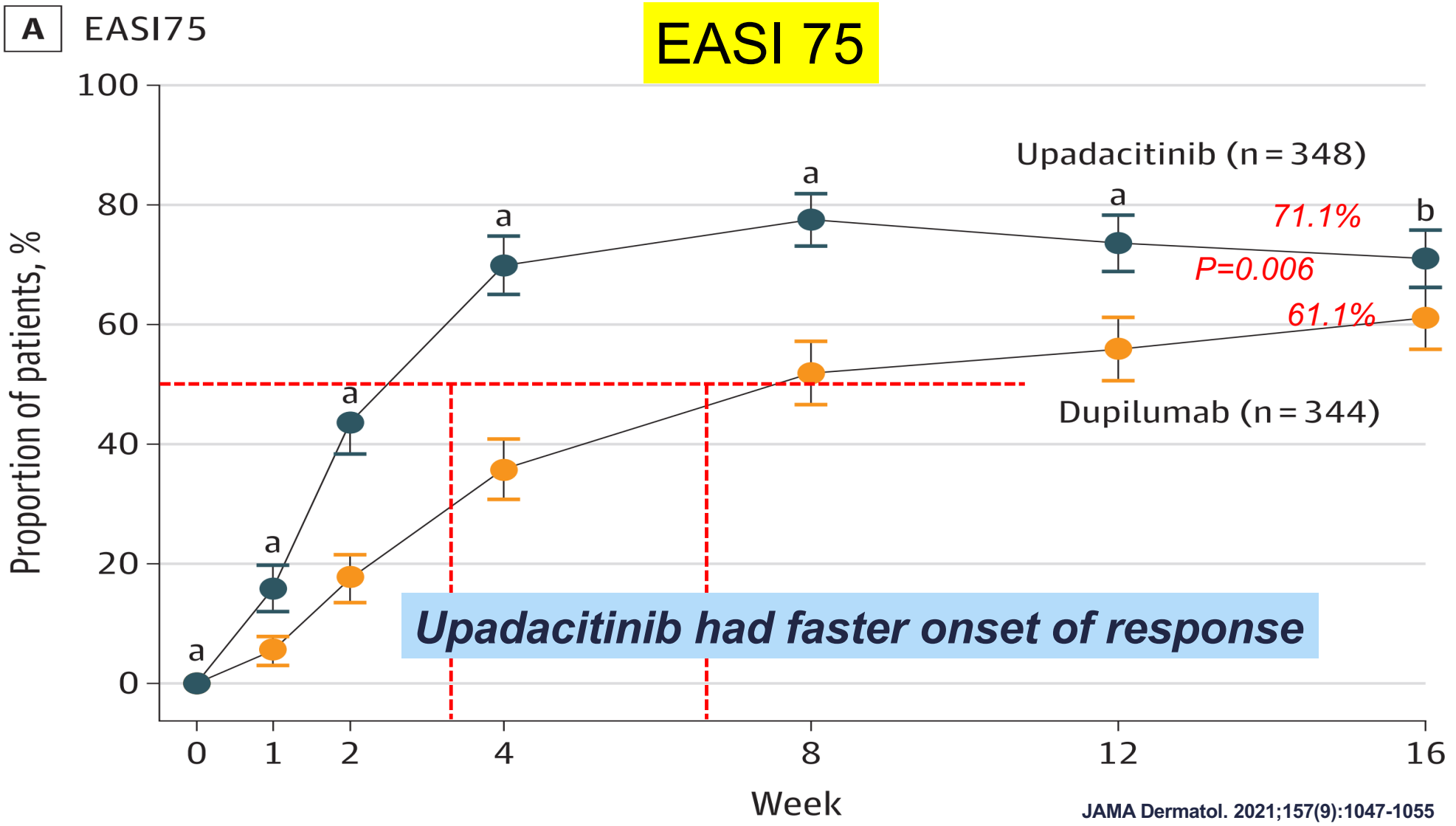
JAMA Dermatology | Original Investigation

Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis

A Randomized Clinical Trial

JAMA Dermatol. 2021;157(9):1047-1055

Andrew Blauvelt, MD, MBA; Henrique D. Teixeira, PhD, MBA; Eric L. Simpson, MD, MCR; Antonio Costanzo, MD; Marjolein De Bruin-Weller, MD; Sebastien Barbarot, MD, PhD; Vimal H. Prajapati, MD; Peter Lio, MD; Xiaofei Hu, PhD; Tianshuang Wu, PhD; John Liu, MD, MS; Barry Ladizinski, MD, MPH, MBA; Alvina D. Chu, MD; Kilian Eyerich, MD



JAMA Dermatol. 2021;157(9):1047-1055

Heads Up Results at Week 16*,[1]

	Dupilumab (300 mg) (n=344)	Upadacitinib (30 mg) (n=348)
EASI 75[a]	61%	71% ✓
EASI 90[b]	39%	61% ✓
EASI 100[c]	8%	28% ✓
Percent Change from Baseline in Worst Pruritus NRS[d]	-49%	-67% ✓
Worst Pruritus NRS Improvement ≥4[e] (Dupilumab, n=336) (Upadacitinib, n=340)	36%	55% ✓

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2021;384:1101-12.DOI: 10.1056/NEJMoa2019380

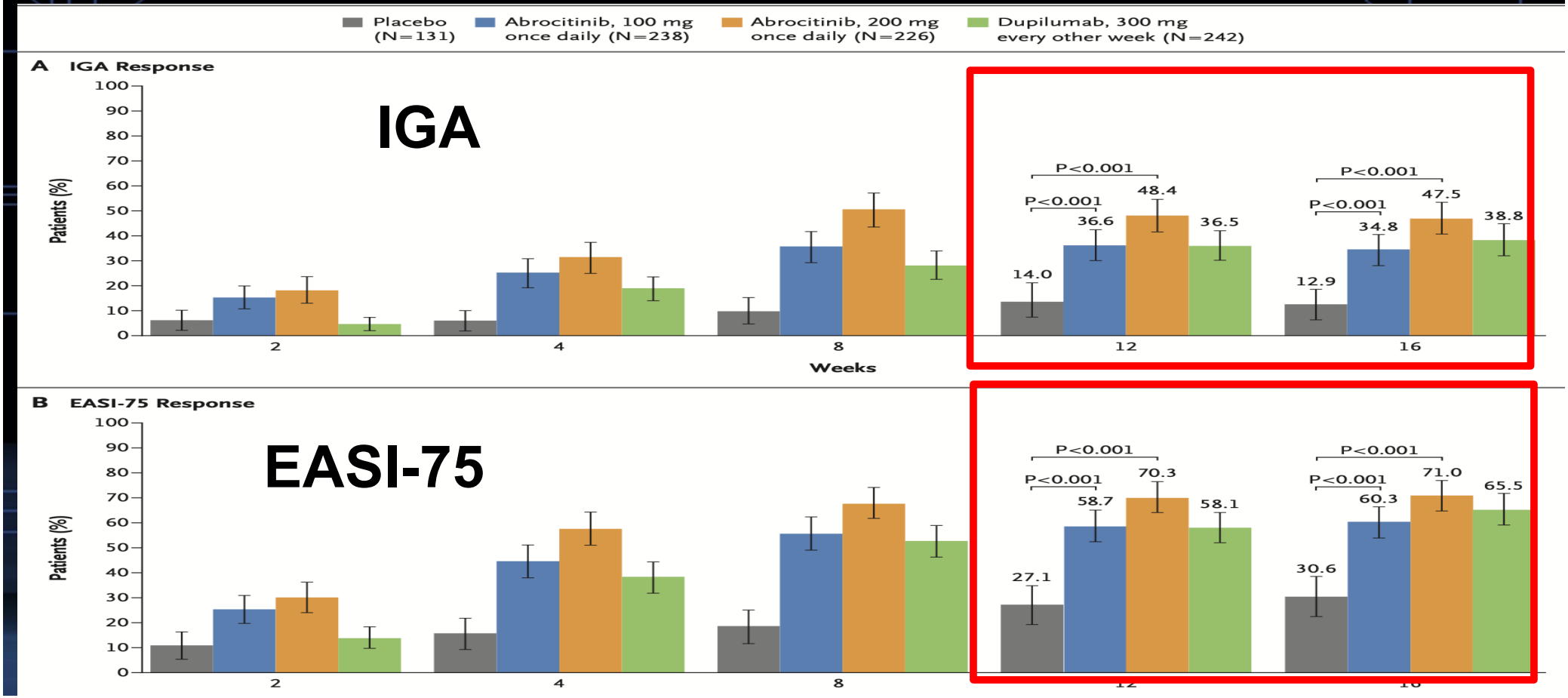
ORIGINAL ARTICLE

Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis

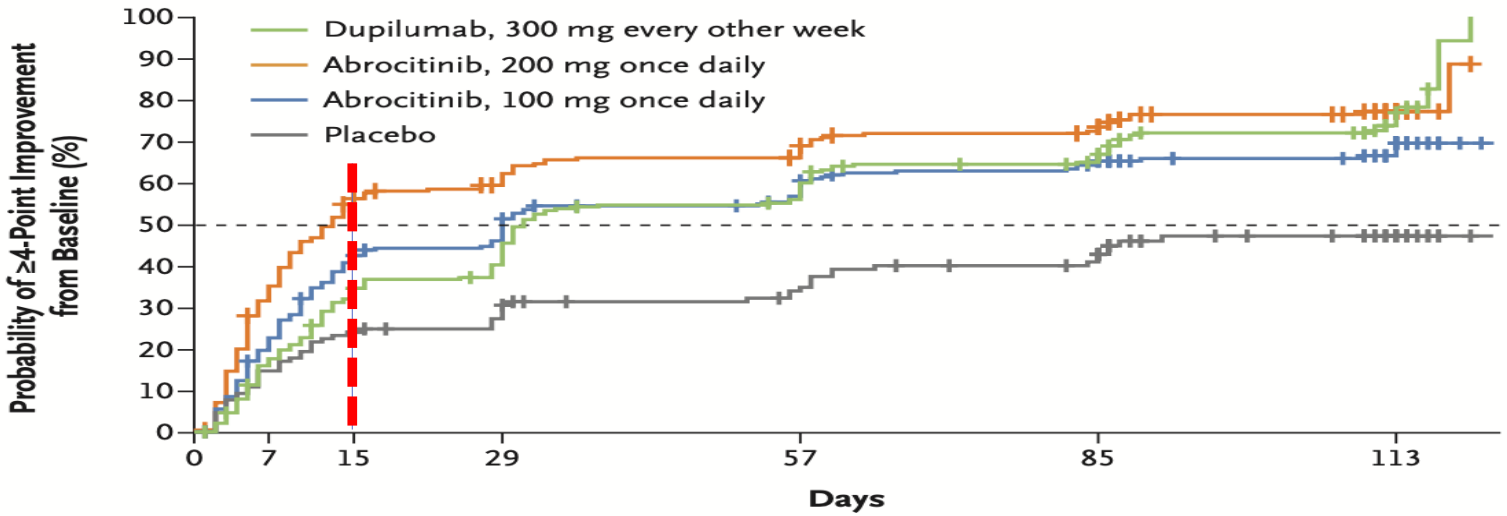
T. Bieber, E.L. Simpson, J.I. Silverberg, D. Thaçi, C. Paul, A.E. Pink, Y. Kataoka, C.-Y. Chu, M. DiBonaventura, R. Rojo, J. Antinew, I. Ionita, R. Sinclair, S. Forman, J. Zdybski, P. Biswas, B. Malhotra, F. Zhang, and H. Valdez, for the JADE COMPARE Investigators*

1. The trial was NOT formally designed to evaluate the superiority of abrocitinib over dupilumab with respect to the two primary end points.
2. Abrocitinib at a dose of either 200 mg or 100 mg once daily resulted in significantly greater reductions in signs and symptoms of moderate-to-severe atopic dermatitis than placebo at weeks 12 and 16.
3. The 200-mg dose, but not the 100-mg dose, of abrocitinib was superior to dupilumab with respect to itch response at week 2.
4. Neither abrocitinib dose differed significantly from dupilumab with respect to most other key secondary end-point comparisons at week 16.

IGA & EASI-75:
Abrocitinib (100 & 200 mg) vs Dupilumab



Abrocitinib (100 & 200 mg) vs Dupilumab: *Itch Response*



No. at Risk

Dupilumab, 300 mg every other week	240	199	160	137	99	73	42
Abrocitinib, 200 mg once daily	226	153	100	86	70	53	24
Abrocitinib, 100 mg once daily	236	187	137	122	93	74	44
Placebo	130	110	99	89	76	65	29

Figure 1. Median Time to Itch Response.

Itch response was defined as an improvement from baseline of at least 4 points in the score on the Peak Pruritus Numerical Rating Scale, on which scores range from 0 to 10, with higher scores indicating greater severity of pruritus.

Safety Of Oral JAK Inhibitors

- **Black box warnings:** in abrocitinib and upadacitinib
  - Serious infection: (opportunistic infections)
  - Malignancy (lymphoma)
  - Thrombosis (DVTs, PEs)
- **Recommended lab monitoring:**
  - LFTs
  - CBC
  - Lipids

Monoclonal Antibodies in AD

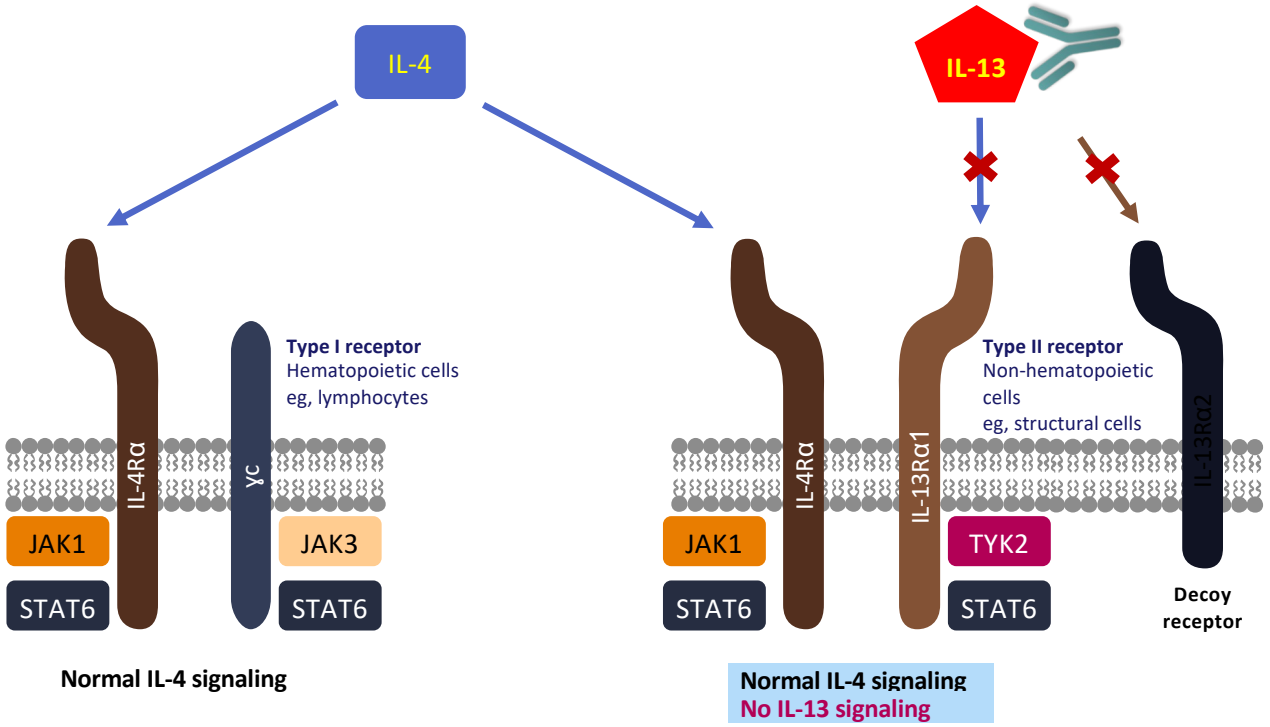
Monoclonal Antibodies in AD

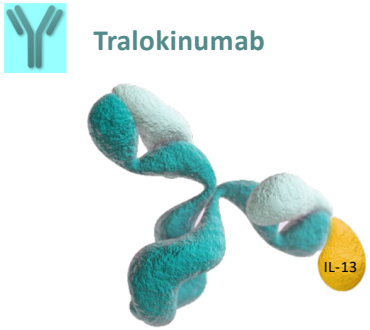
- **Approved for AD**
  - Dupilumab: IL4α Receptor MAb (Dupixent®): Approved ≥ 6 months and older
    - Phase 3 Study 6 month – 5 yo (presented here in later slide)
  - Tralokinumab: IL-13 Mab (Adbry®): Approved 12/21 for ≥ 18 yo
    - Phase 3 Studies completed in adolescents: 12-17 yo
- **Being Studied in AD**
  - Lebrikizumab (IL-13 MAb): Phase 3 completed in ≥ 12 yo
  - Nemolizumab (IL-31 MAb): Phase 2b completed; phase 3 ongoing

Tralokinumab (Adbry®): Selective IL-13 MAb for AD

Tralokinumab: Selective Targeting IL-13: Approved for AD 12/21

- Tralokinumab is a fully human monoclonal antibody that specifically binds to the IL-13 cytokine and inhibits downstream signaling





γc, common gamma chain; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase.
May RD et al. *Br J Pharmacol.* 2012;166:177-93; Popovic B et al. *J Mol Biol.* 2017;429:208-19; Bieber T. *Allergy.* 2020;75:54-62.

Tralokinumab (Adbry®): Selective IL-13 MAb for AD

- Approved for AD patients 18 yrs and older
- 600 mg loading dose -> 300 mg q2 weeks (150 mg pre-filled syringes)
- Can increase dose interval to q 4 weeks at 16 weeks if IGA 0/1 and < 220 lbs

Tralokinumab (Adbry®): Adolescents (12-17 yo) w/ AD

Efficacy and safety of tralokinumab in adolescents with moderate-to-severe atopic dermatitis: results of the phase 3 ECZTRA 6 trial

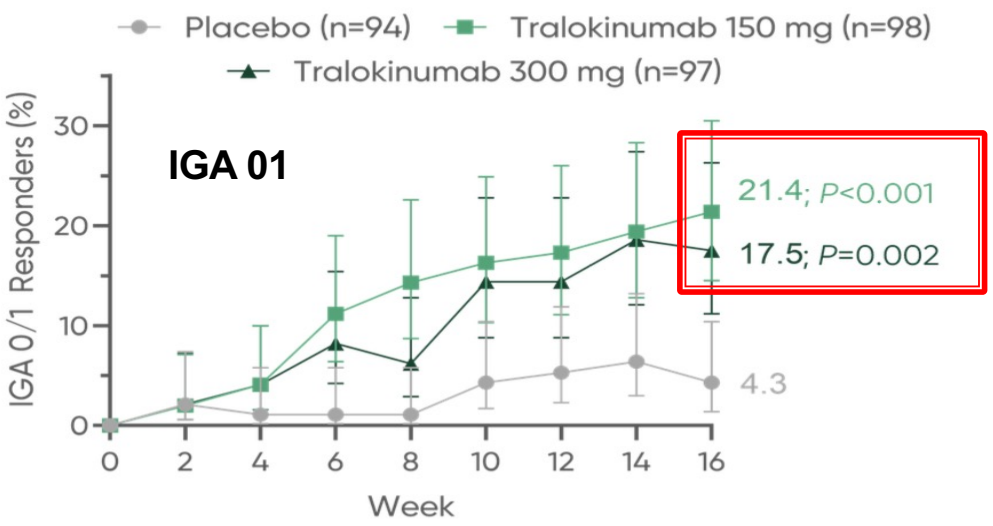
Amy Paller[1], Andrew Blauvelt[2], Weily Soong[3], Shinichi Imafuku[4], Chih-ho Hong[5], Marie L.A. Schuttelaar[6], Petra Amoudruz[7], Azra Kurbasic[7], Lise Soldbro[7], Katja Lophaven[7], Michael Cork[8], Anthony Bewley[9], Eric L. Simpson[10]

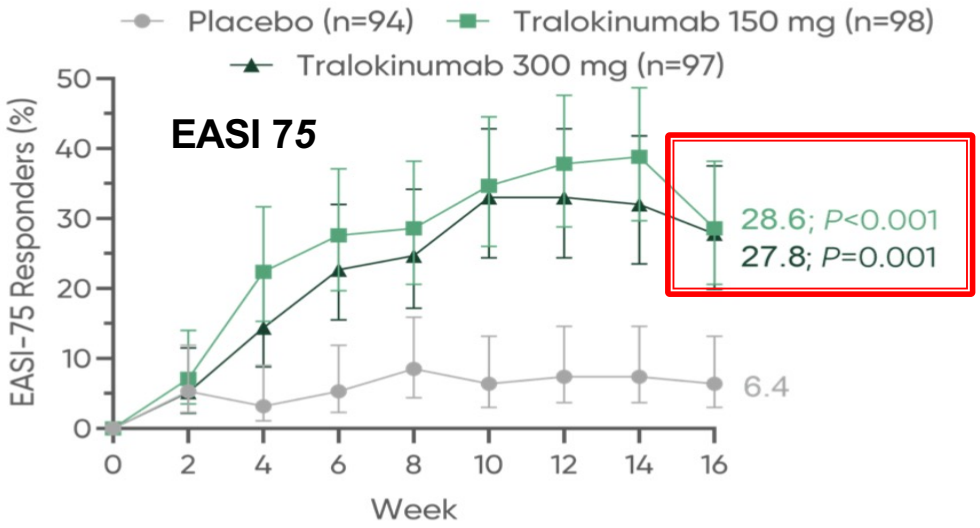
Tralokinumab (Adbry®): Adolescents (12-17 yo) w/ AD

Tralokinumab treatment demonstrated efficacy vs placebo across endpoints at Week 16

At Week 16, significantly greater proportions of patients receiving tralokinumab achieved the primary endpoints of IGA 0/1 and EASI-75 without use of rescue compared to those receiving placebo

150 mg and 300 mg Q2W





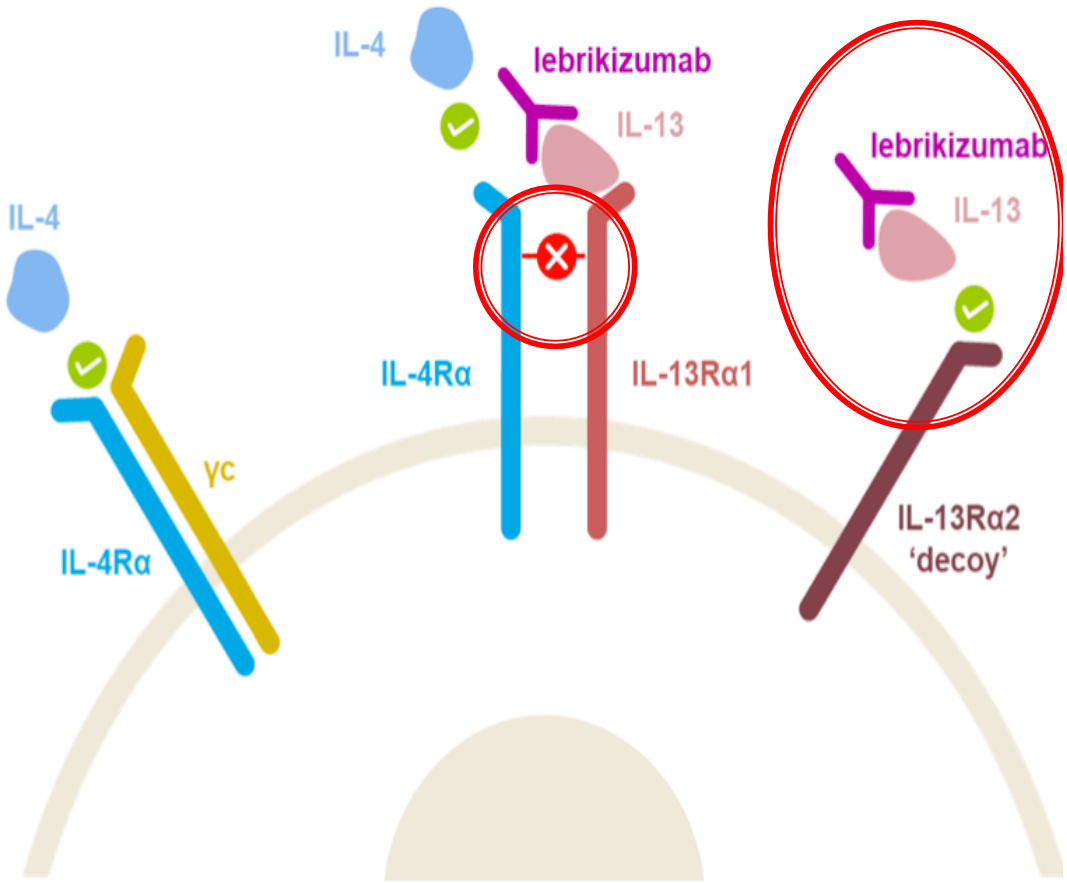
Error bars show 95% confidence intervals. P-values compare respective tralokinumab dose to placebo.
IGA: Investigator's Global Assessment. EASI: Eczema Area and Severity Index.

Safety profiles were comparable to those in Phase 3 adult tralokinumab trials

LEBRIKIZUMAB: IL-13 Selective Mab in AD (COMING, NOT YET APPROVED)

LEBRIKIZUMAB: IL-13 Selective Mab in AD

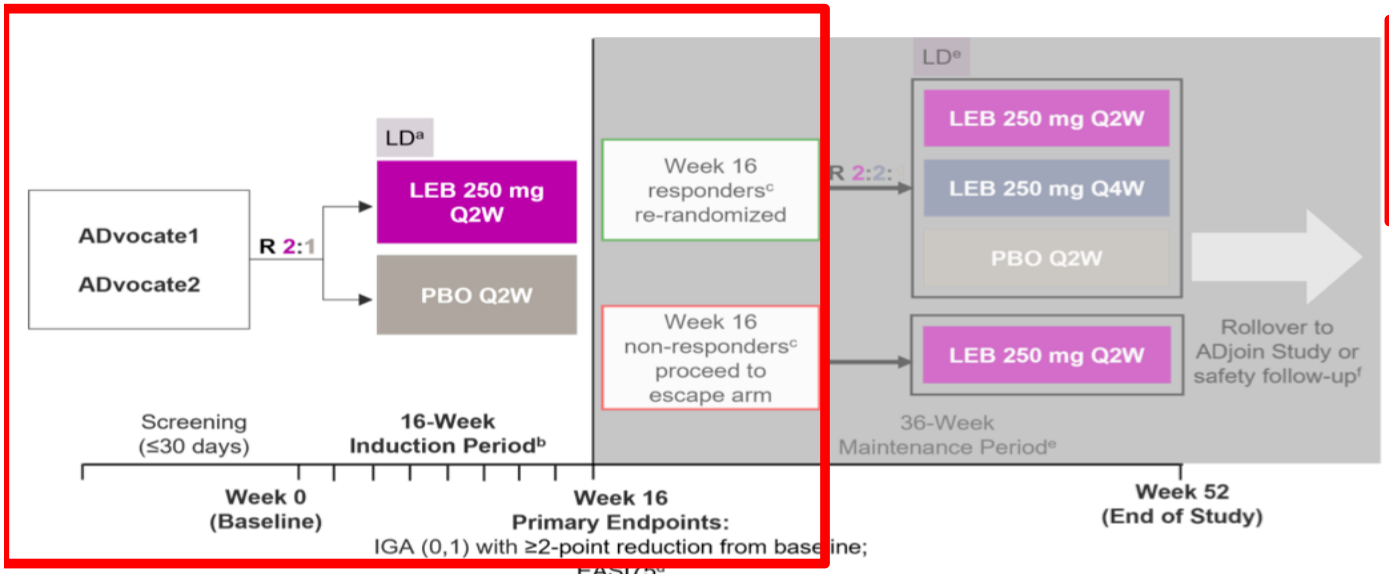
- Lebrikizumab is a novel, high-affinity immunoglobulin G4 monoclonal antibody targeting interleukin (IL)-13
- Lebrikizumab selectively prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex, thus blocking IL-13 signaling[1,2]
- Lebrikizumab does not prevent the binding of IL-13 to the IL-13Rα2 (decoy) receptor, which allows the internalization of IL-13 into the cell[3]



1. Simpson EL, et al. *J Am Acad Dermatol*. 2018;78:863-871.e11.
2. Gonçalves F, et al. *Drugs Context*. 2021;10:2021-1-7.
3. Wulur I, et al. Presented at 4th Inflammatory Skin Disease Summit. 2021.
IL=interleukin

Lebrikizumab: Phase 3 Study Design

STUDY DESIGN



USE OF RESCUE MEDICATION THROUGH WEEK 16

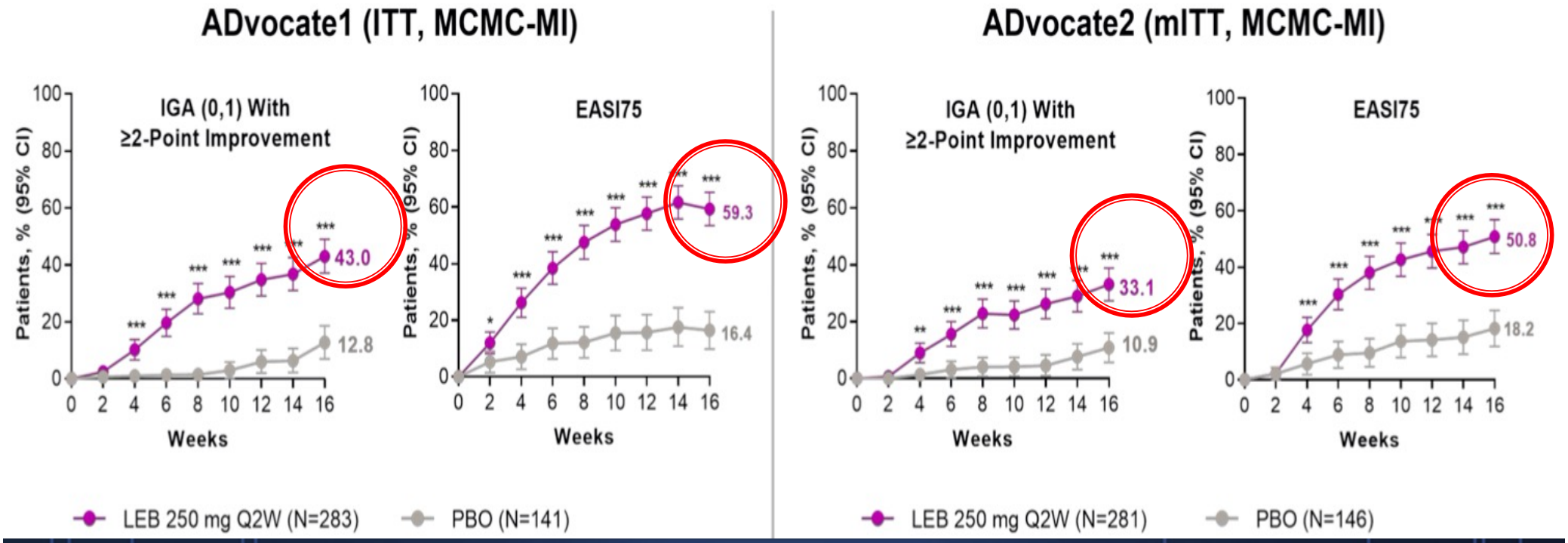
	ADvocate1 (ITT)		ADvocate2 (mITT)	
	PBO Q2W (N=141)	LEB 250 mg Q2W (N=283)	PBO Q2W (N=146)	LEB 250 mg Q2W (N=281)
Any rescue medication[a]	47 (33.3)	30 (10.6)	58 (39.7)	56 (19.9)
Topical rescue medication	44 (31.2)	27 (9.5)	54 (37.0)	52 (18.5)
Low-/mid-potency TCS	38 (27.0)	21 (7.4)	24 (16.4)	28 (10.0)
High-potency TCS	15 (10.6)	6 (2.1)	36 (24.7)	25 (8.9)
Topical calcineurin inhibitor	9 (6.4)	3 (1.1)	6 (4.1)	11 (3.9)
Systemic rescue medication	11 (7.8)	6 (2.1)	9 (6.2)	8 (2.8)

ction Period were considered to be non-responders
EASI75 at Week 16
tors and as a major secondary endpoint by the FDA
eived an LD of LEB 500 mg at Week 16 or at
e Maintenance Period
otherwise, patients participated in a safety follow-up 12 weeks after their last dose
5=75% reduction from baseline in EASI score; FDA=US Food and Drug Administration; LD=loading dose; LEB=lebrikizumab;
nization

Key Eligibility Criteria

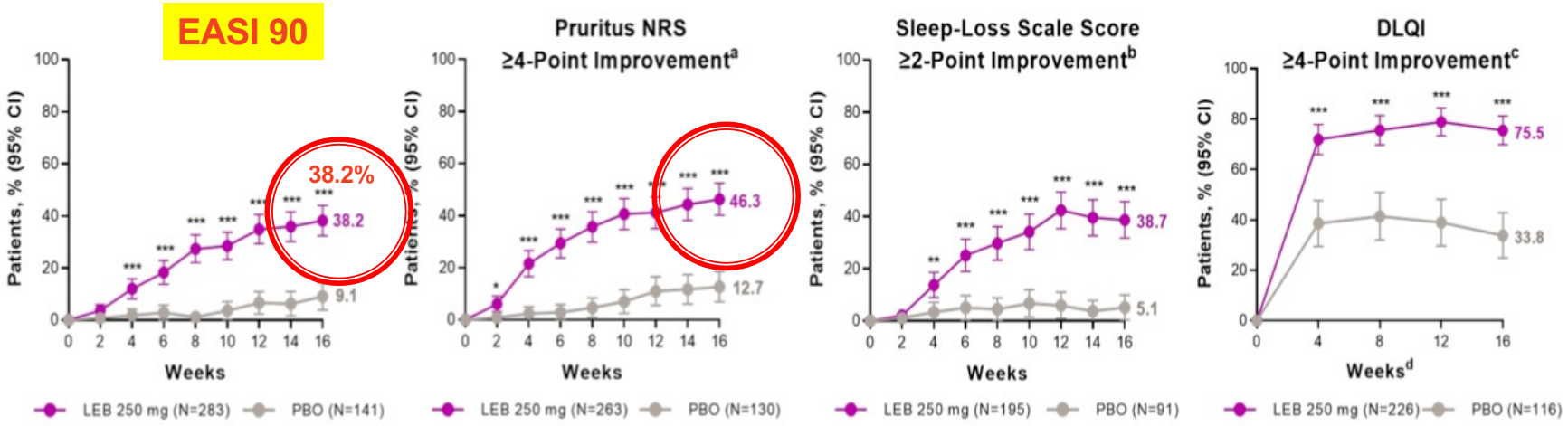
- Adults ≥18 years old and adolescents (≥12 to <18 years old; weighing ≥40 kg)
- Moderate-to-severe AD:
  - Eczema Area and Severity Index (EASI) score ≥16
  - Investigator's Global Assessment (IGA) score ≥3
  - Body surface area % involvement ≥10%
- Chronic AD for ≥1 year for whom topical treatment was inadequate or inadvisable
- Dupilumab and tralokinumab naïve

1^0 Endpoints

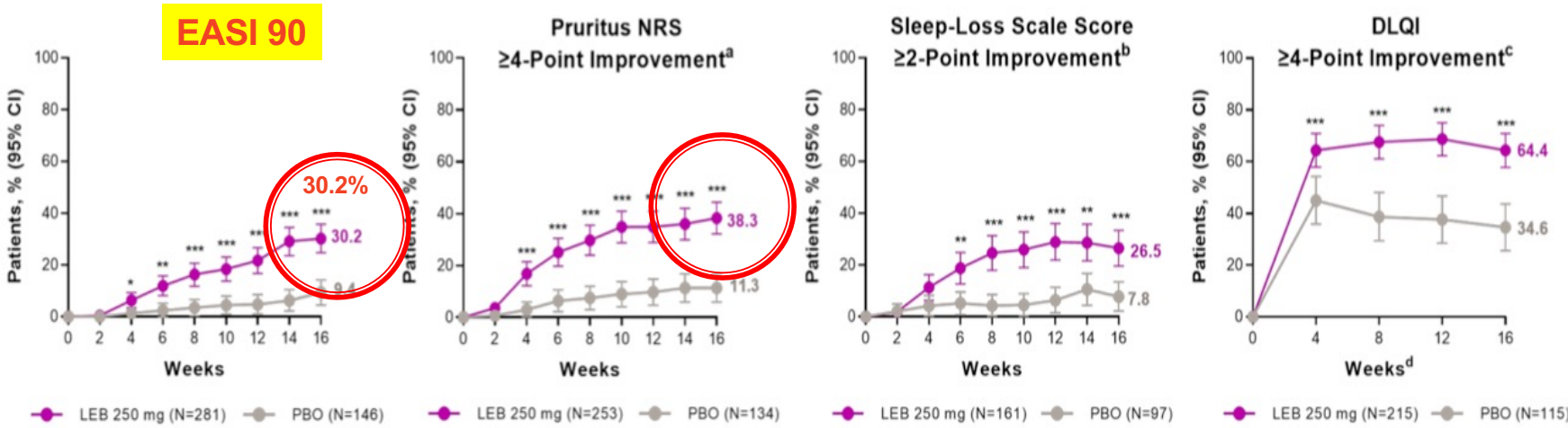


2^0 Endpoints: EASI 90 & ITCH

ADvocate1
(ITT, MCMC-MI)



ADvocate2
(mITT, MCMC-MI)



Transient AEs Through Week 16

	ADvocate1 (Safety Population)		ADvocate2 (Modified Safety Population)	
	PBO Q2W (N=141)	LEB 250 mg Q2W (N=282)	PBO Q2W (N=145)	LEB 250 mg Q2W (N=281)
Any TEAE	72 (51.5)	128 (45.4)	96 (66.2)	149 (53.0)
Mild	34 (24.1)	78 (27.7)	40 (27.6)	73 (26.0)
Moderate	31 (22.0)	44 (15.6)	49 (33.8)	69 (24.6)
Severe	7 (5.0)	6 (2.1)	7 (4.8)	7 (2.5)
Most common TEAEs (≥5% in either LEB group)				
Conjunctivitis[a]	4 (2.8)	21 (7.4)	3 (2.1)	22 (7.8)
Exacerbation of AD	28 (19.9)	15 (5.3)	37 (25.5)	28 (10.0)
Nasopharyngitis	3 (2.1)	11 (3.9)	3 (2.1)	14 (5.0)
Headache	2 (1.4)	9 (3.2)	6 (4.1)	14 (5.0)
Serious AE[b]	1 (0.7)	6 (2.1)	4 (2.8)	2 (0.7)
Death	0	0	1 (0.7)	0
AEs leading to treatment discontinuation[b]	1 (0.7)	3 (1.1)	4 (2.8)	8 (2.8)
Injection site reactions	3 (2.1)	3 (1.1)	1 (0.7)	7 (2.5)
Herpes infections	6 (4.3)	9 (3.2)	6 (4.1)	8 (2.8)

- All conjunctivitis treatment-emergent adverse events (TEAEs) were mild-to-moderate in severity; the majority of conjunctivitis-related TEAEs did not lead to treatment discontinuation

Data are n (%)

[a] Conjunctivitis single preferred term; [b] Deaths are also included as serious AEs and AEs leading to treatment discontinuation

AD=atopic dermatitis; AE=adverse event; LEB=lebrikizumab; PBO=placebo; Q2W=every 2 weeks; TEAE=treatment-emergent adverse event

Take Home Points

- Seeking approval in >12 yo. patients
- Dosing can be stretched to Q4 week after week 16 if patients improve clinically
- Conjunctivitis still an issue
- IGA 0/1 and EASI 75 & 90 highest we have seen yet for a biologic ….BUT…. no comparator trials yet to dupilumab and tralokinumab
- No comparator trial to a JAKinib

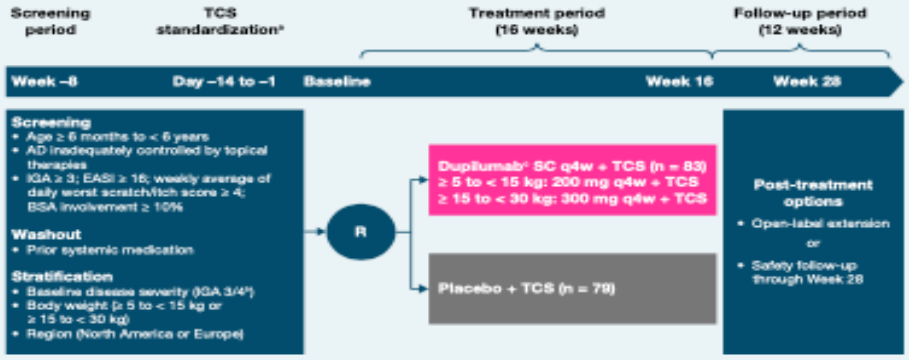
Dupilumab:

1. New indication: age 6 mo – 5 years
2. New Approval: Prurigo Nodularis (9/2022)
3. Studies in Urticaria (Phase 3)

Dupilumab + TCS: Phase 3 Studies 6 months - 5 Years

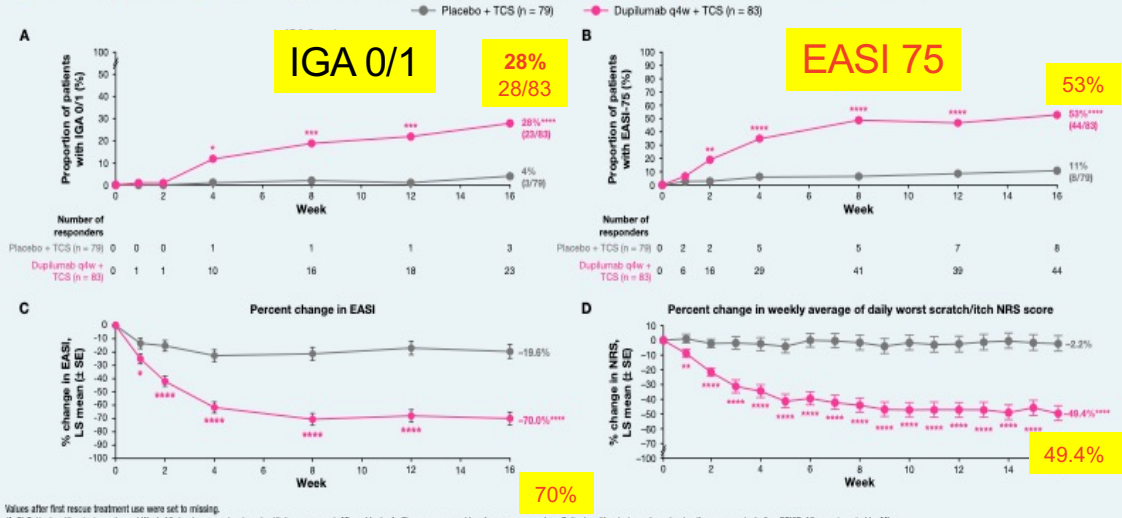
METHODS

Figure 1. Study design LIBERTY AD PRESCHOOL Part B (NCT03346434), a double-blind, placebo-controlled, phase 3 trial.



[a]Starting on Day –14, all patients were to initiate a standardized low-potency TCS treatment regimen (hydrocortisone acetate 1% cream).
[b]Number of patients with IGA 3 was capped to 40.
[c]No loading dose. Weight-tiered doses were assigned by baseline body weight for the duration of the study.
BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; q4w, every 4 weeks; R, randomization; SC, subcutaneous.

Figure 2. Rapid and significant improvements in lesional burden and patient-reported itch through Week 16.



Values after first rescue treatment use were set to missing.
(A, B) Patients with missing values at Week 16 due to rescue treatment, withdrawn consent, AE, and lack of efficacy were considered as non-responders. Patients with missing values due to other reasons including COVID-19 were imputed by MI.
(C, D) Patients with missing values at Week 16 due to rescue treatment, withdrawn consent, AE, and lack of efficacy were imputed by WOCF. Patients with missing values due to other reasons including COVID-19 were imputed by MI. All non-missing data before imputation of WOCF was used for MI.
*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001 vs placebo.
AE, adverse event; EASI-75, 75% improvement from baseline in EASI; LS, least squares; MI, multiple imputation; SE, standard error; WOCF, worst observation carried forward.

6 mo - 5 yrs: 5 to 15 kg is 200 mg q4 weeks (no loading dose)
6 mo - 5 yrs: 15 - 30 kg is 300 mg q4 weeks (no loading dose)

TEAE of special interest	0	1 (1.2)[d]
Conjunctivitis (narrow[e])	0	4 (4.8)
Skin infection (excluding herpes infection)	19 (24.4)	10 (12.0)
Injection-site reactions (HLT)	2 (2.6)	2 (2.4)
Herpes viral infections (HLT)	4 (5.1)[f]	5 (6.0)[g]

[a]Serious TEAEs were atopic dermatitis, hypersensitivity, staphylococcal bacteremia, and staphylococcal cellulitis. All occurred in the placebo + TCS group and none led to study drug discontinuation. [b]Patient discontinued due to AE of nightmares due to blood draws. [c]Patient discontinued due to AE of AD flare. [d]AE of special interest of blepharitis. [e]Standardized MedDRA query containing conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis. [f]Oral herpes (2), eczema herpeticum, herpes simplex. [g]Herpes virus infection (2), varicella (2), oral herpes.

