IV EDICIÓN
INMUNOTERAPIA EN DERMATOLOGÍA

30 de marzo de 2023.
Recinte Modernista Sant Pau

Alopecia areata. Realidades y expectativas 2023

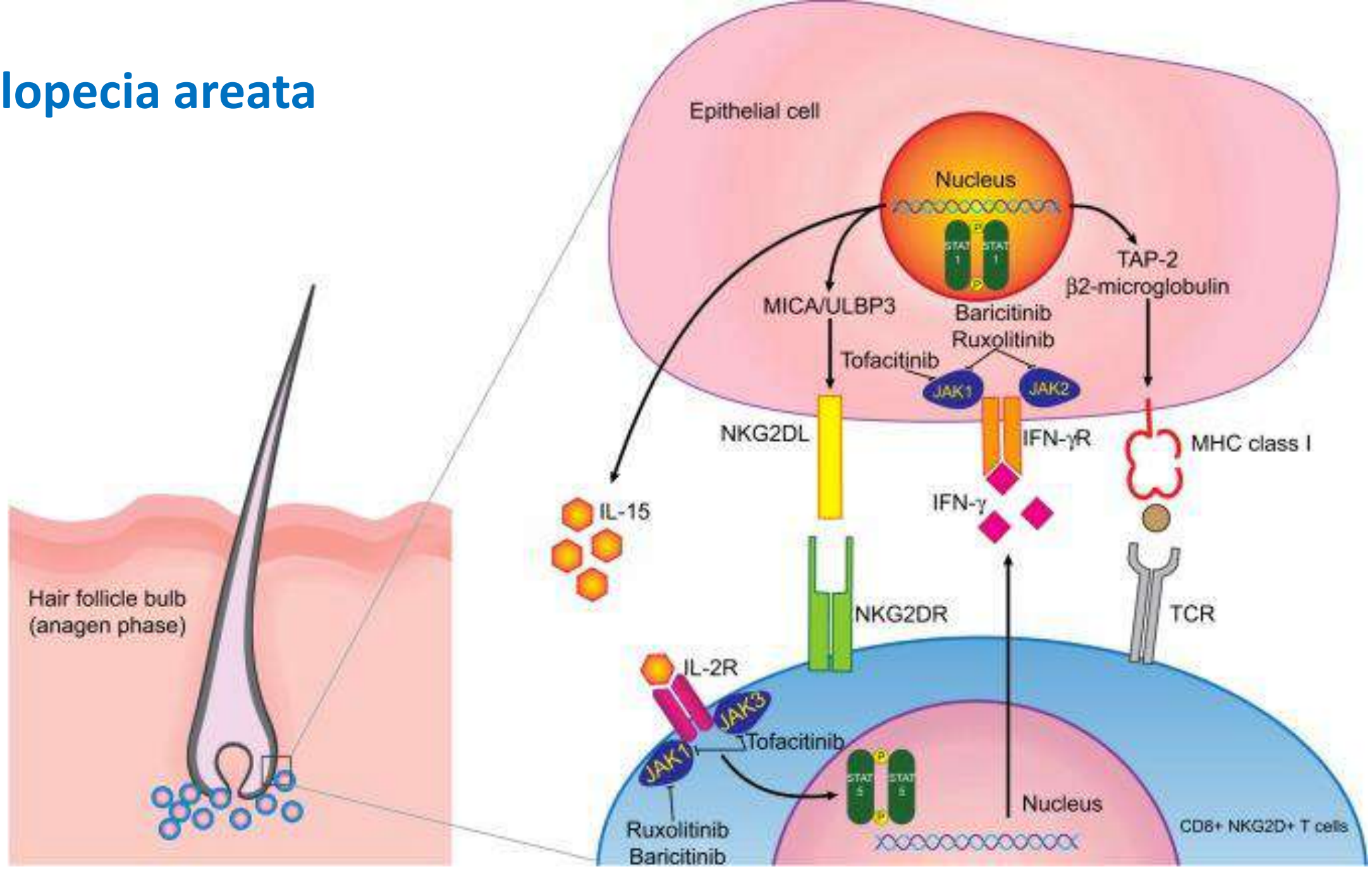
Lluís Puig.

Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona.

HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA

COI disclosure:
L. Puig has perceived consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi, and UCB.