- **severe AD, dupilumab q4w + low-potency TCS rapidly and significantly improved AD signs and symptoms**
- **Dupilumab has demonstrated an acceptable safety profile, similar to that observed in older children and adults**

▪Poster: Paller A., et al Maui Derm NPPA Summer 2022

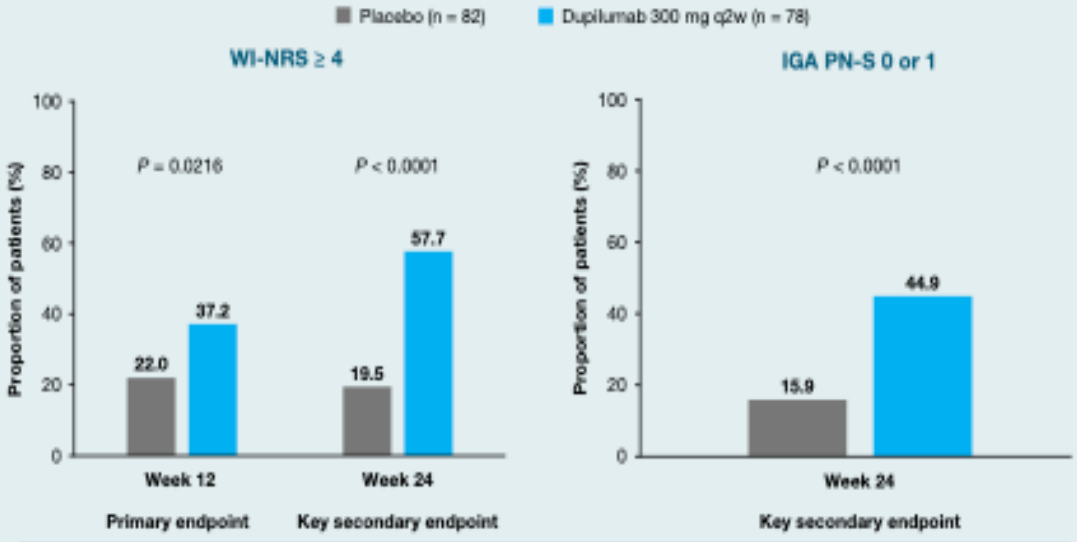
Dupilumab for Prurigo Nodularis

Dupilumab Significantly Improves Itch and Skin Lesions in Patients With Prurigo Nodularis: Results From a Phase 3 Trial (LIBERTY-PN PRIME2)

Gil Yosipovitch[1], Nicholas Mollanazar[2], Sonja Ständer[3], Shawn G. Kwatra[4], Brian S. Kim[5], Sheldon Wang[6], Elizabeth Laws[6], Ashish Bansal[7], John T. O'Malley[8]

[1]University of Miami, Miami, FL, USA; [2]University of Pennsylvania, Philadelphia, PA, USA; [3]University Hospital Münster, Münster, Germany; [4]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [5]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]Sanofi, Bridgewater, NJ, USA; [7]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [8]Sanofi, Cambridge, MA, USA

Figure 3. Proportion of patients with ≥ 4-point improvement in WI-NRS and IGA PN-S 0 or 1



These results were confirmed by a second positive pivotal trial in PN, **PRIME** (NCT04183335), that will be presented at a future meeting

Patients:

1. PN pts with severe itch, high lesion count and impaired QOL
2. Not controlled with topicals; 2/3 had used systemic therapies
3. No new safety signals; c/w known safety profile in AD

Poster Maui Derm NPPA Summer 2022

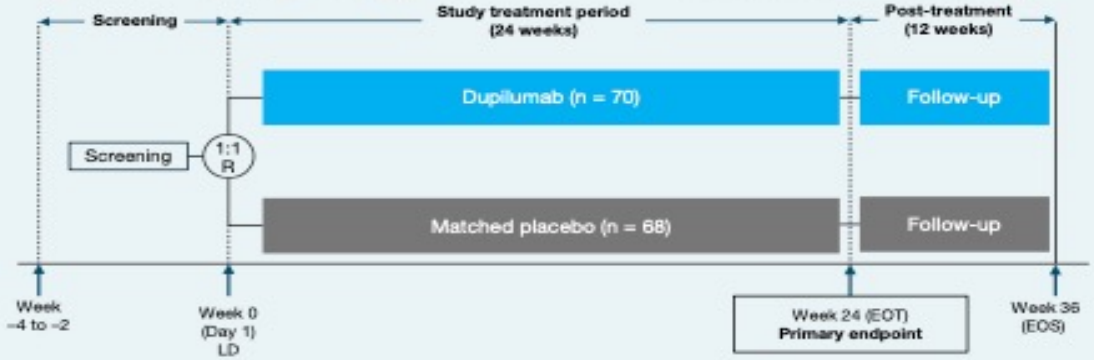
Dupilumab for Itch and Hives in Chronic Spontaneous Urticaria

Dupilumab Significantly Reduces Itch and Hives in Patients With Chronic Spontaneous Urticaria: Results From a Phase 3 Trial (LIBERTY-CSU CUPID Study A)

Marcus Maurer[1,2], Thomas B. Casale[3], Sarbjit S. Saini[4], Moshe Ben-Shoshan[5], Allen Radin[6], Bola Akinlade[6], Chunpeng Fan[7], Deborah Bauer[7], Elizabeth Laws[7], Leda P. Mannent[8], Aleksandra Stjepanovic[8]

[1]Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany; [3]University of South Florida, Tampa, FL, USA; [4]Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA; [5]McGill University Health Centre, Montreal, QC, Canada; [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [7]Sanofi, Bridgewater, NJ, USA; [8]Sanofi, Chilly-Mazarin, France

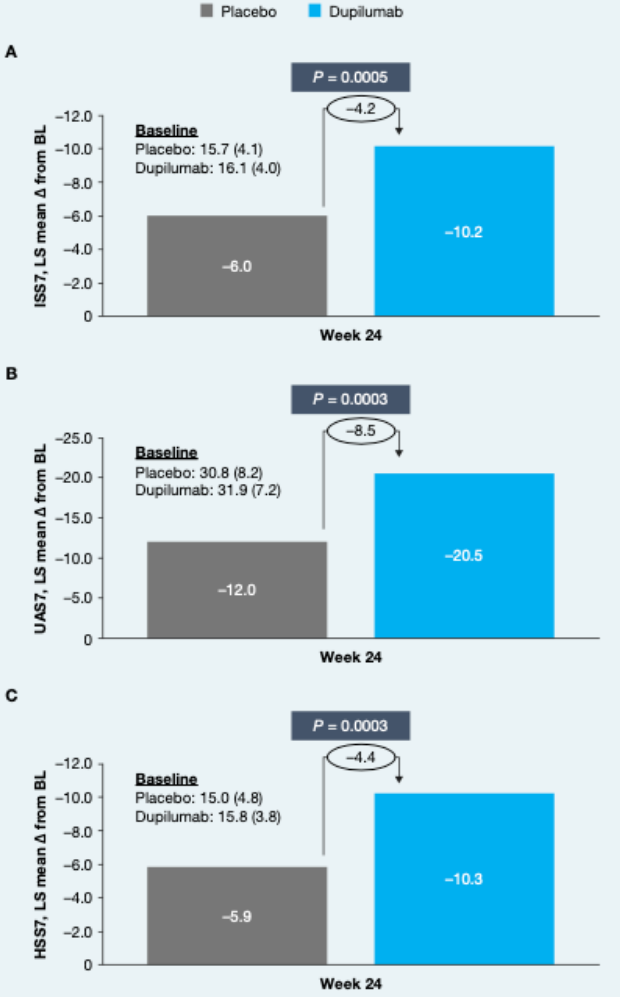
Figure 1. Study design of LIBERTY-CSU CUPID Study A.



Dupilumab dosing: adults (> 18 years) and adolescents (12–17 years) ≥ 60 kg: LD 600 mg (two 300 mg SC injections), followed by 300 mg q2w; adolescents (12–17 years) and children (≥ 6 to < 12 years) ≥ 30 kg to < 60 kg: LD 400 mg (two 200 mg SC injections), followed by 200 mg q2w; children (≥ 6 to < 12 years) ≥ 15 kg to < 30 kg: LD 600 mg (two 300 mg SC injections), followed by 300 mg q4w

EOS, end of study; EOT, end of treatment; LD, loading dose; q2w, every 2 weeks; q4w, every 4 weeks; R, randomization; SC, subcutaneous.

Figure 2. Dupilumab treatment leads to statistically significant improvements in (A) ISS7 (primary endpoint), (B) UAS7 (secondary endpoint), and (C) HSS7 (secondary endpoint).

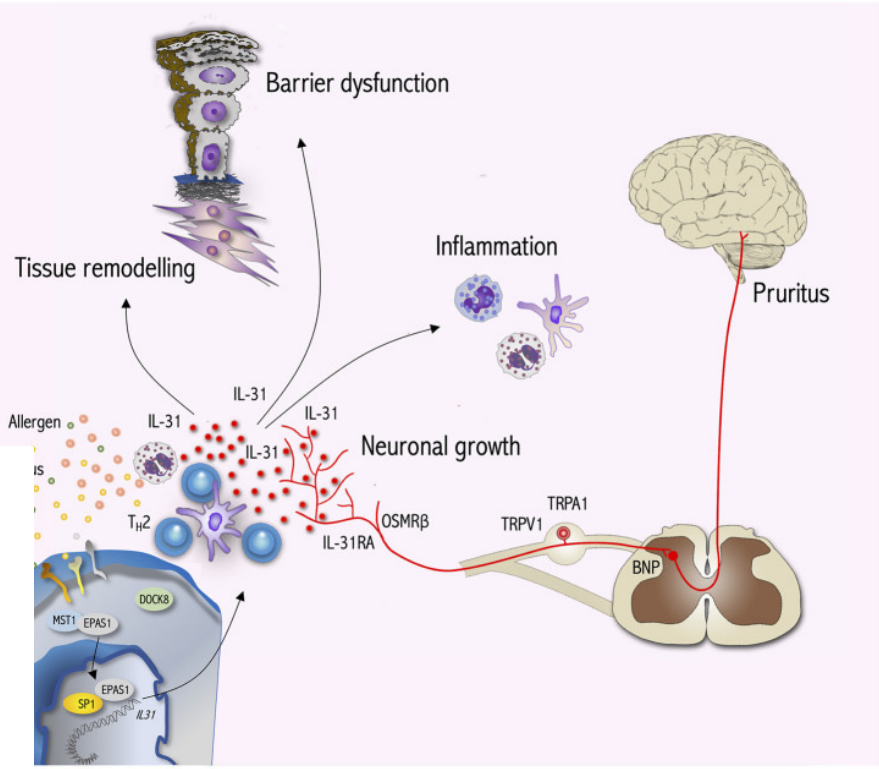


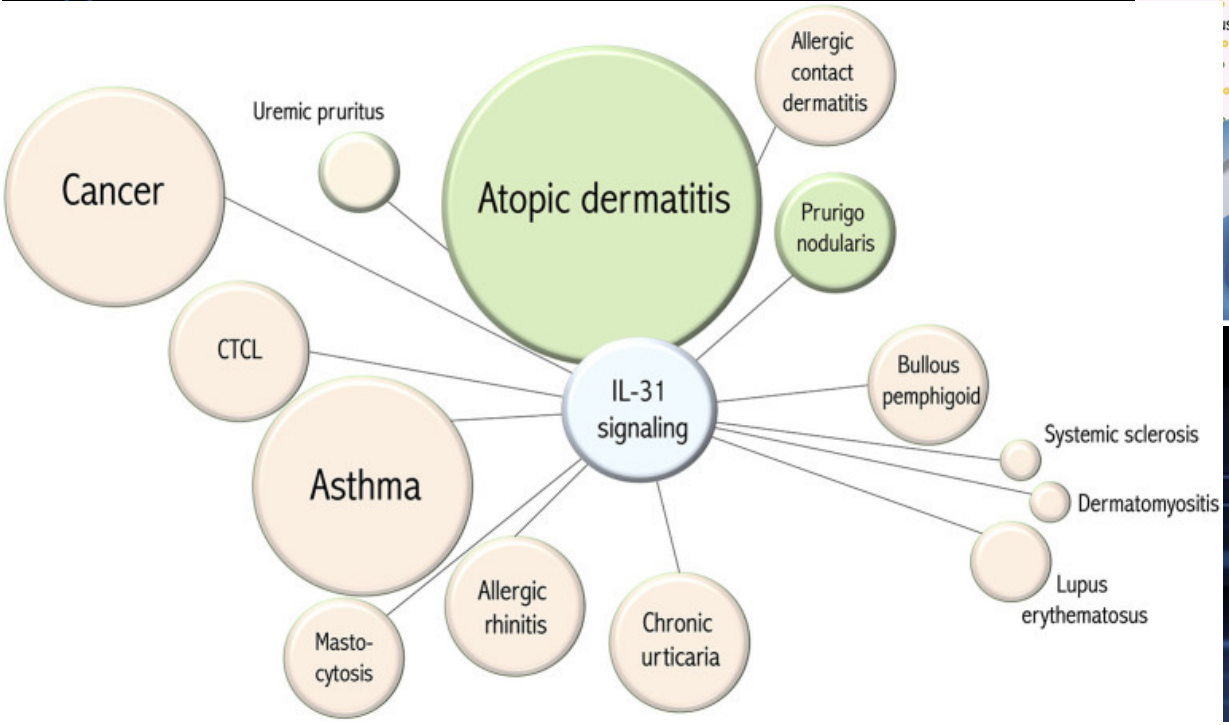
BL data are presented as mean (standard deviation).
ISS7, range 0–21; UAS7 is a composite of ISS7 and HSS7, range 0–42; HSS7, range 0–21. LS, least squares.

Nemolizumab: IL-31 Receptor Antibody (Coming; Not Yet Approved)

IL-31 Signaling

IL-31 also induces a distinct transcriptional program in *sensory neurons*, leading to *nerve elongation and branching* both in vitro and in vivo.

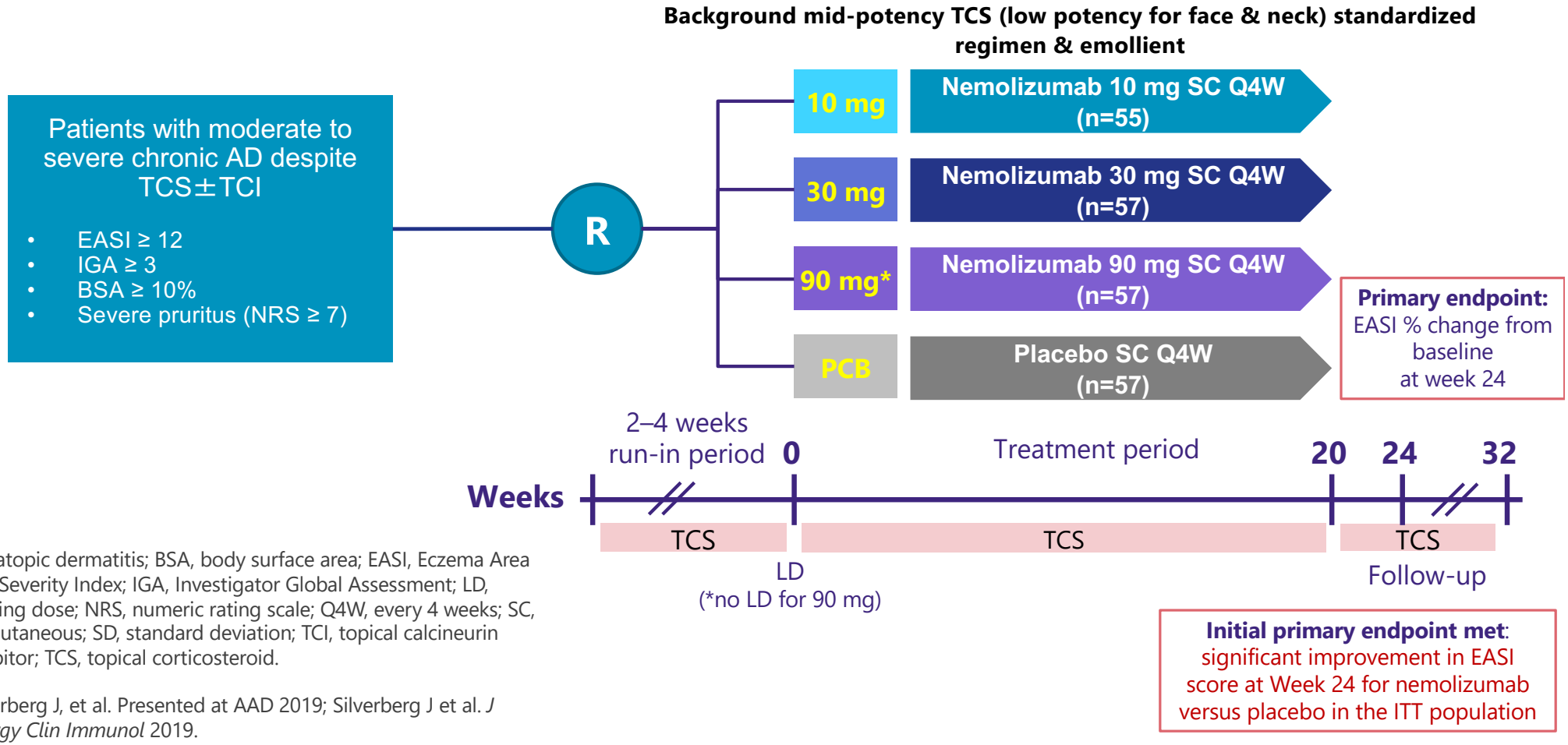




Nemolizumab: IL-31 Receptor Antibody

- Interleukin (IL)-31 affects the inflammatory response, is involved in epidermal barrier disruption in atopic dermatitis (AD) and plays a key role in pruritus.
- **Nemolizumab**, a humanized monoclonal antibody against ***IL-31 receptor A***

Phase 2b Study Design for Nemolizumab in AD

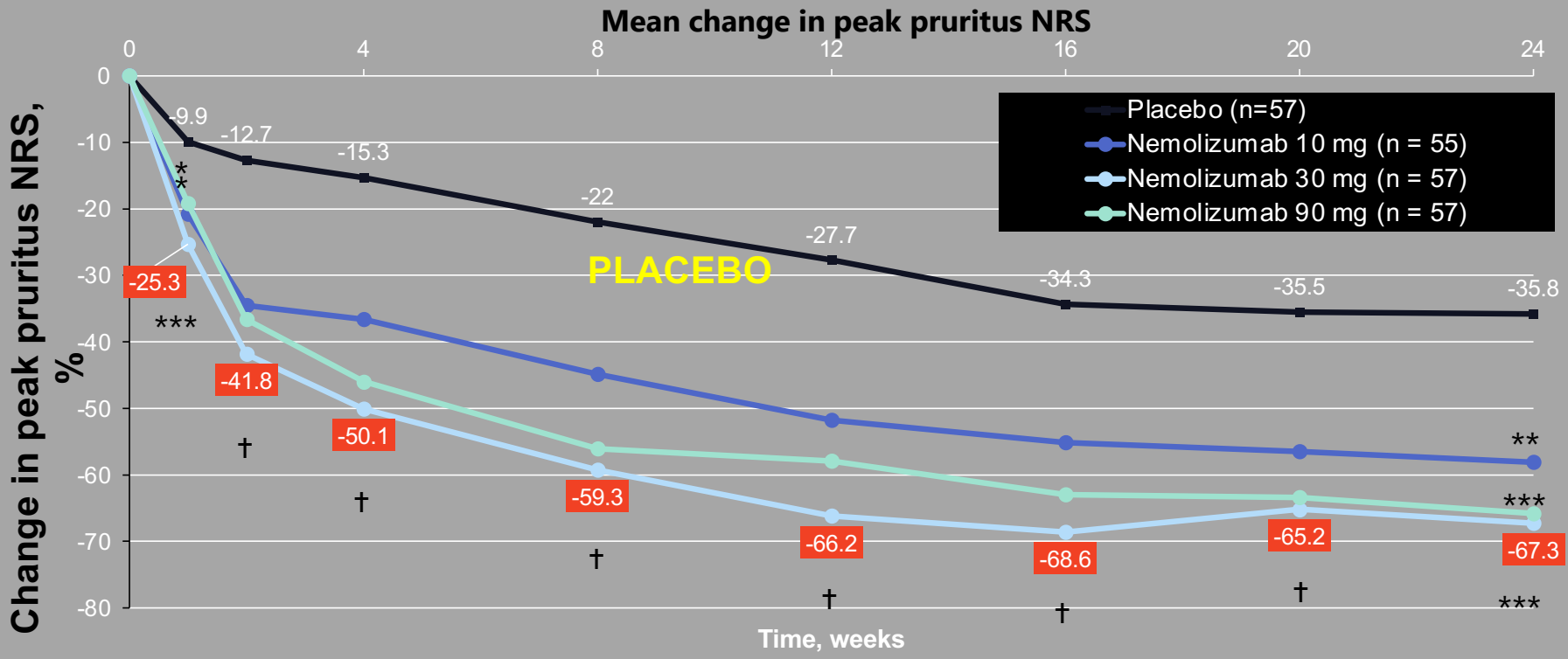


AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; LD, loading dose; NRS, numeric rating scale; Q4W, every 4 weeks; SC, subcutaneous; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Silverberg J, et al. Presented at AAD 2019; Silverberg J et al. *J Allergy Clin Immunol* 2019.

Phase 2b efficacy: nemolizumab + TCS on pruritus

- Improvements in adjusted mean percent change from baseline in NRS-itch score were significant by week 1 and remained significant at all subsequent visits for the nemolizumab 30 mg group.



*P<0.05, **P<0.01, ***P<0.001,
†P<0.001 all doses

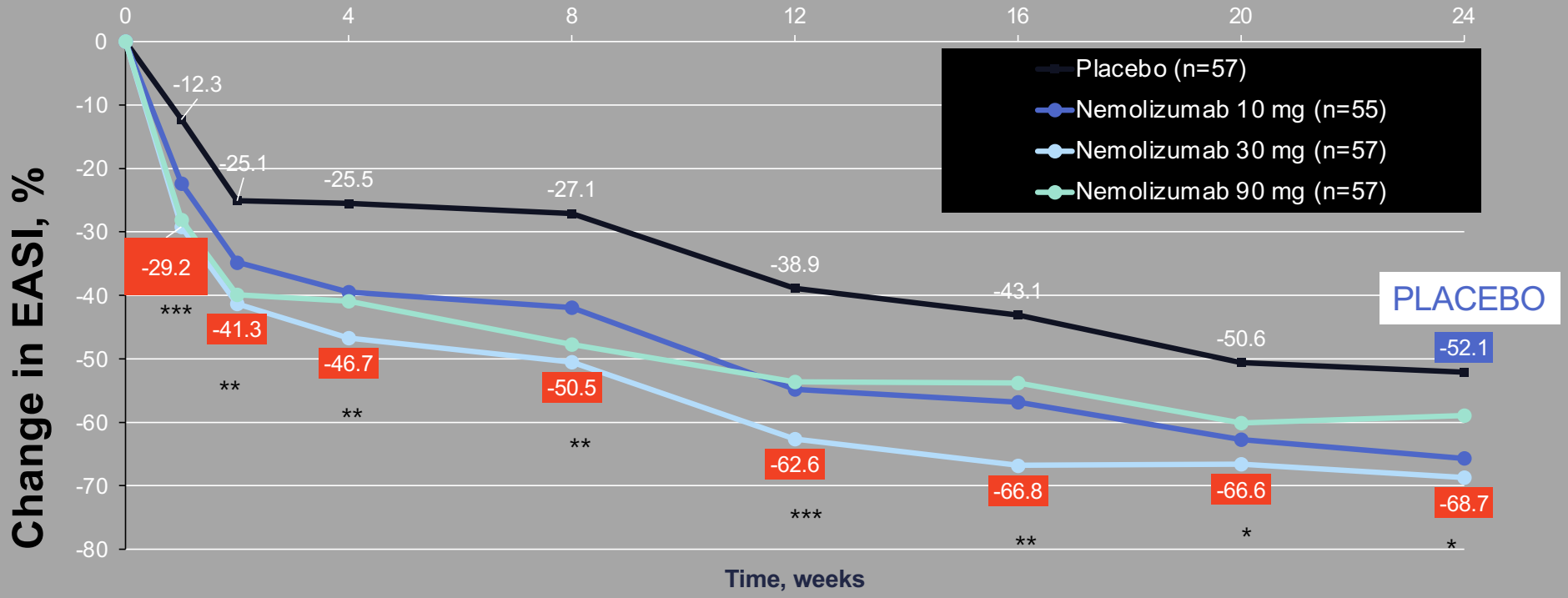
NRS, numeric rating scale; TCS, topical corticosteroid.

Silverberg J, et al. Presented at AAD 2019;
Silverberg J et al. *J Allergy Clin Immunol* 2019.

Phase 2b efficacy: *Nemolizumab + TCS*

EASI (% change from baseline)

- Improvements in EASI score (% change from baseline) were significant by week 1 and remained significant at all subsequent visits for the nemolizumab 30 mg group.

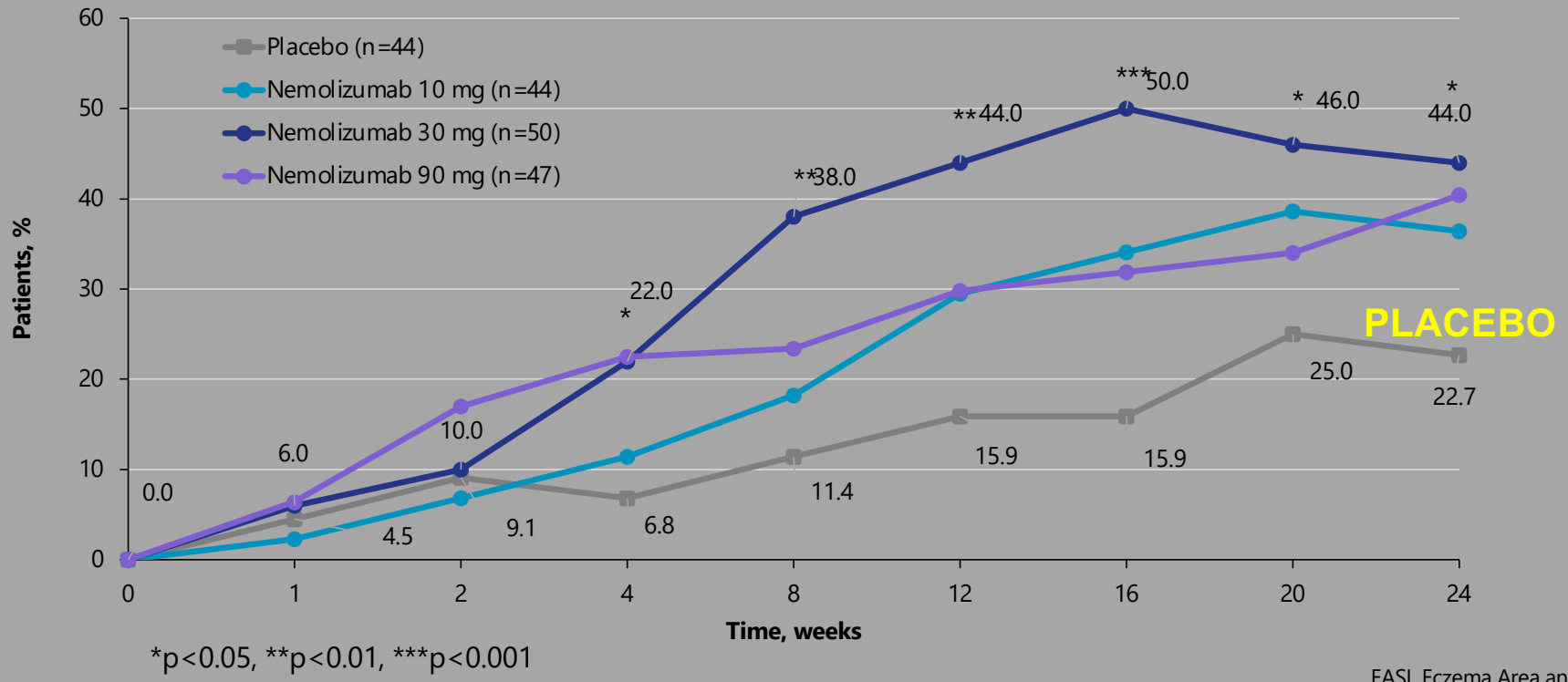


*P<0.05, **P<0.01, ***P<0.001

EASI, Eczema Area and Severity Index; NRS, numeric rating scale; ITT, intent-to-treat.
Silverberg J, et al. Presented at AAD 2019; Silverberg J et al. *J Allergy Clin Immunol* 2019.

EASI≥16 sub-population: efficacy of nemolizumab + TCS on EASI 75

A significantly greater proportion of patients showed a ≥75% improvement in EASI score with nemolizumab 30 mg *vs* placebo from Week 4 onwards [1,2]



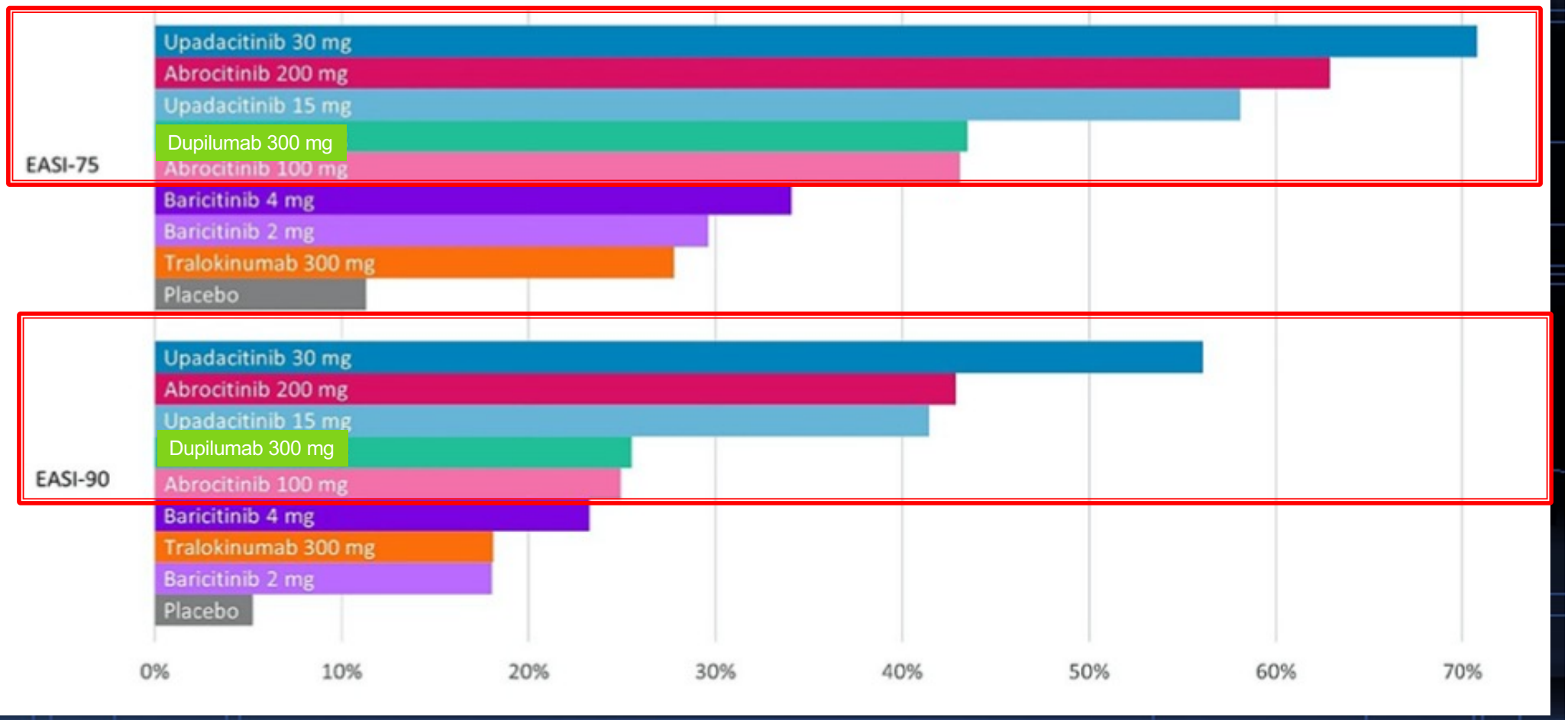
*p<0.05, **p<0.01, ***p<0.001

EASI, Eczema Area and Severity Index.

1. Silverberg J, *et al.* EADV 2020 Abstract 1796, e-Poster P0230, Galderma data on file. 2. Silverberg et al, 2021, JEADV. Nemolizumab is associated with a rapid improvement in atopic dermatitis signs and symptoms: subpopulation (EASI ≥ 16) analysis of randomized phase 2B study

How Do The JAKinibs and IL-13 MAb Compare ?

Meta-analysis of EASI 75 & 90



Silverberg J.I. et al Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysisDermatol Ther (Heidelb) (2022) 12:1181–1196 https://doi.org/10.1007/s13555-022-00721-1

Meta-analysis IGA & Pruritus Scores: ΔNRS ≥4

ΔNRS ≥4

IGA 0/1

Fig. 2 IGA 0/1 versus ΔNRS ≥ 4 absolute response rate estimates for moderate to severe atopic dermatitis (primary endpoint timepoint). *ΔNRS ≥ 4* Pruritus Numerical Rating Scale reduction of ≥ 4 points from baseline, *IGA* Investigator Global Assessment for Atopic Dermatitis

Silverberg J.I. et al Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysisDermatol Ther (Heidelb) (2022) 12:1181–1196 https://doi.org/10.1007/s13555-022-00721-1


BUT WAIT
Ruxolitinib
JACK IN THE BOX
THERE'S MORE

Vitiligo

- Affects 0.5% - 1% of the population
- Only ~25% of identical twins have concordant vitiligo
- 25% - 30% of patients have an associated autoimmune dz (thyroid, adrenal (Addison's), alopecia areata, pernicious anemia)

Photo of Winnie Harlow

FDA Approval July 18,2022
Ruxolitinib (JAK 1,2) Topical Cream
For The Treatment of (non-segmental) Vitiligo
>12 years of age

INSURANCE IS LOOKING FOR REASONS TO DENY COVERAGE. HERE ARE TWO FACTORS THEY LOOK FOR VERY INTENTLY!

Ruxolitinib (JAK 1,2) Topical Cream

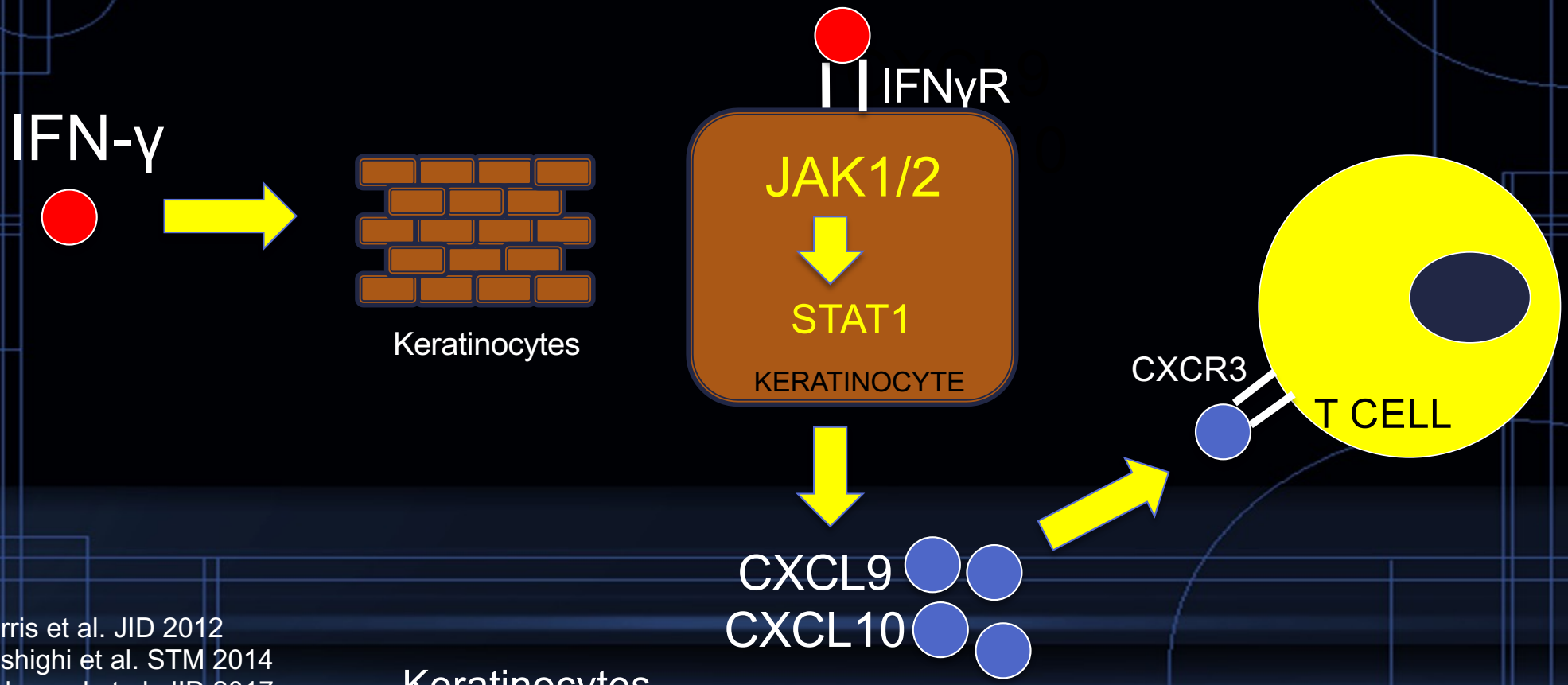
Presented at the American Academy of Dermatology Annual Meeting
March 25–29, 2022; Boston, MA

Efficacy and Safety of Ruxolitinib Cream Monotherapy for the Treatment of Vitiligo: Results From Two 52-Week Phase 3 Studies

David Rosmarin, MD,[1] Thierry Passeron, MD, PhD,[2,3] Amit G. Pandya, MD,[4,5] Pearl Grimes, MD,[6] John E. Harris, MD, PhD,[7] Seemal R. Desai, MD,[5,8] Mark Lebwohl, MD,[9] Mireille Ruer-Mulard, MD,[10] Julien Seneschal, MD, PhD,[11] Albert Wolkerstorfer, MD, PhD,[12] Deanna Kornacki, PhD,[13] Kang Sun, PhD,[13] Kathleen Butler, MD,[13] Khaled Ezzedine, MD, PhD[14]

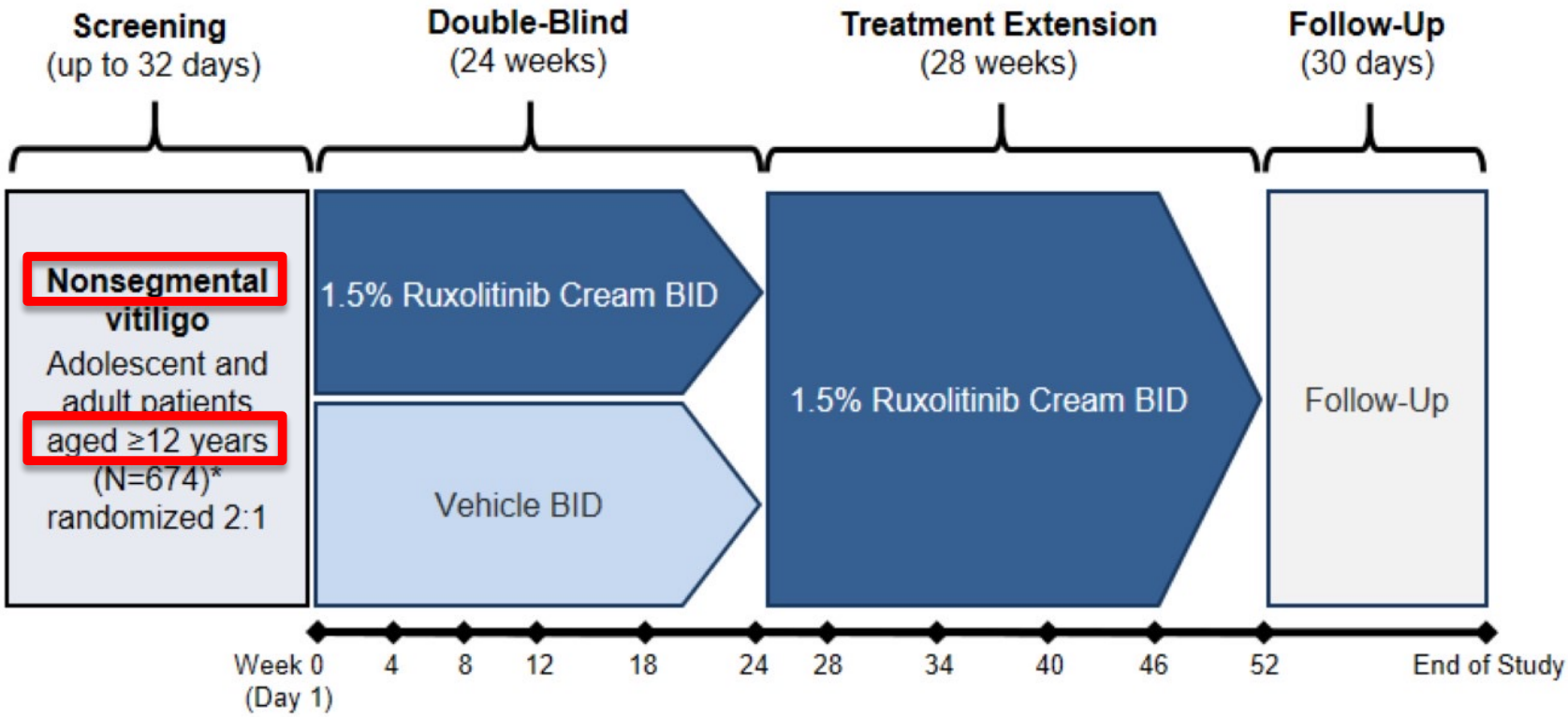
[1]Tufts Medical Center, Boston, MA, USA; [2]Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France; [3]INSERM U1065, C3M, Université Côte d'Azur, Nice, France; [4]Palo Alto Foundation Medical Group, Sunnyvale, CA, USA; [5]University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]The Vitiligo & Pigmentation Institute of Southern California, Los Angeles, CA, USA; [7]University of Massachusetts Medical School, Worcester, MA, USA; [8]Innovative Dermatology, Plano, TX, USA; [9]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [10]Office of Mireille Ruer-Mulard, MD, Martiques, France; [11]Department of Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin Disorders, Hôpital Saint-André, Université de Bordeaux, INSERM, BMGIC, U1035, F-33000, Bordeaux, France; [12]Amsterdam University Medical Center, Amsterdam, Netherlands; [13]Incyte Corporation, Wilmington, DE, USA; [14]Henri Mondor University Hospital and Université Paris-Est Créteil Val de Marne, Paris, France

VITILIGO IS A IFN-γ DRIVEN DISEASE



Harris et al. JID 2012
Rashighi et al. STM 2014
Richmond et al. JID 2017a
Richmond, et al. JID 2017b

TRuE-V1 and TRuE-V2 Study Design

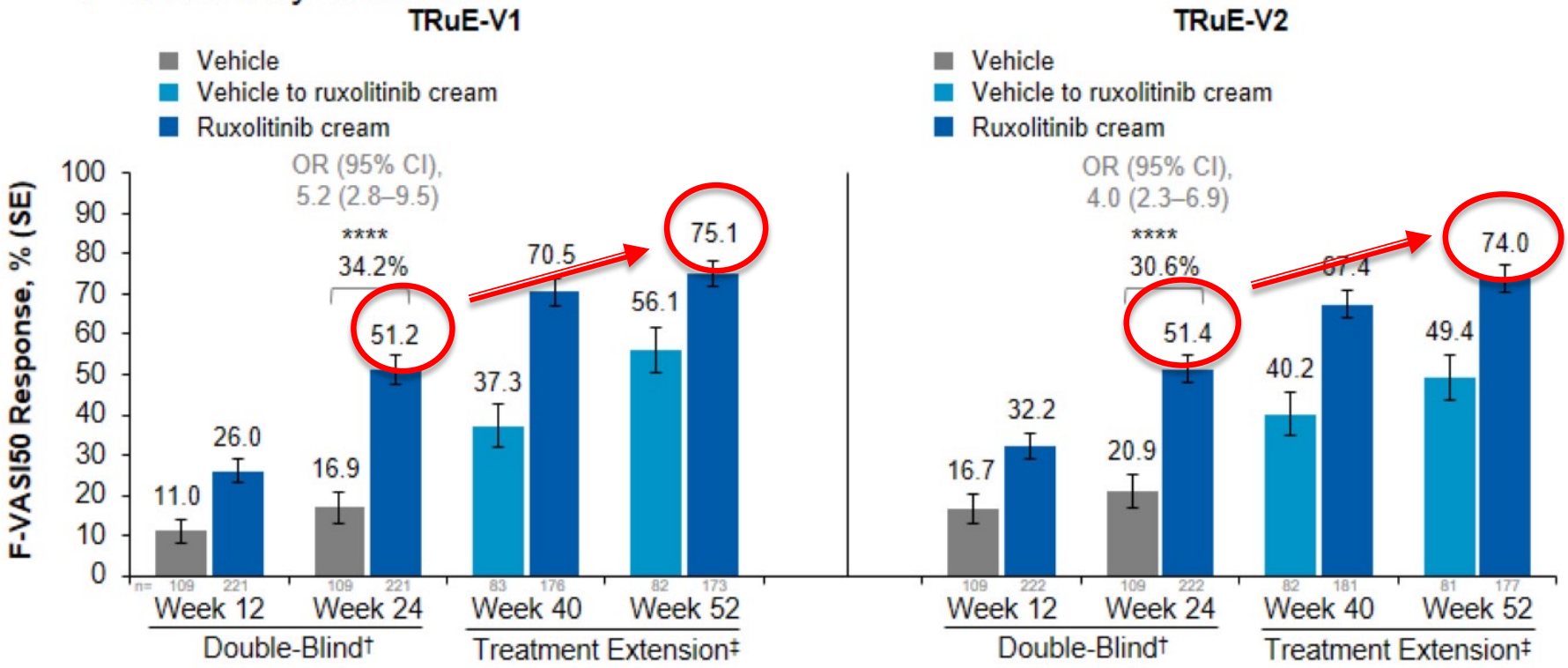


BID, twice daily.

* 1 randomized patient who did not apply ≥1 dose of ruxolitinib cream was excluded from safety analyses. 13 patients from 1 study site were excluded from efficacy analyses for compliance issues.

F-VASI50 Responses

- Approximately 75% of patients who applied ruxolitinib cream from Day 1 achieved F-VASI50 by Week 52

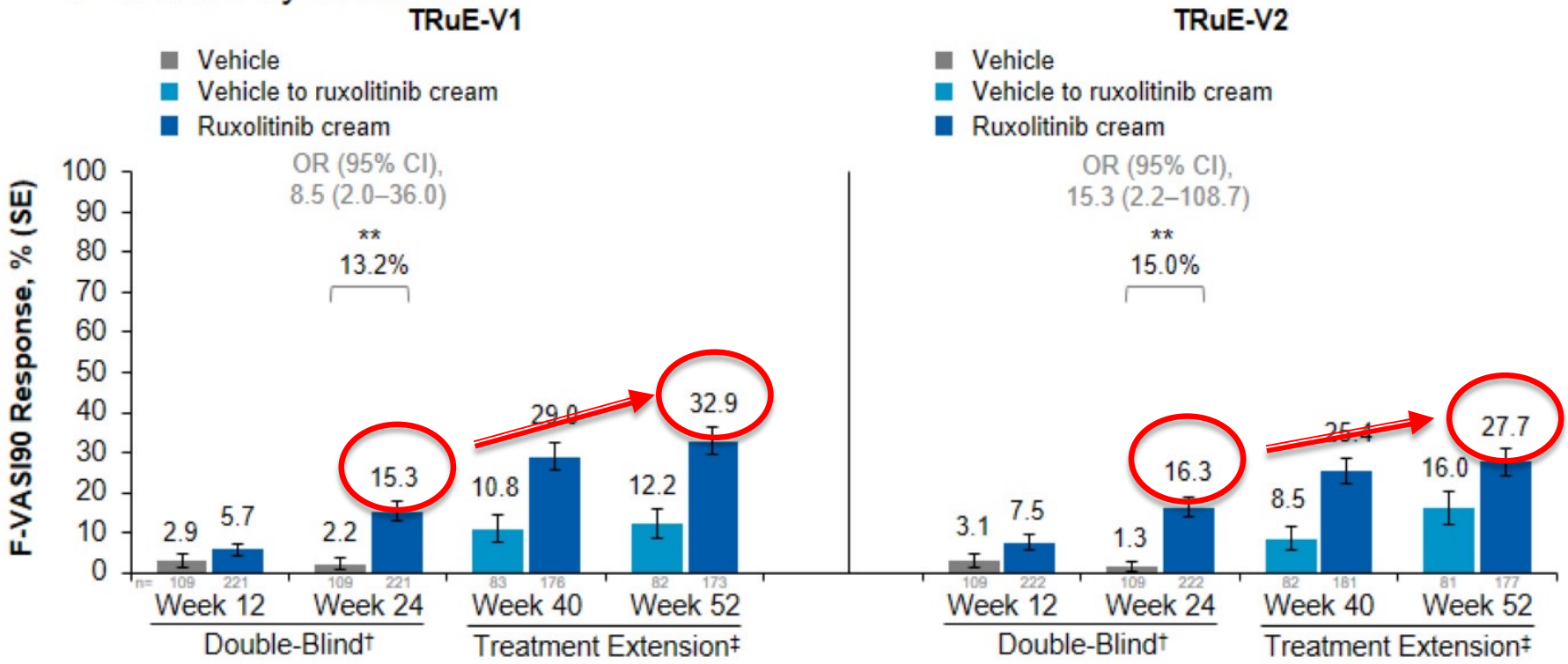


**** $P<0.0001$ for response rate difference for ruxolitinib cream vs vehicle.

† During the double-blind period (up to Week 24), multiple imputation was applied to account for missing values. ‡ During the open-label extension (after Week 24), responses were reported as observed.

F-VASI90 Responses

- Approximately 30% of patients who applied ruxolitinib cream from Day 1 achieved F-VASI90 by Week 52



** $P<0.01$ for response rate difference for ruxolitinib cream vs vehicle.

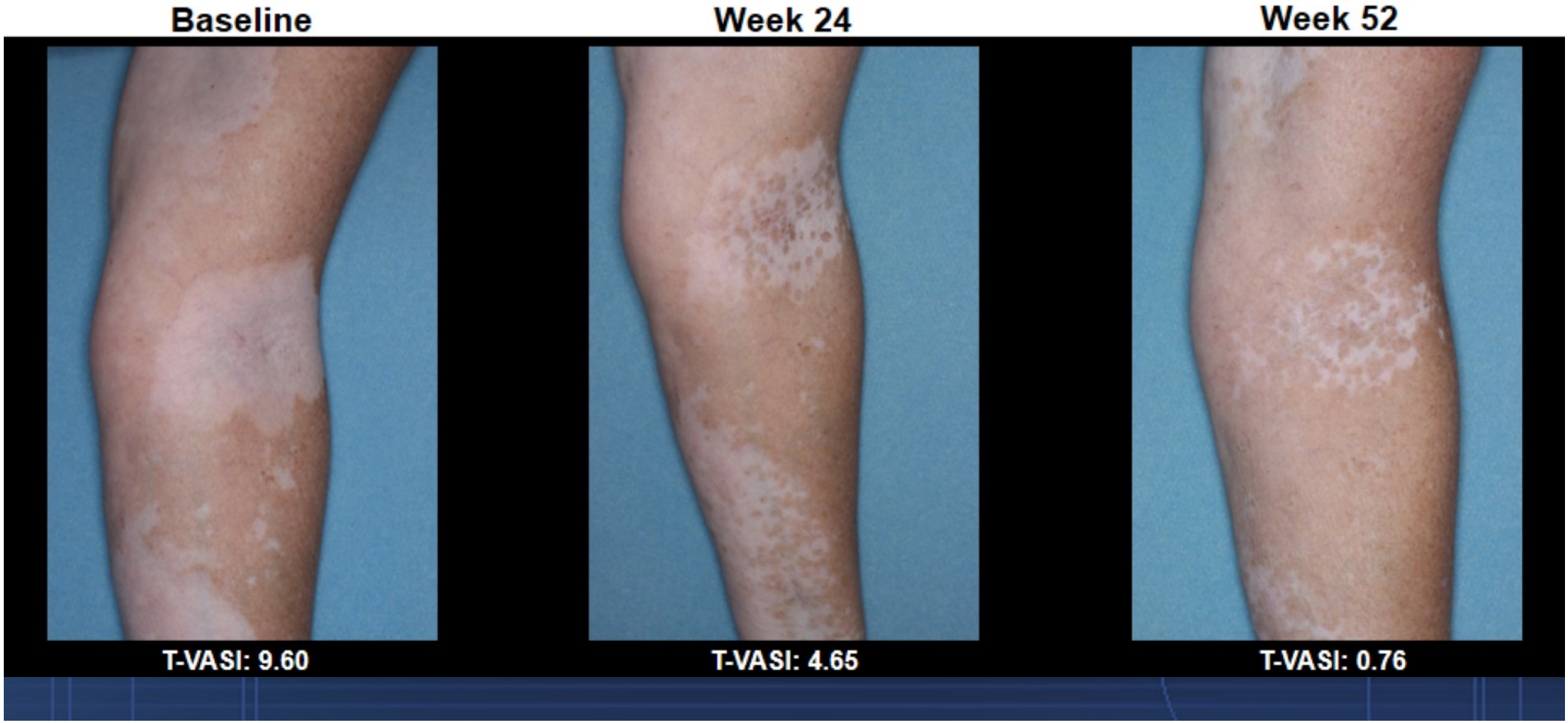
† During the double-blind period (up to Week 24), multiple imputation was applied to account for missing values. ‡ During the open-label extension (after Week 24), responses were reported as observed.

Clinical Images Showing F-VASI Response

1.5% Ruxolitinib Cream BID

Clinical Images Showing T-VASI Response

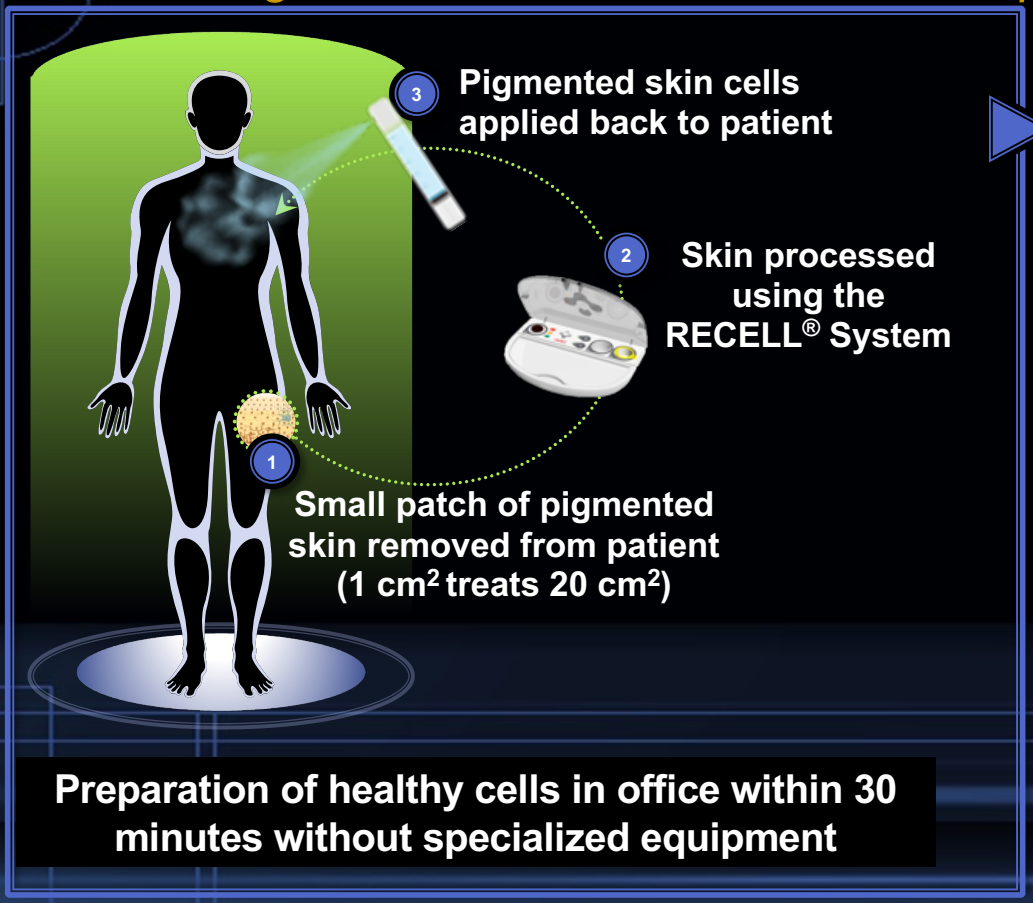
1.5% Ruxolitinib Cream BID



Autologous Cell Harvesting For Vitiligo Refractory To Topical, Systemic and Narrow Band UV Therapy

RECELL® Autologous Cell Harvesting Device

Platform for Regenerative & Restorative Skin Therapies



Preparation of healthy cells in office within 30 minutes without specialized equipment

Technology platform benefits a wide array of skin defects and wounds irrespective of etiology

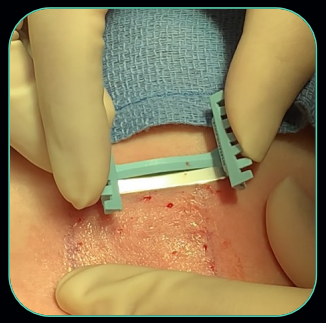
- **Burns *(US approved 2018)***
- Stable vitiligo
- Cancer reconstruction
- Regenerative dermatology
- Soft tissue reconstruction
- Chronic wounds

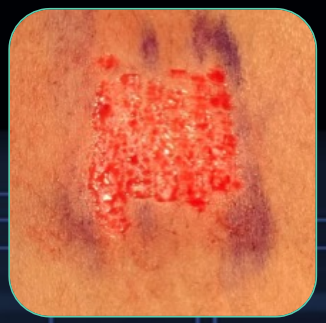
RECELL for vitiligo, cancer reconstruction, regenerative dermatology, soft tissue reconstruction, and chronic wounds is investigational and limited by US Federal Law to investigational use

Cell Harvesting Procedure

1 Obtain Skin Sample

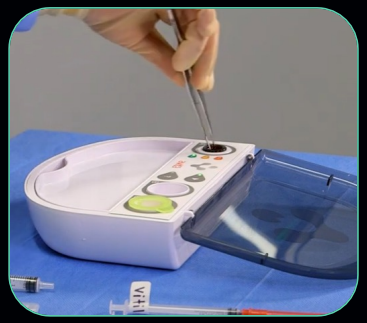
Local anesthetic application followed by thin skin sample harvest using a **tool familiar to the dermatologist**





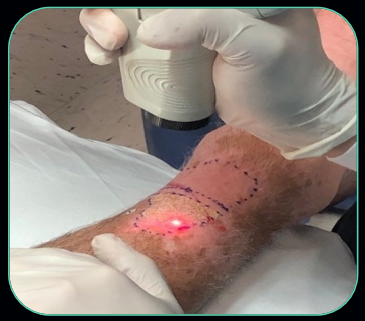
2 Prepare Suspension

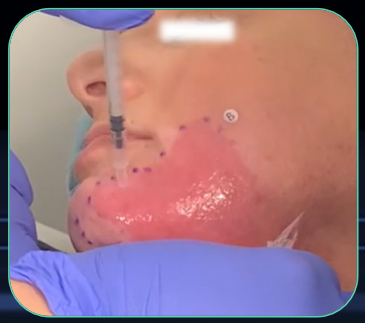
Skin sample subjected to enzymatic and mechanically processing using RECELL System.



3 Ablate & Apply

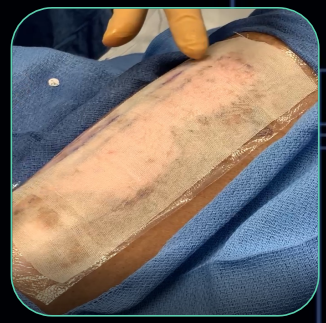
Treatment area is **prepared with epidermal ablation**, and then apply Spray-on Skin™ cell suspension.

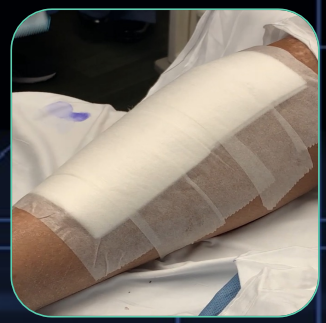




4 Dress & Aftercare

After RECELL apply non-adherent, greasy gauze and protective dressings. Cells should be protected from moisture for 5-7 days.





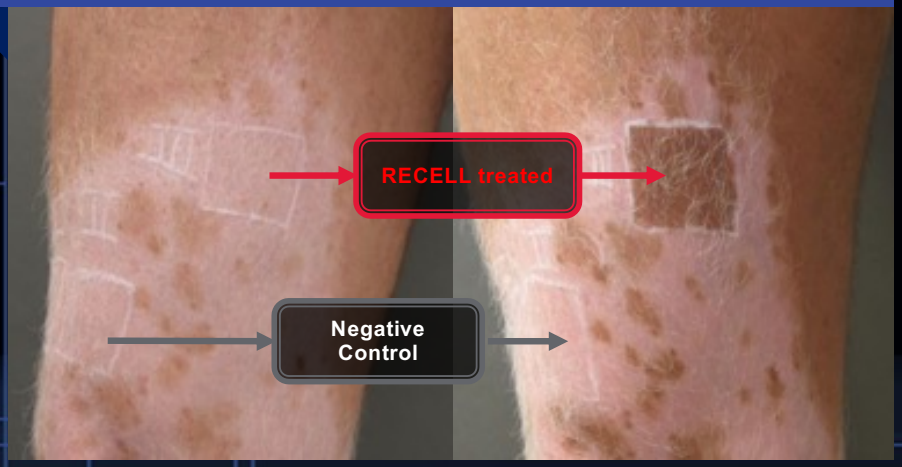
Images courtesy of Dr Mahmoud, Dr Hamzavi, Dr Munavalli, and Dr Robinson

RECELL for vitiligo is investigational and limited by US Federal Law to investigational use

Case Series:
Repigmentation of Stable Vitiligo and Piebaldism

10 patients included in study, with median repigmentation of 78%

6 MONTHS
RECELL-treated area was 100% re-pigmented

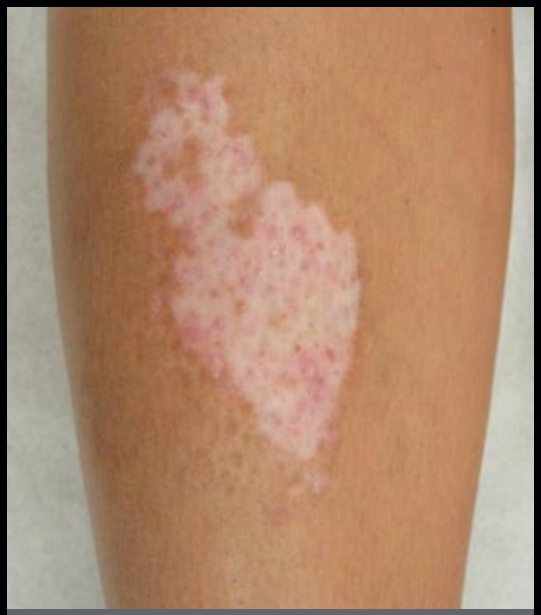


- CO_2 ablation to prepare treatment area
  - Ultrapulse active Fx 200 mJ, 60W, Density 3
- Cells prepared from thin skin sample (0.2-0.3 mm)

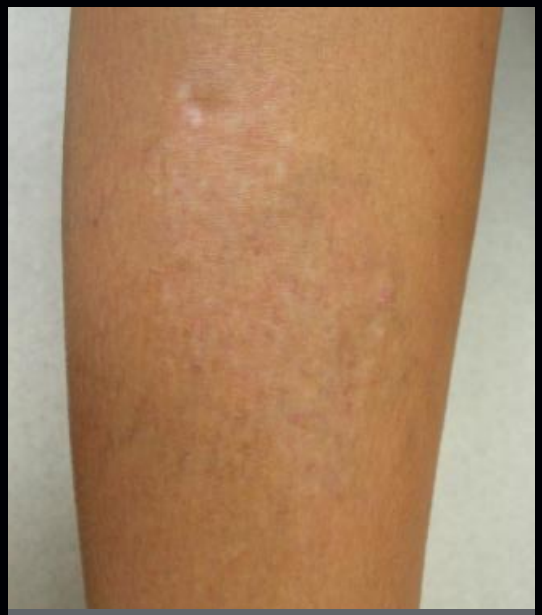
Komen et al. J Am Acad Dermatol. 2015 Jul; 73(1):170-2

RECELL for vitiligo is investigational and limited by US Federal Law to investigational use

RECELL Case:
Repigmentation of Shin



Before RECELL®



6 months

- 33-year-old female with stable vitiligo (>5 yrs)
- Patient unresponsive to creams, UVA, UVB, and punch grafting
- CO2 laser (200 mJ, 60 W, density 3) to the depth of dermal-epidermal junction
- Single application of cell suspension

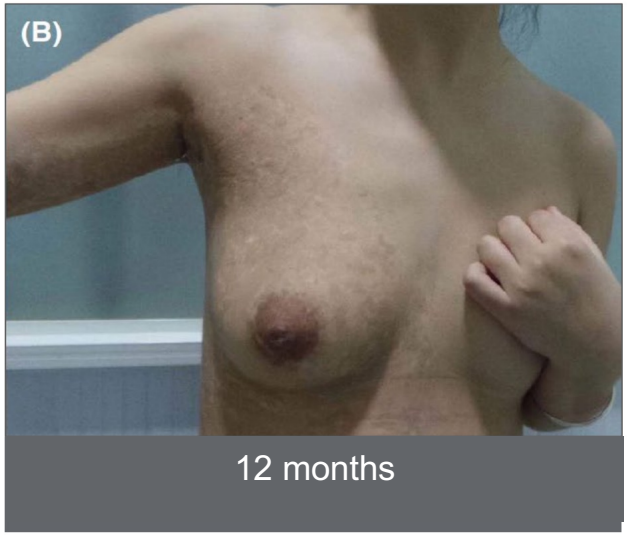
Komen et al. JCAS. 2016; 9(2): 133-5.

RECELL for vitiligo is investigational and limited by US Federal Law to investigational use

Case Series:
Repigmentation of Nipple-Areola Complex

18 patients included in study, 12-month repigmentation rate in nipple-areola complex was 93.2 ± 3.6%

Before RECELL®



12 months

- 23-year-old female with stable vitiligo
- Donor skin harvested from adjacent unaffected areas (0.15-0.2 mm depth)
- Dermabrasion of the vitiligo patches was performed to the depth of dermal-epidermal junction
- Cell suspension applied to both recipient and donor areas (expansion ratio ranged from 1:20 to 1:40)

Yu et al. J Cosmetic Dermatol. 2021 Aug.

RECELL for vitiligo is investigational and limited by US Federal Law to investigational use

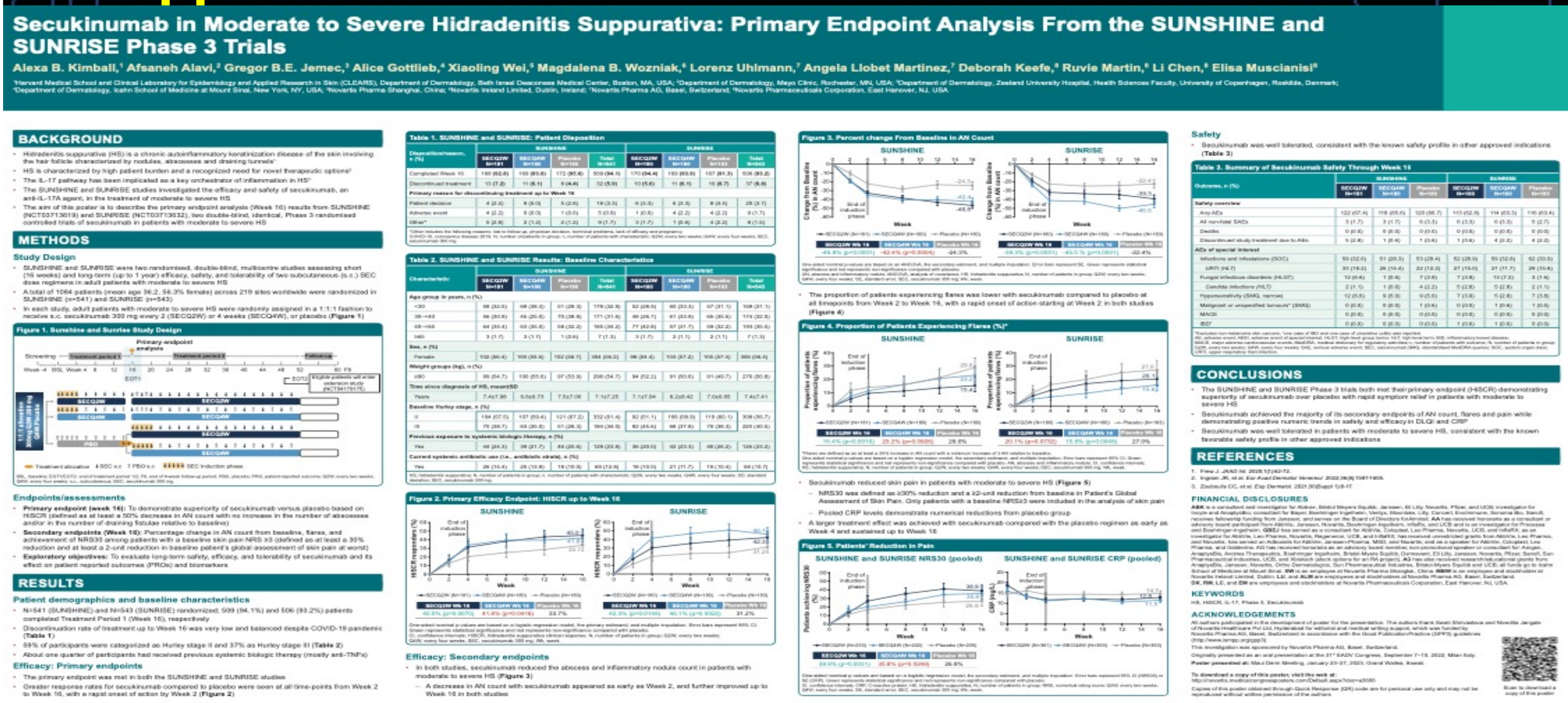
Phase 3 Results: 6 Month Data

- An expert central review committee found:
- **56%** of patients treated with RECELL had repigmentation of more than 50% of the treated area
- **12%** of the control treatments.

Press release 15 Sept 2022

Hidradenitis Suppurativa

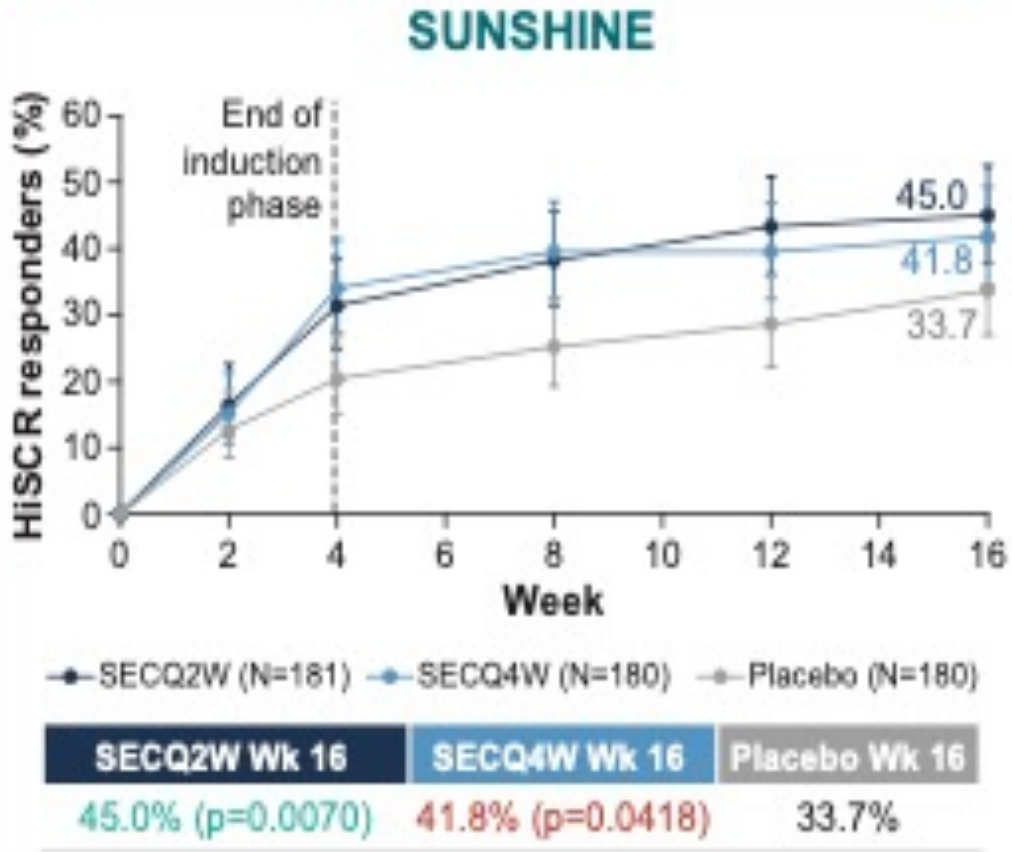
Secukinumab in Moderate to Severe Hidradenitis Suppurativa: SUNSHINE and SUNRISE Phase 3 Trials



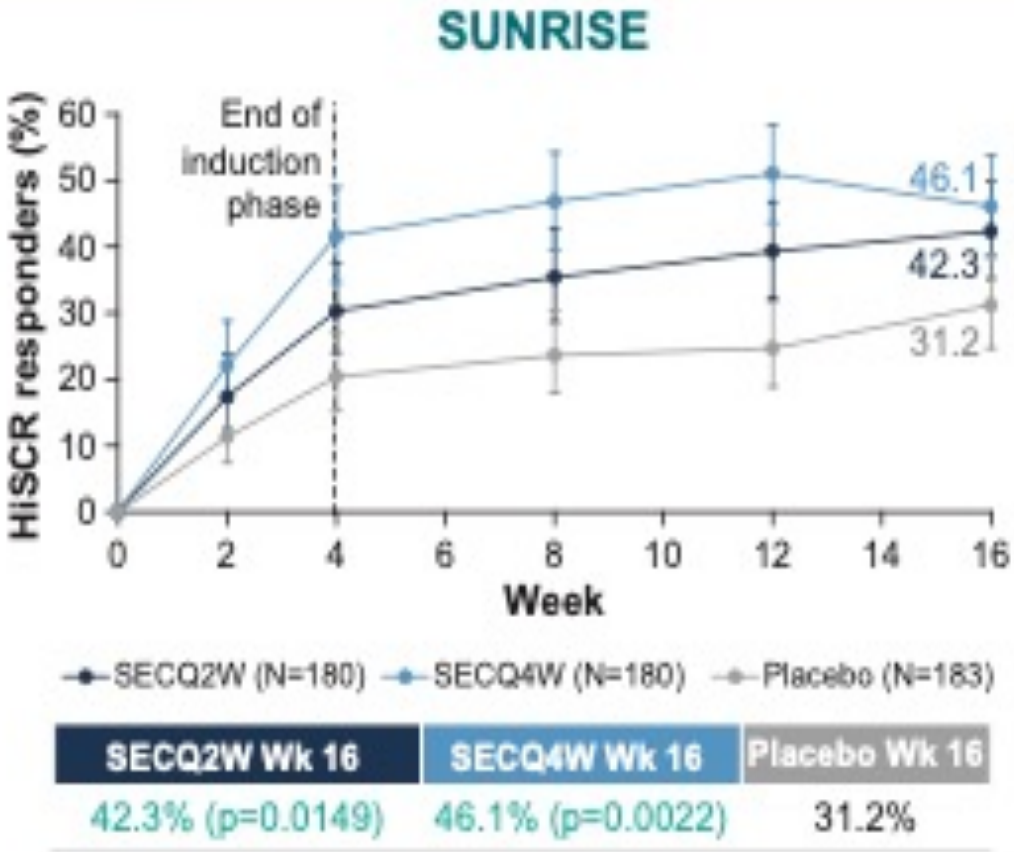
Kimball AB, et al. Presented at: 31st EADV Congress; September 7-10, 2022; Milan, Italy. Oral presentation D3T01.1.

1^0 Efficacy Endpoints: HiSCR up to Week 16

Figure 2. Primary Efficacy Endpoint: HiSCR up to Week 16



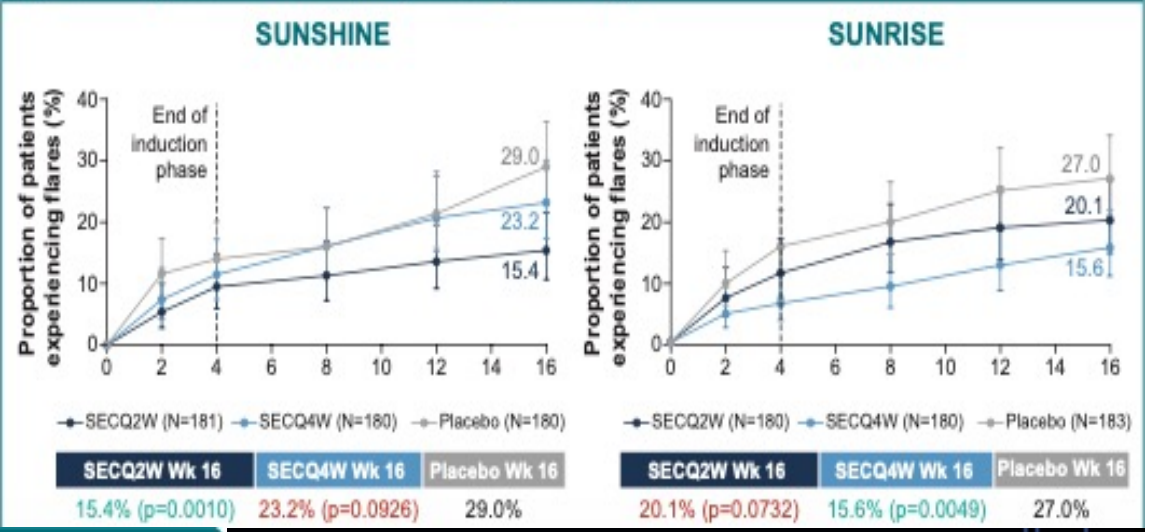
SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
45.0% (p=0.0070)	41.8% (p=0.0418)	33.7%



SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
42.3% (p=0.0149)	46.1% (p=0.0022)	31.2%

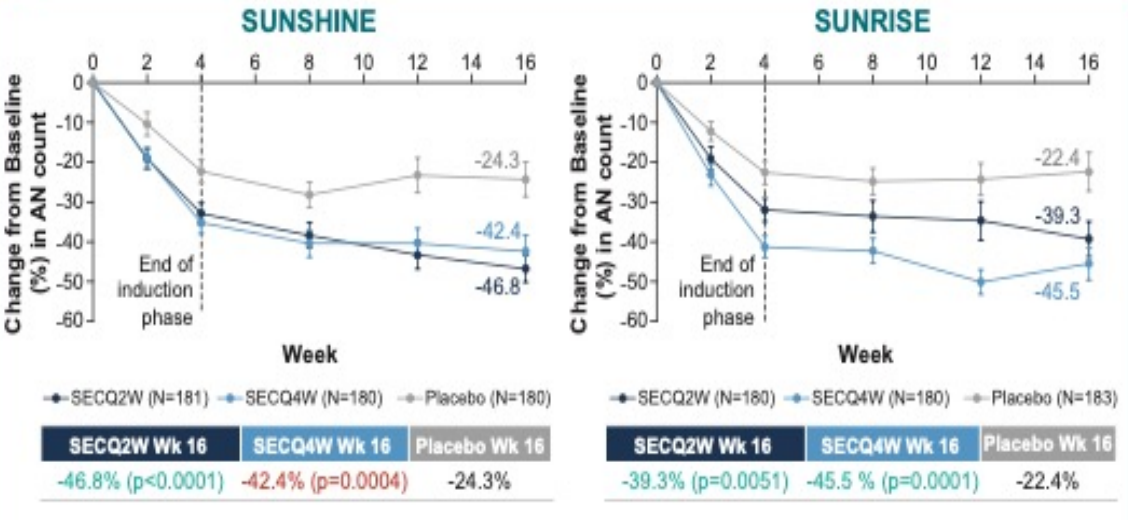
2^0 Efficacy Endpoints: %Change in Nodules/Abscesses and Flares

Figure 4. Proportion of Patients Experiencing Flares (%)*



	SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
SUNSHINE	15.4% (p=0.0010)	23.2% (p=0.0926)	29.0%
SUNRISE	20.1% (p=0.0732)	15.6% (p=0.0049)	27.0%

Figure 3. Percent change From Baseline in AN Count



	SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
SUNSHINE	-46.8% (p<0.0001)	-42.4% (p=0.0004)	-24.3%
SUNRISE	-39.3% (p=0.0051)	-45.5 % (p=0.0001)	-22.4%

GL-N-BK-HS-2300008 | Date of preparation: March 2023

Bimekizumab in patients with moderate-to-severe hidradenitis suppurativa: 48-week efficacy and safety from BE HEARD I & II, two phase 3, randomized, double-blind, placebo-controlled, multicenter studies

Alexa B. Kimball,[1] Christos C. Zouboulis,[2,3] Christopher Sayed,[2,4] Joslyn S. Kirby,[5] Errol Prens,[2,6] John R. Ingram,[2,7] Amit Garg,[8] Robert Rolleri,[9] Edward Muller,[10] Paulatsya Joshi,[10] Gregor Jemec[2,11,12]

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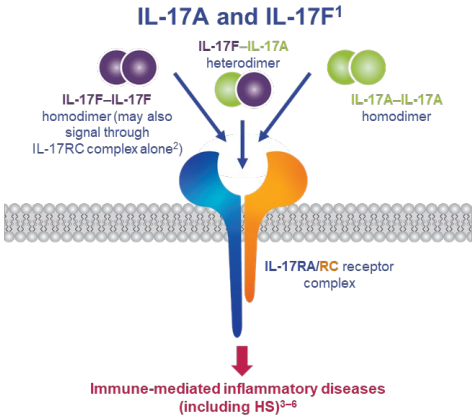
AAD Late-Breaking Research Program | March 17–21 2023 **Session S042**

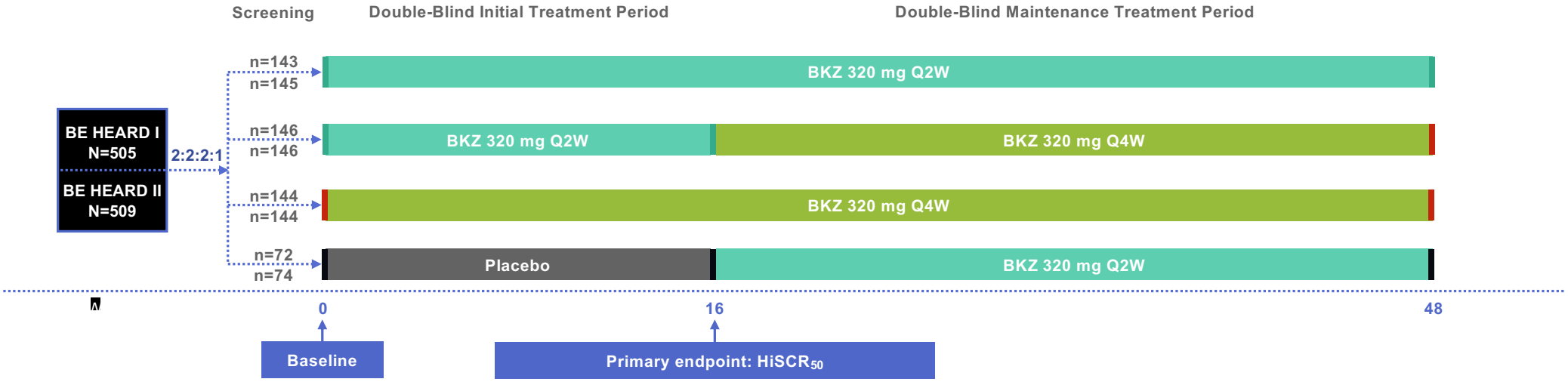
Background and BE HEARD I and II Study Design

Patients

- **Included**: patients with a diagnosis of moderate-to-severe HS with ≥5 inflammatory lesions (abscess and inflammatory nodule [AN] count)
- **Excluded**: patients with >20 draining tunnels



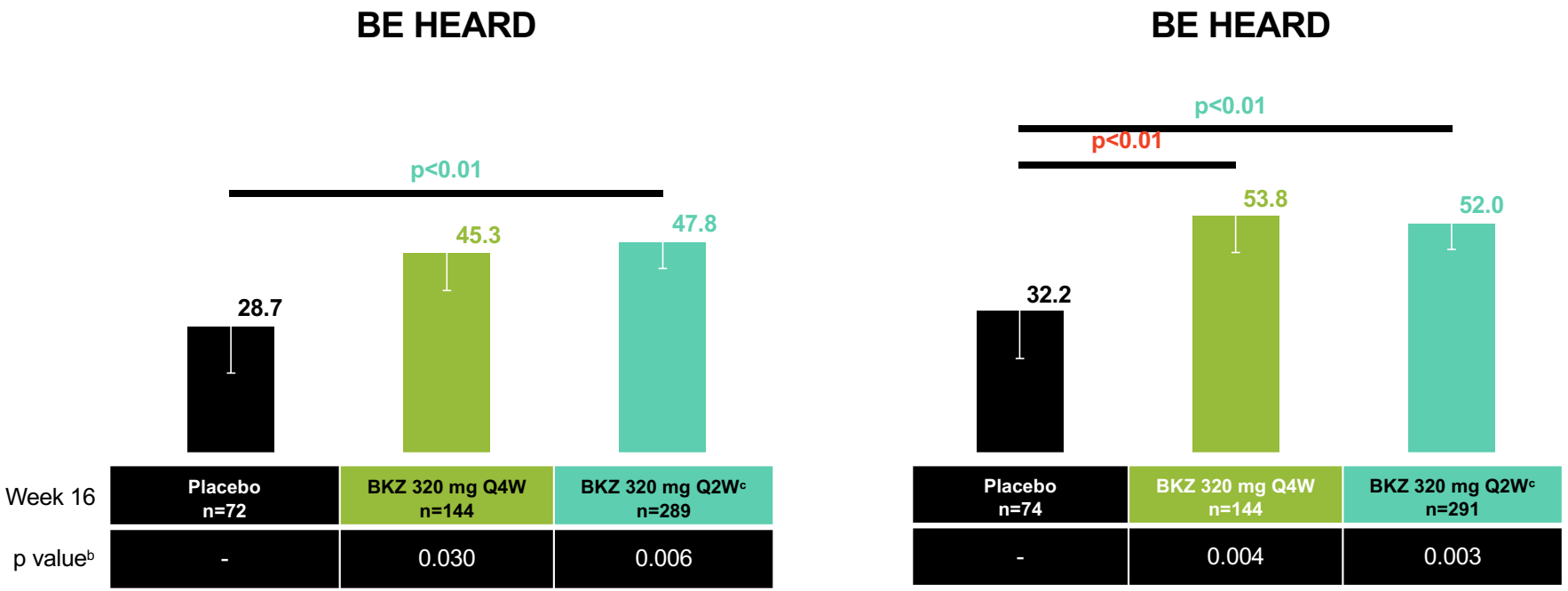
Study Design



1. Yang XO et al. *J Exp Med* 2008;205:1063–75; **2.** Goepfert A et al. *Immunity* 2020;52:499–512; **3.** Glatt S et al. *Ann Rheum Dis* 2018;77:523−32; **4.** Zouboulis CC et al. *J Eur Acad Dermatol Venereol* 2020;34:846–61; **5.** Schlapbach C et al. *J Am Acad Dermatol* 2011;65:790–98; **6.** Maroof A et al. *Translational data suggesting a pivotal role for IL-17A and IL-17F in hidradenitis suppurativa*. Poster 3776; SHSA 2022. AN: abscess and inflammatory nodule; BKZ: bimekizumab; $HiSCR_{50}$: ≥50% reduction from baseline in the total AN count with no increase from baseline in abscess or draining tunnel count; HS: hidradenitis suppurativa; IL: interleukin; Q2W: every two weeks; Q4W: every four weeks; RA: receptor A; RC: receptor C.

Primary Endpoint: HiSCR$_{50}$ Response at Week 16 (mNRI [All-ABX][a])

BE HEARD I met the primary endpoint of HiSCR$_{50}$ for BKZ 320 mg Q2W versus placebo
BE HEARD II met the primary endpoint of HiSCR$_{50}$ for both BKZ dose regimens versus placebo

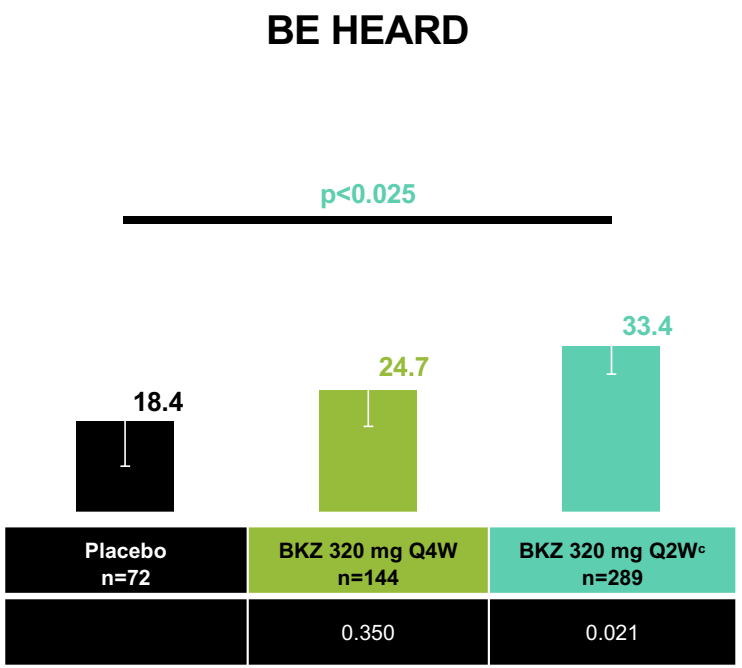


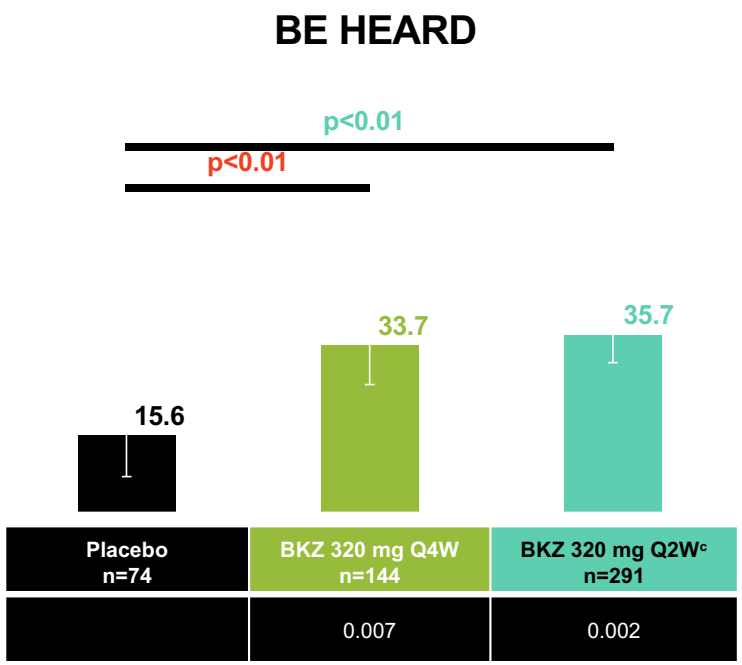
Randomized set. [a] **mNRI (All-ABX): Patients who take any systemic antibiotic (new or increased dose)** or who discontinue due to AE or lack of efficacy **are treated as non-responders at all subsequent visits**. Other missing data were imputed via multiple imputation. Primary analysis method; [b] p value (from Wald test) reported for **adjusted responder rates**, obtained from logistic regression with treatment, Hurley

Q2W: every two weeks; Q4W: every four weeks

Secondary Endpoint: HiSCR$_{75}$ Response at Week 16 (mNRI [All-ABX][a])

BE HEARD I met the secondary endpoint of HiSCR$_{75}$ for BKZ 320 mg Q2W versus placebo
BE HEARD II met the secondary endpoint of HiSCR$_{75}$ for both BKZ dose regimens versus placebo





Randomized set. [a] **mNRI (All-ABX): Patients who take any systemic antibiotic (new or increased dose)** or who discontinue due to AE or lack of efficacy **are treated as non-responders at all subsequent visits**. Other missing data were imputed via multiple imputation. Primary analysis method; [b] p value (from Wald test) reported for **adjusted responder rates**, obtained from logistic regression with treatment, Hurley stage at

Q2W: every two weeks; Q4W: every four weeks

Safety Topics of Interest: Weeks 0–48

	BE HEARD I				BE HEARD II			
	Placebo/BKZ 320 mg Q2W[a] (n=65) 100 PY=0.59	BKZ 320 mg Q4W/Q4W (n=143) 100 PY=1.18	BKZ 320 mg Q2W/Q4W (n=145) 100 PY=1.24	BKZ 320 mg Q2W/Q2W (n=141) 100 PY=1.21	Placebo/BKZ 320 mg Q2W[a] (n=69) 100 PY=0.68	BKZ 320 mg Q4W/Q4W (n=142) 100 PY=1.31	BKZ 320 mg Q2W/Q4W (n=146) 100 PY=1.35	BKZ 320 mg Q2W/Q2W (n=144) 100 PY=1.33
Infections and infestations	43 (66.2)	87 (60.8)	89 (61.4)	91 (64.5)	34 (49.3)	76 (53.5)	85 (58.2)	85 (59.0)
Serious infections	1 (1.5)	2 (1.4)	3 (2.1)	5 (3.5)	1 (1.4)	1 (0.7)	1 (0.7)	2 (1.4)
Opportunistic infections[c]	1 (1.5)	3 (2.1)	3 (2.1)	1 (0.7)	0	3 (1.4)	1 (0.7)	1 (0.7)
Fungal infections	12 (18.5)	35 (24.5)	32 (22.1)	33 (23.4)	10 (14.5)	35 (24.6)	39 (26.7)	40 (27.8)
Candida infections	4 (6.2)	22 (15.4)	21 (14.5)	20 (14.2)	4 (5.8)	26 (18.3)	29 (19.9)	27 (18.8)
Oral candidiasis	3 (4.6)	13 (9.1)	16 (11.0)	15 (10.6)	3 (4.3)	14 (9.9)	25 (17.1)	22 (15.3)
Neutropenia	0	0	1 (0.7)	0	0	0	0	0
Any hypersensitivity reaction[d]	15 (23.1)	26 (18.2)	30 (20.7)	38 (27.0)	10 (14.5)	23 (16.2)	28 (19.2)	23 (16.0)
Dermatitis and eczema	8 (12.3)	15 (10.5)	20 (13.8)	22 (15.6)	9 (13.0)	17 (12.0)	20 (13.7)	14 (9.7)
Adjudicated suicidal ideation/behavior	1 (1.5)	2 (1.4)	0	1 (0.7)	0	0	1 (0.7)	0
Adjudicated MACE	0	0	1 (0.7)	2 (1.4)	0	0	0	0
Hepatic events	7 (10.8)	2 (1.4)	7 (4.8)	12 (8.5)	2 (2.9)	7 (4.9)	7 (4.8)	3 (2.1)
>5 x ULN elevation of AST/ALT	0	0[e]	2 (1.4)[f]	2 (1.4)[e]	1 (1.4)	2 (1.4)	0[g]	1 (0.7)[h]
Malignancies	1 (1.5)	0	0	0	0	1 (0.7)	0	2 (1.4)
Definite or probable adjudicated IBD[i]	1 (1.5)	1 (0.7)	1 (0.7)	0	0	2 (1.4)	1 (0.7)	1 (0.7)

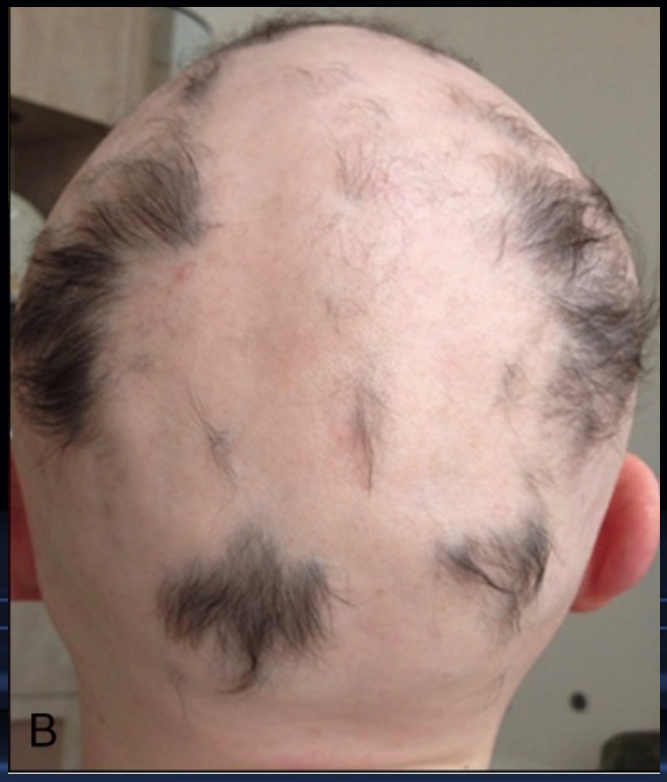
Across the program, one patient with significant cardiovascular history died of congestive heart failure (BE HEARD I: BKZ Q2W/Q2W group).