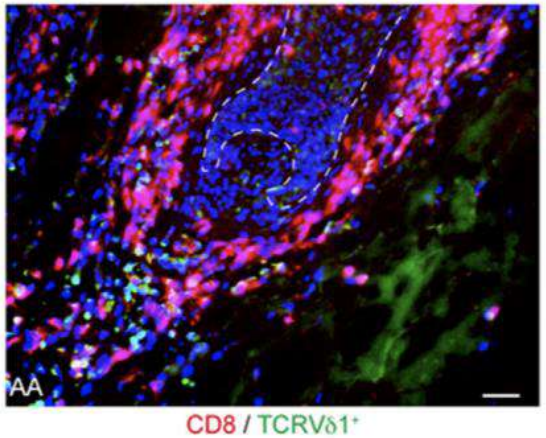
Alopecia areata

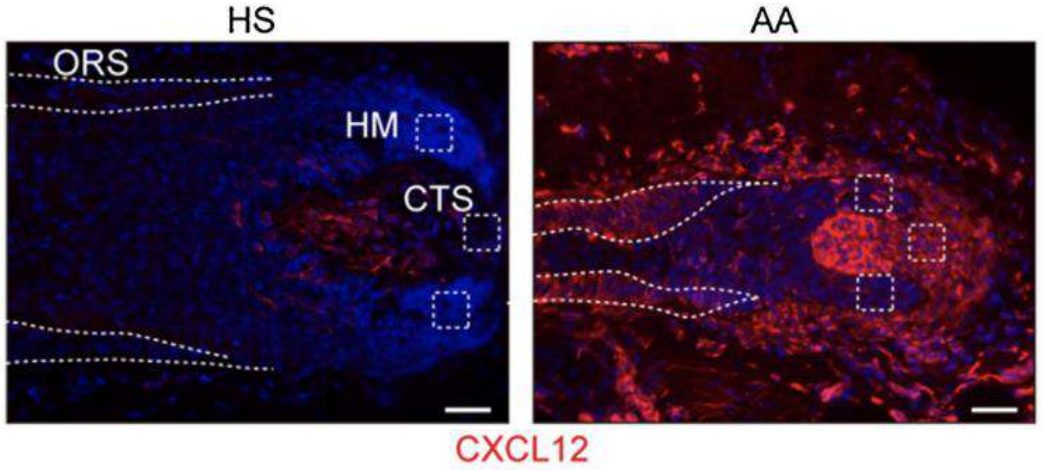


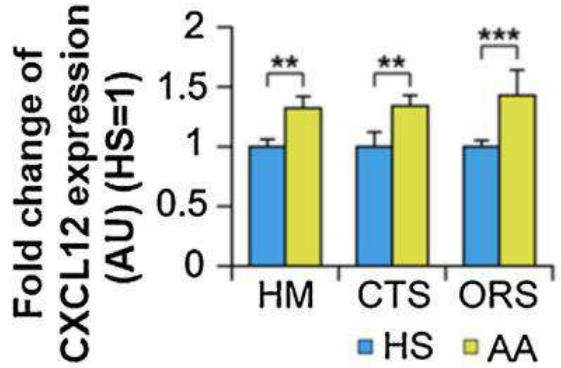
Triyangkulsri K, Suchonwanit P. Role of janus kinase inhibitors in the treatment of alopecia areata. Drug Des Devel Ther. 2018 Jul 27;12:2323-2335

Pro-inflammatory Vδ1+ T-cells infiltrates are present in and around the hair bulbs of non-lesional and lesional alopecia areata hair follicles

- It is widely accepted that NKG2D+ cells are critically involved in alopecia areata (AA) pathogenesis. However, besides being expressed in CD8+ T-cells and NK cells, NKG2D is also found in human γδT-cells. AA lesional hair follicles (HFs) overexpress NKG2D and γδTCR activating ligands, e.g. MICA and CD1d, and chemoattractants for γδT-cells, such as CXCL10.
- In healthy human scalp skin, the few skin-resident γδT-cells were found to be mostly Vδ1+ , nonactivated (CD69NKG2Ddim) and positive for CXCL10, and CXCL12 receptors. These Vδ1+ T-cells predominantly localized in/around the HF infundibulum. In striking contrast, the number of Vδ1+ Tcells was significantly higher around and even inside the proximal (suprabulbar and bulbar) epithelium of lesional AA HFs. These cells also showed a pro-inflammatory phenotype, i.e. higher NKG2D, and IFN-γ and lower CD200R expression. Importantly, more pro-inflammatory Vδ1+ T-cells were seen also around non-lesional AA HFs. Lesional AA HFs also showed significantly higher expression of CXCL12.
- Our pilot study introduces **skin-resident γδT-cells as a previously overlooked, but potentially important, mostly (auto-)antigen-independent, new innate immunity protagonist in AA pathobiology. The HF infiltration of these activated, IFN-γ-releasing cells already around non-lesional AA HFs suggest that Vδ1+ T-cells are involved in the early stages of human AA** pathobiology, and may thus deserve therapeutic targeting for optimal AA management.