Active medication set, MedDRA (Version 19.0). Hepatic events category includes events in the SMQ "Drug related hepatic disorders - comprehensive search (SMQ)", excluding the following two sub-SMQs: "Liver neoplasms, benign (incl. cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)"; Hepatic events category includes all post-baseline assessments including those at unscheduled visits but excluding any that occur more than 140 days after the last administration of study medication, counting a patient only once. [a] TEAEs reported for the Placebo/BKZ 320 mg group may have occurred while the patient was receiving either placebo or BKZ; [b] [c]

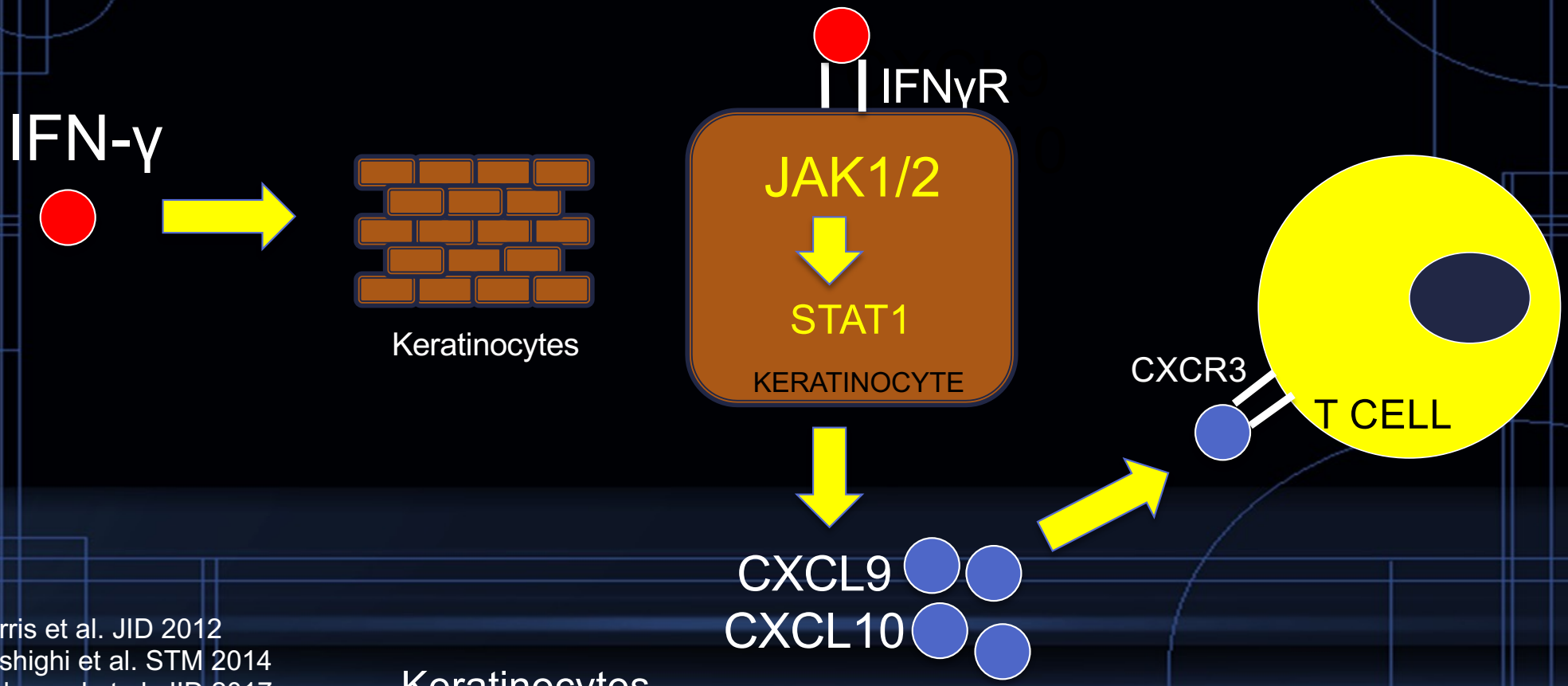
Opportunistic infections were localized mucocutaneous events, as defined by internal company conventions; [d] There were no incidences of anaphylactic reactions related to BKZ; [e] n=140; [f] n=144; [g] n=145; [h] n=143; [i] In patients with no history of IBD. ALT: alanine aminotransferase; AST: aspartate aminotransferase; BKZ: bimekizumab; IBD: inflammatory bowel disorder; MACE: major adverse cardiac event; PY: patient-years; Q2W: every two weeks; Q4W: every four weeks; SMQ: standardized MedDRA queries; TEAE: treatment-emergent adverse event; ULN: upper limit of normal.


BUT WAIT
Baricitinib
Ritlecitinib
JACK IN THE BOX
THERE'S MORE

ALOPECIA AREATA



ALOPECIA AREATA IS A IFN-γ DRIVEN DISEASE



Harris et al. JID 2012
Rashighi et al. STM 2014
Richmond et al. JID 2017a
Richmond, et al. JID 2017b

On June 13th, 2022, the US FDA approved *Olumiant® (Baricitinib),* a Janus kinase (JAK 1,2) inhibitor, as a first-in-disease systemic treatment for adult patients with severe alopecia areata.

Baricitinib (JAK1,2) For Alopecia Areata

The NEW ENGLAND JOURNAL of MEDICINE

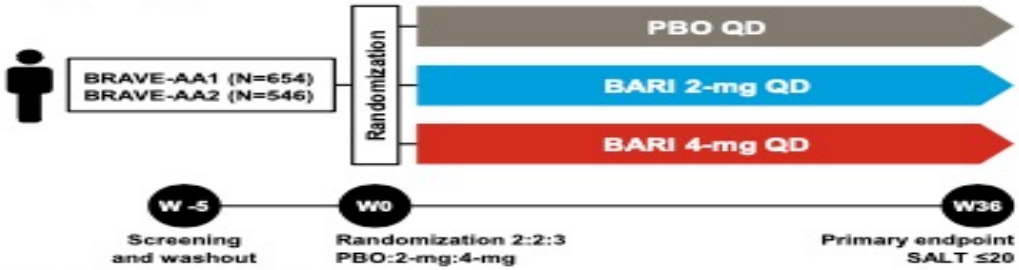
ESTABLISHED IN 1812 MAY 5, 2022 VOL. 386 NO. 18

Two Phase 3 Trials of Baricitinib for Alopecia Areata

Brett King, M.D., Ph.D., Manabu Ohyama, M.D., Ph.D., Ohsang Kwon, M.D., Ph.D., Abraham Zlotogorski, M.D., Justin Ko, M.D., Natasha A. Mesinkovska, M.D., Ph.D., Maria Hordinsky, M.D., Yves Dutronc, M.D., Wen-Shuo Wu, M.D., Jill McCollam, Pharm.D., Chiara Chiasserini, Sc.D., Guanglei Yu, Ph.D., Sarah Stanley, Ph.D., Katrin Holzwarth, M.D., Amy M. DeLozier, M.P.H., and Rodney Sinclair, M.D., for the BRAVE-AA Investigators*

METHODS

Study Design[a], BRAVE-AA1 and BRAVE-AA2

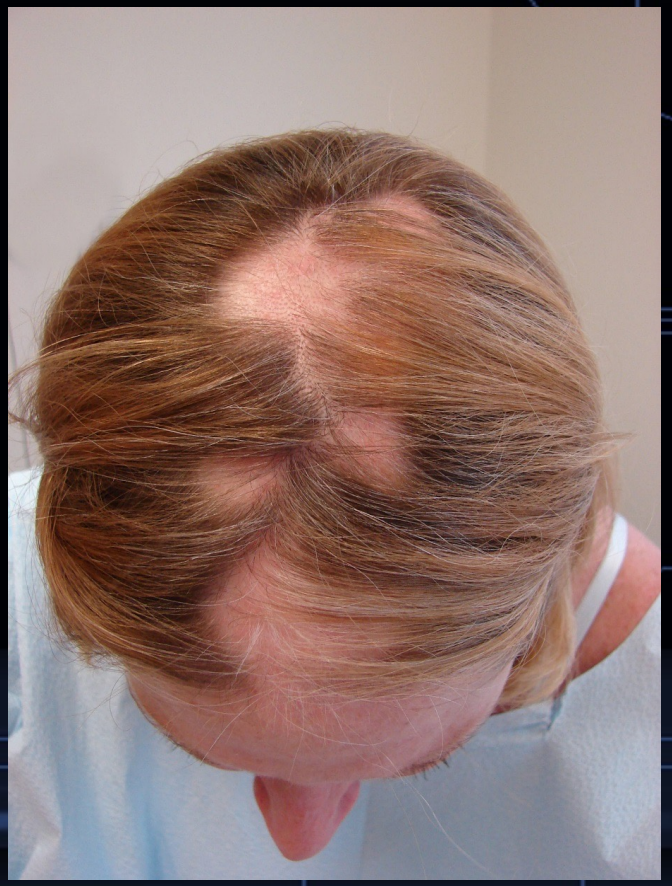


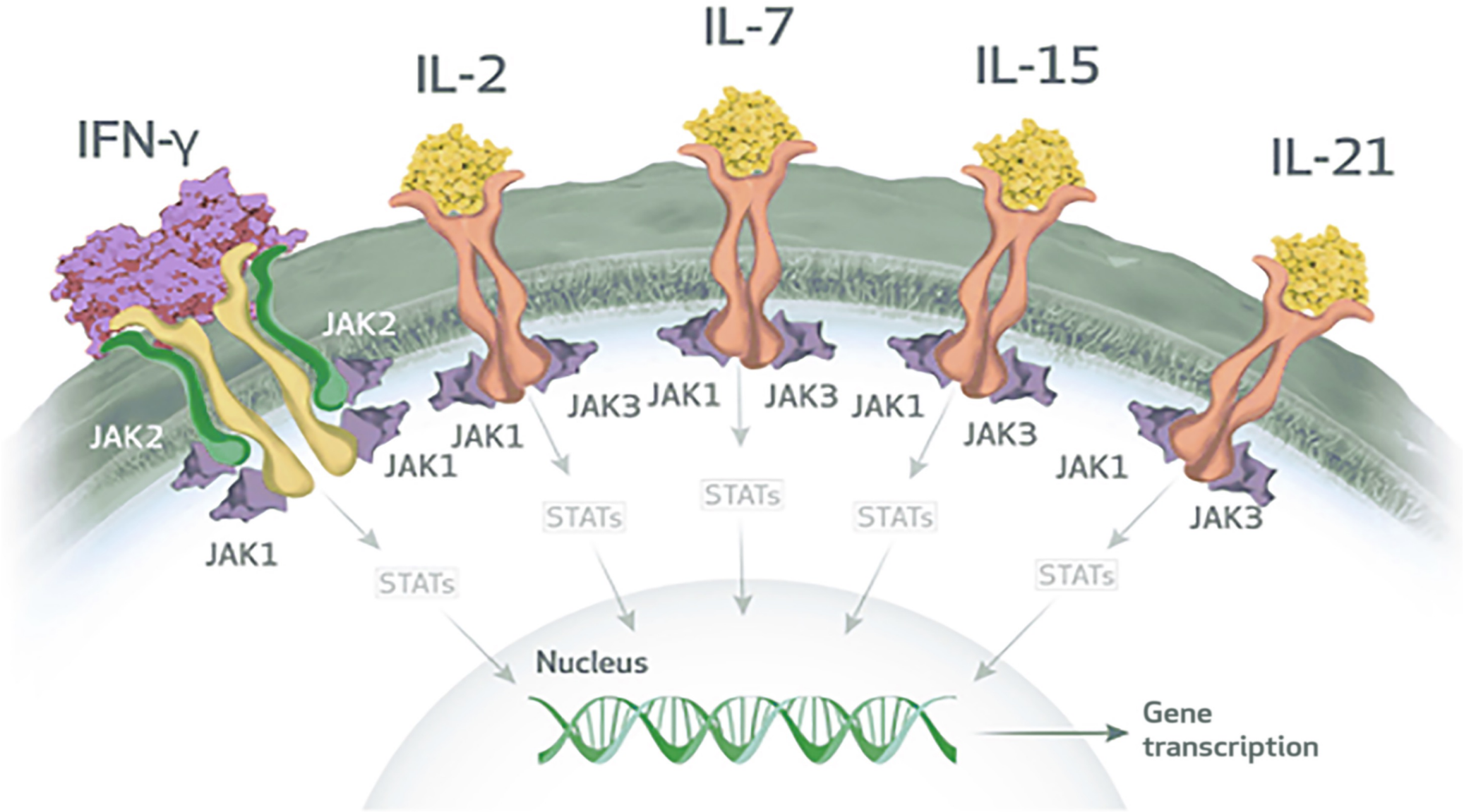
[a] Figure is not the full study design, but only the PBO-controlled period of both trials.

Key Eligibility Criteria

- Male or female ≥18 years old; ≤60 years for males and ≤70 years for females
- Hair loss involving ≥50% of the scalp, as measured by SALT
- Current episode of AA >6 months to <8 years[a]
- No spontaneous improvement in the 6 months prior to screening

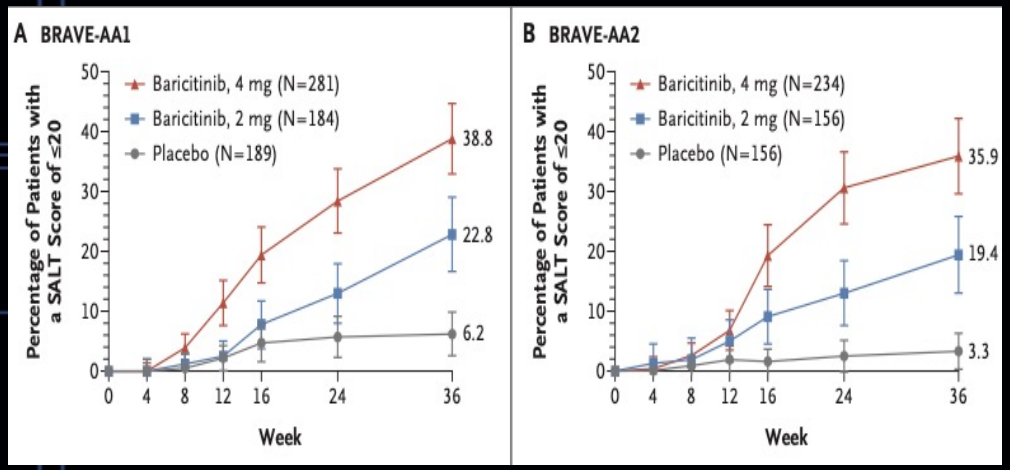
[a] Patients who had AA for 8 years could be enrolled if episodes of regrowth (spontaneous or due to being under treatment) had been observed on the affected areas over the past 5 years.



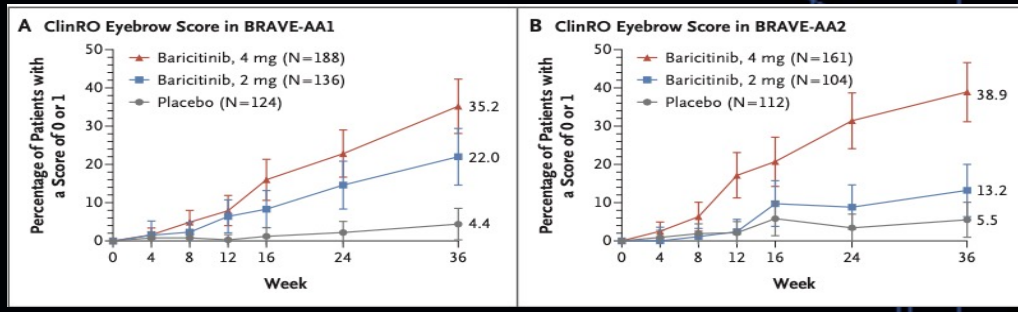

IFN-γ
IL-2
IL-7
IL-15
IL-21
JAK2
JAK2
JAK1
JAK1
JAK1
JAK3
JAK1
JAK3
JAK1
JAK3
JAK1
JAK3
STATs
STATs
STATs
STATs
STATs
Nucleus
Gene transcription

Baricitinib: Scalp, Eyebrow & Eyelash Regrowth

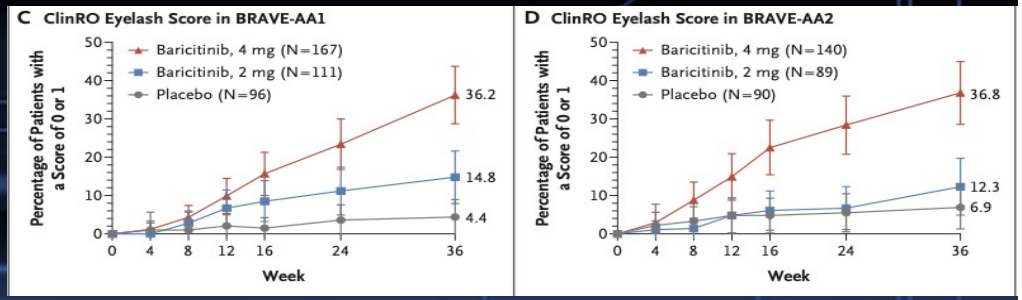
SCALP: 80% SCALP COVERAGE



EYEBROW: IGA 0/1



EYELASH: IGA 0/1



Baricitinib: 2mg & 4 mg for Alopecia Areata

- **Demographic:** Average age 37.5 years with a mean duration of 12.2 years with a average onset of age 25
- **Scalp:**
  - 35.2% patients treated with baricitinib 4 mgs/day achieved 80% scalp coverage
  - 21.7% patients treated with baricitinib 2 mgs/day achieved 80% scalp coverage
- 2-5% of placebo group regrew hair.
- **Eyebrow:** 4 mgs/day: 31% regrowth Placebo: 3%
- **Eyelash:** 4 mgs/day 33.5% regrowth Placebo: 3%

Dosage Recommendations For Baricitinib in Alopecia Areata (PI)

- *2 mg once daily orally, with or without food*
- **Inadequate response:** Increase to 4 mg once daily
- **Severe AA:** 4 mg once daily, w/ or w/o food.
  - Nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss
  - Once patients achieve an adequate response to treatment with 4 mg, decrease the dosage to 2 mg once daily.

Pooled Safety Data and AA and AD

- Pooled data in 2,500 patients for AA and atopic dermatitis
- Acne 2.9%
- Headache 6.6%
- Diarrhea 3.1%
- Severe side effects: 10/2500

Oral Ritlecitinib (PF06651600)JAK3/TEC Inhibitor Efficacy: Phase 2b/3 Trial

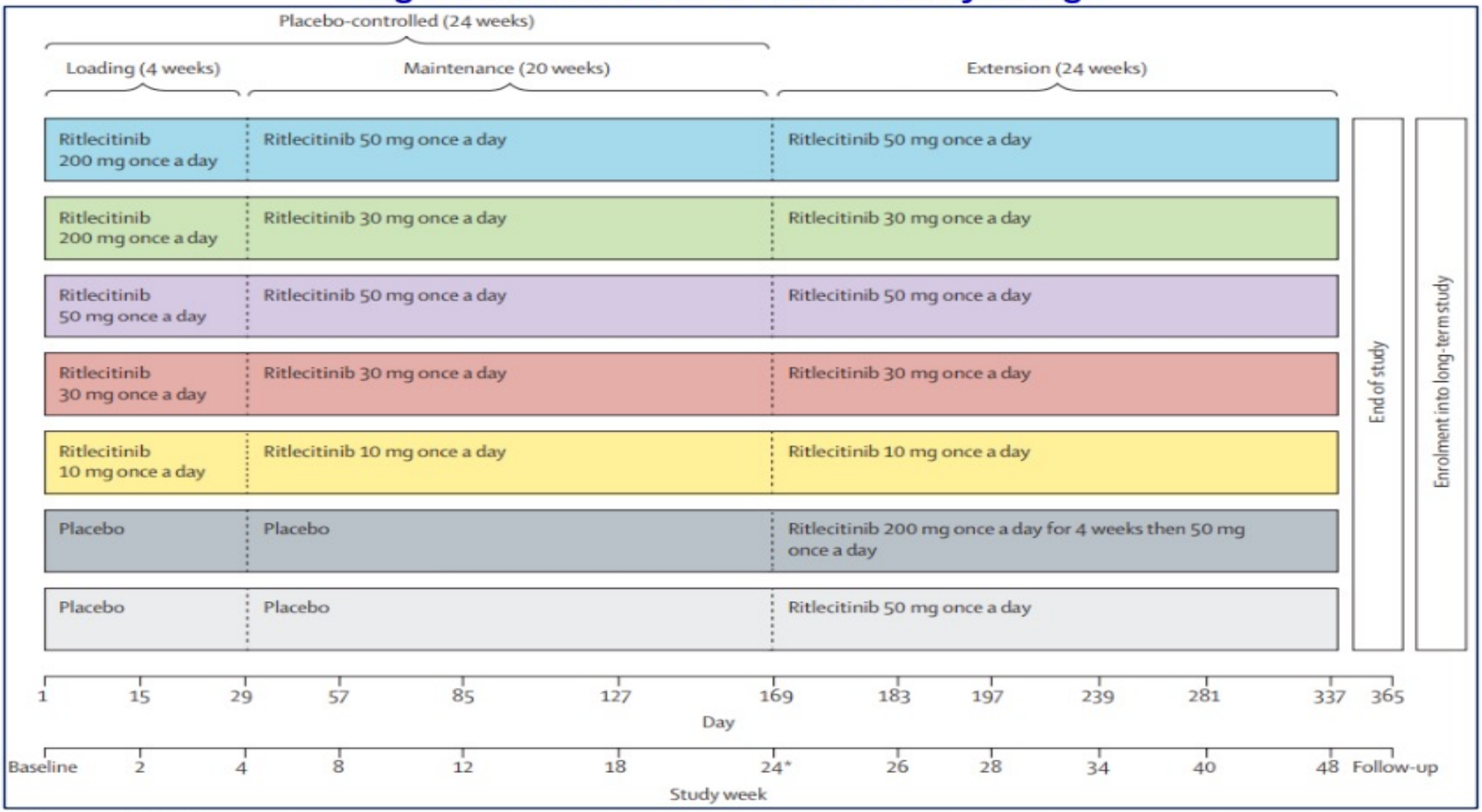
Efficacy of the oral JAK3/TEC inhibitor ritlecitinib (PF-06651600) in patients with alopecia areata over 48 weeks: results from the ALLEGRO phase 2b/3 randomized, double-blind, placebo-controlled trial

Natasha Mesinkovska[1], Jerry Shapiro[2], Brett King[3], Rodney Sinclair[4], Xingqi Zhang[5], Charles Lynde[6], Walter Gubelin Harcha[7], Jacek C Szepietowski[8], Dalia Wajsbrot[9], Liza Takiya[9], Robert Wolk[9]

[1]School of Medicine, University of California, Irvine, CA, USA; [2]New York University School of Medicine, New York, NY, USA; [3]Yale University School of Medicine, New Haven, CT, USA; [4]Sinclair Dermatology, Melbourne, Victoria, Australia; [5]The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [6]Department of Medicine, University of Toronto, Toronto, ON, Canada; [7]Skinmed, Santiago de Chile, Chile; [8]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; [9]Pfizer Inc, USA

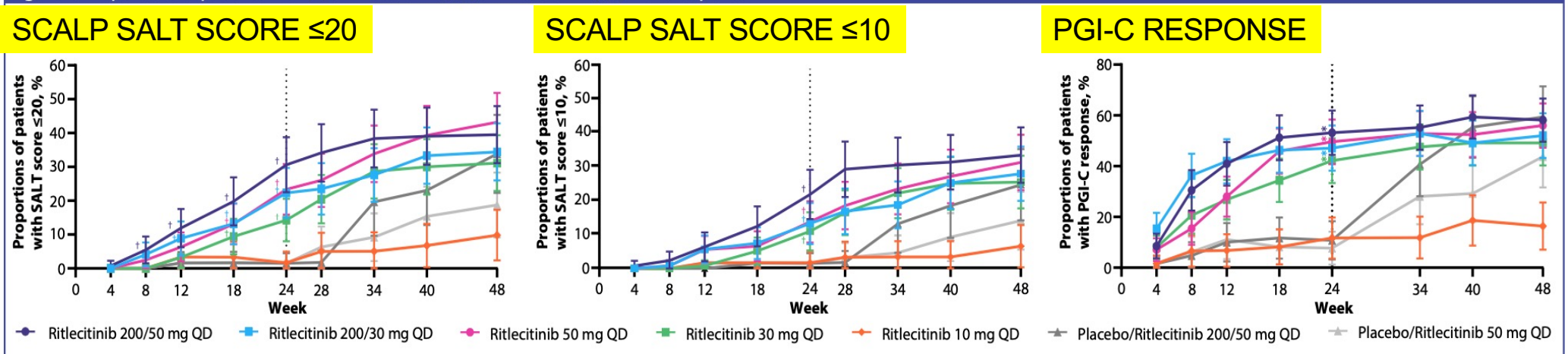
- AA is mediated by T-Cells and NK cell attack on hair follicles
- Cytokines IFN-γ and IL-15 mediated by JAK-STAT pathways
- Oral Ritlecitinib (PF06651600)JAK3/TEC Inhibitor
  - Impacts JAK-STAT (JAK3) and TEC (T-cell receptor signaling via TEC kinases)
- Efficacy: 50 mg & 30 mg doses, with 200 mg week load dose demonstrated efficacy as early as week 8 and 12 respectively
- Safety: severe AEs 0.8 – 3.2%; 69-75% mild/mod AE

Figure 1. ALLEGRO Phase 2b/3 Study Design[3]



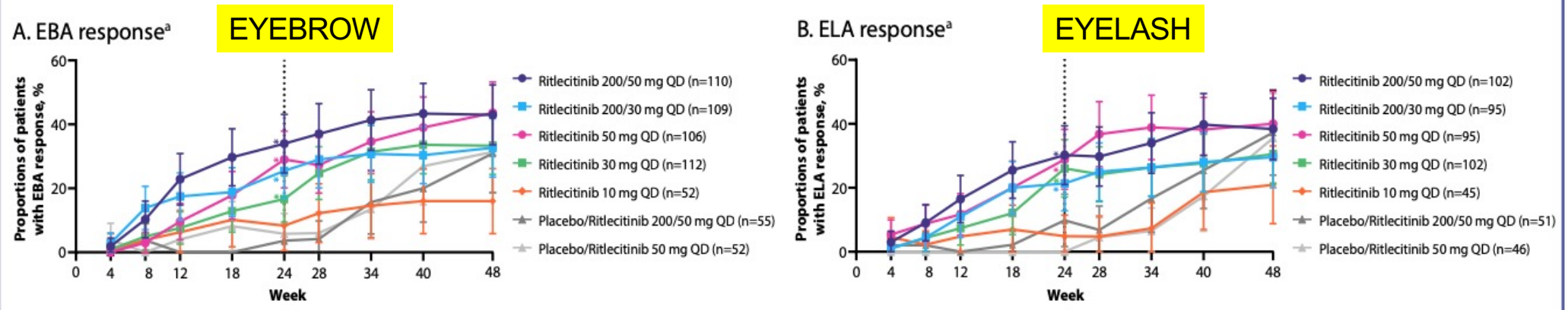
King et al 2023

Figure 2: Proportions of patients with (A) SALT score ≤20, (B) SALT score ≤10, (C) PGI-C response



PGI-C, Patient's Global Impression of Change; QD, once daily; SALT, Severity of Alopecia Tool.
† Statistically significant vs placebo based on pre-established testing procedures for the overall study at an overall significance level (α) of 0.05.
* Nominal P values: P≤0.05 vs. placebo at Week 24 (not shown for SALT score ≤20 and SALT score ≤10).
[a] PGI-C score of "moderately improved" or "greatly improved."

Figure 3: Proportions of patients with (A) eyebrow assessment (EBA) or (B) eyelash assessment (ELA) response



EBA, eyebrow assessment; ELA, eyelash assessment; QD, once daily.
* Nominal P values: P≤0.05 vs. placebo at Week 24.
[a] ≥2-grade improvement or score of 3 among patients without normal EBA/ELA at baseline. EBA and ELA scales range from 0=none to 3=normal.

Table 3. Summary of the Efficacy Outcomes in ALLEGRO Phase 2b/3 (Full set Analysis)*[3]

		Ritlecitinib once daily				
	Placebo† n=131	10 mg‡ n= 63	30 mg n=132	50 mg n= 130	200 mg/30 mg n= 130	200 mg/50 mg n= 132
SALT score 20 or less response at week 24 (Primary endpoint)§‖						
n/N (%)	2/130 (2%)	1/59 (2%)	17/119 (14%)	29/124 (23%)	27/121 (22%)	38/124 (31%)
Difference from placebo (95% CI)	-	0.16 (-4.05 to 7.58)	12.75 (6.69-20.36)	21.85 (14.65-30.23)	20·78 (13.65-29.18)	29.11 (21.17-37.91)
p value	-	-	<0.0002	<0.0001	<0.0001	<0.0001
SALT score 10 or less response at week 24 (Key secondary endpoint)‖¶						
n/N (%)	2/130 (2%)	1/59 (2%)	13/119 (11%)	17/124 (14%)	16/121 (13%)	27/124 (22%)
Difference from placebo (95% CI)	-	0.16 (-4.05 to 7.58)	9.39 (3.86-16.46)	12.17 (6.27-19.53)	11.68 (5.82-19.07)	20.24 (13.23-28.49)
p value	-	-	0·0019	0·0002	0·0003	<0·0001
SALT score 10 or less response at week 24#**						
Estimated response rate (%)	1.54%	1.65%	10.62%	13.42%	12.87%	21.29%
Difference from placebo (95% CI)	-	0·12 (-3.67 to 3.91)	9.09 (3.10-15.07)	11.88 (5.42-18.33)	11.33 (4.93-17.74)	19.75 (11.91-27.59)
p value	-	-	0.0029	0.0003	0.0005	< 0.0001
PGI-C response†† at week 24						
Estimated response rate (%)	9.23%	11.36%	41.95%	49.17%	45.40%	52.19%
Difference from placebo (95% CI)	-	2.15 (-6.91 to 11.22)	32.72 (21.95-43.50)	39.96 (28.85- 51.06)	36.18 (25.22-47.14)	42.96 (31.68-54·25)
p value	-	-	< 0.0001	< 0.0001	< 0.0001	< 0.0001

JAK INVASION

JAK1 JAK2 JAK3 TYK2

NOT ALL JAK inhibitors are the same!

PSORIASIS

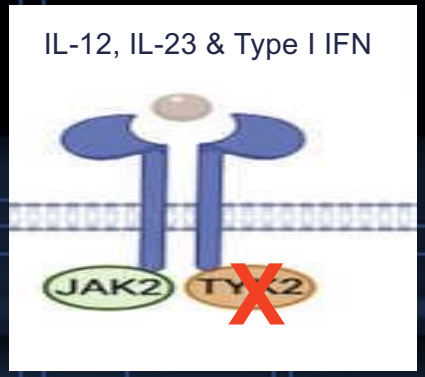
Deucravacitinib (SOTYKTU™)

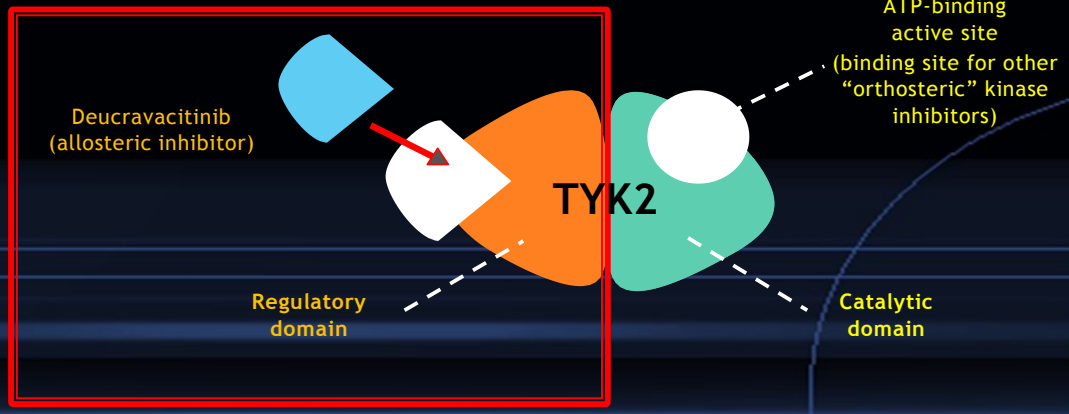
Oral, Selective Tyrosine Kinase 2 (TYK2) Allosteric Inhibitor ("Allo-TYK2") For PsO

FDA Approved Sept 9, 2022

Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 (TYK2) Allosteric Inhibitor For PsO

- Oral, selective tyrosine kinase 2 (TYK2) inhibitor [1]. ***Once daily 6 mg dosing.***
- Binds to the TYK2 regulatory domain with high selectivity and inhibits TYK2 via an ***"allosteric mechanism"***
- ***Locks the TYK2 receptor in its "inactive state"***
  - Inhibits TYK2-mediated signaling by cytokines involved in psoriasis pathogenesis (eg, IL-23, IL-12, and Type 1 interferon)[1,2]
  - **≥100-fold** greater selectivity for TYK2 vs **JAK1/3**
  - **≥2000-fold** greater selectivity for TYK2 vs **JAK2**[1,2]



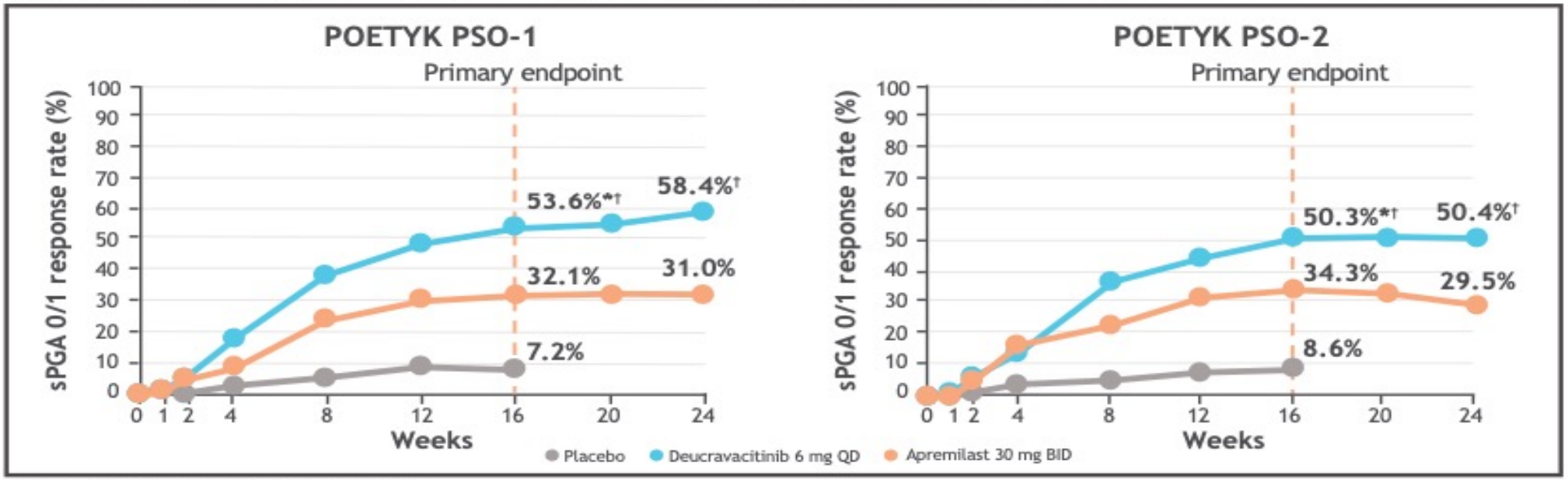


1. Burke JR et al. *Sci Transl Med*. 2019;11:1-16. **2.** Wrobleski ST et al. *J Med Chem*. 2019;62:8973-8995

Armstrong A., et al Poster Maui Derm NPPA Summer 2021 Encore

Clear or Almost Clear at Week 16 Through Week 24
Deucravacitinib v Apremilast v Placebo

Figure 4. sPGA 0/1 response[a] at Week 16 (coprimary endpoint) and through Week 24



Missing data were imputed with nonresponder imputation.
[a]Response defined as sPGA score of 0 or 1 with ≥2-point improvement from baseline.
*$P<0.0001$ vs placebo. †$P<0.0001$ vs apremilast.
BID, twice daily; QD, once daily; sPGA, static Physician's Global Assessment.

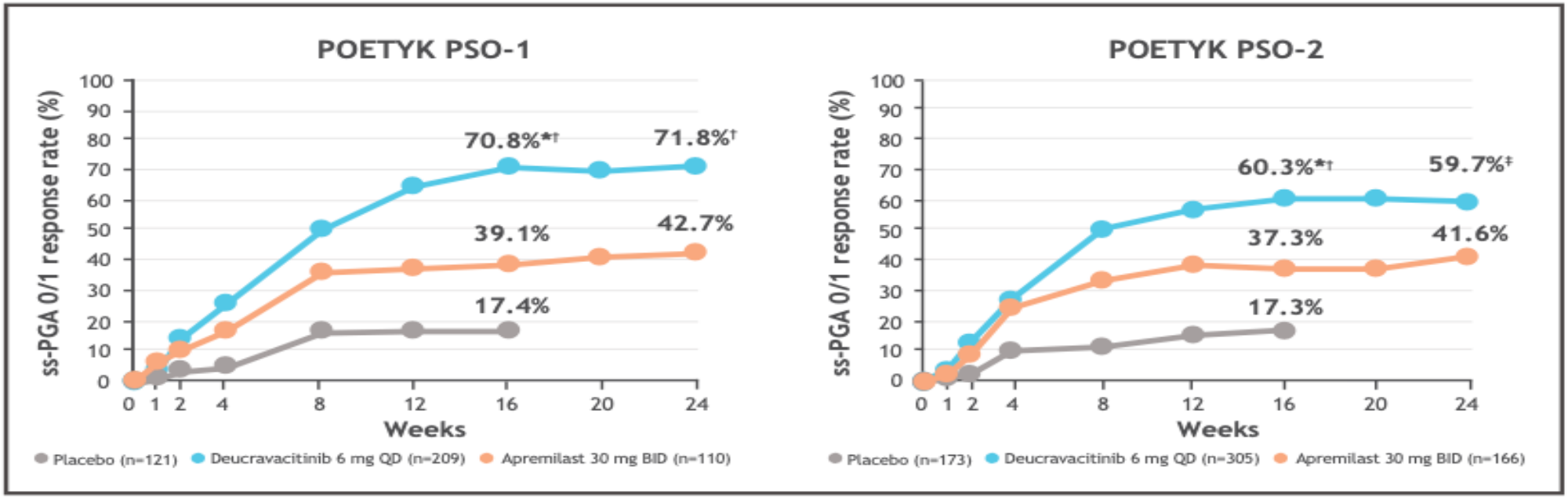
Armstrong A., et al Poster Maui Derm NPPA Summer 2021 Encore

Key secondary endpoints

- Statistical significance was achieved for deucravacitinib vs placebo and apremilast for multiple ranked secondary endpoints in both trials (**Tables 2** and **3**)

Scalp Psoriasis
Deucravacitinib v Apremilast v Placebo

Figure 5. Scalp psoriasis: ss-PGA 0/1[a] responses through Week 24



Missing data were imputed with nonresponder imputation.
[a]Included patients with a baseline ss-PGA score of ≥3.
*P<0.0001 vs placebo. †P<0.0001 vs apremilast. ‡P=0.0002 vs apremilast.
BID, twice daily; QD, once daily; ss-PGA, scalp-specific Physician's Global Assessment.

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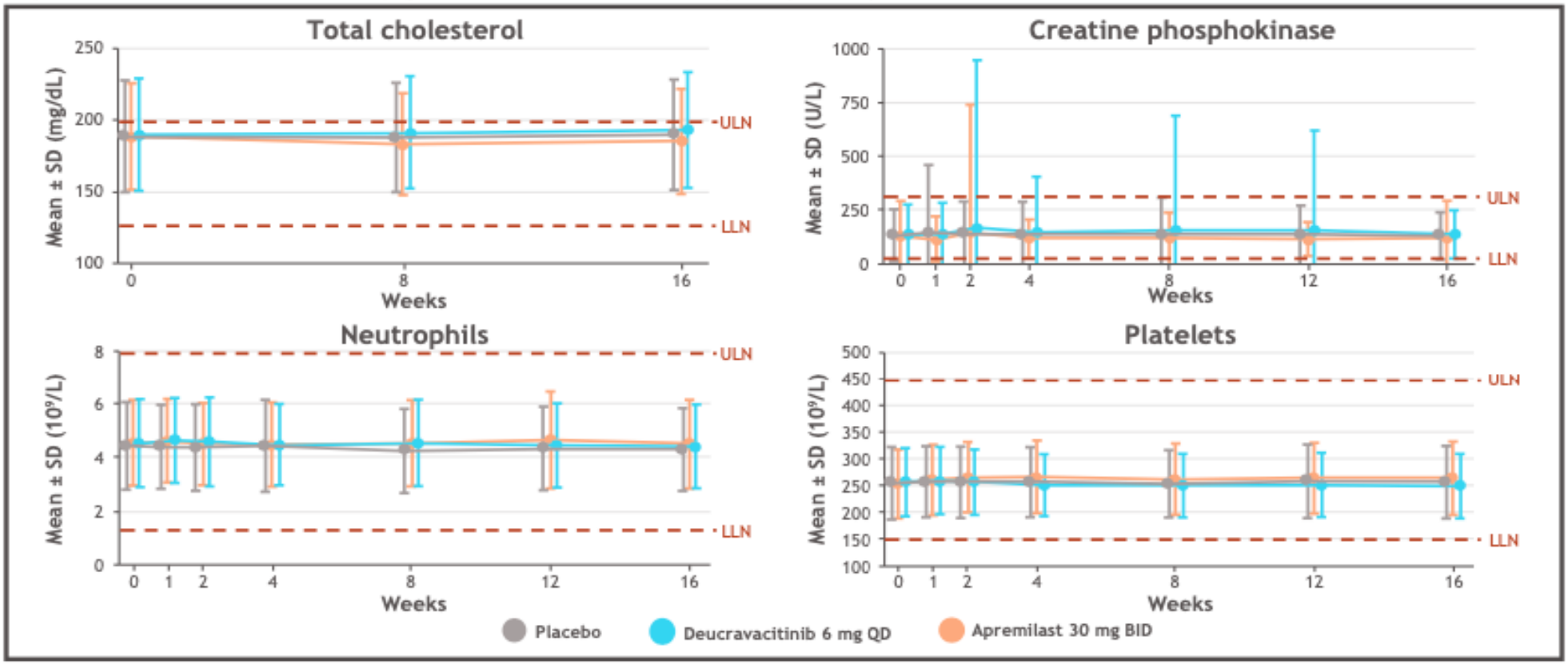
- Significantly greater improvement from baseline in PSSD symptom scores was observed for deucravacitinib vs apremilast at Week 16 in both trials (**Figure 6**)
- Significantly greater improvement from baseline for deucravacitinib vs apremilast was also seen at Week 24 in both trials

Laboratory Parameters of Interest

Figure 9. Selected laboratory parameters of interest (integrated), Weeks 0–16



BID, twice daily; LLN, lower limit of normal; QD, once daily; ULN, upper limit of normal.