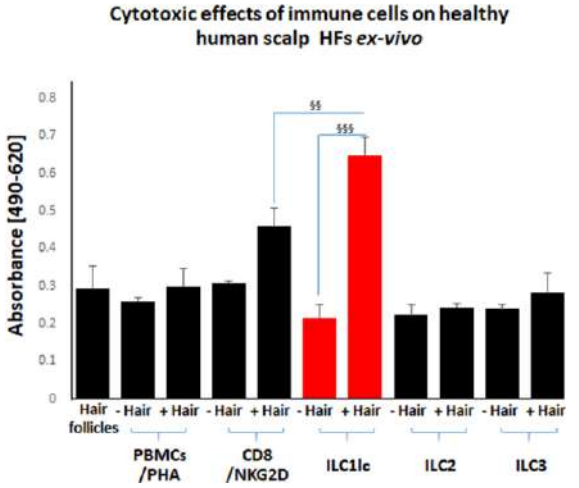
Uchida Y, et al. J Dermatol Sci. 2020 Nov;100(2):129-138.

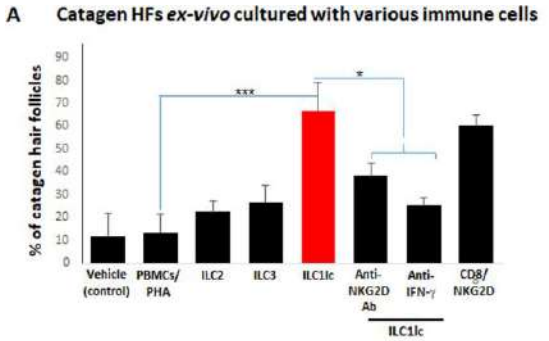
ILC1 cells are pathogenic in alopecia areata

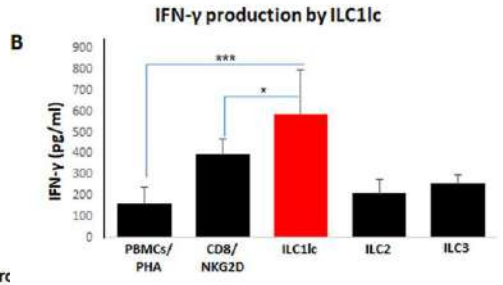
Abstract Here, we have explored the involvement of innate lymphoid cells-type 1 (ILC1) in the pathogenesis of alopecia areata (AA), because we found them to be significantly increased around lesional and non-lesional HFs of AA patients. To further explore these unexpected findings, we first co-cultured autologous circulating ILC1-like cells (ILC1lc) with healthy, but stressed, organ-cultured human scalp hair follicles (HFs). ILClc induced all hallmarks of AA ex vivo: they significantly promoted premature, apoptosis-driven HF regression (catagen), HF cytotoxicity/dystrophy, and most important for AA pathogenesis, the collapse of the HFs physiological immune privilege. NKG2D-blocking or IFNγ-neutralizing antibodies antagonized this. In vivo, intradermal injection of autologous activated, NKG2D+/IFNγ-secreting ILC1lc into healthy human scalp skin xenotransplanted onto SCID/beige mice sufficed to rapidly induce characteristic AA lesions. This provides the first evidence that ILC1lc, which are positive for the ILC1 phenotype and negative for the classical NK markers, suffice to induce AA in previously healthy human HFs ex vivo and in vivo, and further questions the conventional wisdom that AA is always an autoantigen-dependent, CD8 +T cell-driven autoimmune disease.

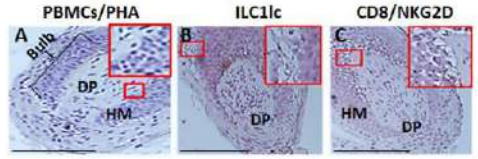
Editor's evaluation

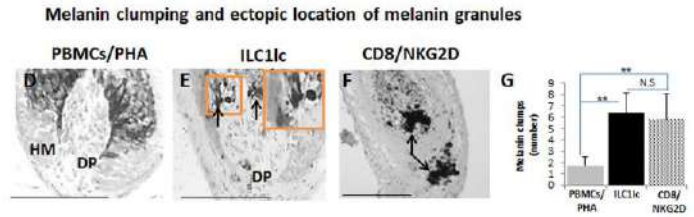
This manuscript provides fundamental data that implicate ILC1-like cells in alopeia areata. The data are solid in the use of cultured human hair follicles co-cultured with ILC-1-like cells and demonstration that alopecia phenotypes emerge. The authors also provide compelling evidence that injection of ILC1-like cells induces alopecia in a mouse model grafted with human hair follicle-containing skin. This work will be of interest to immunologists, skin biologists, and scientists interested in autoimmune disorders.

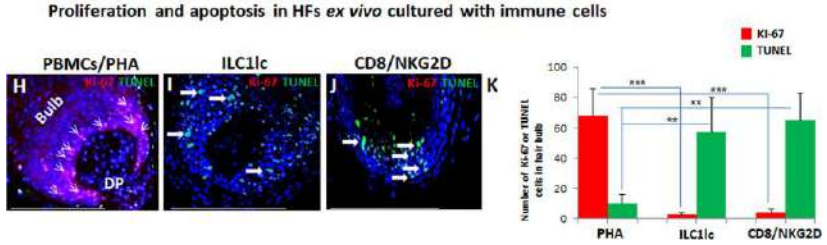






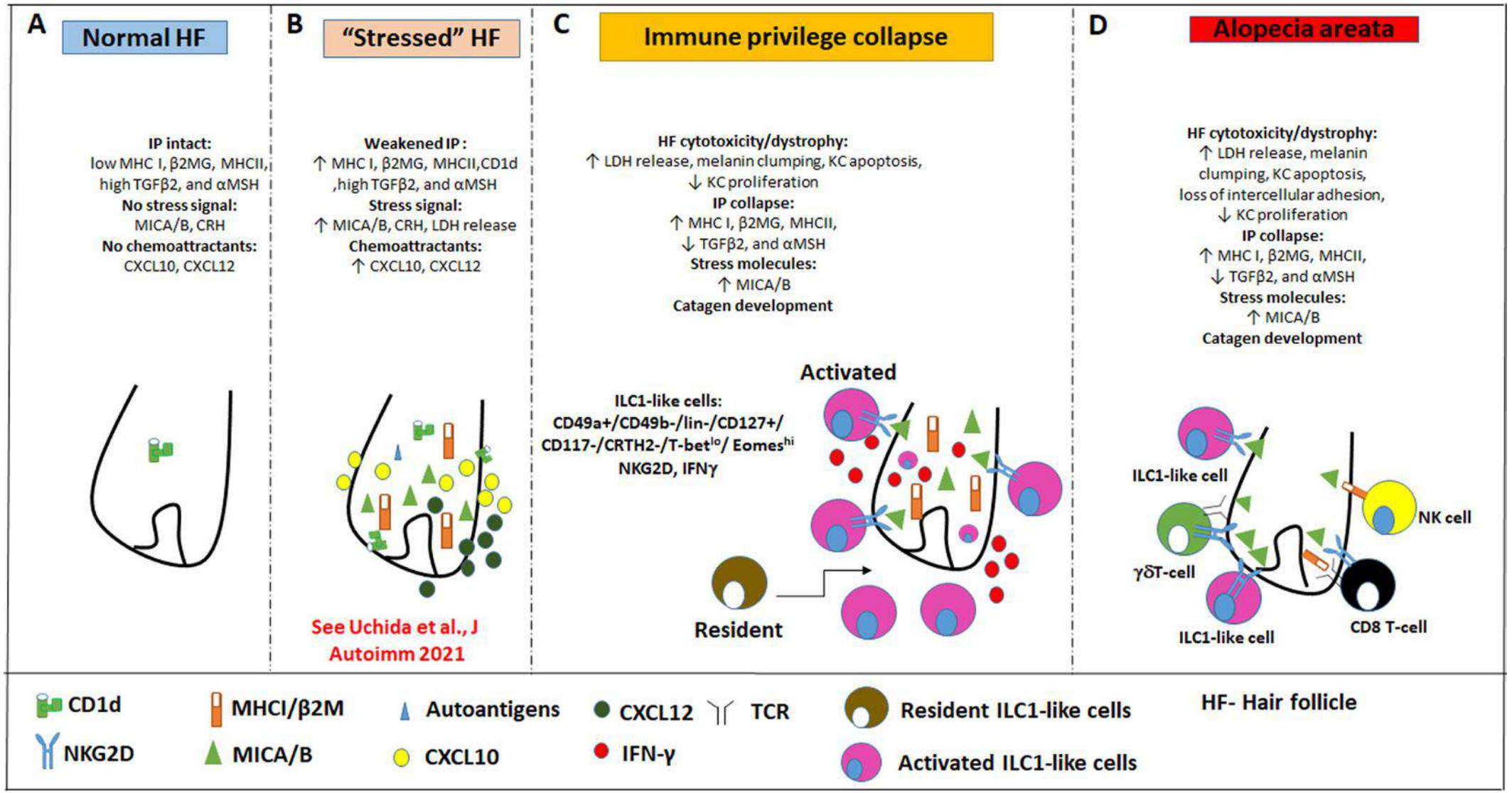






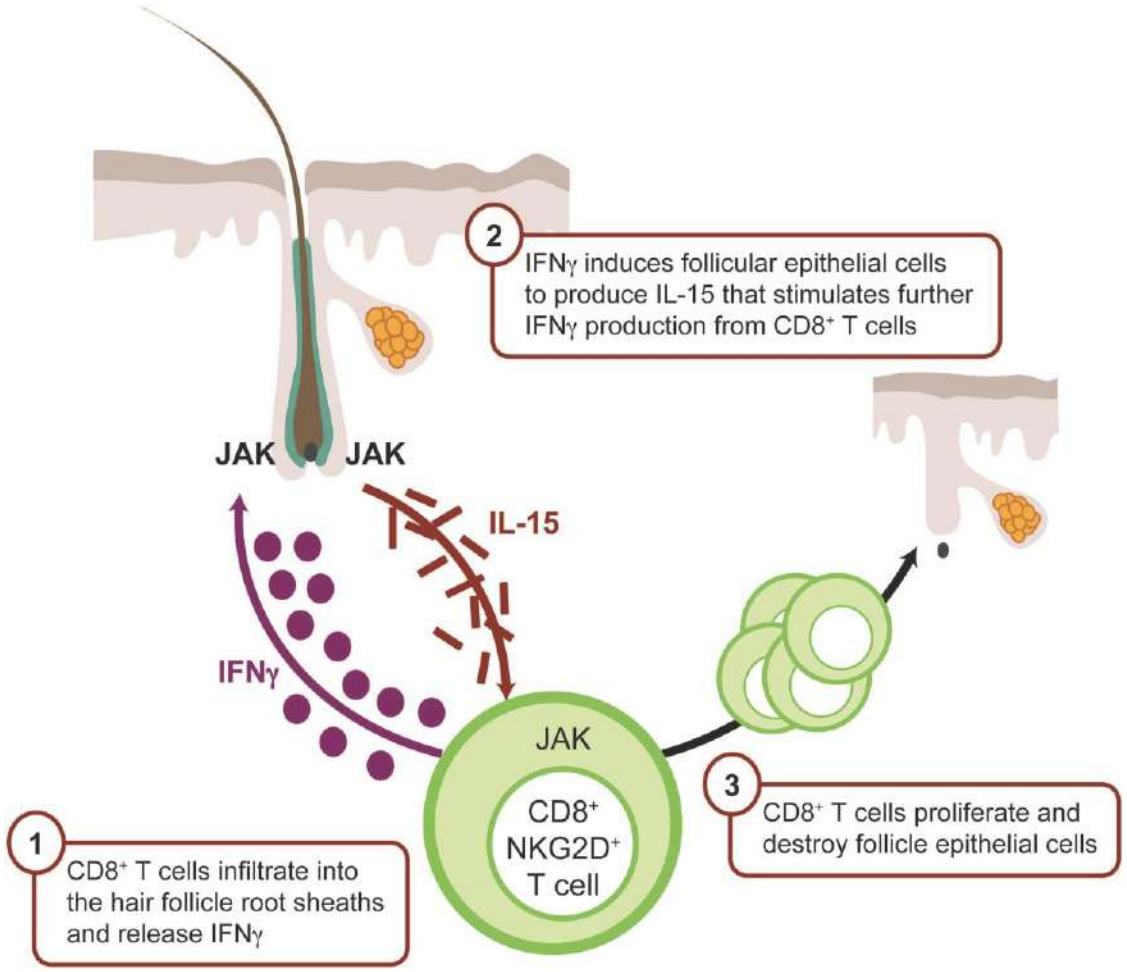
Laufer Britva R, et al. Elife. 2023 Mar 17;12:e80768.