Armstrong A., et al Poster Maui Derm NPPA Summer 2021 Encore

Deucravacitinib (PI)

- ***No laboratory requirement***

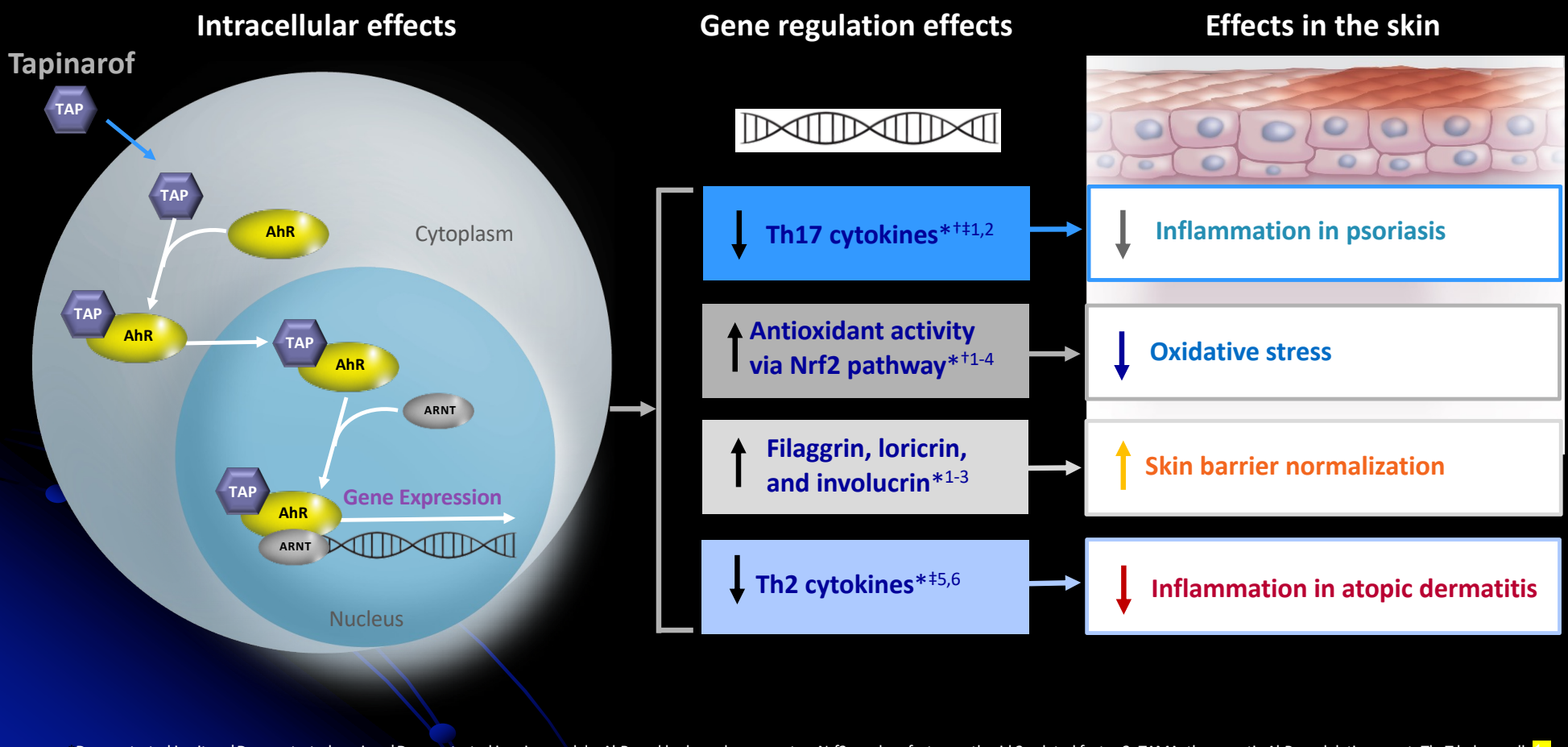
- *It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of Janus Kinase (JAK) inhibition.*
- Cases of elevated CPK and rhabdomyolysis were reported in subjects treated with deucravacitinib resulting in interruption or discontinuation of deucravacitinib dosing.
- Elevated triglycerides and LFTs were reported
- Malignancies, including lymphomas were reported in the clinical trials: risk: benefit of continuing therapy should be considered
- Avoid use in patients with an active or serious infection.
- Consider the risks and benefits of treatment prior to initiating deucravacitinib in patients:
  - with chronic or recurrent infection (example: Hep B, C)
  - who have been exposed to TB
  - with a hx of a serious or an opportunistic infection
  - with underlying conditions that may predispose them to infection.
  - Herpes virus reactivation (e.g., herpes zoster, herpes simplex):

Approved New Non-Steroidal Topical Therapies Targeting Psoriasis

- **Tapinarof 1% Cream (VTAMA®)** : **aryl hydrocarbon receptor agonist; QD treatment of mild, moderate and severe PsO in adults ≥ 18 yo**
- **Roflumilast 0.3% Cream (ZORYVE™): PDE-4 inhibitor; QD treatment of mild, moderate and severe plaque PsO, including intertriginous PsO age ≥ 12 yo**

Tapinarof (VTAMA®) Cream in Mild-Moderate-Severe Psoriasis

Biologic Effects of Tapinarof



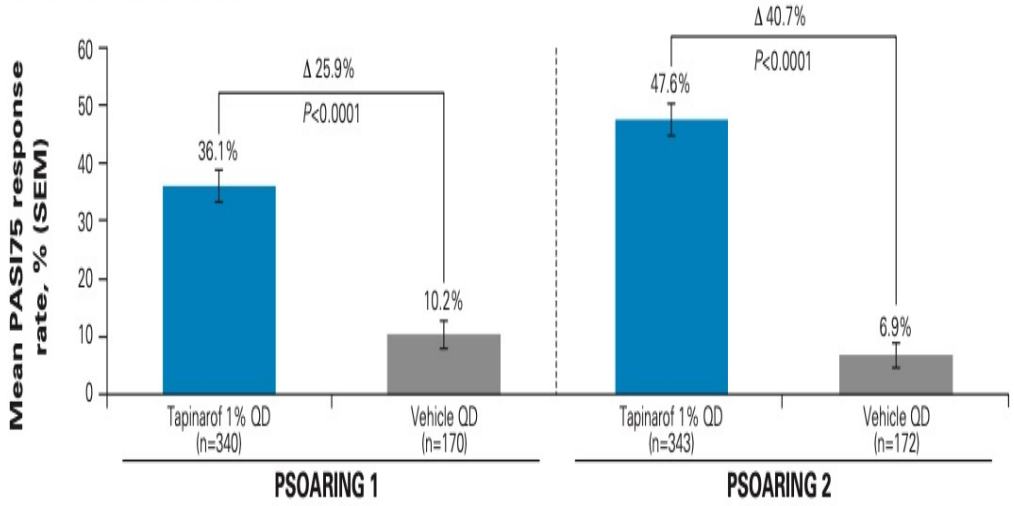
*Demonstrated in vitro. †Demonstrated ex vivo. ‡Demonstrated in mice models. AhR, aryl hydrocarbon receptor; Nrf2, nuclear factor erythroid 2-related factor 2; TAMA, therapeutic AhR modulating agent; Th, T helper cell.

1. Bissonnette R, et al. *J Am Acad Dermatol*. 2021;84(4):1059-1067. 2. Smith SH et al. J Inv Dermatol 2017;137:2110–2119. 3. Furue M et al. J Dermatological Sci. 2015;80:83–88. 4. Tsuji G et al. J Invest Dermatol. 2012;132:59–68. 5. Dermavant DOF [DMVT-505 Th2 Polarization; Apr 2015]. 6. Dermavant DOF [DMVT-505 AD Mouse Model; Oct 2016].

PASI 75 Week 12

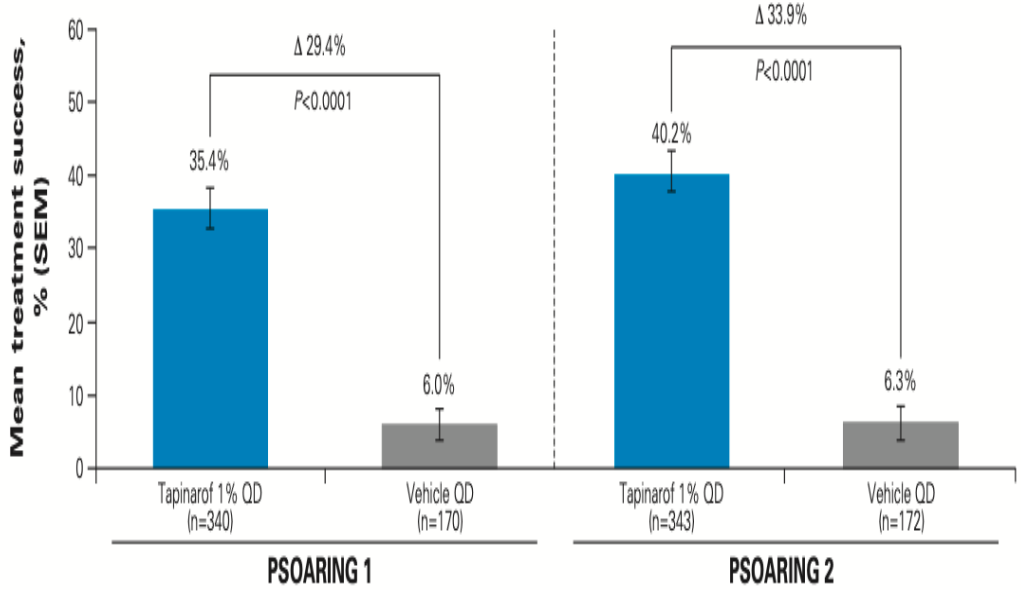
PGA Response Week 12

Figure 4. PASI75 Response at Week 12



ITT, MI. *P* value based upon Cochran-Mantel-Haenszel analysis stratified by baseline PGA score. ITT, intent-to-treat; MI, multiple imputation; PASI75, ≥75% improvement in Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily; SEM, standard error of mean

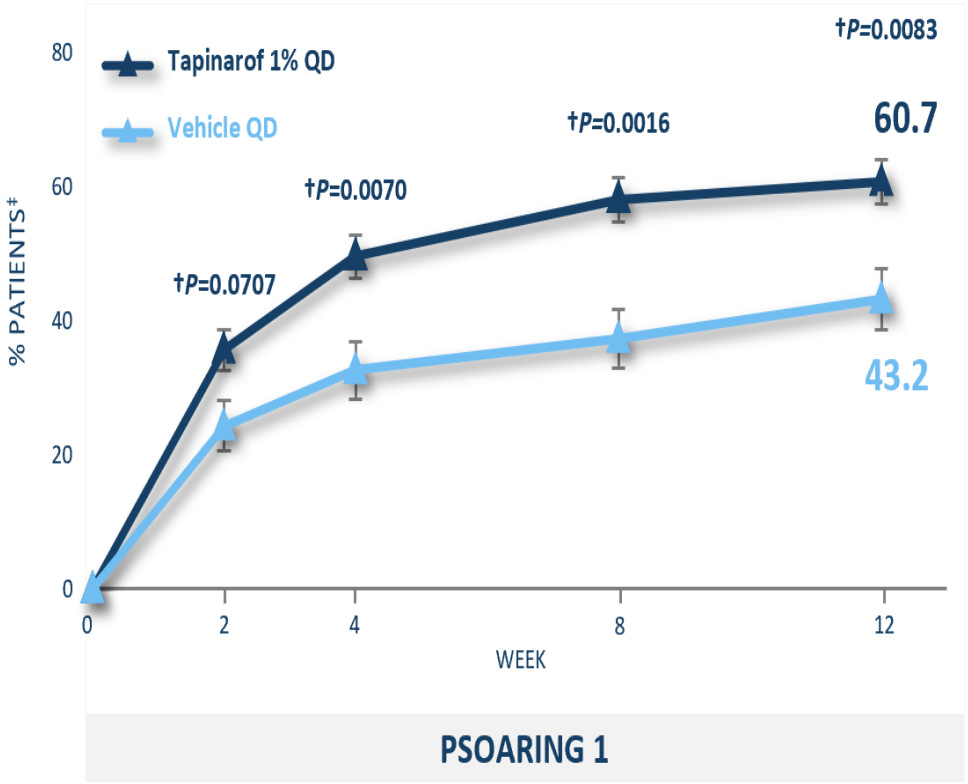
Figure 2. PGA Response at Week 12



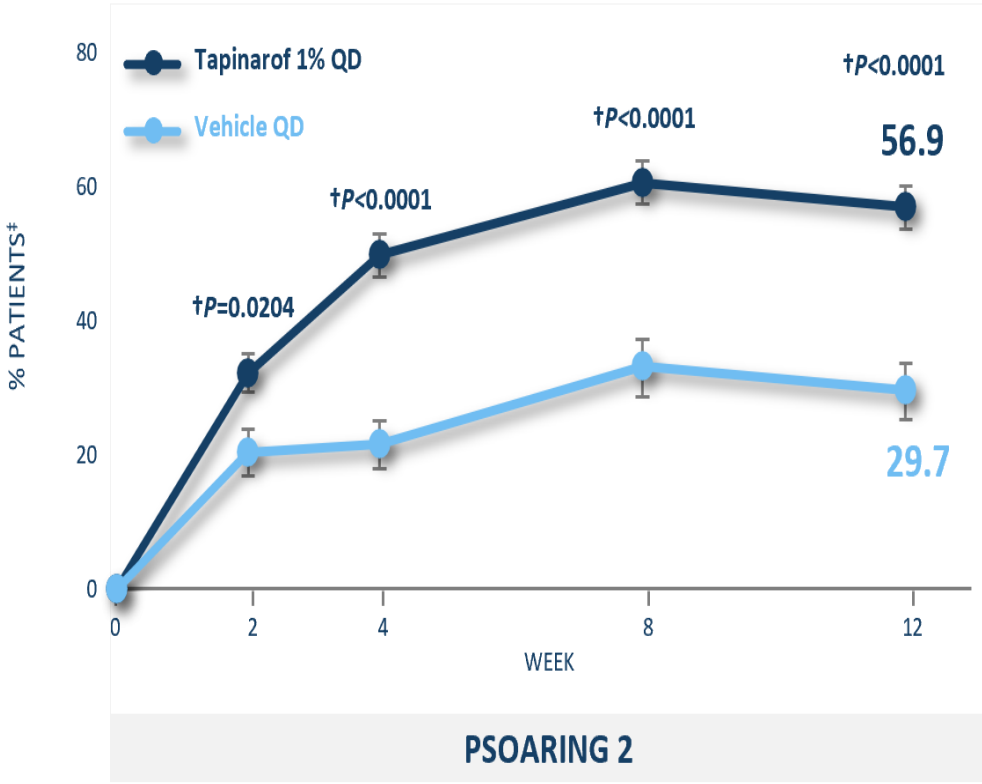
Lebwohl M. et al Poster: Maui Derm NPPA Summer 2021

Phase 3 PSOARING Program – Improvement in Peak Pruritus NRS of ≥4-point

Minimum 4-point Improvement in Peak Pruritus NRS from Baseline to Week 12 *(ITT, MI)**



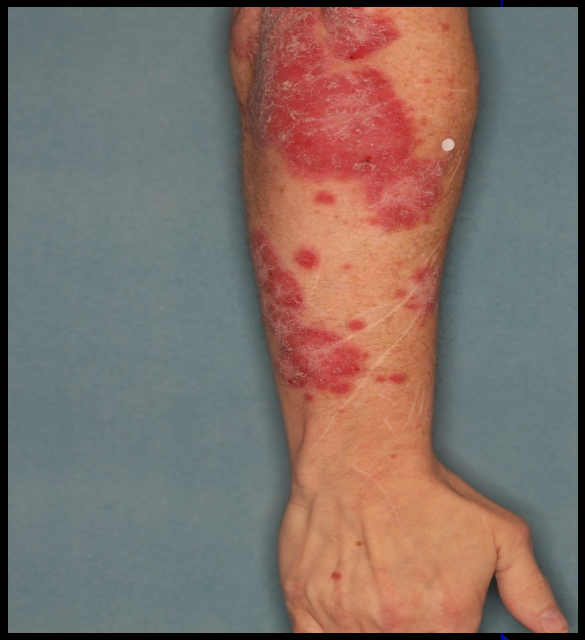
PSOARING 1



PSOARING 2

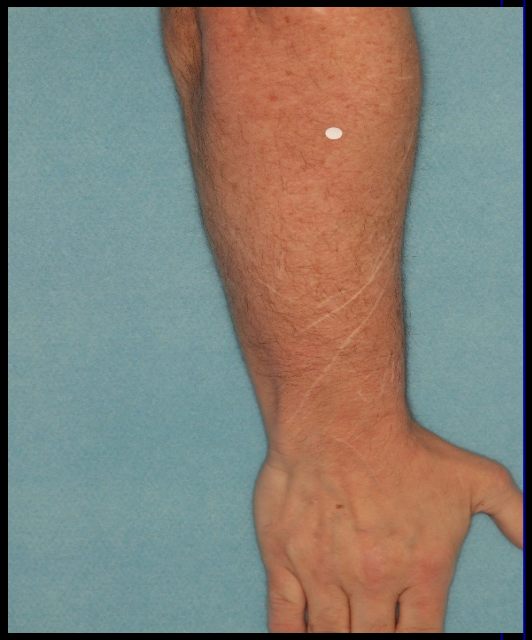
Tapinarof 1% QD Clinical Response of Patient with Plaque Psoriasis

Baseline



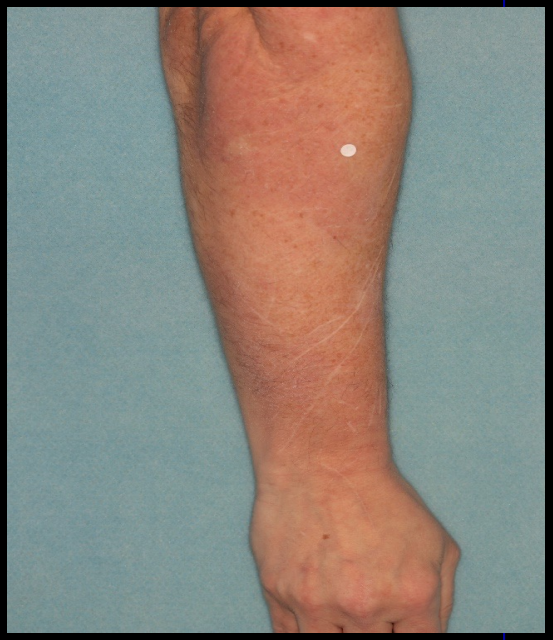
- PGA = 3
- PASI = 17.6

Week 4



- PGA = 2
- PASI = 4

Week 12



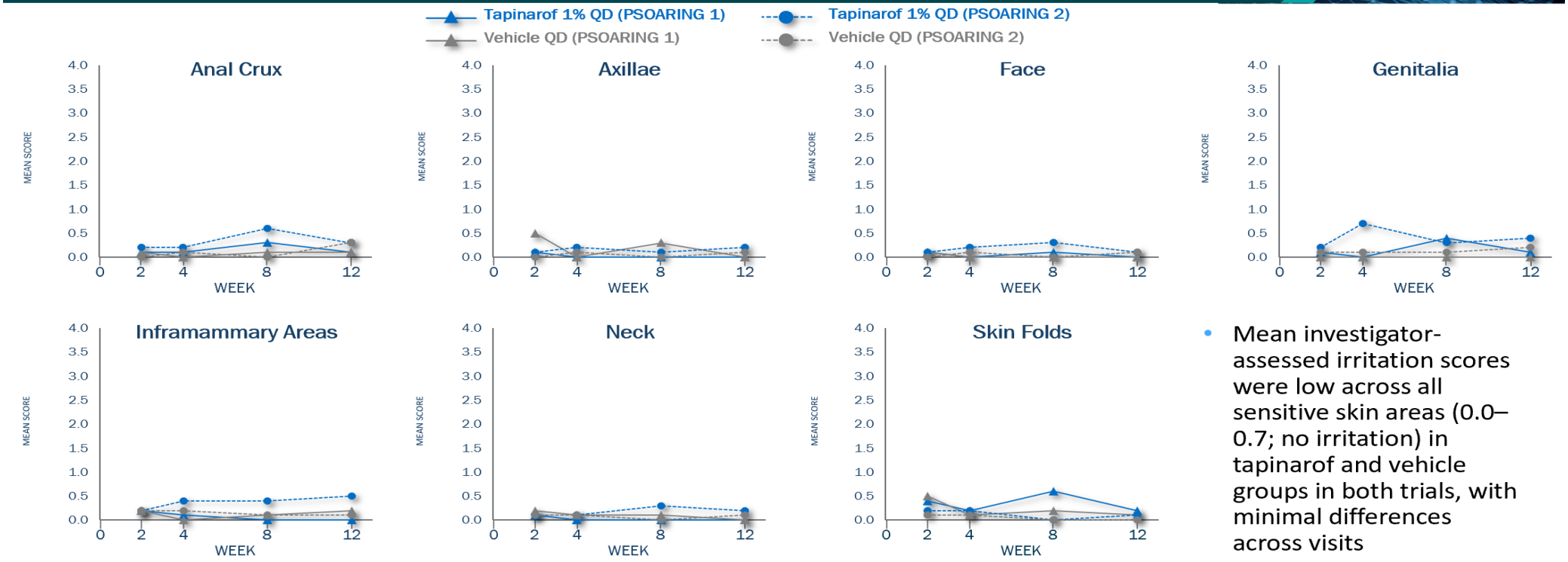
- PGA = 0
- PASI = 0

PGA and PASI are global efficacy assessments. Example of one representative target lesion of a patient treated with tapinarof 1% QD; individual results may vary. Photographs demonstrate improvement in PGA and PASI at Week 4 and 12. PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; QD, once daily.

Lebwohl, Stein Gold, Strober, et al. Poster Presentation, Fall Clinical Virtual meeting 2020

Tapinarof Phase 3 PSOARING Program – Local Tolerability

Investigator-assessed local tolerability in sensitive skin areas



- Mean investigator-assessed irritation scores were low across all sensitive skin areas (0.0–0.7; no irritation) in tapinarof and vehicle groups in both trials, with minimal differences across visits

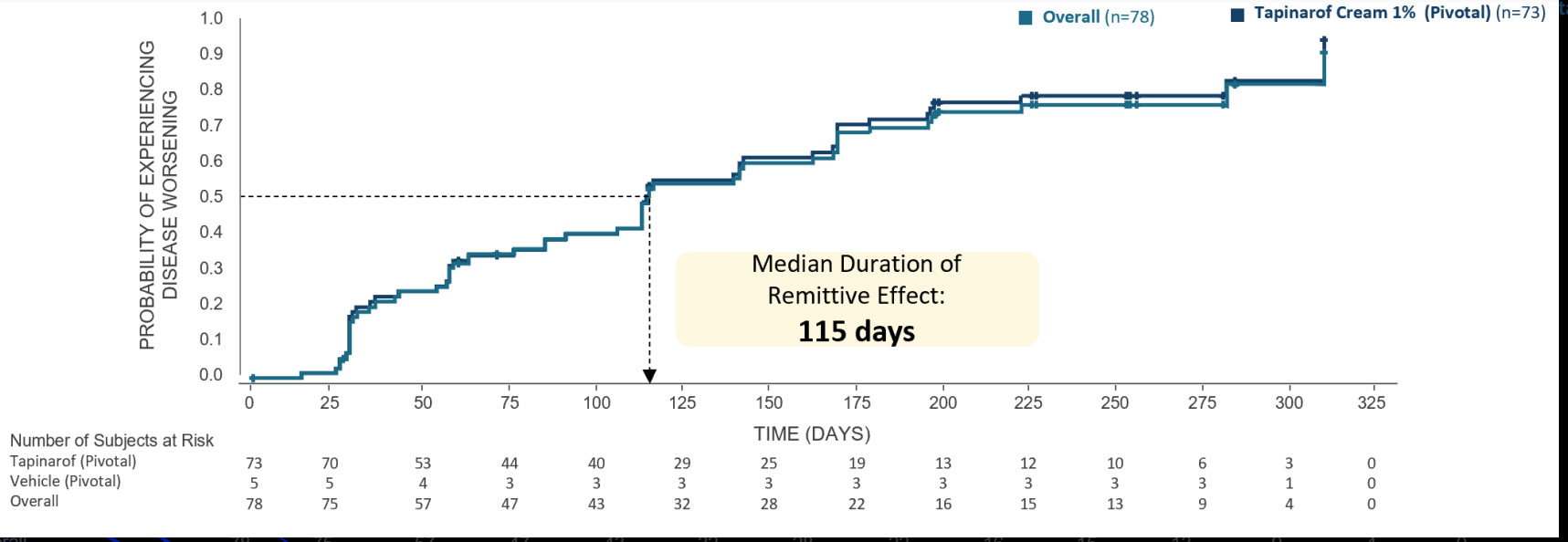
*Investigator-assessed irritation scores (0–4) assess the presence and overall degree of irritation at the application sites according to the Local Tolerability Scale (dryness, erythema, and peeling) – no irritation (0), mild (1), moderate (2), severe (3), very severe (4). The score ideally represents an "average" across all application sites. Scores were not assessed at baseline.
QD, once daily.

Stein Gold L, et al. Poster presentation at Innovations in Dermatology 2021, Mar 16–20, 2021.

Tapinarof Phase 3 PSOARING LTE Interim Analysis

Remittive effect for patients entering with PGA=0 was **~4 months**

Remittive Effect: Maintenance of PGA of 0 or 1 While Off Therapy *(ITT, OC)*



- Remittive effect off-treatment was defined as maintenance of PGA 0 (clear) or 1 (almost clear) while off therapy after achieving complete disease clearance (PGA of 0)
- The duration of remittive effect was likely an underestimate as study end, not disease worsening, truncated the duration for some patient:
  - Patients entering the study with PGA of 0: **115 days** (85.0; 162.0)*
  - Patients entering the study with, or achieving, a PGA of 0 (n=299): **119.3 days** (81.8)†

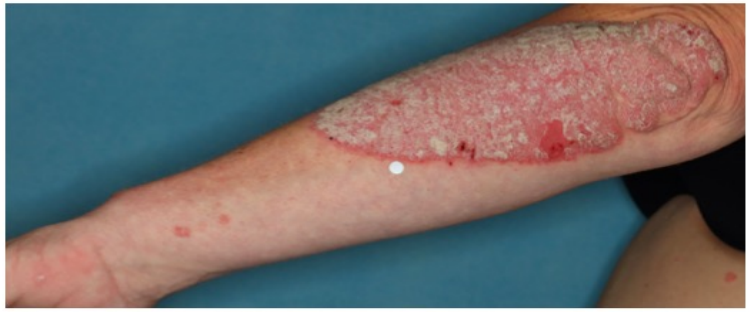
*Kaplan-Meier estimated median, 95% confidence interval. †Mean, standard deviation. CI, confidence interval; ITT, intention-to-treat, LTE, long term extension; OC, observed cases; PGA, Physician Global Assessment.

1. Strober B, et al. Poster presentation at the Innovations in Dermatology 2021, Mar 16–20, 2021.

Tapinarof 1% Cream: Remittive Effect x 24 Weeks

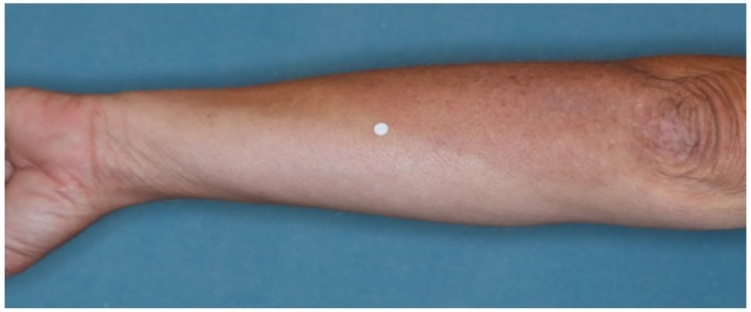
PSOARING 1

BASELINE



- PGA= 4
- DLQI=6
- PASI=19.8

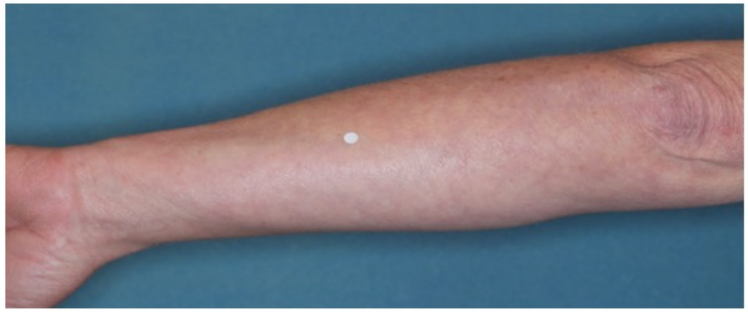
WEEK 12



- PGA=1
- DLQI=0
- PASI=3.8

PSOARING 3 (LTE)

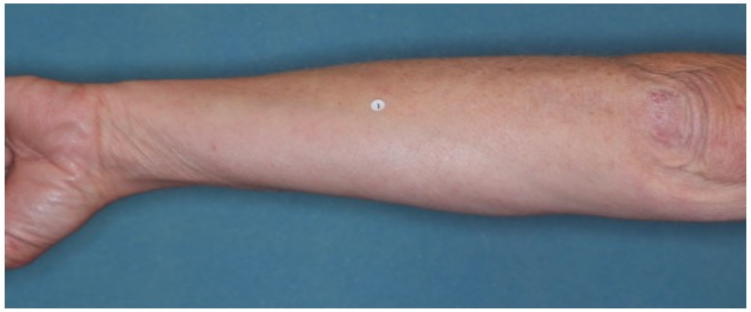
WEEK 36 (LTE Week 24)



Off Treatment for 12 weeks*

- PGA=1
- DLQI=0
- PASI=1.2

WEEK 48 (LTE Week 36)



Off Treatment for 24 weeks*

- PGA=2
- DLQI=2
- PASI=5.4

Tapinarof 1% QD AE Profile Consistent with Previous Studies[1,2]

Patients, n (%)	PSOARING 1		PSOARING 2	
	Tapinarof 1% QD (n=340)	Vehicle QD (n=170)	Tapinarof 1% QD (n=343)	Vehicle QD (n=172)
Folliculitis	70 (20.6)	2 (1.2)	54 (15.7)	1 (0.6)
Contact dermatitis	13 (3.8)	1 (0.6)	16 (4.7)	0 (0.0)
Headache	5 (1.5)	1 (0.6)	1 (0.3)	0 (0.0)
Pruritus	4 (1.2)	0 (0.0)	2 (0.6)	0 (0.0)
Dermatitis	1 (0.3)	0 (0.0)	4 (1.2)	0 (0.0)
Study discontinuation due to AESI				
Folliculitis	6 (1.8)	0 (0.0)	3 (0.9)	0 (0.0)
Contact dermatitis	5 (1.5)	0 (0.0)	7 (2.0)	0 (0.0)
Headache	1 (0.3)	0 (0.0)	2 (0.6)	0 (0.0)
Severity of folliculitis, **n (%) among subset of patients with AESI of folliculitis**				
Mild	51 (63.8)	1 (50.0)	44 (72.1)	0 (0.0)
Moderate	28 (35.0)	1 (50.0)	17 (27.9)	1 (100.0)
Severe	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)

Folliculitis: non-infectious "keratosis pilaris like" follicular plugging

- The most common (≥1% in any group) TEAEs were folliculitis, contact dermatitis, headache, pruritus, and dermatitis
- Folliculitis was mostly mild or moderate in severity in both studies and study discontinuation due to folliculitis was low: 1.8% (6/340) vs 0.0% (0/170) and 0.9% (3/343) vs 0.0% (0/172) in PSOARING 1 and 2, respectively

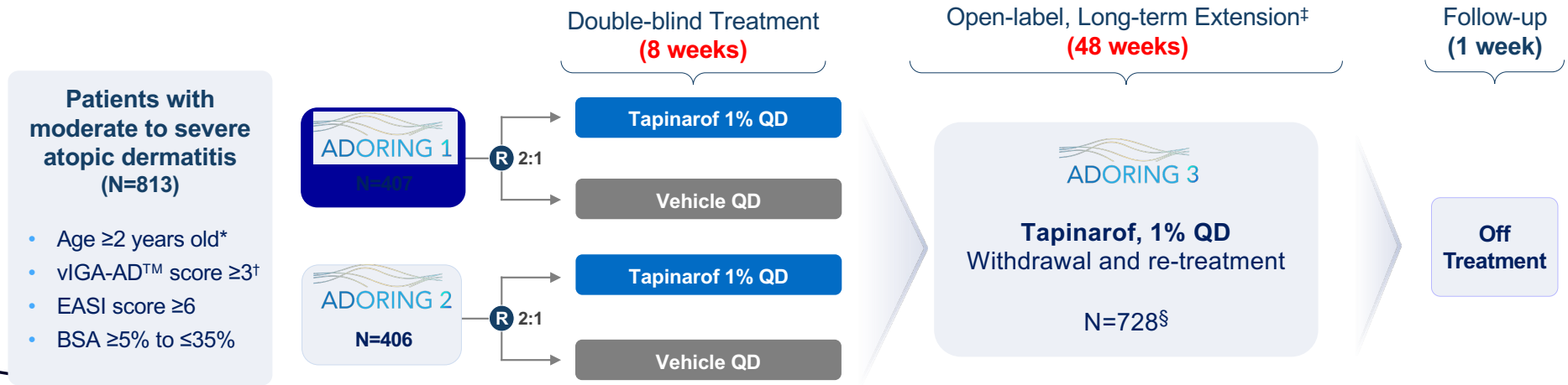
AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; TEAE, treatment-emergent adverse event.

1. Robbins K, et al. *J Am Acad Dermatol*. 2019;80:714–721; 2. Stein Gold L, et al. *J Am Acad Dermatol*. 2020; doi: 10.1016/j.jaad.2020.04.181. 3. Lebwohl, Stein Gold, Strober, et al. Poster Presentation. Fall Clinical Virtual meeting 2020

Tapinarof (VTAMA®) Cream in Mild-Moderate-Severe ATOPIC DERMATITIS

ADORING Phase 3 Program

- **Two Identical Pivotal Trials Followed by an Open-Label, Long-Term Extension Trial**



Primary Endpoint:
- Proportion of patients with a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline at Week 8

Secondary Endpoints:
- EASI75 from baseline at Week 8
- %BSA affected from baseline at Week 8
- EASI90 from baseline at Week 8
- Achievement of a ≥4-point PP-NRS reduction at Week 8¶

Safety:
- TEAEs, SAEs

PROs:
- LTS
- DLQI/ CDLQI/ IDQOL
- EQ-5D-5L/ EQ-5D-Y
- POEM
- DFI
- PP-NRS

*A minimum of ~15% of patients will be enrolled into the following age groups: 2–6 years, 7–11 years, 12–17 years, and ≥18 years. Adults (≥18 years) will comprise a maximum of approximately 20% of enrolled patients. †Patients with a vIGA-AD™ score of 4 (severe) will represent a minimum of ~10% of the total randomized population; the remainder will have a vIGA-AD™ score of 3 (moderate). ‡Patients electing not to participate in ADORING 3 will attend a follow-up visit 1 week after completion of the treatment period in ADORING 1 or 2. §Includes eligible patients from ADORING 1 and 2, the Maximal Usage PK trial, and ~125 additional patients aged 2 to <18 years enrolling directly into ADORING 3. ¶In patients ≥12 years with a baseline patient reported PP-NRS score ≥4. BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatitis Family Impact; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI75, ≥75% improvement in Eczema Area and Severity Index score; EASI90, ≥90% improvement in Eczema Area and Severity Index score; EQ-5D-5L, 5-level EuroQol-5 Dimension; EQ-5D-Y, child-friendly EuroQol-5 Dimension version; IDQOL, Infants' Dermatitis Quality of Life Index; LTS, Local Tolerability Scale; PK, pharmacokinetic; POEM, Patient Oriented Eczema Measure; PP-NRS, Patient-Reported Peak Pruritus-Numeric Rating Scale; PROs, patient reported outcomes; QD, once daily; R, randomized; SAE, serious adverse event; TEAE, treatment-emergent adverse event; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis. vIGA-AD™ is the trademark of Eli Lilly and Co.

This slide is subject to the Disclaimer at the beginning of this slide deck

ADORING 1 & 2 Baseline Demographics and Disease Characteristics

- **80% Pediatric Patients and Well Balanced Across Pediatric Age Cohorts**

	ADORING 1			ADORING 2		
	Tapinarof 1% QD (n=270)	**Vehicle QD** (n=137)	**Overall** (n=407)	**Tapinarof 1% QD** (n=271)	**Vehicle QD** (n=135)	**Overall** (n=406)
Age, mean (SD)	15.6 (16.62)	15.6 (16.49)	15.6 (16.56)	16.4 (16.24)	16.7 (16.05)	16.5 (16.16)
Age group, n (%)						
2–6 years	76 (28.1)	39 (28.5)	115 (28.3)	65 (24.0)	32 (23.7)	97 (23.9)
7–11 years	75 (27.8)	37 (27.0)	112 (27.5)	64 (23.6)	32 (23.7)	96 (23.6)
12–17 years	67 (24.8)	34 (24.8)	101 (24.8)	89 (32.8)	44 (32.6)	133 (32.8)
≥18 years	52 (19.3)	27 (19.7)	79 (19.4)	53 (19.6)	27 (20.0)	80 (19.7)
Male, n (%)	130 (48.1)	66 (48.2)	196 (48.2)	117 (43.2)	58 (43.0)	175 (43.1)
Weight, kg, mean (SD)	46.69 (27.251)	47.69 (27.725)	47.03 (27.381)	51.52 (29.148)	54.03 (32.005)	52.36 (30.112)
BMI, kg/m^2, mean (SD)	21.38 (6.307)	22.06 (6.557)	21.61 (6.392)	22.65 (7.460)	23.25 (8.257)	22.85 (7.729)
vIGA-AD™, n (%)						
3 – Moderate	244 (90.4)	122 (89.1)	366 (89.9)	228 (84.1)	113 (83.7)	341 (84.0)
4 – Severe	26 (9.6)	15 (10.9)	41 (10.1)	43 (15.9)	22 (16.3)	65 (16.0)
EASI, mean (SD)	12.24 (5.007)	12.86 (5.633)	12.45 (5.228)	13.45 (5.615)	13.09 (4.689)	13.33 (5.322)
BSA affected (%), mean (SD)	16.45 (8.666)	17.71 (9.500)	16.87 (8.964)	17.13 (8.743)	15.84 (7.888)	16.70 (8.480)
PP-NRS (all), mean (SD)	6.8 (2.33)	6.5 (2.39)	6.7 (2.35)	6.7 (2.37)	6.9 (2.09)	6.8 (2.28)
PP-NRS (≥12 years), mean (SD)	6.5 (2.40)	6.3 (2.31)	6.4 (2.36)	6.3 (2.36)	6.5 (2.21)	6.4 (2.31)
PP-NRS (<12 years), mean (SD)	7.0 (2.25)	6.6 (2.46)	6.9 (2.33)	7.1 (2.32)	7.4 (1.82)	7.2 (2.17)

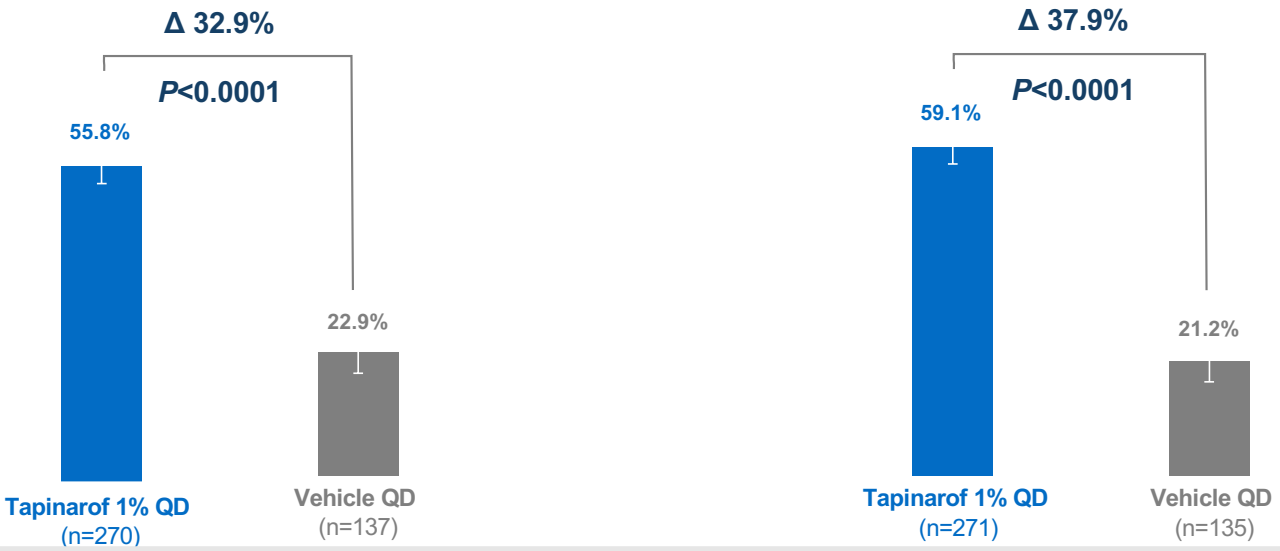
- Baseline disease characteristics reflect moderate to severe population, aged 2–81 years, and mean PP-NRS of 6.7–6.8

BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus-Numeric Rating Scale; QD, once daily; SD, standard deviation; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis. vIGA-AD™ is the trademark of Eli Lilly and Co.
Source: 1; 14.1.2.1.

ADORING 1 & 2 – EASI75

- **Greater Than 55% of Tapinarof-Treated Patients Achieved At Least 75% Improvement In EASI by Week 8**

EASI75 from Baseline at Week 8 *(ITT, MI*)*



*Estimand. P value based upon Cochran-Mantel-Haenszel analysis stratified by baseline vIGA-AD™ score and age group.
EASI75, ≥75% improvement in Eczema Area and Severity Index score; ITT, intention-to-treat; MI, multiple imputation; QD, once daily; SE, standard error; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis. vIGA-AD™ is the trademark of Eli Lilly and Co.
Source: 14.2.2.1.1.

ADORING 1 & 2 Summary of TEAEs – Safety Population

- **Tapinarof Demonstrated a Favorable Safety Profile in AD Patients Down to 2 Years of Age**

Patients, n (%)	**Tapinarof 1% QD** (n=270)	**Vehicle QD** (n=137)	**Tapinarof 1% QD** (n=271)	**Vehicle QD** (n=133)
AESI (treatment emergent)				
Contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Follicular event	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
TEAE leading to treatment discontinuation	6 (2.2)	6 (4.4)	4 (1.5)	5 (3.8)
TEAE leading to trial discontinuation	5 (1.9)	5 (3.6)	4 (1.5)	4 (3.0)

- Very low rates of treatment and trial discontinuation due to adverse events
- Trial and treatment discontinuation greater in vehicle-treated group than Tapinarof-treated group
- 91% of subjects from ADORING 1 & 2 elected to enroll into the Phase 3 ADORING 3, a 48 week open-label, long-term safety study

Follicular event includes folliculitis, application site folliculitis, follicular eczema, and keratosis pilaris.
AD, atopic dermatitis; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; QD, once daily; TEAE, treatment-emergent adverse event.
Source: 14.3.1.1.

Roflumilast 0.3% Cream (ZORYVE™) Plaque (Mild-Moderate-Severe) Psoriasis

Roflumilast: PDE - 4 Inhibitor

Roflumilast: PDE-4 inhibitor (200-300x more powerful inhibitor than apremilast)

Indications Being Pursued

1. **Psoriasis: approved 7/2022**
2. Atopic Dermatitis
3. Seborrheic Dermatitis (ARQ 154-304)
4. Vitiligo (ARQ 252-213)

Vehicles

- Cream
- Foam
- Lotion

Roflumilast Cream 0.3%, a Once-Daily, Potent Phosphodiesterase-4 Inhibitor, in Chronic Plaque Psoriasis Patients: Efficacy and Safety From DERMIS-1 and DERMIS-2 Phase 3 Trials

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Disclosures: Mark Lebwohl, Leon H. Kircik, Angela Moore, Linda Stein Gold, Zoe D. Draelos, Melinda J. Gooderham, Kim A. Papp, Jerry Bagel, Neal Bhatia, James Del Rosso, Laura K. Ferris, Lawrence J. Green, Adelaide A. Hebert, Terry Jones, Steven E. Kempers, David M. Pariser, Paul S. Yamauchi, and Matthew Zirwas are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; Robert C. Higham, Lynn Navale, and David R. Berk are employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.