Pathobiology of alopecia areata

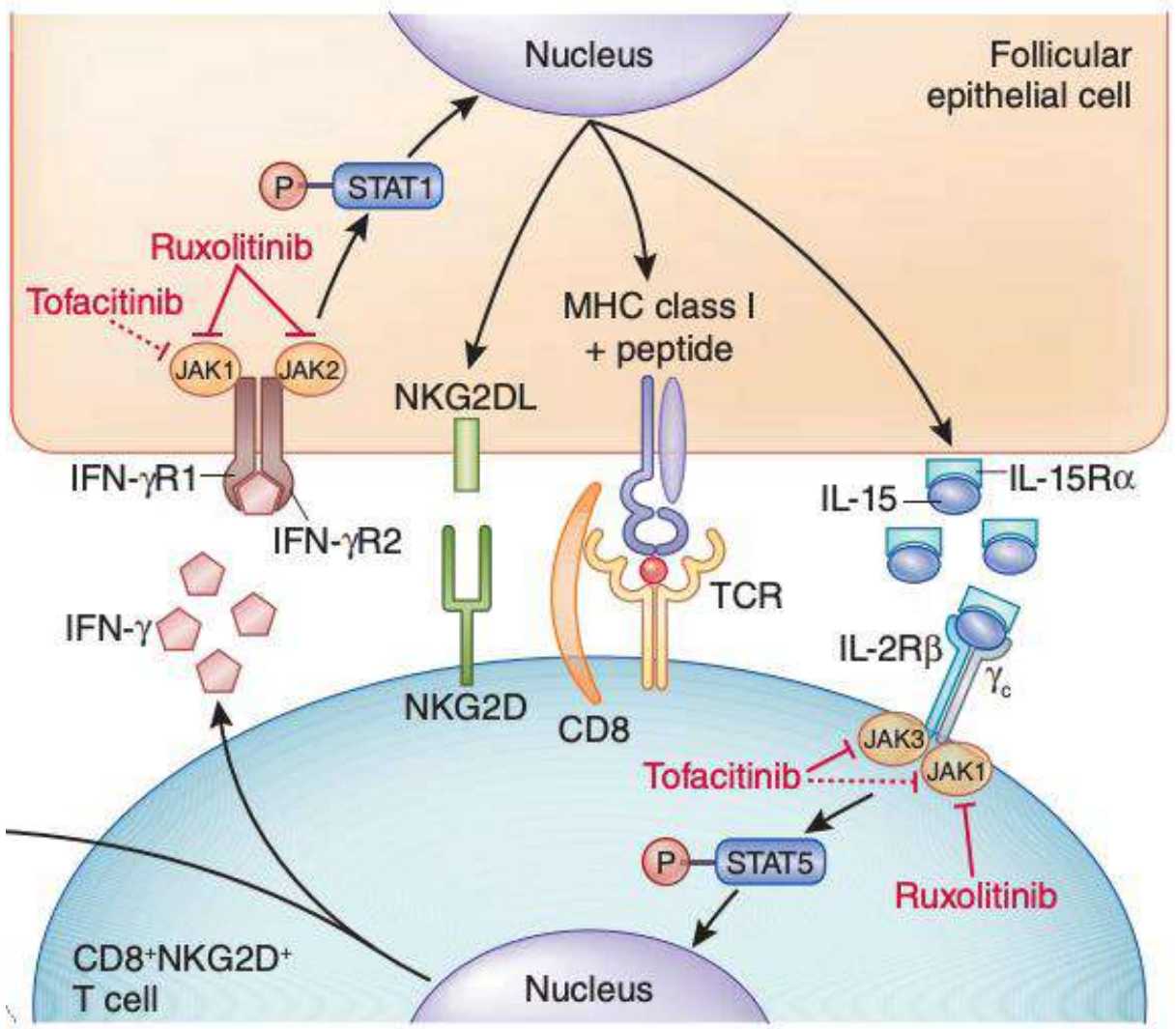


Laufer Britva R, et al. Elife. 2023 Mar 17;12:e80768.