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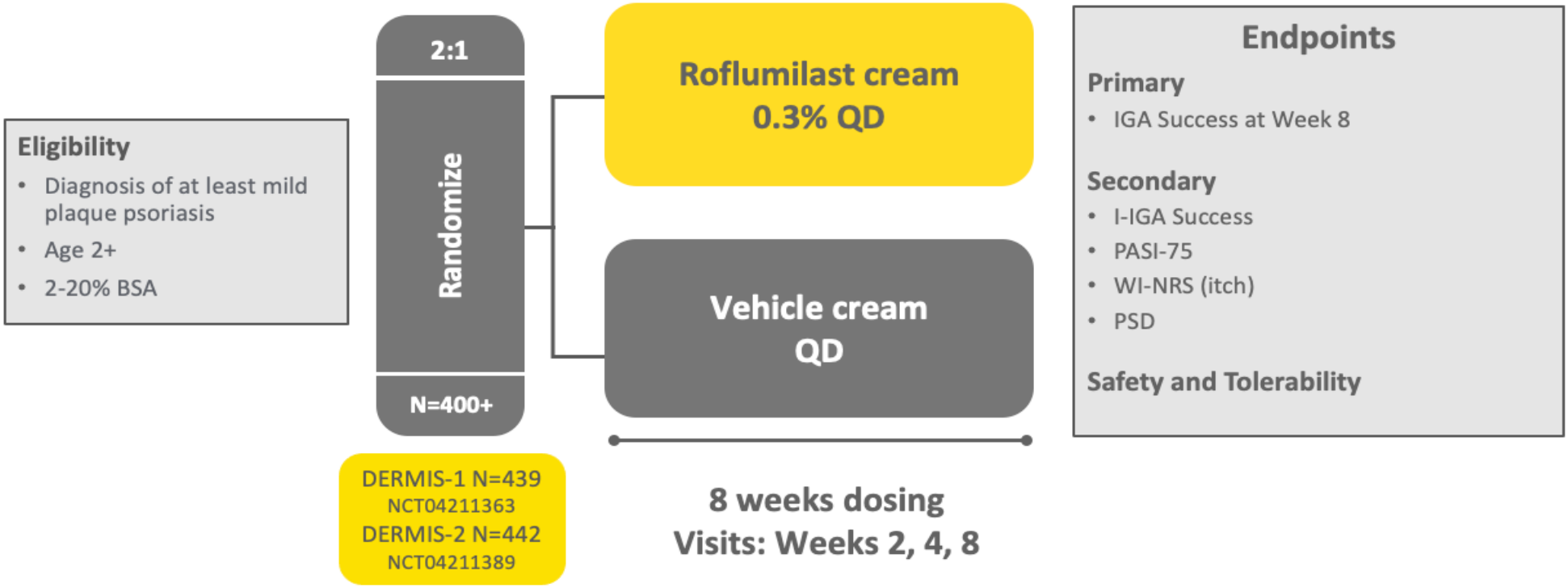
Presented at the European Academy of Dermatology and Venereology Spring Symposium 2021, 06-07 May 2021

DERMIS-1 & DERMIS-2: Phase 3 PsO Identical Study Design and Endpoints

Randomized, Double-blind, Vehicle-controlled, Multicenter Studies
(Two identical, parallel phase 3 studies)

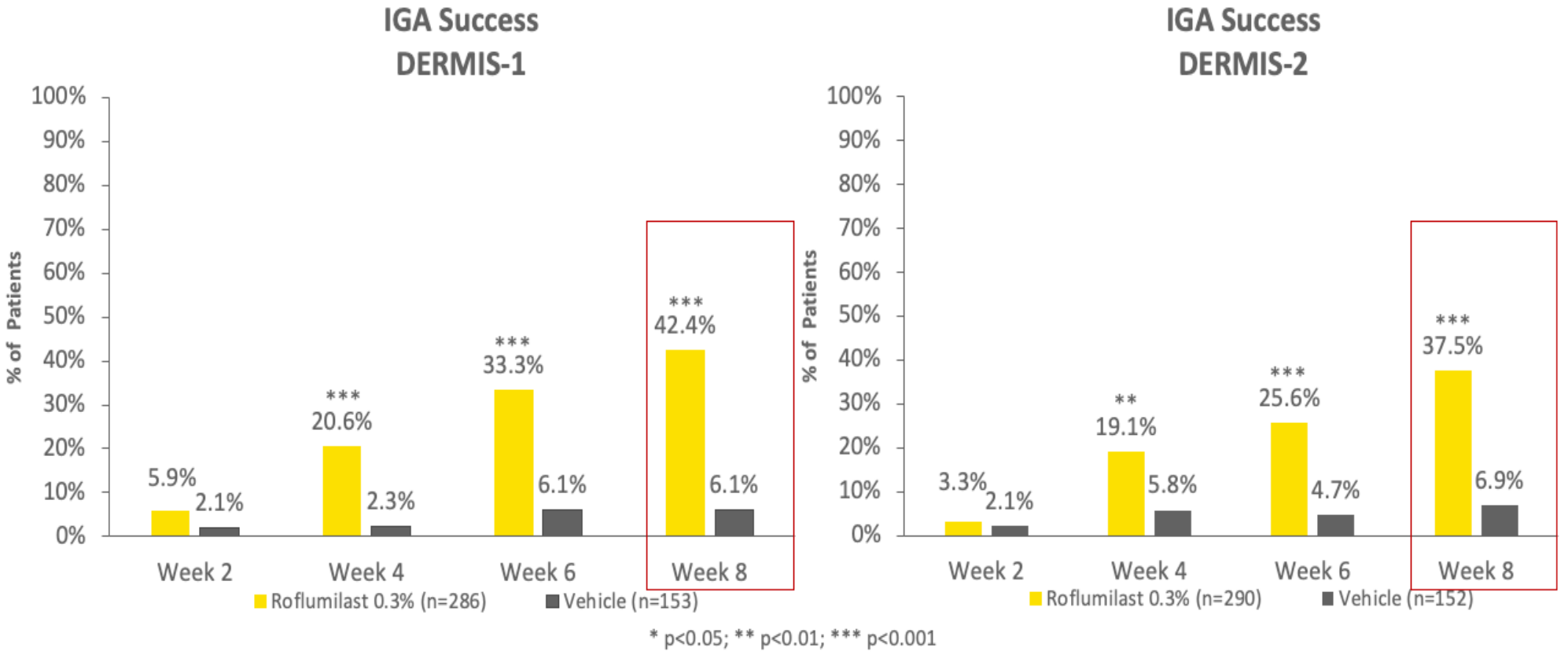


BSA: body surface area; IGA: Investigator's Global Assessment; I-IGA: intertriginous-IGA; PASI-75: Psoriasis Area and Severity Index-75% reduction; PSD: Psoriasis Symptom Diary; QD: once daily; WI-NRS: Worst Itch Numeric Rating Scale

Presented at the European Academy of Dermatology and Venereology Spring Symposium 2021, 06-07 May 2021

Efficacy on IGA Success in Both Phase 3 Studies

I-IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline



Intent-to-treat population; missing scores imputed using multiple imputations

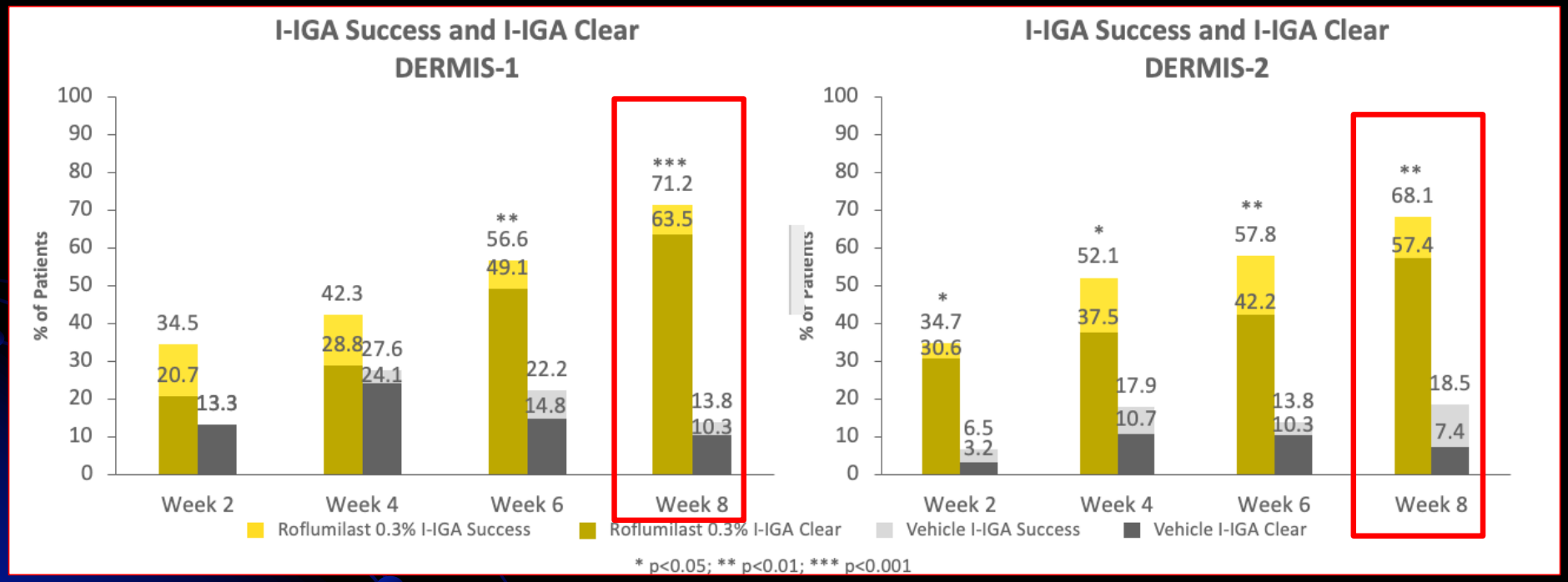
IGA: Investigator's Global Assessment

Presented at the European Academy of Dermatology and Venereology Spring Symposium 2021, 06-07 May 2021

Roflumilast Was Highly Effective for *Intertriginous Plaques* in DERMIS-1 and DERMIS-2

Exactly where you DON'T want to use steroids

I-IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline

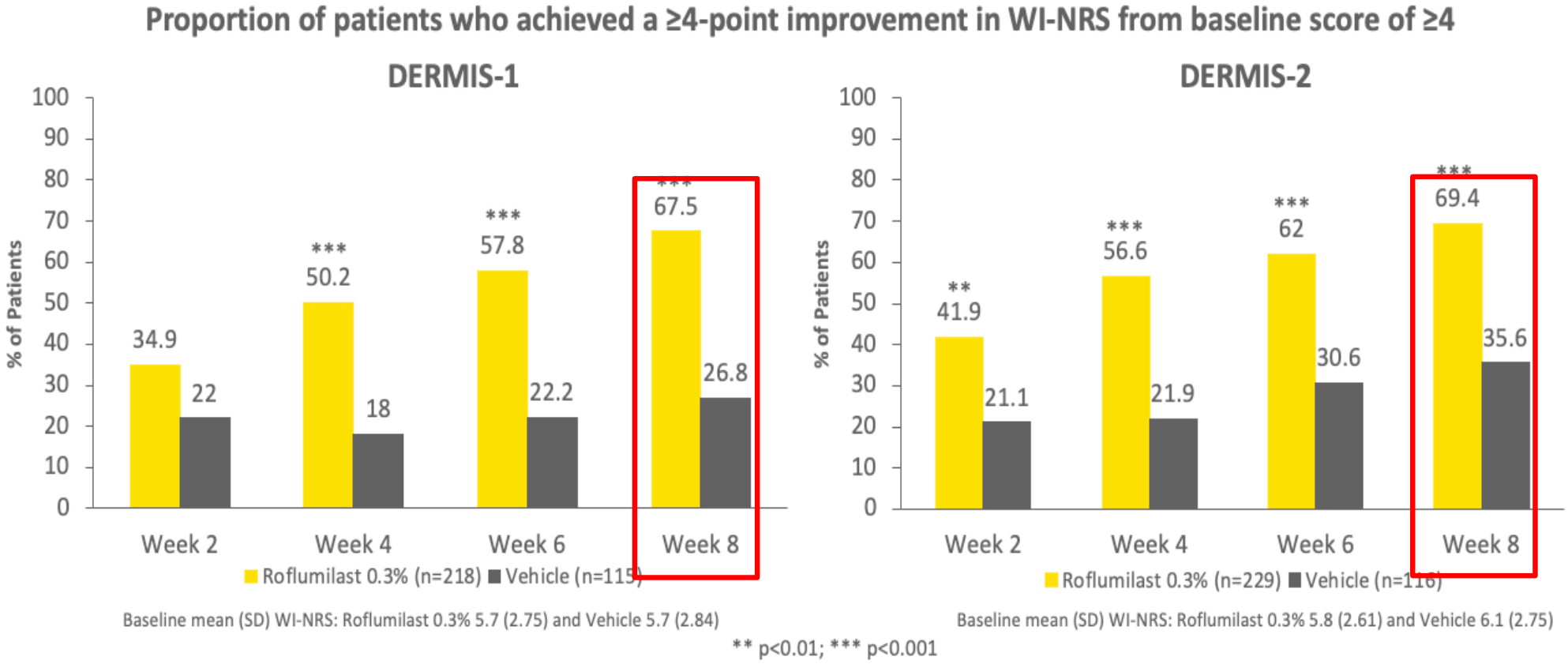


I-IGA-intent-to-treat population: patients with intertriginous area involvement with severity of the intertriginous lesions at least mild (I-IGA ≥2) at baseline. Observed data. P values for I-IGA success

I-IGA: Intertriginous-Investigator's Global Assessment

Presented at the European Academy of Dermatology and Venereology Spring Symposium 2021, 06-07 May 2021

Rapid Itch Response in Both DERMIS-1 and DERMIS-2

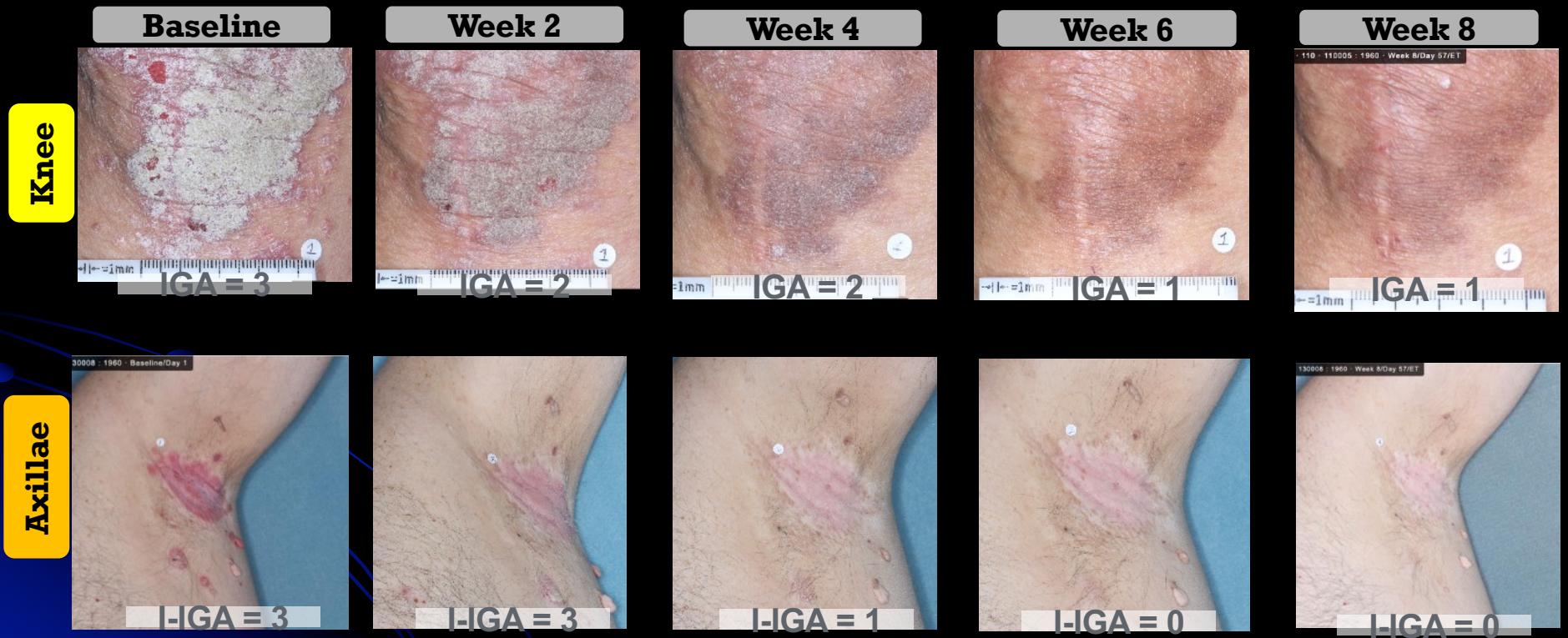


Evaluated in a subset of the intent-to-treat population of patients with WI-NRS pruritus score ≥4 at baseline; missing scores imputed using multiple imputations

SD: standard deviation; WI-NRS: Worst Itch Numeric Rating Scale

Presented at the European Academy of Dermatology and Venereology Spring Symposium 2021, 06-07 May 2021

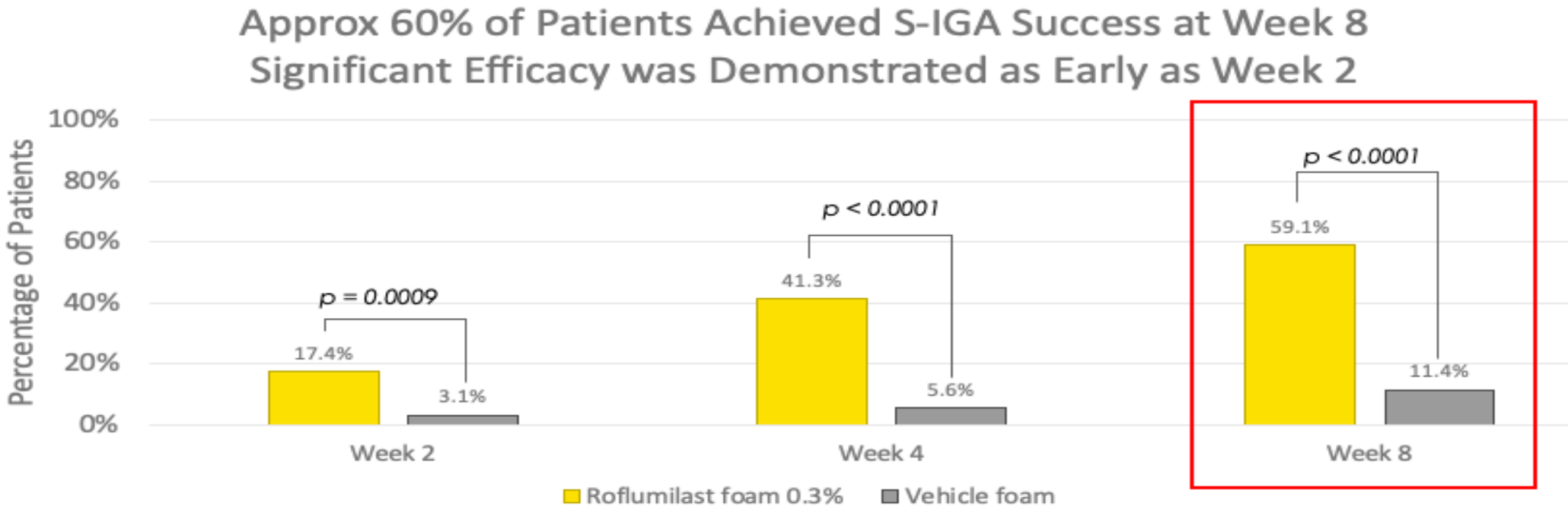
Roflumilast Cream 0.3%: DERMIS-1 & DERMIS-2



IGA: Investigator's Global Assessment; I-IGA: intertriginous-IGA

Presented at the European Academy of Dermatology and Venereology Spring Symposium 2021, 06-07 May 2021

Roflumilast Foam for Scalp Psoriasis (Not Yet Available)

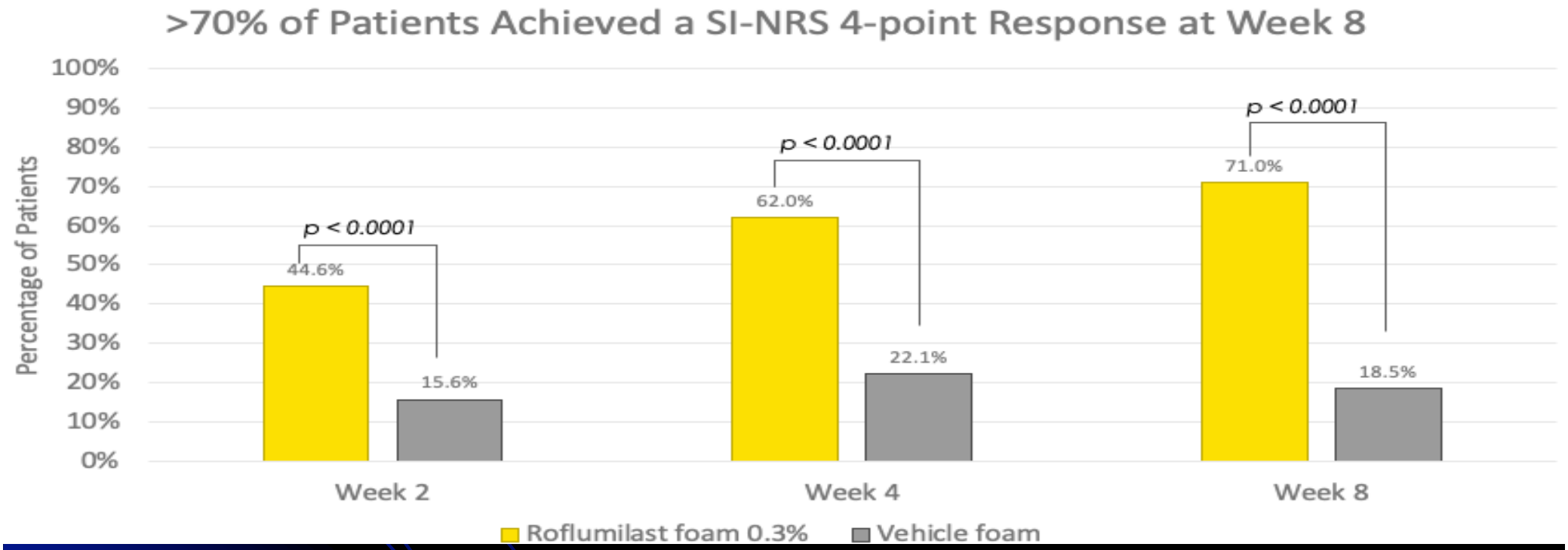


34.3% of patients on roflumilast achieved S-IGA = 0 (clear) versus 3.4% on vehicle

Intent-to-treat population; S-IGA: Scalp-Investigator's Global Assessment
IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline

Presented at the American Academy of Dermatology Virtual Annual Meeting, April 23-25, 2021

Scalp Itch: Roflumilast-Treated Patients had SI-NRS 4-point Response as Early as Week 2



Evaluated in patients with SI-NRS Score ≥4 at Baseline
Intent-to-treat population; SI-NRS: Scalp worst itch numeric rating scale

Presented at the American Academy of Dermatology Virtual Annual Meeting, April 23-25, 2021

Efficacy and Safety of Roflumilast Foam 0.3% in Patients With Seborrheic Dermatitis in a Phase 3 Trial

Andrew Blauvelt[1], Javier Alonso-Llamazares[2], Neal Bhatia[3], Zoe D. Draelos[4], Janet DuBois[5], Seth B. Forman[6], Melinda Gooderham[7], Scott T. Guenthner[8], Adelaide A. Hebert[9], Edward Lain[10], Angela Y. Moore[11], Kim A. Papp[12], Linda Stein Gold[13], Matthew Zirwas[14], Saori Kato[15], Scott Snyder[15], David Krupa[15], Patrick Burnett[15], David R. Berk[15], David H. Chu[15]

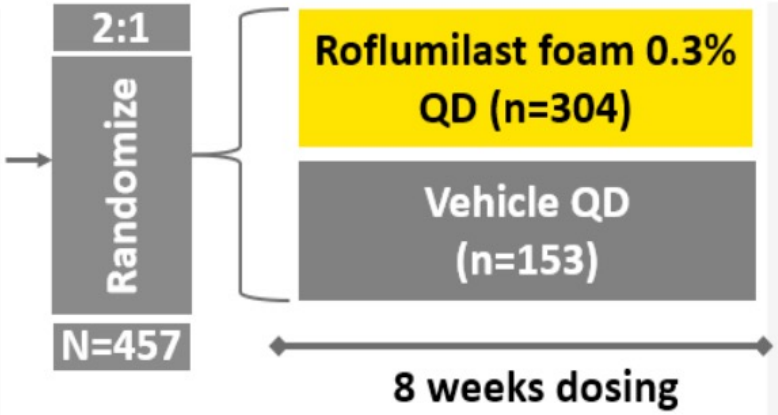
[1]Oregon Medical Research Center, Portland, OR, USA.; [2]Driven Research LLC, Coral Gables, FL, USA; [3]Therapeutics Clinical Research, San Diego, CA, USA; [4]Dermatology Consulting Services, High Point, NC, USA; [5]DermResearch, Inc., Austin, TX, USA; [6]ForCare Medical Center, Tampa, FL, USA; [7]SKiN Centre for Dermatology, Probity Medical Research and Queen's University, Peterborough, ON, Canada; [8]The Dermatology Center of Indiana, PC, and The Indiana Clinical Trials Center, PC, Plainfield, IN, USA; [9]UT Health McGovern Medical School, Houston, TX, USA [10]Sanova Dermatology, Austin, TX, USA; [11]Arlington Research Center, Arlington, TX, USA and Baylor University Medical Center, Dallas, TX, USA; [12]Probity Medical Research and K Papp Clinical Research, Waterloo, ON, Canada; [13]Henry Ford Medical Center, Detroit, MI, USA; [14]Dermatologists of the Central States, Probity Medical Research, and Ohio University, Bexley, OH, USA; [15]Arcutis Biotherapeutics, Inc., Westlake Village, CA, USA.

Presented at the European Academy of Dermatology and Venereology (EADV) Congress, September 7-11, 2022, Milano, Italy.

Study Design

Eligibility

- Diagnosis of at least moderate seborrheic dermatitis (IGA ≥3)
- Age ≥9
- ≤20% BSA



Endpoints[a]

- Primary: IGA Success (0 or 1 With a 2-Grade Improvement) at Week 8
- Secondary:
  - IGA Success at Weeks 2 and 4
  - IGA of Clear at Week 8
  - WI-NRS at Weeks 2, 4, and 8
  - Erythema Score of 0 at Week 8
  - Scaling Score of 0 at Week 8
- Safety & tolerability

*As this study is a single pivotal trial, the statistical significance of the primary endpoint was assessed at the 1% significance level (2-sided). To control for multiple testing, the 1% alpha was partitioned to .0033 for WI-NRS endpoints and .0067 for other secondary endpoints

AE, adverse event; BSA, body surface area; IGA, Investigator Global Assessment; QD, once daily; SAE, serious adverse event; SD, seborrheic dermatitis; WI-NRS, Worst Itch Numeric Rating Scale.

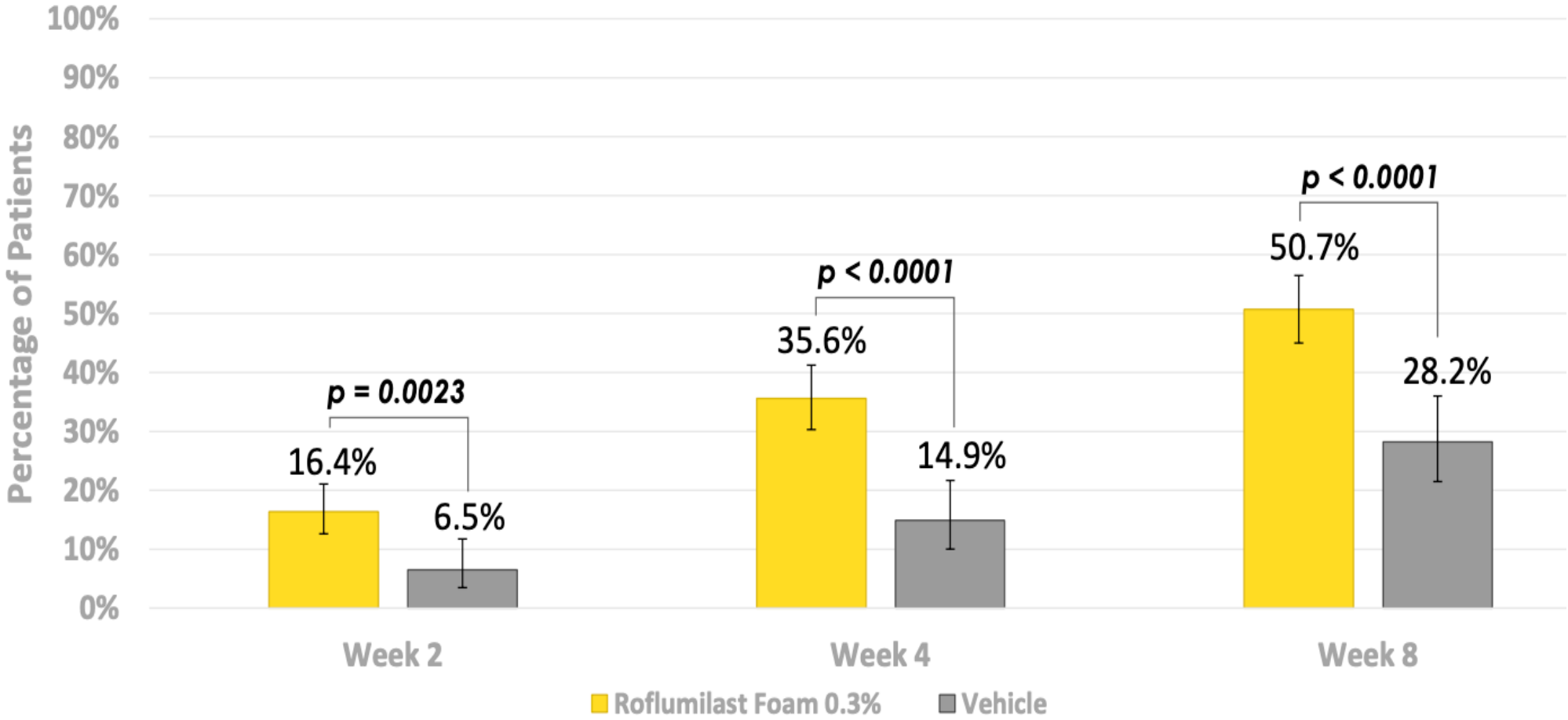
Presented at the European Academy of Dermatology and Venereology (EADV) Congress, September 7-11, 2022, Milano, Italy.

	Roflumilast Foam 0.3% (n=304)	Vehicle (n=153)
IGA score, n (%)		
3 (moderate)	287 (94.4)	141 (92.2)
4 (severe)	17 (5.6)	12 (7.8)
Erythema score, n (%)		
2 (mild)	0	1 (0.7)
3 (moderate)	282 (92.8)	141 (92.2)
4 (severe)	22 (7.2)	11 (7.2)
Scaling score, n (%)		
2 (mild)	0	0
3 (moderate)	256 (84.2)	130 (85.0)
4 (severe)	48 (15.8)	23 (15.0)
WI-NRS, mean score (Std Dev)	5.06 (2.34)	4.74 (2.29)
WI-NRS score ≥4, n (%)	206 (67.8)	98 (64.1)
BSA, mean % (Std Dev)	2.89 (2.03)	2.98 (2.57)

	Roflumilast Foam 0.3% (n=304)	Vehicle (n=153)
Age in years, mean (SD)	43.2 (16.8)	41.8 (17.5)
Sex		
Male, n (%)	153 (50.3)	75 (49.0)
Female, n (%)	151 (49.7)	78 (51.0)
Race, n (%)		
American Indian or Alaska Native	4 (1.3)	0
Asian	18 (5.9)	10 (6.5)
Black or African American	36 (11.8)	15 (9.8)
Native Hawaiian or Other Pacific Islander	0	1 (0.7)
White	234 (77.0)	122 (79.7)
More than 1 race	1 (0.3)	1 (0.7)
Other	11 (3.6)	4 (2.6)
Ethnicity		
Hispanic or Latino	69 (22.7)	28 (18.3)
Not Hispanic or Latino	235 (77.3)	125 (81.7)

Patients, n (%)	Roflumilast Foam 0.3% (n=304)	Vehicle (n=153)
Scalp	291 (95.7)	136 (88.9)
Face	186 (61.2)	98 (64.1)
Eyelids Involved	29 (9.5)	13 (8.5)
Ears	146 (48.0)	79 (51.6)
Neck	33 (10.9)	13 (8.5)
Trunk	28 (9.2)	18 (11.8)
Other	11 (3.6)	4 (2.6)

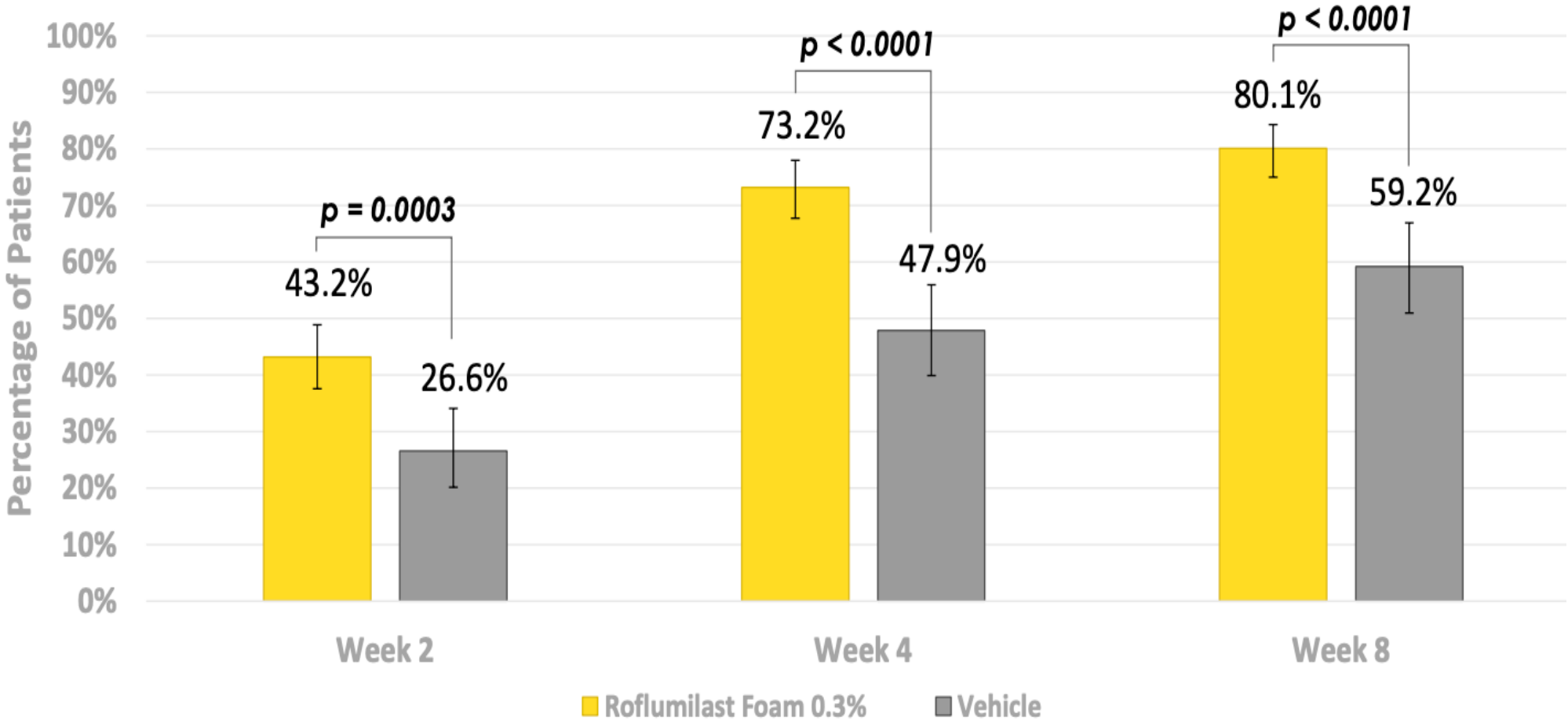
>50% of Patients Achieved IGA of Clear



IGA Clear = IGA Score of 0. Intent-to-treat population; missing scores imputed using multiple imputations, p-values are not adjusted for multiple testing. Error bars represent 95% confidence interval.

IGA, Investigator Global Assessment.

80% of Patients Achieved IGA Success at Week 8



IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline. Intent-to-treat population; missing scores imputed using multiple imputations. Error bars represent 95% confidence interval. Statistical significance was concluded at the 1% significance level (2-sided).

IGA, Investigator Global Assessment

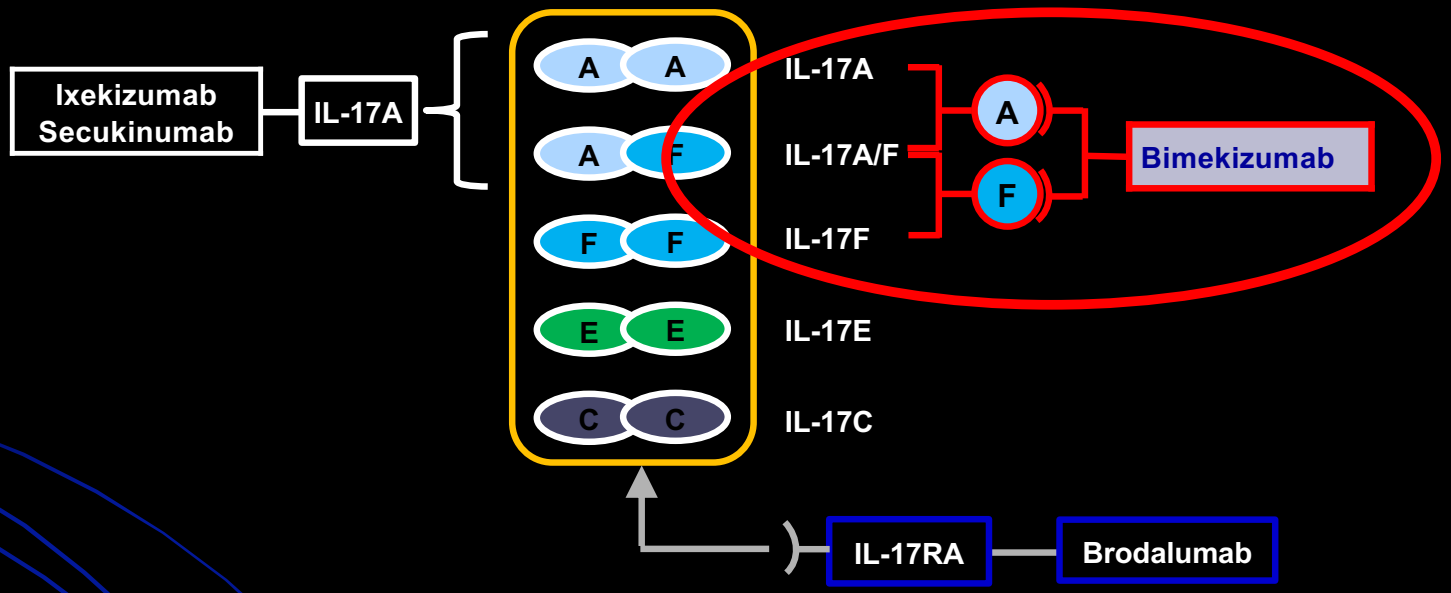
n (%)	Roflumilast Foam 0.3% (n=304)	Vehicle (n=153)
Patients with any TEAE	70 (23.0)	33 (21.6)
Patients with any treatment-related TEAE	8 (2.6)	5 (3.3)
Patients with any treatment-emergent SAE*	1 (0.3)	0
Patients who discontinued study due to AE†	2 (0.7)	3 (2.0)
Most common TEAE (>1% in any group), pr		
COVID-19		5 (3.3)
Urinary tract infection	4 (1.3)	3 (2.0)
Nausea	5 (1.6)	0
Nasopharyngitis	4 (1.3)	1 (0.7)
Application site pain	1 (0.3)	3 (2.0)
Sinusitis	0	2 (1.3)

No Safety Signal

IL-17 Inhibitors

- **Secukinumab:** approved in 2015 as Cosentyx®
- **Ixekizumab:** approved in 2016 as Taltz®
- **Brodalumab:** approved in 2017 as Siliq®
- **Bimekizumab…….**

Targeting the IL17 Family of Cytokines



Adapted From: Lønnberg A, Zachariae C, Skov L. Clin Cosmet Investig Dermatol. (2014) 7: 251—259

Bimekizumab Comparator Trials

ORIGINAL ARTICLE

Bimekizumab versus Adalimumab in Plaque Psoriasis

R.B. Warren, A. Blauvelt, J. Bagel, K.A. Papp, P. Yamauchi, A. Armstrong, R.G. Langley, V. Vanvoorden, D. De Cuyper, C. Cioffi, L. Peterson, N. Cross, and K. Reich

ORIGINAL ARTICLE

Bimekizumab versus Secukinumab in Plaque Psoriasis

Kristian Reich, M.D., Ph.D., Richard B. Warren, M.D., Ph.D., Mark Lebwohl, M.D., Melinda Gooderham, M.D., Bruce Strober, M.D., Ph.D., Richard G. Langley, M.D., Carle Paul, M.D., Ph.D., Dirk De Cuyper, M.D., Veerle Vanvoorden, M.Sc., Cynthia Madden, M.D., Christopher Cioffi, Ph.D., Luke Peterson, M.S., and Andrew Blauvelt, M.D.

Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial

Kristian Reich, Kim A Papp, Andrew Blauvelt, Richard G Langley, April Armstrong, Richard B Warren, Kenneth B Gordon, Joseph F Merola, Yukari Okubo, Cynthia Madden, Maggie Wang, Christopher Cioffi, Veerle Vanvoorden, Mark Lebwohl

Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial

Kenneth B Gordon, Peter Foley, James G Krueger, Andreas Pinter, Kristian Reich, Ronald Vender, Veerle Vanvoorden, Cynthia Madden, Katy White, Christopher Cioffi, Andrew Blauvelt

HEAD TO HEAD COMPARATOR TRIALS IN PsO

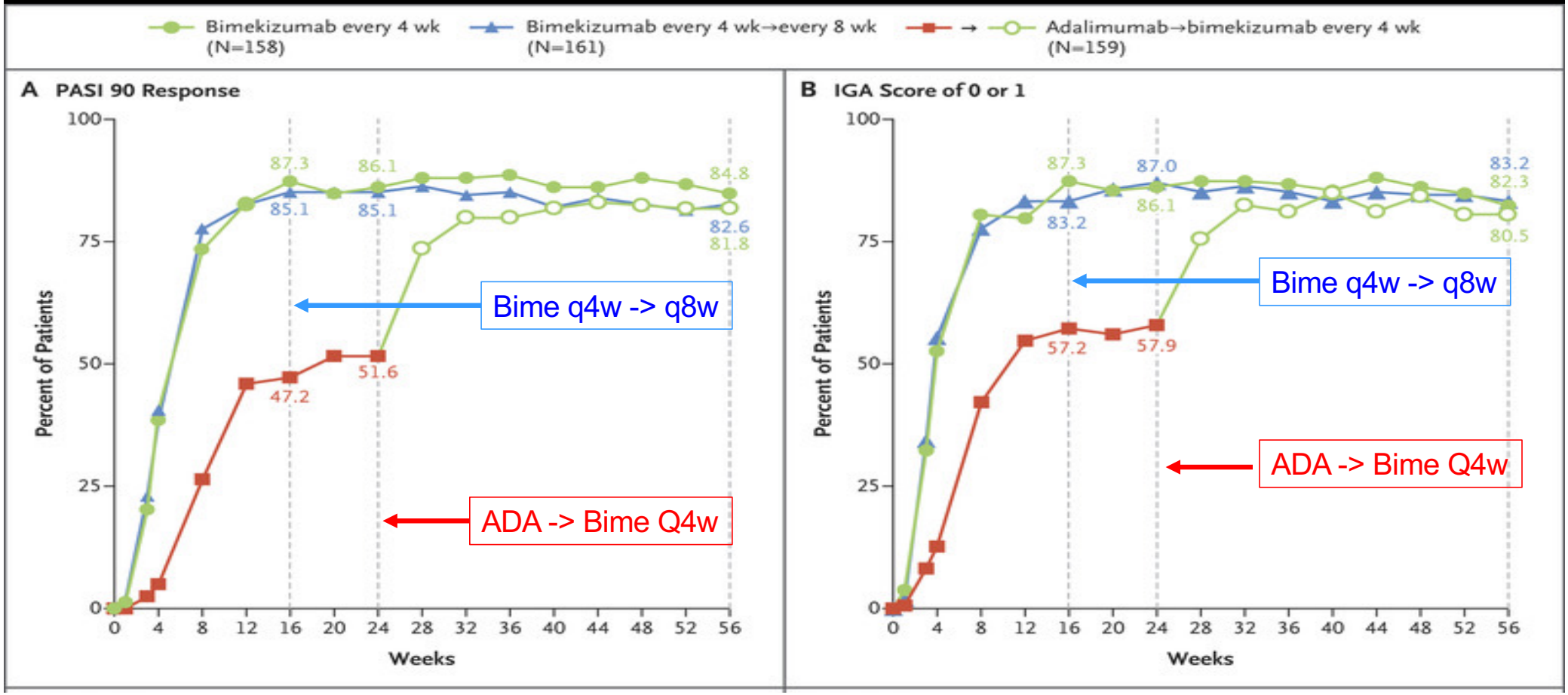
Bimekizumab vs. Adalimumab (TNFi)

Bimkizumab vs Ustekinumab (IL-12/23i)

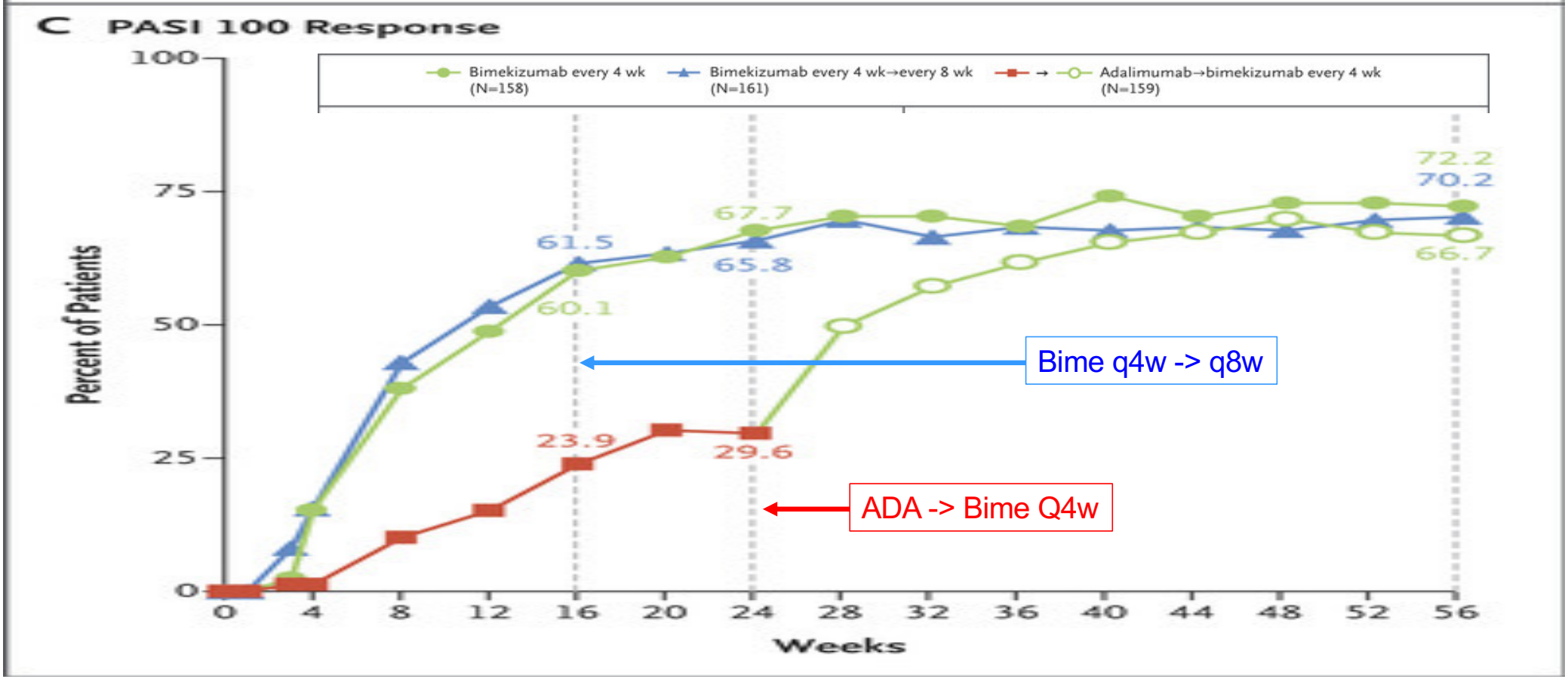
Bimekizumab vs Secukinumab (IL-17-Ai)

Bimekizumab Dose = 320 mg

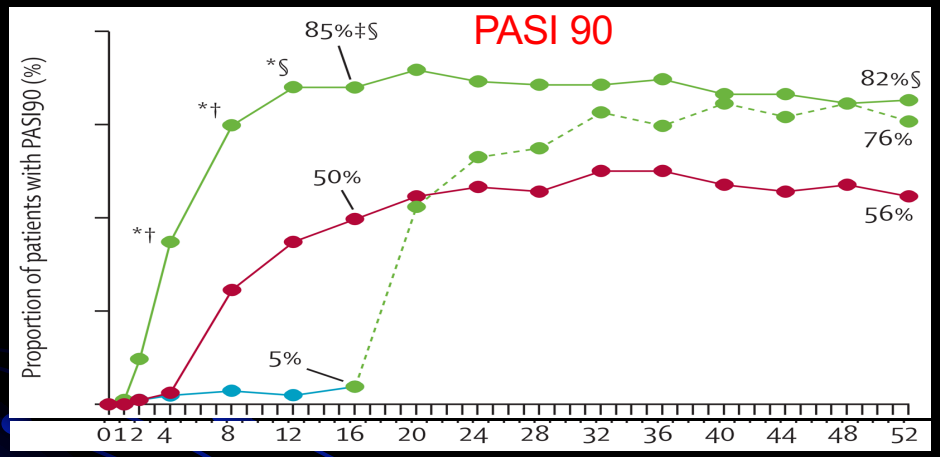
Bimekizumab vs. Adalimumab
PASI 90 and IGA 0/1

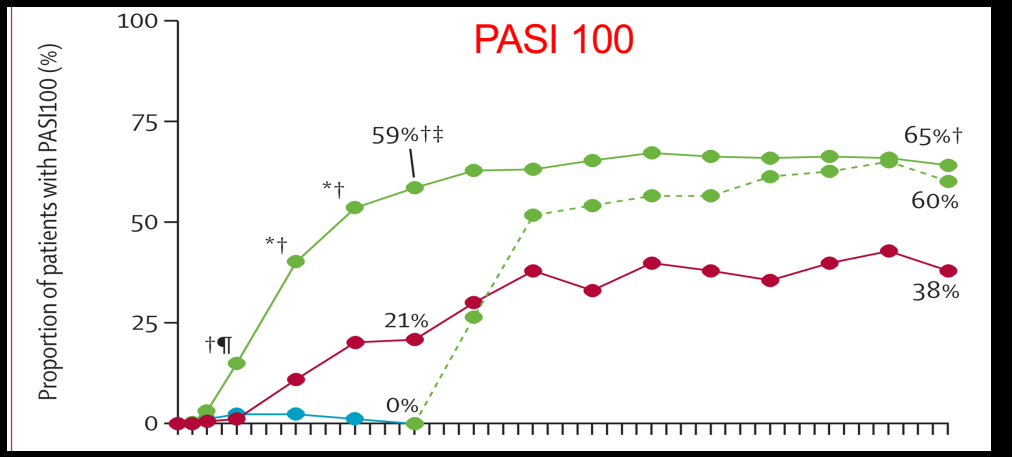


Bimikizumab vs. Adalimumab: PASI 100

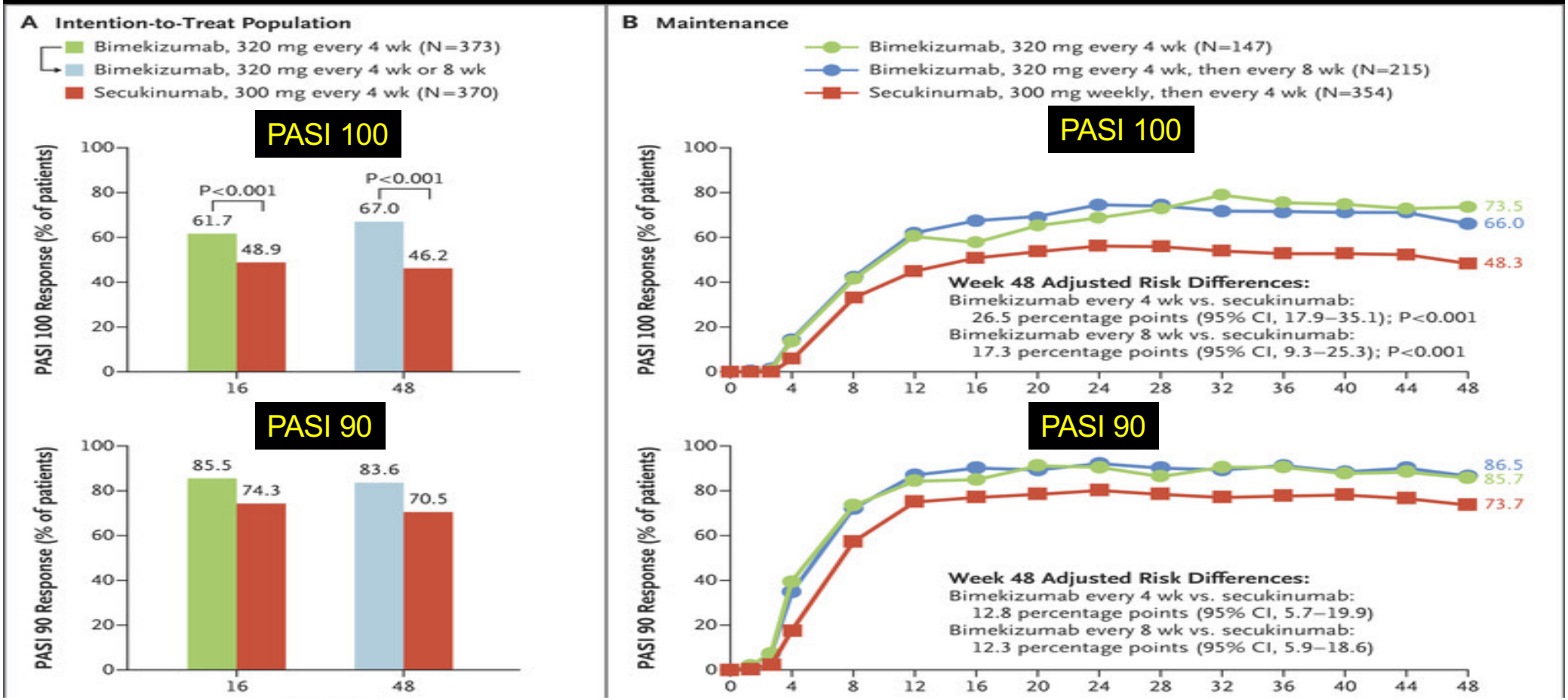


BIMEKIZUMAB VS USTEKINUMAB





Bimekizumab vs Secukinumab: PASI 100 & 90



Candida Signal With Bimekizumab

IL-17 pathway antagonist	%
Bimekizumab	
BE READY (Weeks 16–56)	10.0–15.1
BE VIVID (Weeks 0–52)	18.2
BE SURE (Weeks 24–56)	9.4–14.5
Secukinumab	
ERASURE (Weeks 0–52)	0.8–2.0
FIXTURE (Weeks 0–52)	2.3–4.7
Ixekizumab	
UNCOVER-1/2/3 (Weeks 0–60)	3.4
Brodalumab	
AMAGINE 1 (Weeks 0–52)	2.8
AMAGINE 2 (Weeks 0–52)	4.5
AMAGINE 3 (Weeks 0–52)	5.0

BIME: oral candidiasis seen;
Not vulvo-vaginal due to different immune-protective pathway in vagina vs oral-pharynx

Data slide modified from
B. Strober MD, PhD talk Maui Derm 2022

IL-17 Plays an Important Role in Oral Candidiasis….Less So in Vulvovaginal Candida

- ***Candida*** **hyphal transition (invasive state) triggers an innate immune response at the epithelia, inducing signalling of neutrophil movement to vaginal mucosa via S100A8 alarmin and IL-1β**

Vulvovaginal candidiasis

- ***S100A8 alarmin and IL-1β*** **play a central role in neutrophil recruitment against *Candida* in the vaginal cavity**
- ***IL-17 plays a minor role*** **in vulvovaginal candidiasis**

Oral candidiasis

- ***IL-17 plays a central role*** **in neutrophil recruitment against *Candida* in the oral cavity**
- **Thus, IL-17 inhibition plays a major role in oral candidiasis**

Inhibiting IL-17 with anti-IL-17 therapy predisposes for oral candidiasis, but not vulvovaginal candidiasis, due to different mechanisms of innate cell recruitment at the different anatomical sites

- 1. Willems HME, et al. J. Fungi 2020;6;27–47. 2. Jabra-Rizk MA, et al. Infect Immun 2016;84:2724–2739. 3. Yano J, et al. Infect Immun 2018;86:e00684-17.

Bimekizumab: Approval Delayed…Manufacturing Issue

- **Brussels (Belgium), 13th May 2022 – 08:00 CEST – Regulated Information – Inside Information** – UCB, a global biopharmaceutical company, announced today that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) regarding the Biologics License Application (BLA) for bimekizumab for the treatment of adults with moderate to severe plaque psoriasis.
- The letter indicates that the FDA cannot approve the application in its current form. The CRL states that certain pre-approval inspection observations must be resolved before approval of the application. We are cooperating with the FDA and are working to address these observations as expeditiously as possible.

BIMEKIZUMAB: PsA Data Phase 3

Bimekizumab PsA Dose = 160 mg

Bimekizumab in Patients with Active Psoriatic Arthritis and an Inadequate Response to Tumour Necrosis Factor Inhibitors: 16-Week Efficacy and Safety from BE COMPLETE, a Phase 3, Multicentre, Randomised, Placebo-Controlled Study

Joseph F. Merola,[1] Iain B. McInnes,[2] Christopher Ritchlin,[3] Philip J. Mease,[4] Robert Landewé,[5] Akihiko Asahina,[6] Yoshiya Tanaka,[7] Richard B. Warren,[8] Laure Gossec,[9] Dafna D. Gladman,[10] Frank Behrens,[11] Barbara Ink,[12] Deepak Assudani,[12] Rajan Bajracharya,[12] Jason Coarse,[13] Laura C. Coates[14]

[1]Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK; [3]Department of Medicine, University of Rochester, Rochester, New York, USA; [4]Swedish Medical Center and Providence St. Joseph Health and University of Washington, Seattle, Washington, USA; [5]Amsterdam Rheumatology & Clinical Immunology Center, Amsterdam, and Zuyderland MC, Heerlen, The Netherlands; [6]Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan; [7]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan; [8]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester, UK; [9]Sorbonne Université, Pitié Salpêtrière Hospital, Paris, France; [10]Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Institute of Medical Science, University of Toronto, Ontario, Canada; [11]Rheumatology University Hospital and Fraunhofer Institute for Translational Medicine & Pharmacology ITMP, Goethe University, Frankfurt am Main, Germany; [12]UCB Pharma, Slough, UK; [13]UCB Pharma, Raleigh, North Carolina, USA; [14]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Diseases, University of Oxford and Oxford Biomedical Research Centre, Oxford University Hospitals NHS Trust, Oxford, UK.

EULAR 2022 | Congress | 1–4 June 2022

Presentation number: OP0255

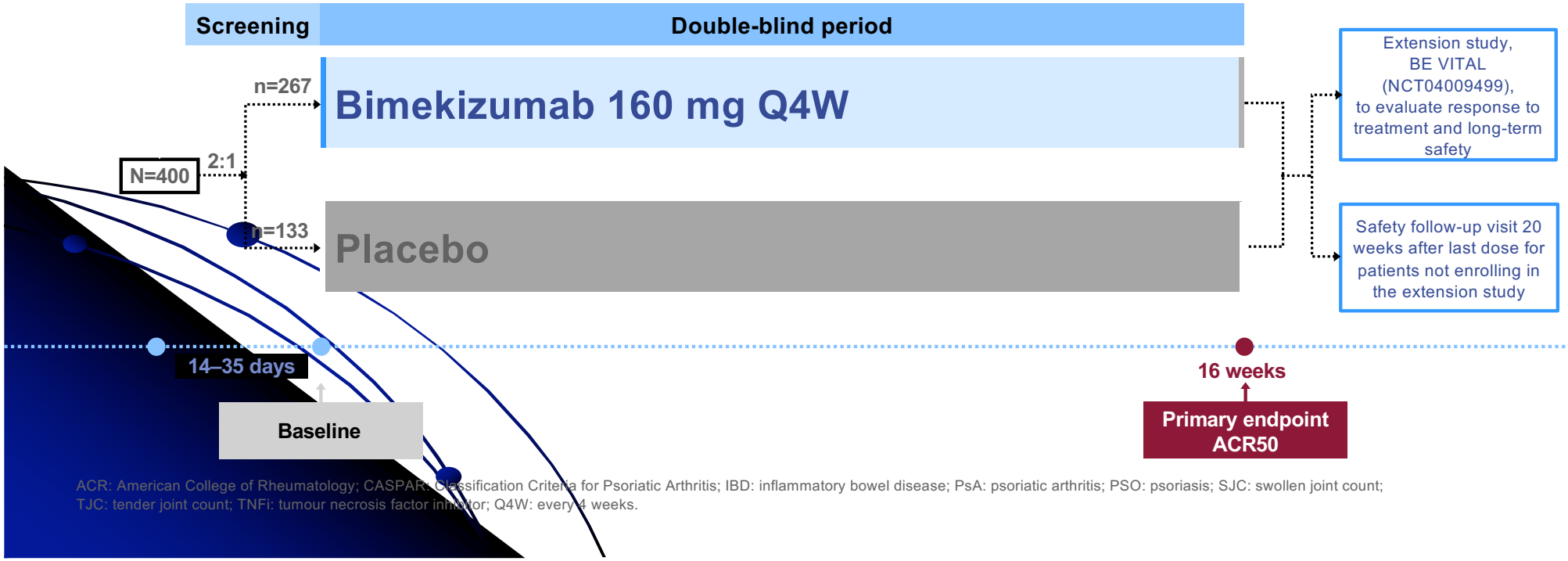
Study Design: BE COMPLETE

Key inclusion criteria

- ✓ Adult-onset PsA fulfilling CASPAR criteria with a duration of ≥6 months
- ✓ TJC ≥3/68 and SJC ≥3/66
- ✓ ≥1 active psoriatic lesions and/or a documented history of PSO
- ✓ Inadequate response or intolerance to 1 or 2 TNFi for either PsA or PSO

Key exclusion criteria

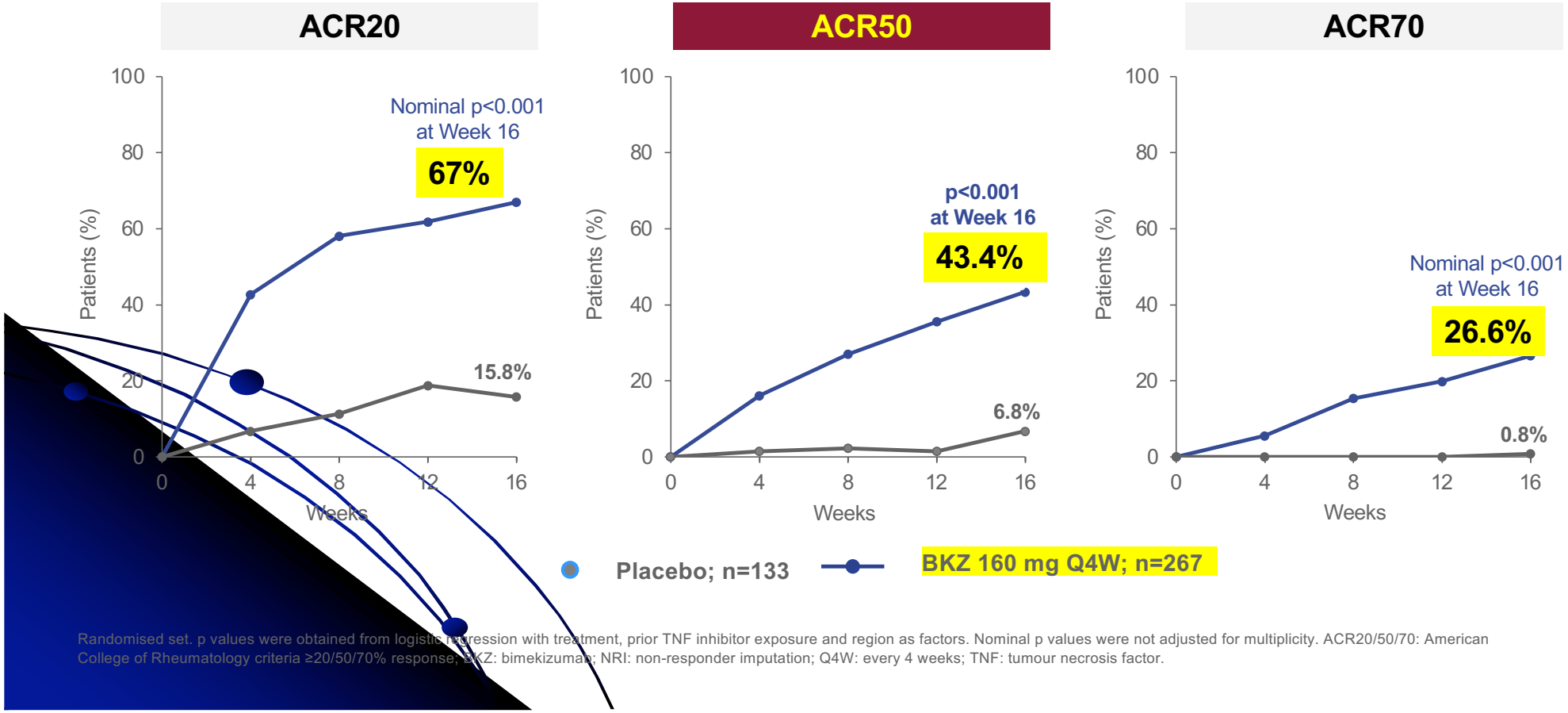
- X Current or prior exposure to any biologics other than TNFi for treatment of PsA or PSO
- X Active, symptomatic IBD at baseline or screening (prior history was not an exclusion criterion)



ACR: American College of Rheumatology; CASPAR: Classification Criteria for Psoriatic Arthritis; IBD: inflammatory bowel disease; PsA: psoriatic arthritis; PSO: psoriasis; SJC: swollen joint count; TJC: tender joint count; TNFi: tumour necrosis factor inhibitor; Q4W: every 4 weeks.

Efficacy: ACR Response Criteria to Week 16 (NRI)

BKZ demonstrated improvements vs placebo in achievement of all ACR response criteria at Week 16



Randomised set. p values were obtained from logistic regression with treatment, prior TNF inhibitor exposure and region as factors. Nominal p values were not adjusted for multiplicity. ACR20/50/70: American College of Rheumatology criteria ≥20/50/70% response; BKZ: bimekizumab; NRI: non-responder imputation; Q4W: every 4 weeks; TNF: tumour necrosis factor.

Bimekizumab in bDMARD-Naïve Patients with Psoriatic Arthritis: 24-Week Efficacy & Safety from BE OPTIMAL, a Phase 3, Multicentre, Randomised, Placebo-Controlled, Active Reference Study (ADALIMUMAB)

Iain B. McInnes,[1] Laura C. Coates,[2] Robert Landewé,[3] Philip J. Mease,[4] Christopher T. Ritchlin,[5] Yoshiya Tanaka,[6] Akihiko Asahina,[7] Laure Gossec,[8] Alice B. Gottlieb,[9] Richard B. Warren,[10] Barbara Ink,[11] Deepak Assudani,[11] Jason Coarse,[12] Rajan Bajracharya,[11] Joseph F. Merola[13]

[1]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK; [2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Diseases, University of Oxford and Oxford Biomedical Research Centre, Oxford University Hospitals NHS Trust, Oxford, UK; [3]Amsterdam Rheumatology & Clinical Immunology Center, Amsterdam, and Zuyderland MC, Heerlen, The Netherlands; [4]Swedish Medical Center and Providence St. Joseph Health and University of Washington, Seattle, Washington, USA; [5]Department of Medicine, University of Rochester, Rochester, New York, USA; [6]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka; [7]Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan; [8]Sorbonne Université, Pitié Salpêtrière Hospital, Paris, France; [9]Department of Dermatology; The Icahn School of Medicine at Mt Sinai, New York, New York, USA; [10]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester, UK; [11]UCB Pharma, Slough, UK; [12]UCB Pharma, Raleigh, North Carolina, USA; [13]Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA.

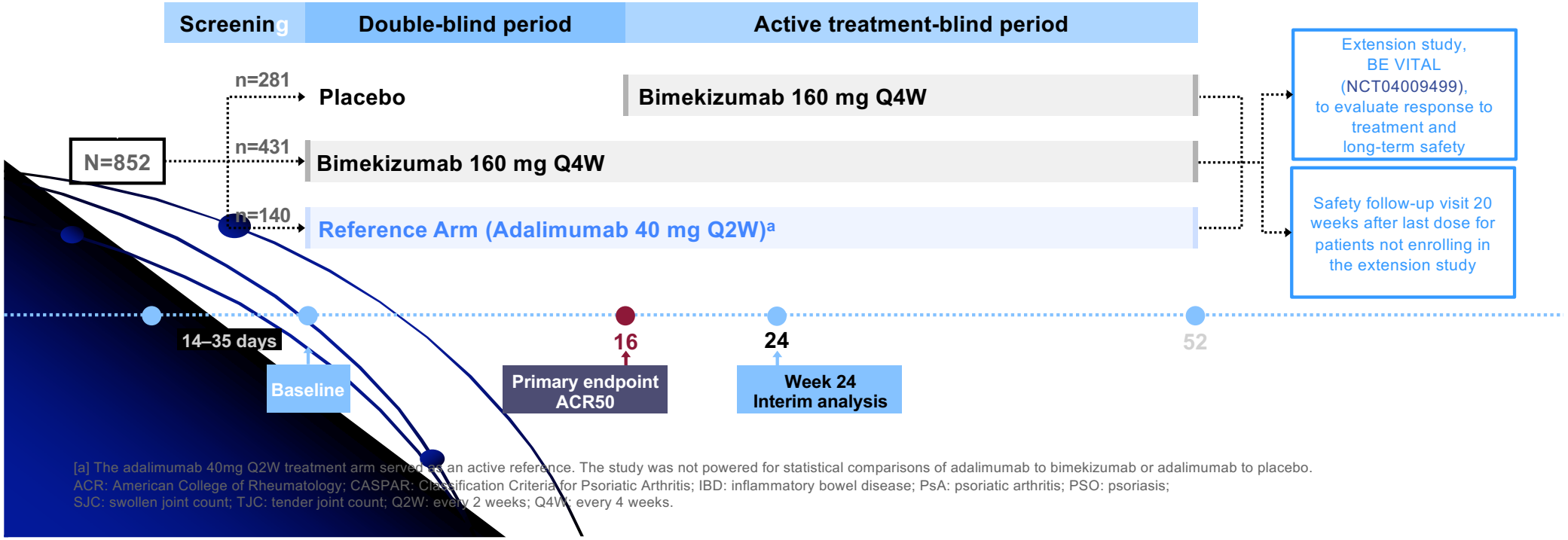
EULAR 2022 | Congress | 1–4 June 2022

Presentation number: LB0001

Study Design: BE OPTIMAL

Key inclusion criteria
- ✓ ≥18 years of age with adult-onset PsA fulfilling CASPAR criteria with a duration of ≥6 months
- ✓ TJC ≥3/68 and SJC ≥3/66
- ✓ ≥1 active psoriatic lesions and/or a documented history of PSO

Key exclusion criteria
- ✗ Current or prior exposure to any biologics for treatment of PsA or PSO
- ✗ Active, symptomatic IBD at baseline or screening (prior history was not an exclusion criterion)

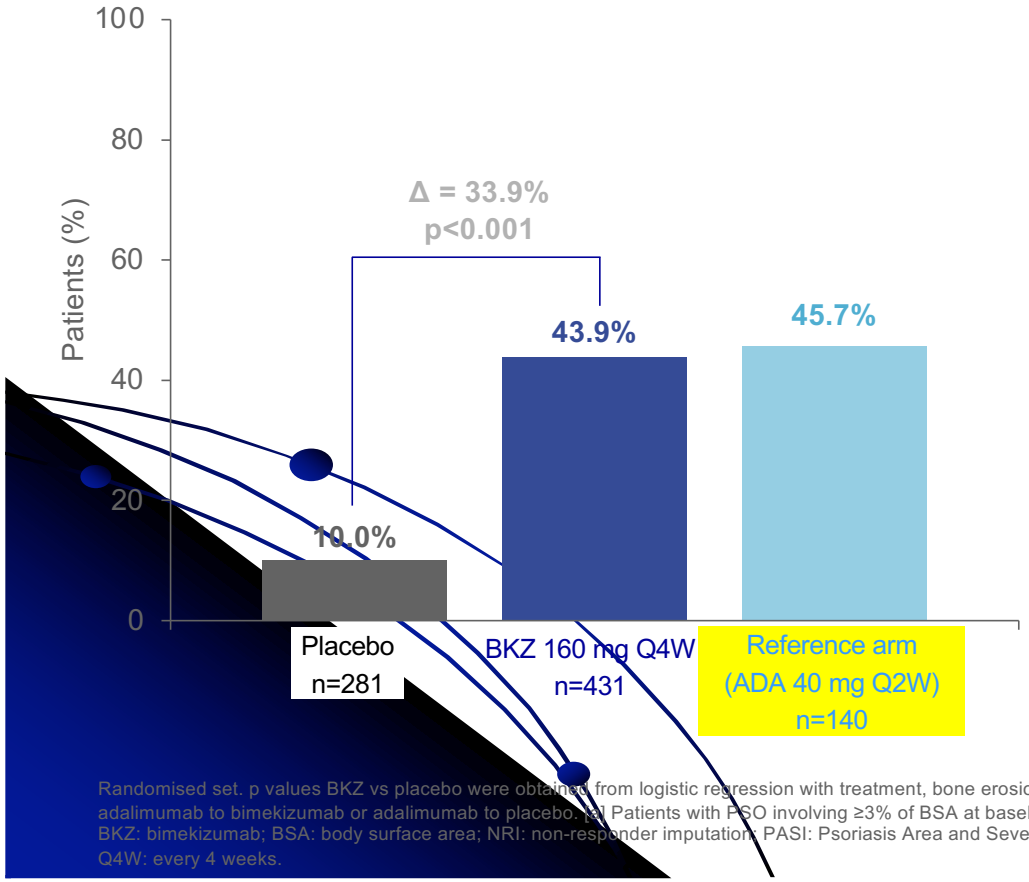


[a] The adalimumab 40mg Q2W treatment arm served as an active reference. The study was not powered for statistical comparisons of adalimumab to bimekizumab or adalimumab to placebo.
ACR: American College of Rheumatology; CASPAR: Classification Criteria for Psoriatic Arthritis; IBD: inflammatory bowel disease; PsA: psoriatic arthritis; PSO: psoriasis; SJC: swollen joint count; TJC: tender joint count; Q2W: every 2 weeks; Q4W: every 4 weeks.

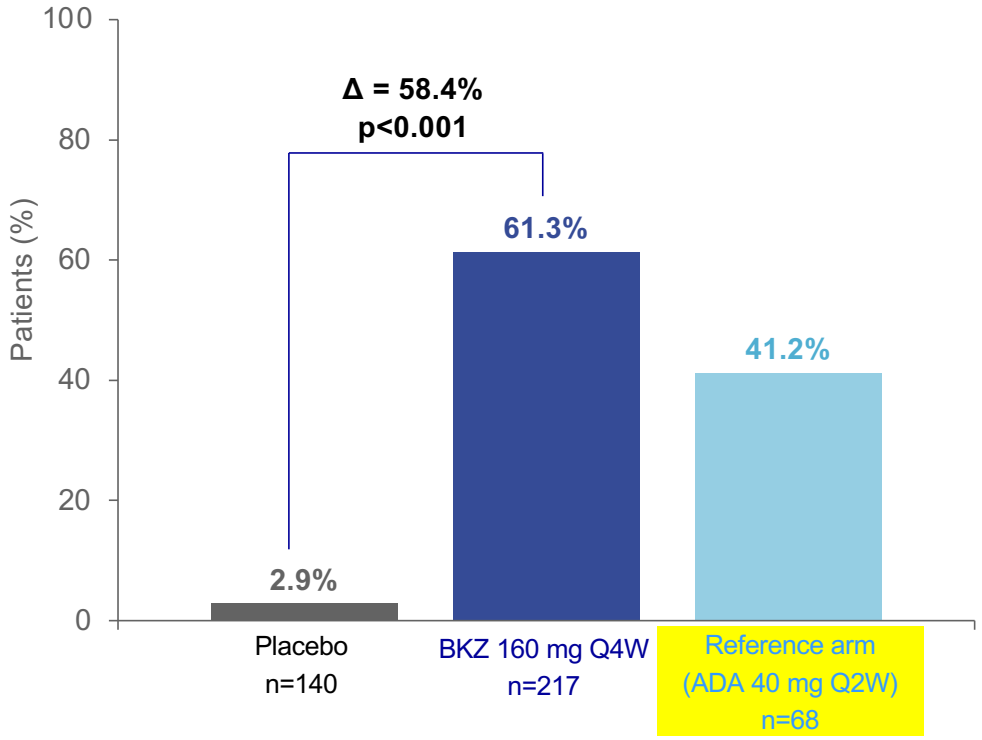
Efficacy: ACR50 and PASI-90 Responses at Week 16 (NRI)

BKZ demonstrated superiority vs placebo in improvements in joint and skin outcomes at Week 16

Primary Endpoint: ACR50



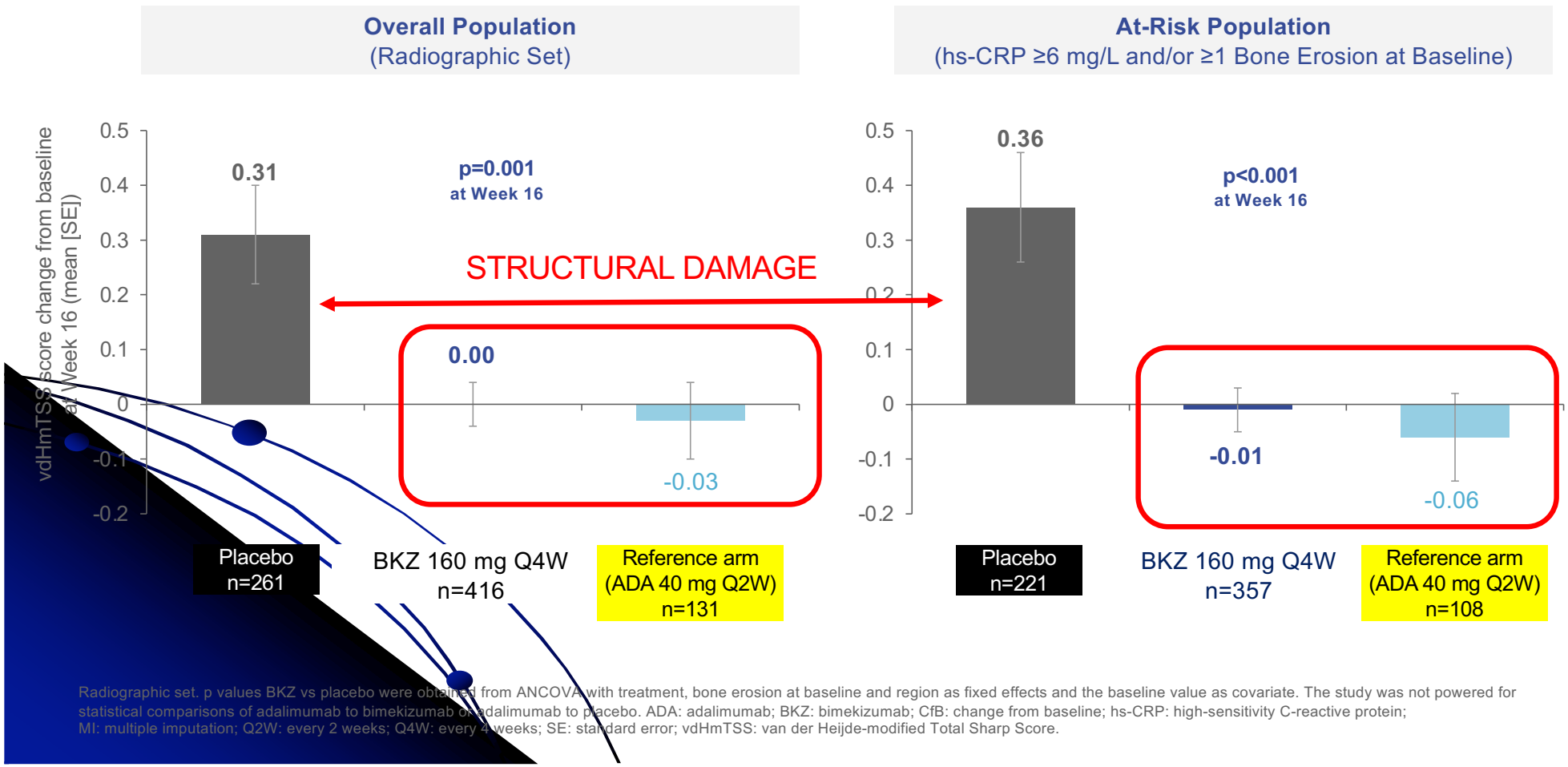
PASI90[a]



Randomised set. p values BKZ vs placebo were obtained from logistic regression with treatment, bone erosion at baseline and region as factors. The study was not powered for statistical comparisons of adalimumab to bimekizumab or adalimumab to placebo. [a] Patients with PSO involving ≥3% of BSA at baseline. ACR50: American College of Rheumatology criteria ≥50% response; ADA: adalimumab; BKZ: bimekizumab; BSA: body surface area; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PASI90: ≥90% improvement in PASI; PSO: psoriasis; Q2W: every 2 weeks; Q4W: every 4 weeks.

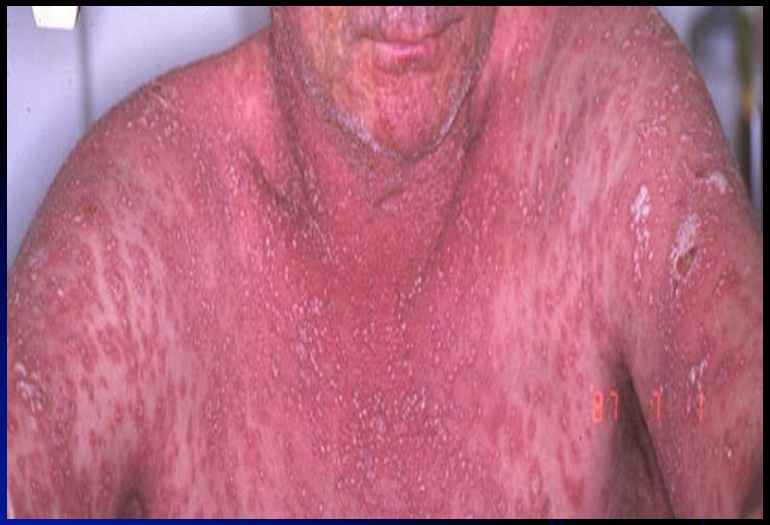
Efficacy: Radiographic Outcomes at Week 16 (MI)

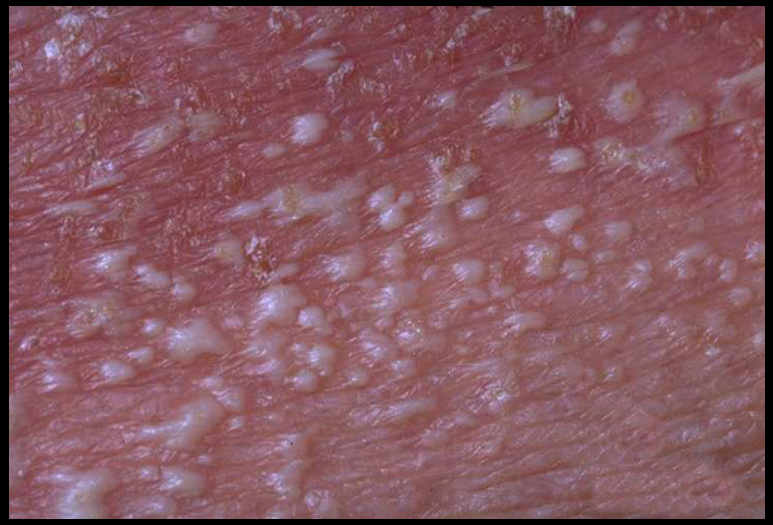
BKZ demonstrated superiority vs placebo in inhibition of structural progression at Week 16



Radiographic set. p values BKZ vs placebo were obtained from ANCOVA with treatment, bone erosion at baseline and region as fixed effects and the baseline value as covariate. The study was not powered for statistical comparisons of adalimumab to bimekizumab or adalimumab to placebo. ADA: adalimumab; BKZ: bimekizumab; CfB: change from baseline; hs-CRP: high-sensitivity C-reactive protein; MI: multiple imputation; Q2W: every 2 weeks; Q4W: every 4 weeks; SE: standard error; vdHmTSS: van der Heijde-modified Total Sharp Score.

SPESOLIMAB (SPEVIGO™):
IL-36Receptor Monoclonal Antibody for the Treatment of Generalized Pustular Psoriasis (GPP)
FDA Approved Sept 2, 2022





H. Bachelez, et al Trial of Spesolimab for GeneralizedPustular PsoriasisN Engl J Med 2021; 385:2431-2440DOI: 10.1056/NEJMoa2111563

SPESOLIMAB for GPP

BACKGROUND: The IL-36 pathway in GPP is supported by:

- Finding of loss-of-function mutations in the interleukin-36 receptor antagonist gene (IL36RN) and associated genes (CARD14, AP1S3, SERPINA3, and MPO)
- Over-expression of interleukin-36 cytokines in GPP skin lesions.

Spesolimab, a humanized anti–interleukin-36 receptor monoclonal antibody

Phase 2 Trial:,multicenter, randomized, double-blind, placebo-controlled trial: examined the efficacy and safety of spesolimab in adults presenting with a moderate-to-severe GPP flare.

Intervention: 53 patients were randomly assigned in a 2:1 ratio to receive either a single 900-mg intravenous dose of spesolimab or placebo.

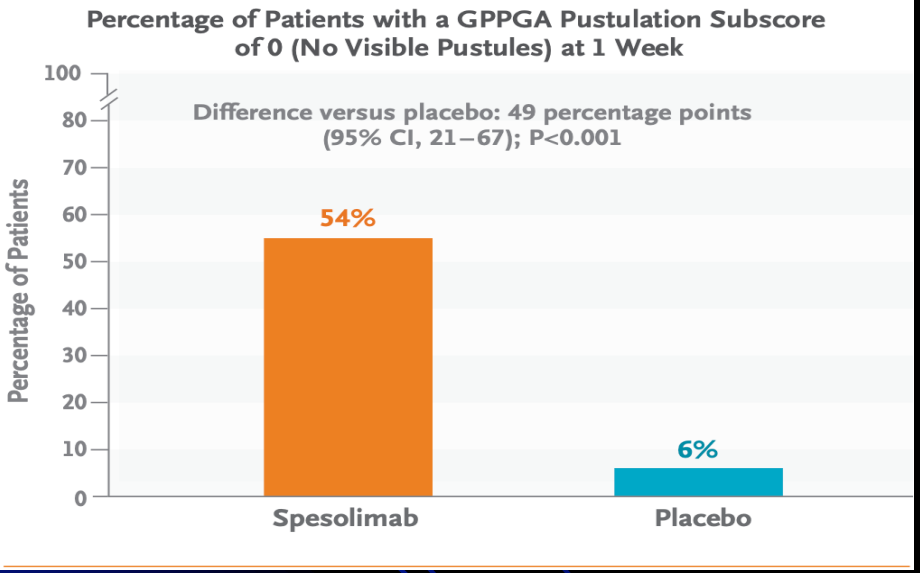
- most patients in the placebo group, were given open-label spesolimab and were followed for 12 weeks

1^0 end point: was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub-score of 0 (range, 0 [no visible pustules] to 4 [severe pustulation]) at the end of week 1.

H. Bachelez, et al Trial of Spesolimab for GeneralizedPustular PsoriasisN Engl J Med 2021; 385:2431-2440DOI: 10.1056/NEJMoa2111563

1⁰ Endpoint and SAEs

Primary End Point



Summary of Adverse Events

Serious Adverse Events at 1 Week	
Spesolimab (N=35)	Placebo (N=18)
6%	0%

Infections at 1 Week	
Spesolimab (N=35)	Placebo (N=18)
17%	6%

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) at 12 Weeks (open-label)
Spesolimab (N=51): 4%
Rate per 100 patient-years, 15.9

GPPGA 0-1: Speso: 15 of 35 patients (43%); Placebo: 2 of 18 patients (11%)

Infections at week 12: Speso: 24 of 51 (47%)

H. Bachelez, et al Trial of Spesolimab for GeneralizedPustular PsoriasisN Engl J Med 2021; 385:2431-2440DOI: 10.1056/NEJMoa2111563

SKIN – GUT (SINTAX*) Therapeutic Approach

*SINTAX: Small Intestinal Axis…..via Mesenteric Lymph Nodes)

EDP1815: Phase 2 Mild-Moderate PsO

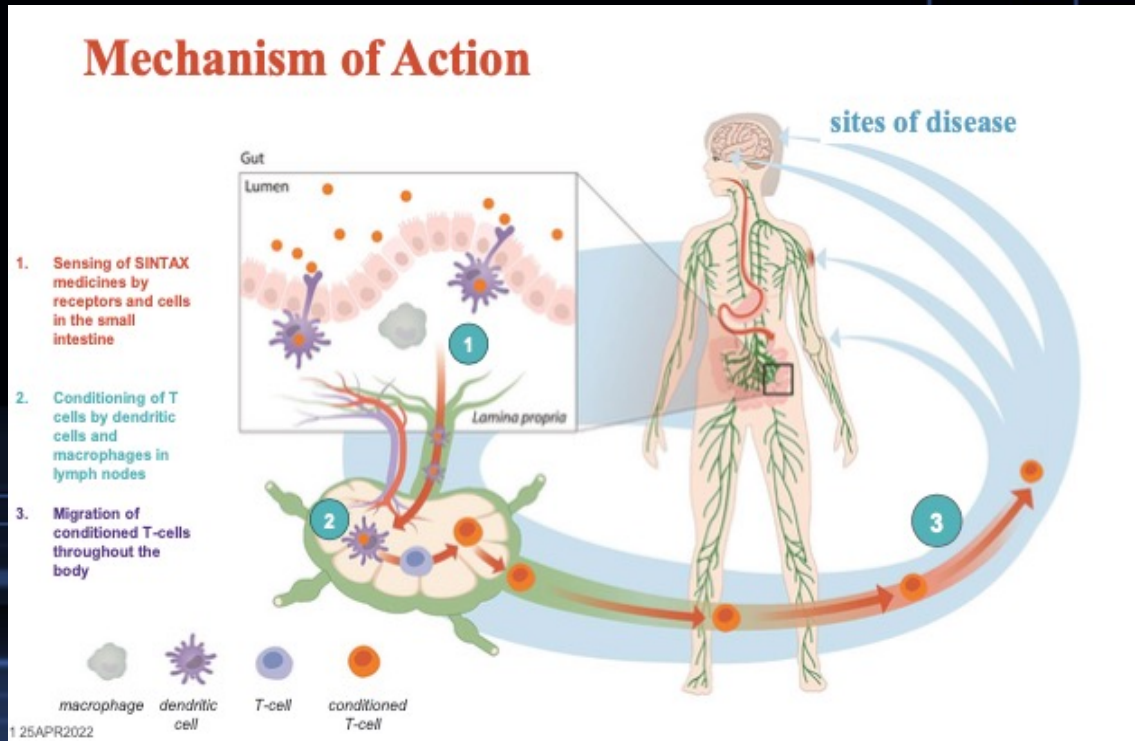
Single strain Prevotella Histicola a small intestine commensal bacteria, non living and harvested from a duodenal biopsy and put into a capsule

No gut colonization or impact on microbiome

3-Step MOA:

1. Impacts gut TLR-2
2. Conditioning of T-cells by dendritic cells and macrophages in the mesenteric lymph nodes
3. Migration of effector CD4+ T-cells throughout the body to sites of inflammation

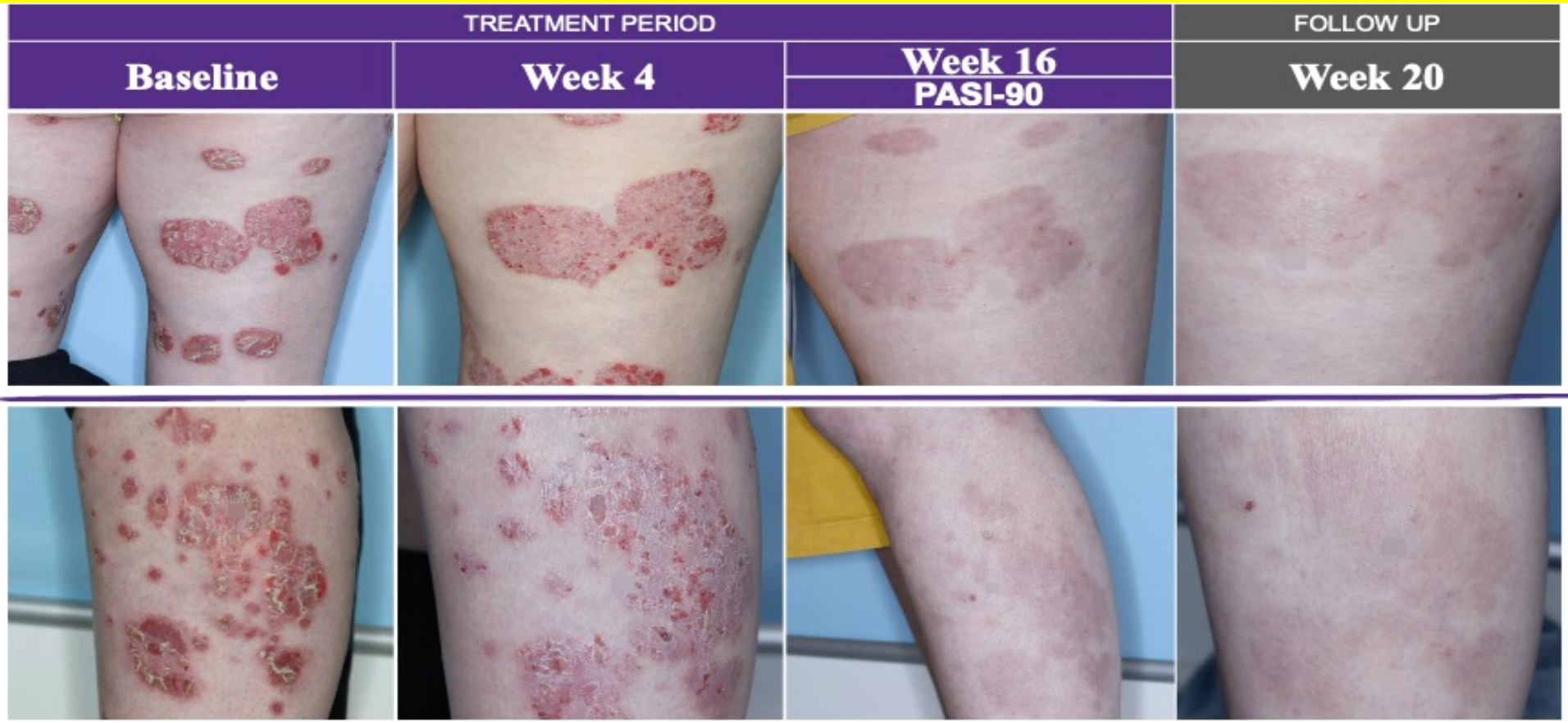
Being studied in PsO and Atopic Dermatitis



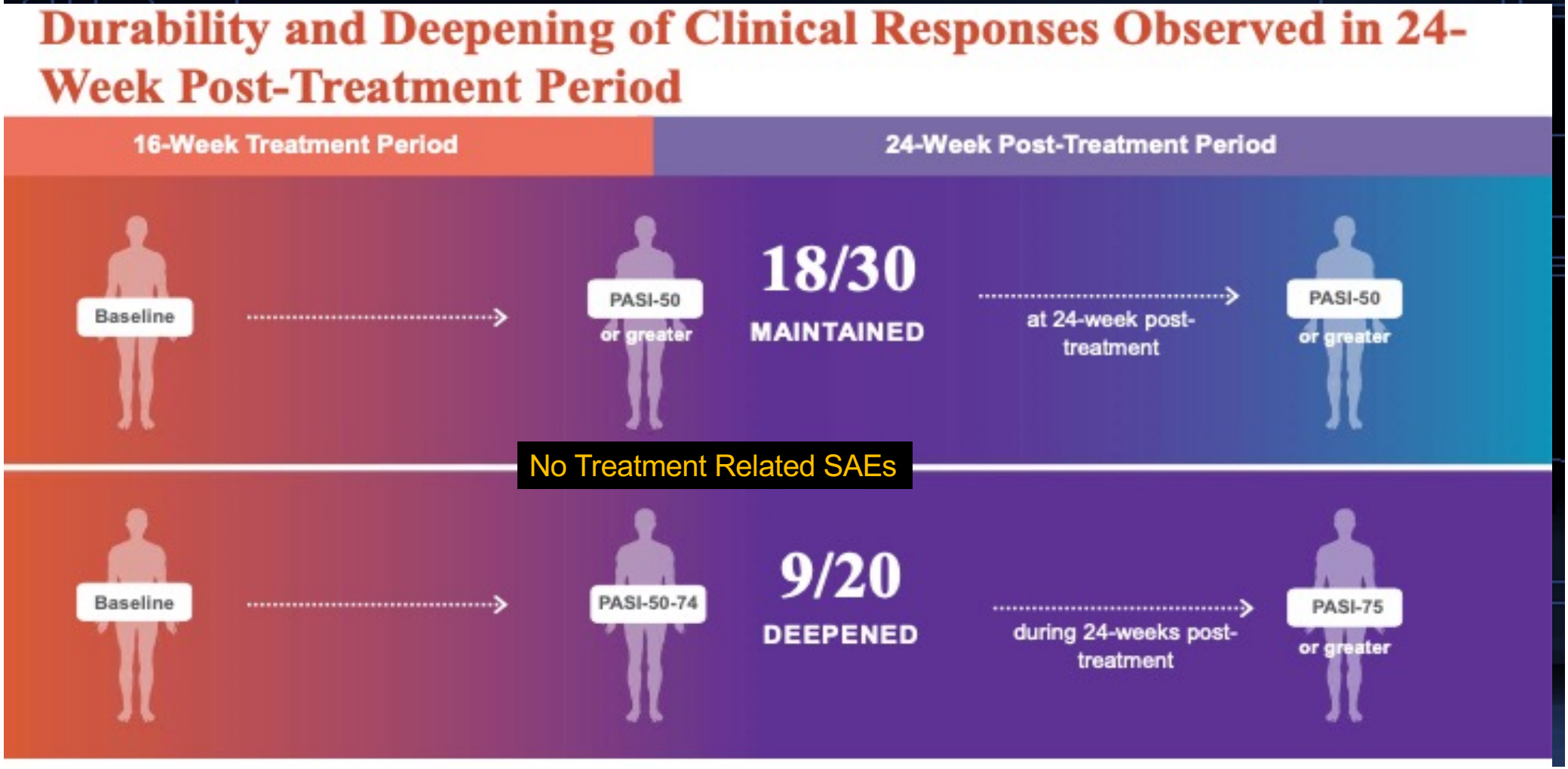
J Exp Med (2006) 203 (3): 497–500. https://doi.org/10.1084/jem.20060227

EDP1815: Phase 2 Mild-Moderate PsO

16-week study; 3 doses of QD EDP1815 in localize PsO (BSA 3-10%)
-25-32% of EDP 1815 pts achieve PASI-50 (12% placebo)
-20% of EDP 1815 pts achieve PGA-0/1 (9% placebo)



EDP: 1815 Phase 2 Durability of Response



Personalized/Precision Medicine in Psoriasis Management

Personalized/Precision Medicine in Psoriasis Management

Correlating RNA to Drug Response is the missing predictive link between a patient's genetic markers and response to different drug classes.

- New patients/switching patients
- Painless, minimally invasive test
- Patch placed on skin for 5 minutes
- RNA is used to evaluate over 7,000 biomarkers per test sample … comparable to a biopsy
- Predicts biologic drug response to better select the best therapy
- Turnaround time for result = 14 days
- ***Commercially available now!***

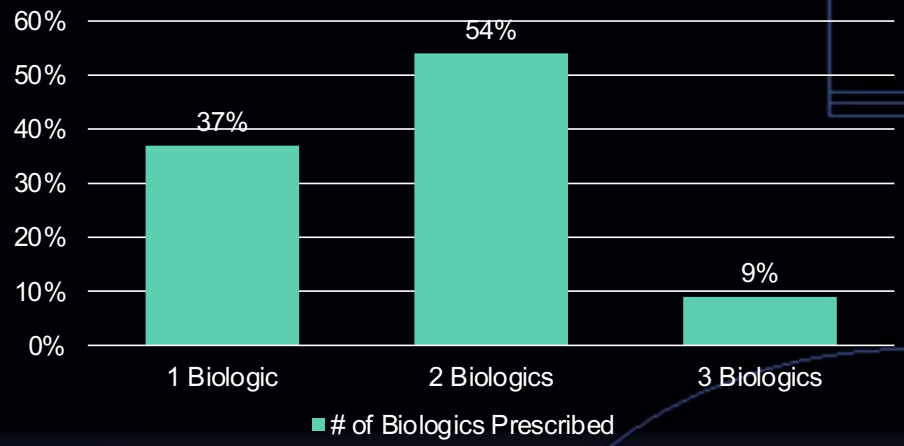
mind.px™

Why Do We Need This Test?

CorEvitas Response Rates[1]

Biologic Class	CorEvitas Response Rates
TNFαi	46.0%
IL-17i	55.9%
IL-23i	50.7%

How many different biologics are typically needed to find the right biologic for the patient to achieve an adequate response?[2]



Prescribing the right biologic the first time = no need to switch.

1. Enos C, O'Connell K, Harrison R, McLean R, Dube B, Van Voorhees A. Psoriasis Severity, Comorbidities, and Treatment Response Differ among Geographic Regions in the United States. *JID Innovations*. 2021;1(2):100025. doi:10.1016/j.xjidi.2021.100025
2. Strober B, Pariser D, Deren-Lewis A, et al. A Survey of Community Dermatologists Reveals the Unnecessary Impact of Trial-and-Error Behavior on the Psoriasis Biologic Treatment Paradigm. *Dermatol Ther (Heidelb)* (2021).

Obtaining The Transcriptome

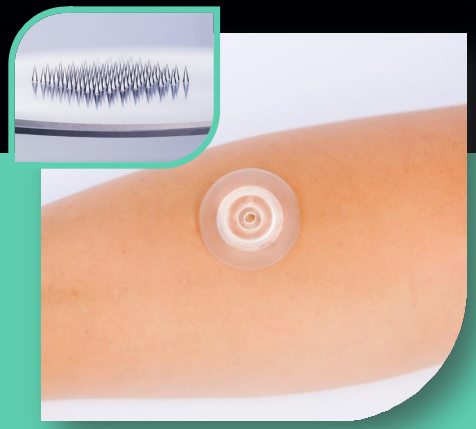
Minimally invasive extraction of transcriptome

High positive predictive value (PPV) for all three biologic classes >92% of the time

Clinically validated, highly actionable STAMP study (n=296)[1]

PPV[1]	Balanced Accuracy[2]
>92%	76%

APPLY

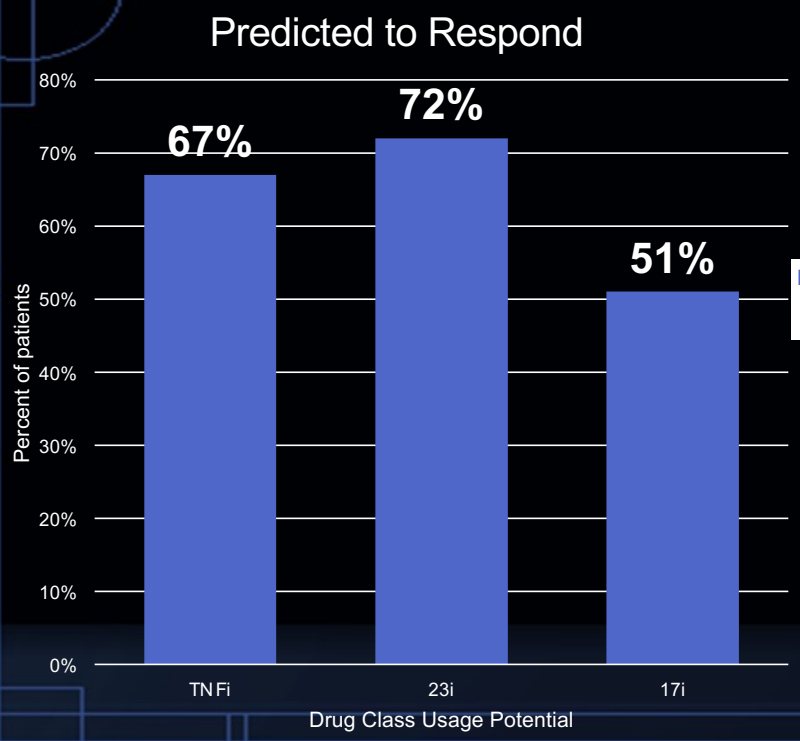


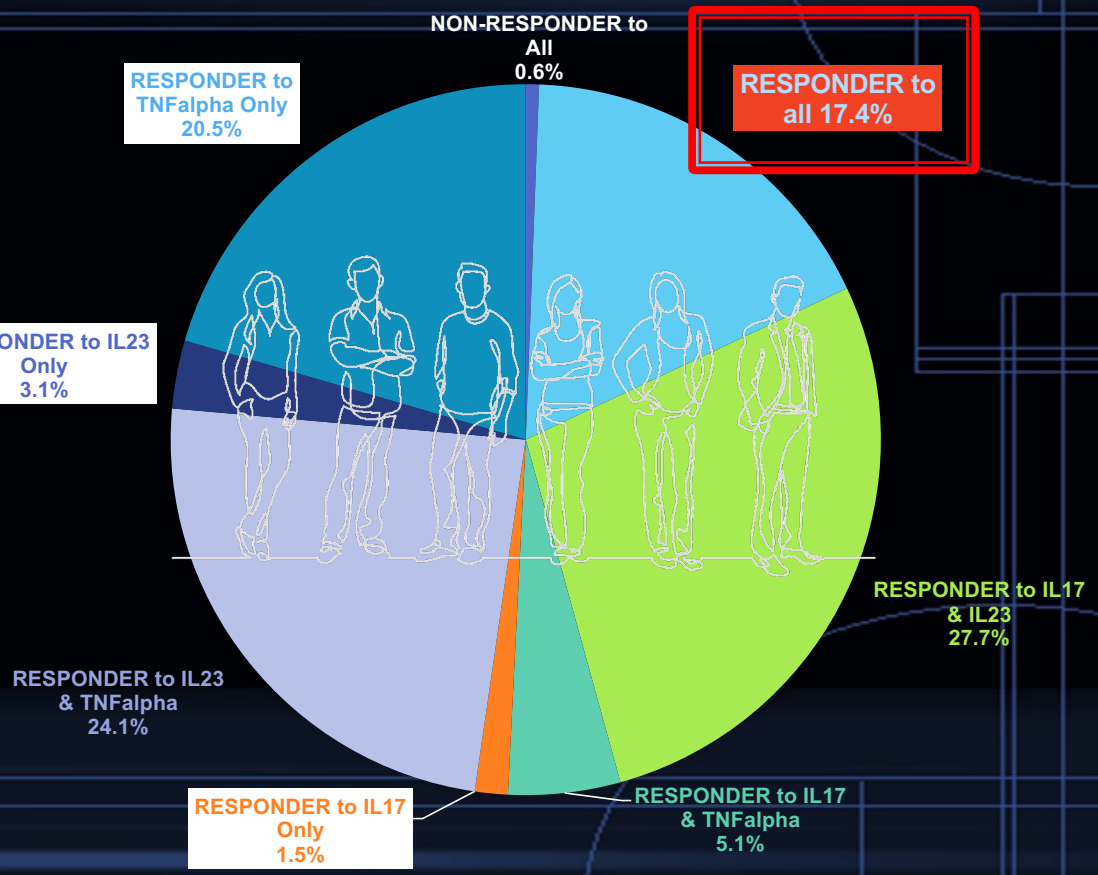
EXTRACT

SEQUENCE & ANALYZE

1. Data on file at Mindera Health. 2. Bagel J, Wang Y, Montgomery III, P, et al. A Machine Learning-Based Test for Predicting Response to Psoriasis Biologics. *SKIN The Journal of Cutaneous Medicine*, 2021;5(6):621-638.

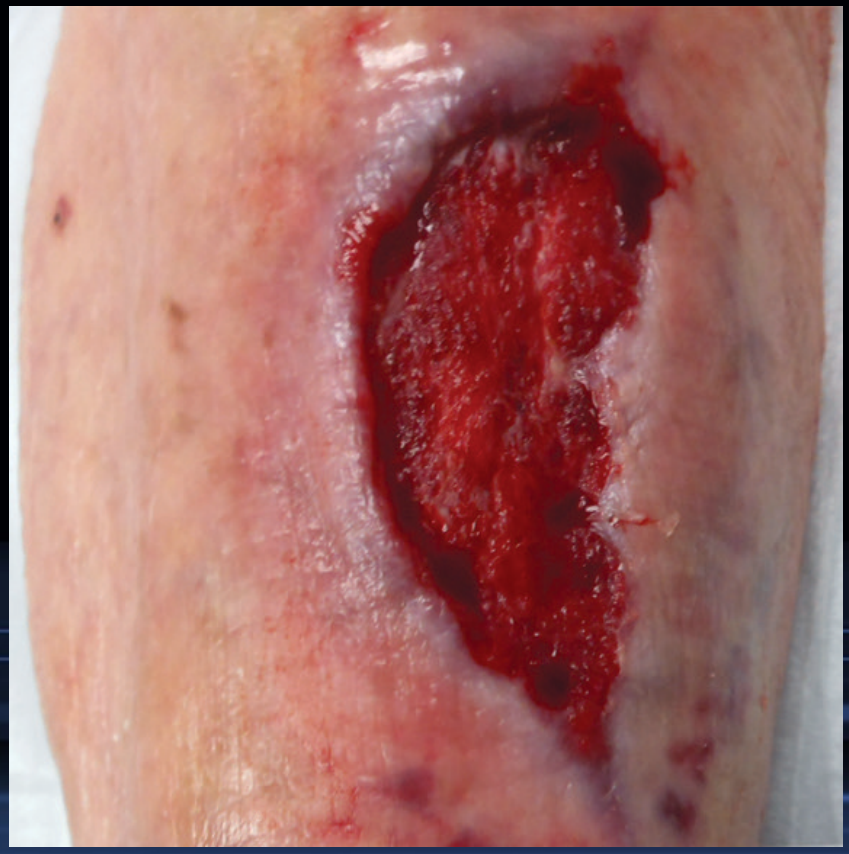
Likely Responses





1. Bagel J, Wang Y, Montgomery III, P, et al. A Machine Learning-Based Test for Predicting Response to Psoriasis Biologics. *SKIN The Journal of Cutaneous Medicine*, 2021;5(6):621-638.

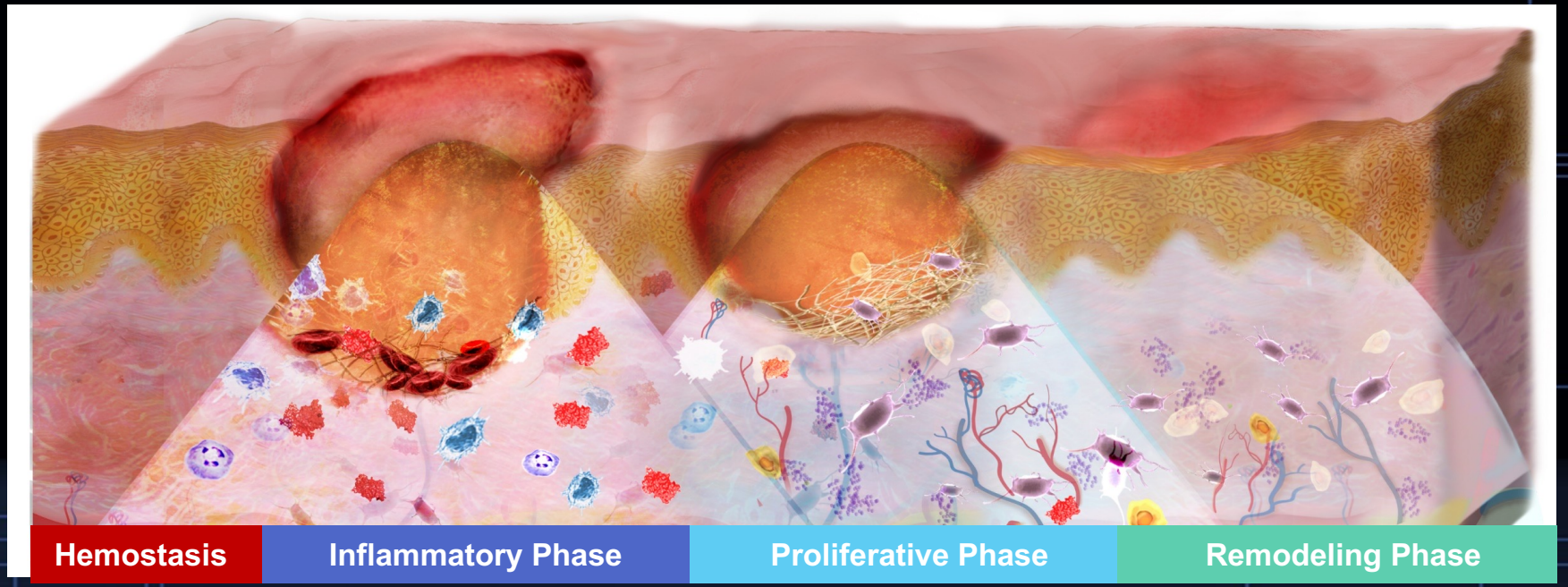
Wounds



What If I Told You It Was Traumatic and On The Leg Of A 93 yo Female

The Acute Wound Healing Process Consists of Four (4) Overlapping Phases[1,2]

Normal wound healing is an orderly, sequential process[1,2]



1. Kane D, Krasner D, eds. *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*. 2nd ed. Wayne, PA: Health Management Publications Inc.; 1997:1-4. 2. Broughton G, et al. *Plast Reconstr Surg*. 2006;117:12S-34S.

3 Products To Assist In Wound Healing In The Dermatology Clinic

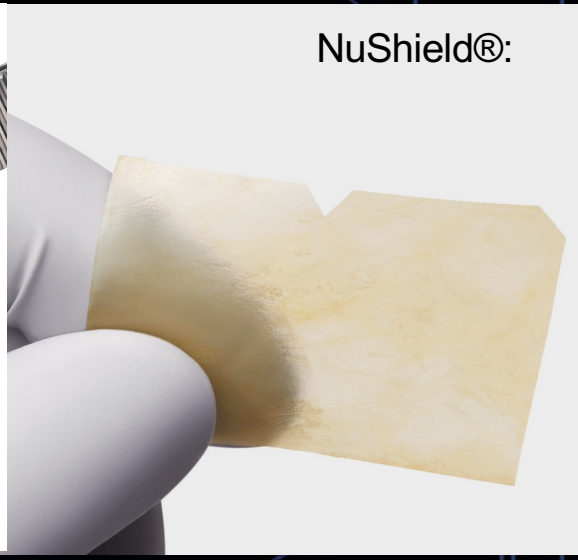
PuraPly® AM:

Provides a sustained antimicrobial barrier effect[1,2]
Controls bioburden and biofilm regrowth[1-3]

Affinity®:

Fresh Amniotic Membrane Wound Covering; Tissue Growth Factors

NuShield®:



A complete dehydrated placental allograft covering

PuraPly® AM: An Advanced Antimicrobial Barrier

PHMB (PolyHexaMethylene Biguanide)

PHMB is a positively-charged polymer that kills bacteria by binding and disrupting negatively-charged cell membranes.

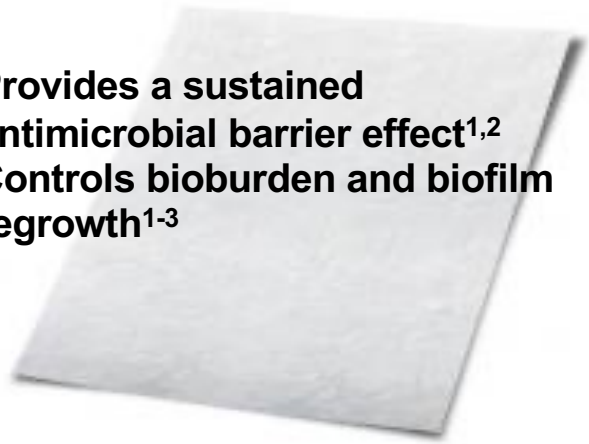
It does not rely on cellular activity, it is effective against quiescent cells within biofilm.

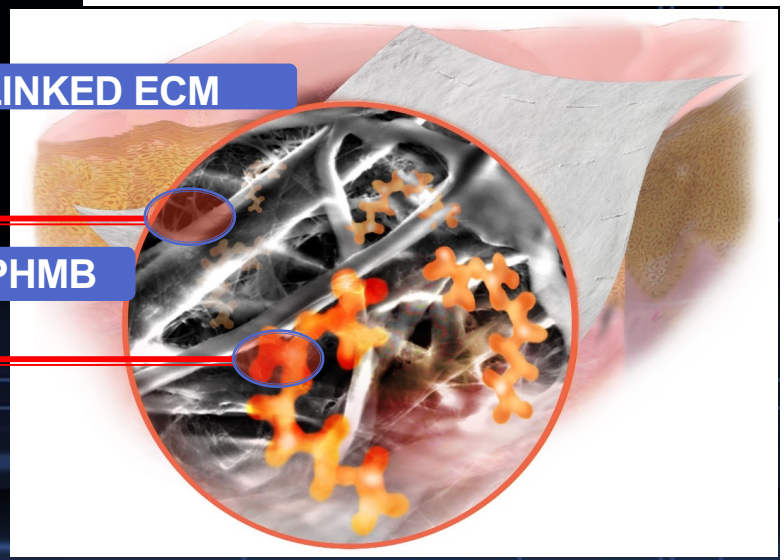
Will not damage key cells (eg, fibroblasts) involved in wound healing[6]

High tissue compatibility and low cytotoxicity[5,7,8]

No known instances of bacteria acquiring resistance[4,5,7,9]

Provides a sustained antimicrobial barrier effect[1,2]
Controls bioburden and biofilm regrowth[1-3]





1. Data on file. PDR-0001. Organogenesis Inc. 2. Data on file. PDR-0002. Organogenesis Inc. 3. PuraPly Antimicrobial [package insert]. Canton, MA: Organogenesis Inc; 2020. 4. Brantley J, et al. Wounds Int. 2016;7(3):1-5. 5. Gilbert P, Moore LE. J Appl Microbiol. 2005;99(4):703-715. 6. Zou SB, et al. Int Wound J. 2013;10(3):306-312. 7. Hubner NO, et al. Skin Pharmacol Physiol. 2010;23(suppl):17-27. 8. Sood A, et al. Adv Wound Care. 2014;3(8):511-529. 9. Sim W, et al. Antibiotics. 2018;7(4):e93.

Properties of Human Amnion and Chorion[1]

Property	Amnion	Chorion
Extracellular matrix (ECM): structural matrix	Collagens I, III, IV, V, VI, elastin	Collagens I, III, IV, V, VI, tropoelastin
ECM: glycoproteins	Fibronectin, laminins, nidogen	Fibronectin, laminins, nidogen
ECM: proteoglycans	Chondroitin, dermatan sulfate, hyaluronan, decorin, biglycan	Chondroitin, dermatan sulfate, hyaluronan, decorin, biglycan, versican, perlican
Selected growth factors*	EGF, HGF, TGF-β1, TGF-β3, bFGF, KGF, NGF, VEGF, PDGF, PIGF, TGF-α	HGF, TGF-β1, TGF-α, bFGF, VEGF, PDGF, PIGF
	Mucin	Interferon α
	Defensins	Defensins
	TIMPS, CTGF, IL-1RA	TIMP-1
	Groα, sICAM, IL-6, IL-8, MCP-1, MIF, serpin E1, SDF-1a, IL-10, IL-4, G-CSF	IL-6, IL-8, IL-4, SDF-1a, IL-10, GCSF

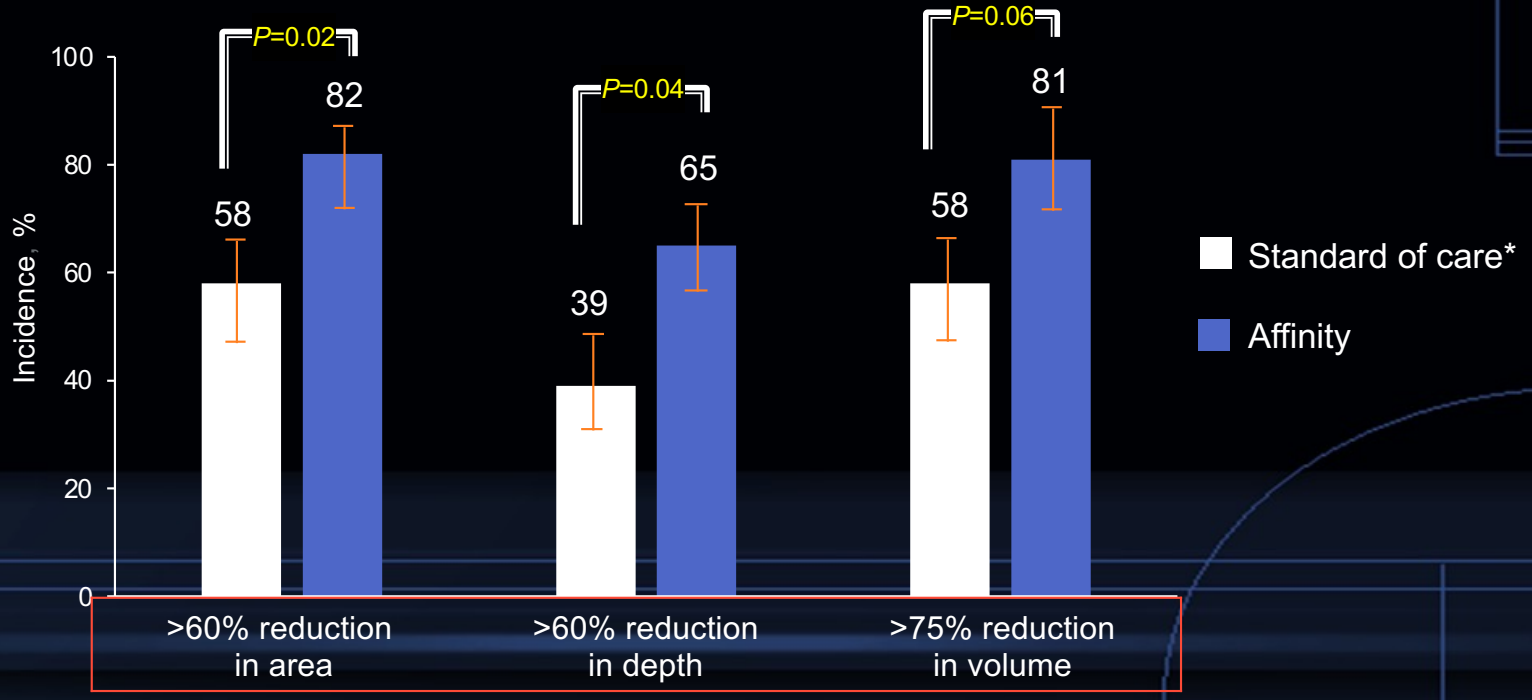
*Most amniotic growth factors are also present in chorion. 1. Table reproduced from Brantley, et al. *Adv Wound Care*. 2015;4(9):545-559.

Fresh Amniotic Membrane Wound Covering: Affinity®

Cytokines	TGF-α	TIMP-1	TIMP-2	IL-1ra	IL-10
Growth factors	aFGF	VEGF	VEGF-D	ANG	ANG-2
	bFGF	EG-VEGF	PDGF-BB	TSP-1	APL4
	EGF	GAL	IGF-II	TGF-β3	PIGF
	HGF	IGF-I	TGF-β1	IGFBP-1	IGFBP-5

More wounds in the Affinity group achieved >60% reduction in area and depth and >75% reduction in volume

Incidence of reduction from baseline in ulcer area, depth, and volume



Note: Affinity is intended for use as a wound covering and barrier.

*Debridement, infection elimination, dressings, and offloading by total contact casting.

Serena TE, et al. *J Comp Eff Res*. 2020;9(1):23-34.

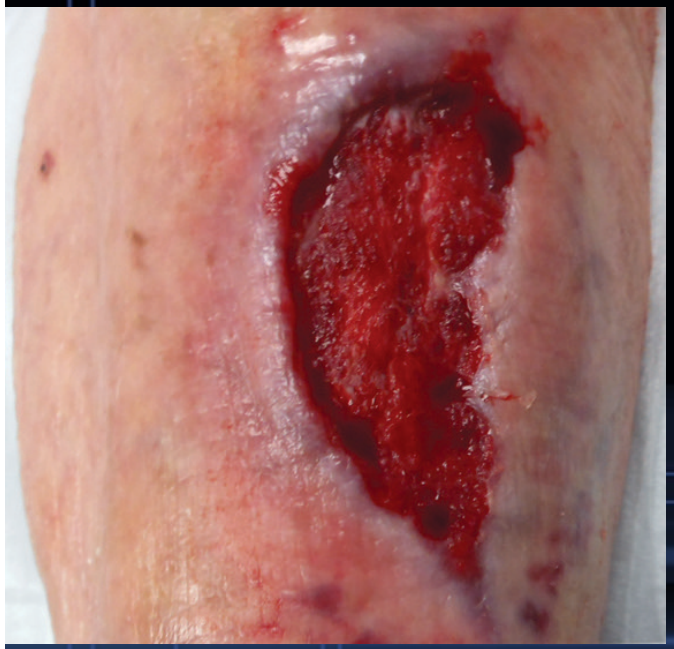
Dehydrated Placental Allograft Covering: NuShield®

- Complete dehydrated placental allograft wound [1-3]
- Convenient “in-office” shelf life
- Retains growth factor/cytokine content
- Analytical testing demonstrated: 640 components (growth factors, cytokines, and chemokines)[1,5]
  ….***unknown how many are bioactive***

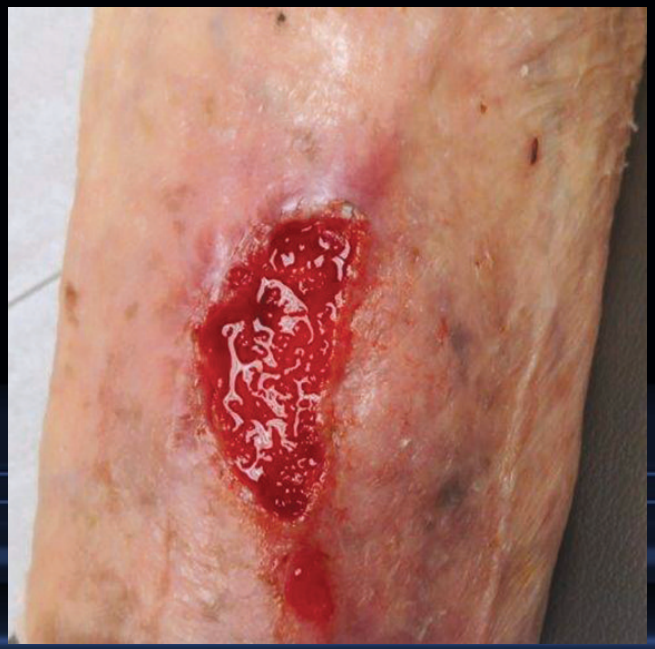
1. McQuilling JP, et al. *Int Wound J*. 2019;16(3):827-840. 2. Niknejad H, et al. *Eur Cells Mater.* 2008;15:88-99. 3. Caporusso J, et al. *Wounds*. 2019;31(4 Suppl):S19-S27. 4. Data on file. Description of BioLoc Process. Organogenesis Inc. 5. McQuilling JP, et al. *Wound Repair Regen*. 2019;27(6):609-621.

NuShield: Case Study Traumatic Wound 93 yo F

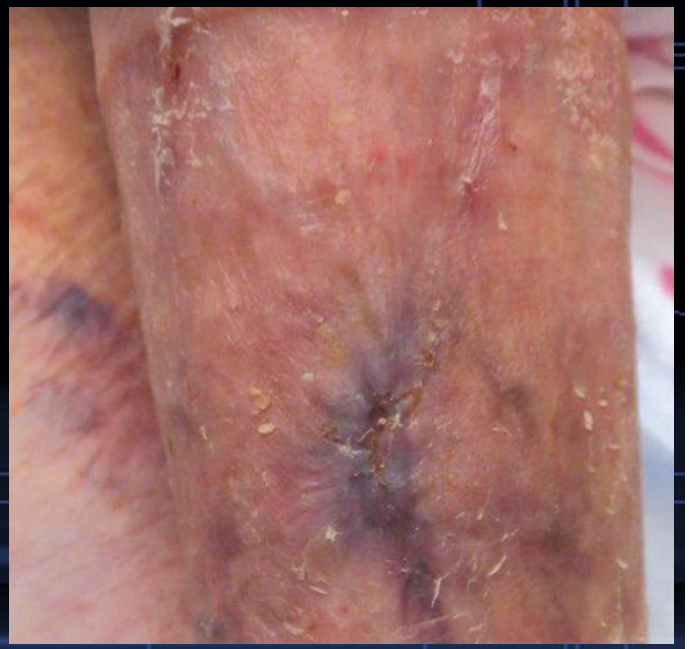
Week 1



Week 5



Week 11



Organogenesis Website: June 5, 2022

Progeria

Progeria

- Limited growth
- Full-body alopecia
- Wrinkled skin
- Kidney failure
- Loss of eyesight
- Atherosclerosis
- Arthritis, osteoporosis Fx
- Scleroderma prevalent
- Distinctive appearance: large head, narrow, wrinkled face, beak nose
- Death in teenage years

- LMNA gene codes for a structural protein called prelamin A
- Prelamin A processed to final form, called lamin A
- Lamin A, Lamin B1, Lamin B2, Lamin C, make up the nuclear lamina: provides shape and stability to the inner nuclear envelope
- Point mutation in LMNA gene leads to abn Lamin A called Progerin

Progeria

- Lonafarnib approved to treat Progeria 11-2020
- Interferes with Progerin synthesis
  - Inhibits farnesyltransferase
- Improves nuclear lamina: Better cellular replication, improved fibroblast function
- Studies demonstrated longer life, lower mortality
- 150mg/m^2 BID (comes as 50mg capsule/$750 per)
- Nausea, vomiting, diarrhea, anorexia, fatigue
- COST: $86,000/month (Most expensive US drug)

NCT00425607 & NCT00916747
JAMA. 2018 Apr 24;319(16):1687-1695
Drugs. 2021;81(2):283-289

Anifrolumab: FDA Approved 8-2-2021

- Human monoclonal antibody, binds to IFN-1 receptor, blocking Type-1 IFN action
- That includes: IFN-alfa, IFN-beta and IFN-kappa
- Most SLE have increased Type-1 IFN signaling
- Approval based primarily on TULIP-2, Phase 3
- 362 uncontrolled SLE; randomized 1:1; received fixed dose 300mg IV Q4w versus placebo Q4w
- Objective improvement by BICLA scale (48%)
- Improvements sustained 3 year; only 7% discontinued
- SQ delivery and Discoid LE trials underway

Arthritis Rheumatol. 2021;73:816-825
N Engl J Med 2020;382:211-221

Fespixon (ON 101) cream

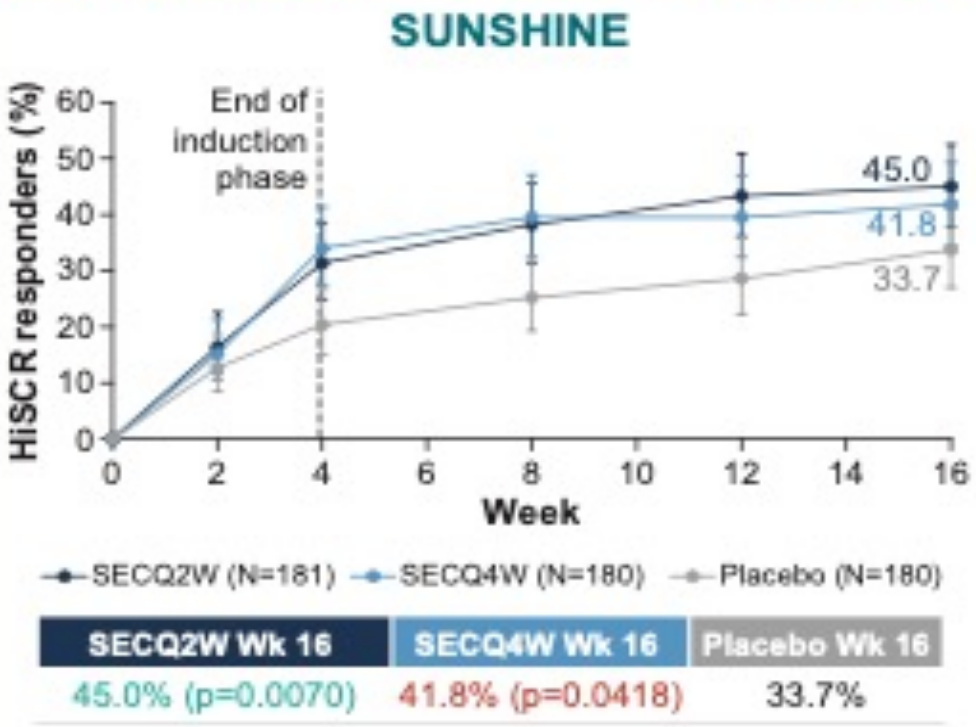
- Diabetic Foot Ulcers; Ph 3 trials[1] FastTrack, out 2023?
- Extracts from plant extracts *Plectranthus amboinicus* and *Centella asiatica* act as Macrophage regulators:
  - M1 proinflammatory and M2 proregenerative
  - Plant extracts balance the ratio to accelerate wound healing
- Small trials, n=54, mean age 57, mean wound 4.8 cm^2
- Apply to wounds b.i.d. with sterile gauze dressing
- Significant wound healing seen in patients
- Approved in Taiwan based on Phase 3 Internatl study[2]

1. https://clinicaltrials.gov/ct2/show/NCT01898923
2. JAMA Netw Open. 2021 Sep 1;4(9):e2122607. doi: 10.1001/jamanetworkopen.2021.22607.

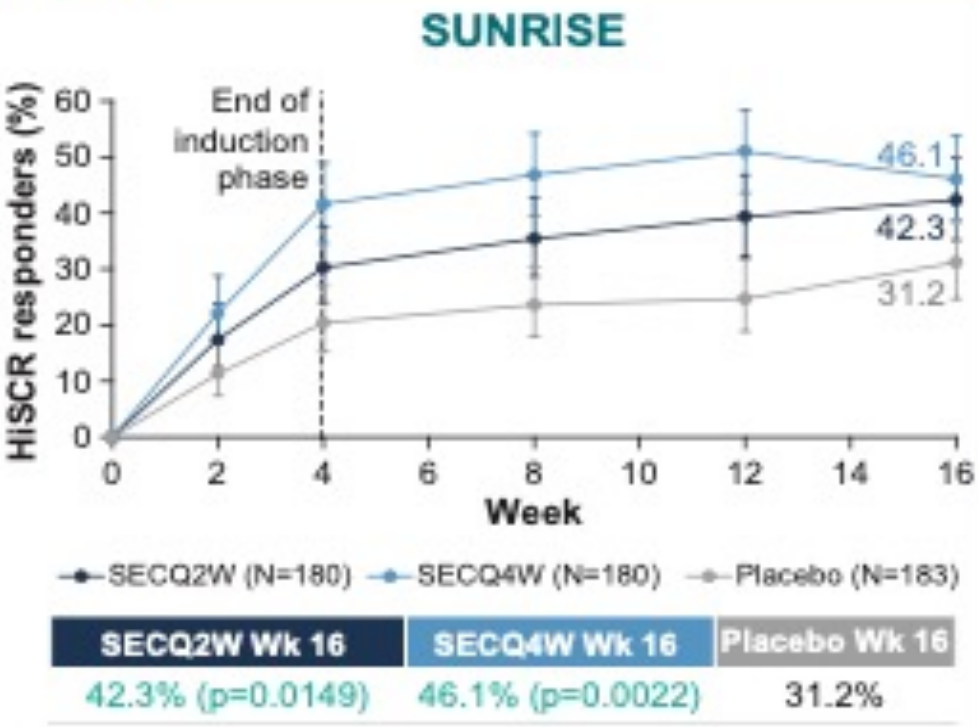

OPTIMISM

Secukinumab in Hidradenitis

Figure 2. Primary Efficacy Endpoint: HiSCR up to Week 16



SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
45.0% (p=0.0070)	41.8% (p=0.0418)	33.7%



SECQ2W Wk 16	SECQ4W Wk 16	Placebo Wk 16
42.3% (p=0.0149)	46.1% (p=0.0022)	31.2%

One-sided nominal p-values are based on a logistic regression model, the primary estimand, and multiple imputation. Error bars represent 95% CI.
Green represents statistical significance and red represents non-significance compared with placebo.
CI, confidence intervals; HiSCR, hidradenitis suppurativa clinical response; N, number of patients in group; Q2W, every two weeks; Q4W, every four weeks; SEC, secukinumab 300 mg; Wk, week.

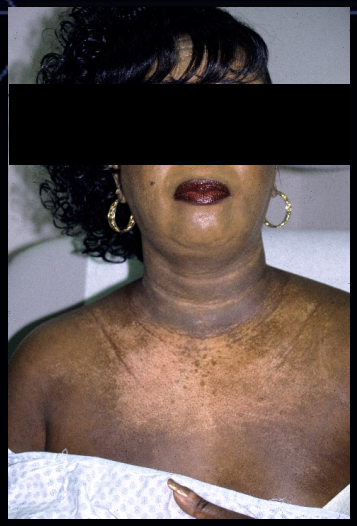
Arbovirus Vaccines

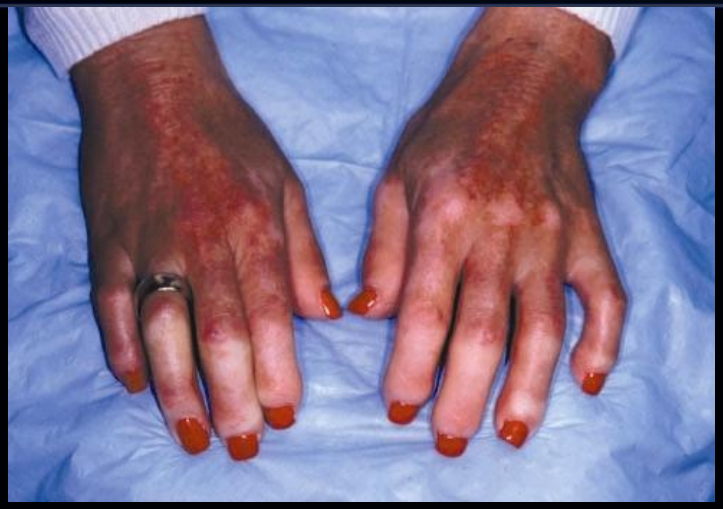
- **Entering Phase III: Zika**
- Two DNA
- Two mRNA
- Whole inactivated virus
- Live attenuated virus

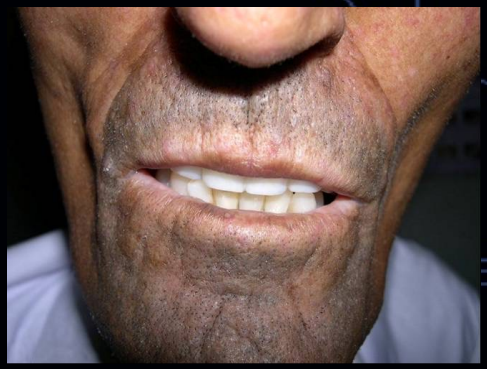
- **Entering Phase III: Chikungunya**
- VLP subunit
- Live attenuated virus

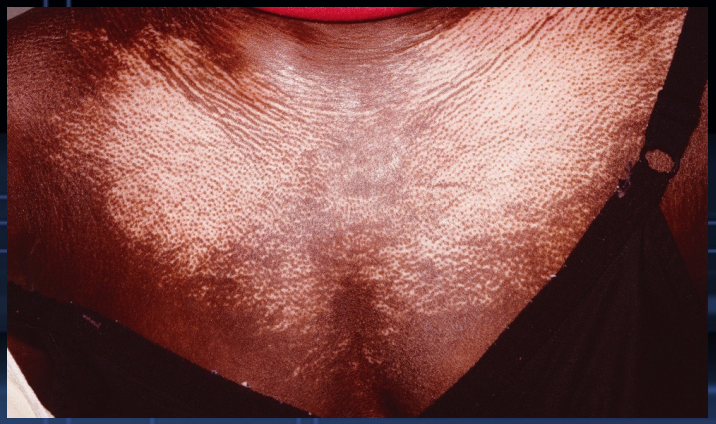
Hum Vaccin Immunother. 2020 Aug 11;1-5. doi: 10.1080/21645515.2020.1796428
JAMA. 2020;323(14):1369-1377

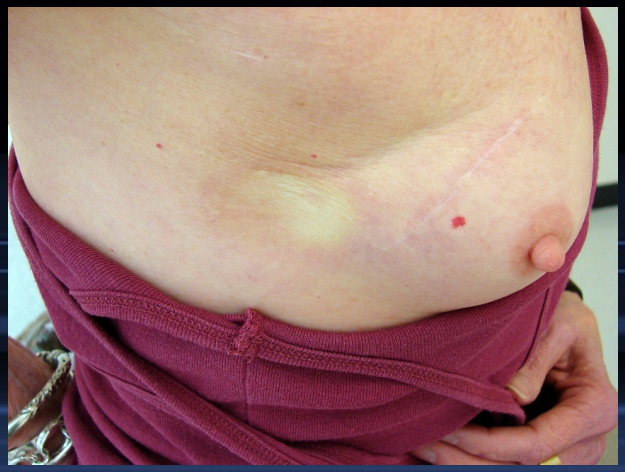
No Really Great Options

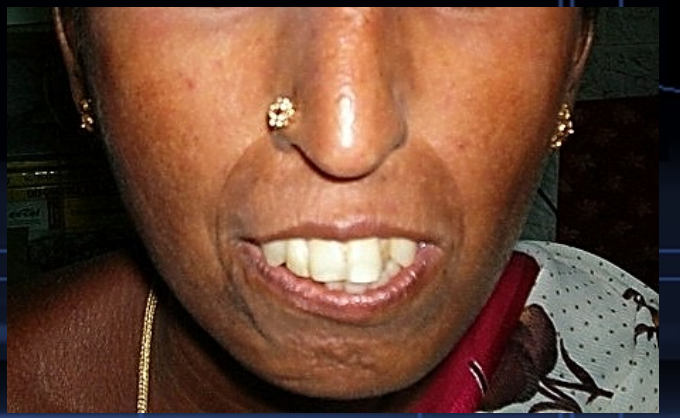












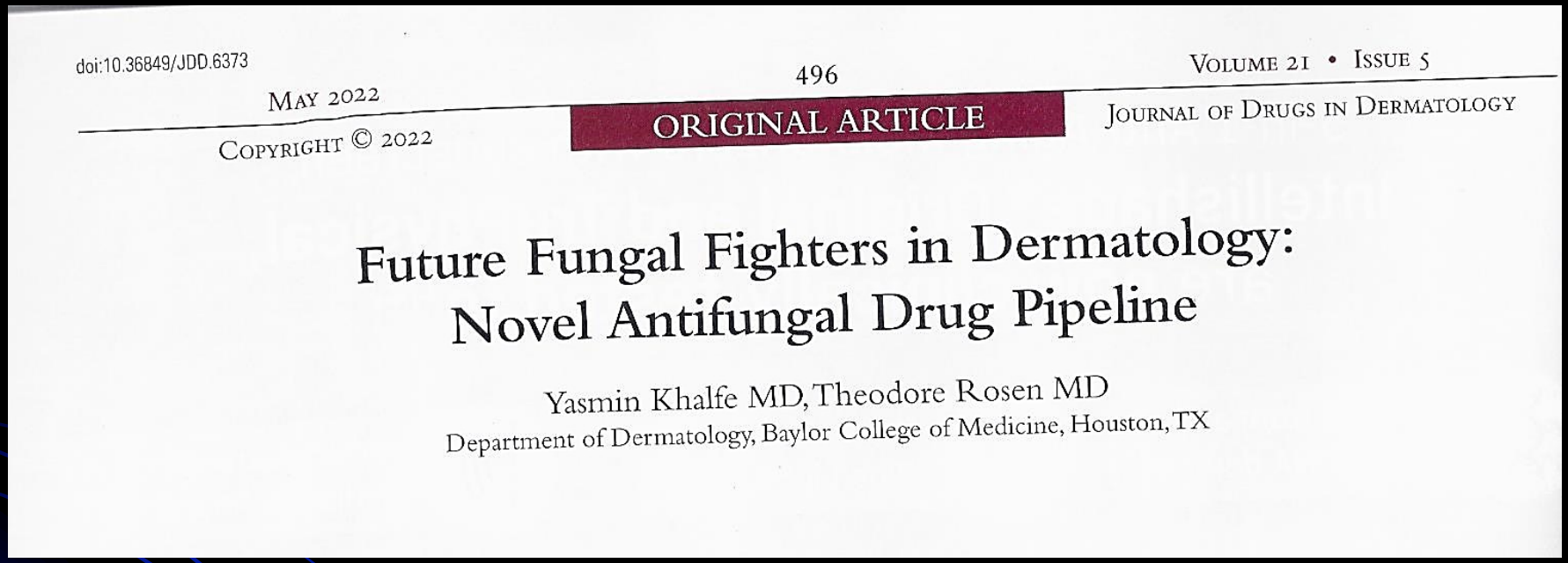
Scleroderma (Systemic and Localized)

Drug	Mechanism of Action	Given	Phase
Vasculan (Ifetroban)	Thromboxan A2 Receptor Antagonist	PO	2a (SSc)
HZN-825 (SAR100842)	Lysophosphtidic Acid Receptor 1 Antagonist	PO	2a (done); 2b (SSc)
CM-101	Chemokine CCL24 Inhibitor	IV	Preclinical (SSc)
Cannabidiol EHP-101	Cannabinoid Type 2 receptor agonist Hypoxia-inducible factor pathway	PO	2a (SSc)
FCX-013 + Veledimex	Genetically modified fibroblasts + stimulator of MMP-1	Intradermal	1/2a (Morphea)
TLY012	TNF-related apoptosis-inducing ligand Binds to fibroblast death receptor DR5	IV	1/2a later in 2021 (SSc)

Dermatology Drugs

- Recent meaningful additions...NOT just “me too”
- Rich and varied pipeline…topical and systemic
- The future is bright: New drug classes in many categories, some of which we didn’t even talk about

New Antifungals: Read This Paper!



doi:10.36849/JDD.6373

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ORIGINAL ARTICLE

JOURNAL OF DRUGS IN DERMATOLOGY

Future Fungal Fighters in Dermatology: Novel Antifungal Drug Pipeline

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