IFNγ-driven inflammation in alopecia areata is JAK mediated

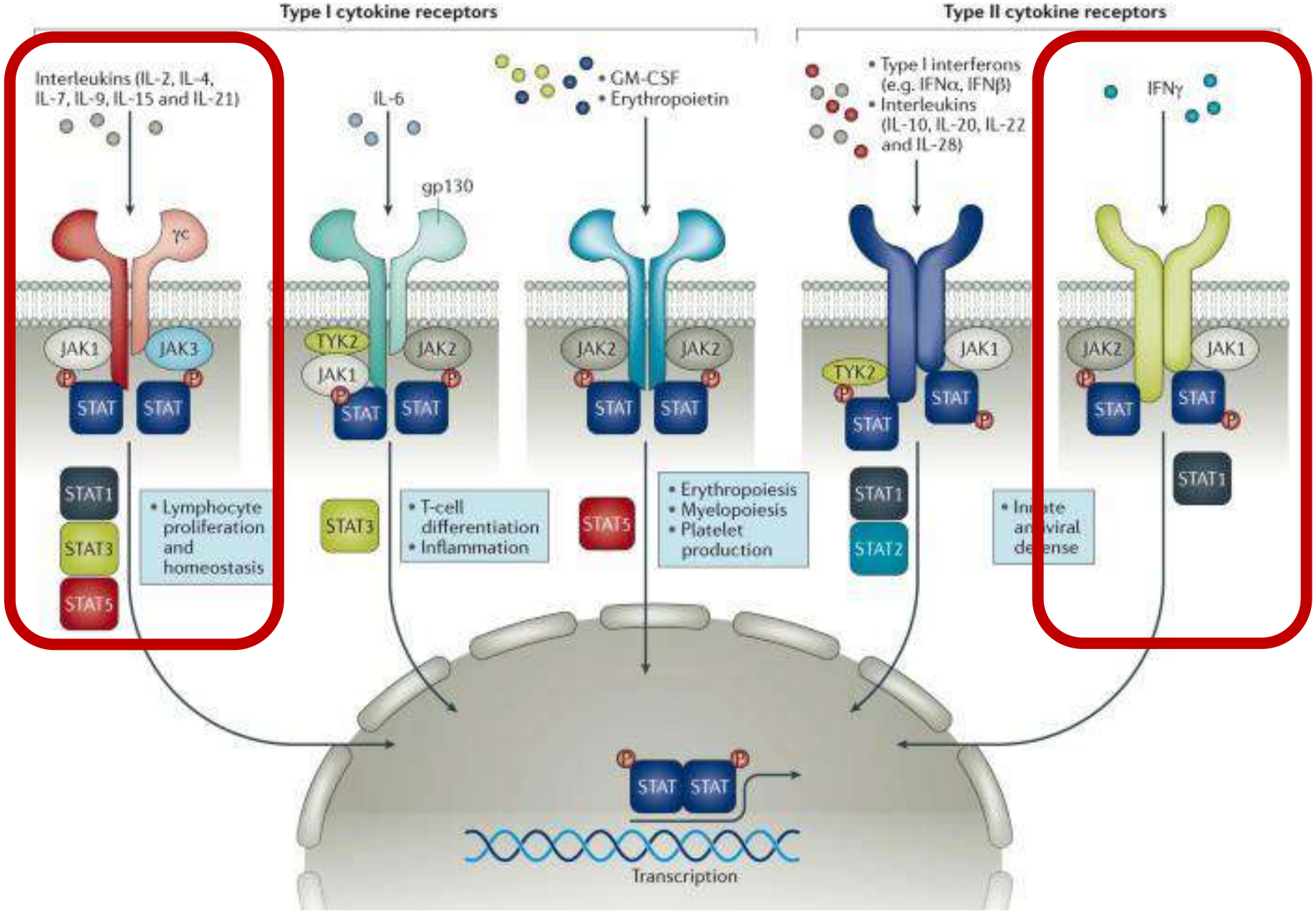


Howell MD, et al. Front Immunol. 2019 Oct 9;10:2342.



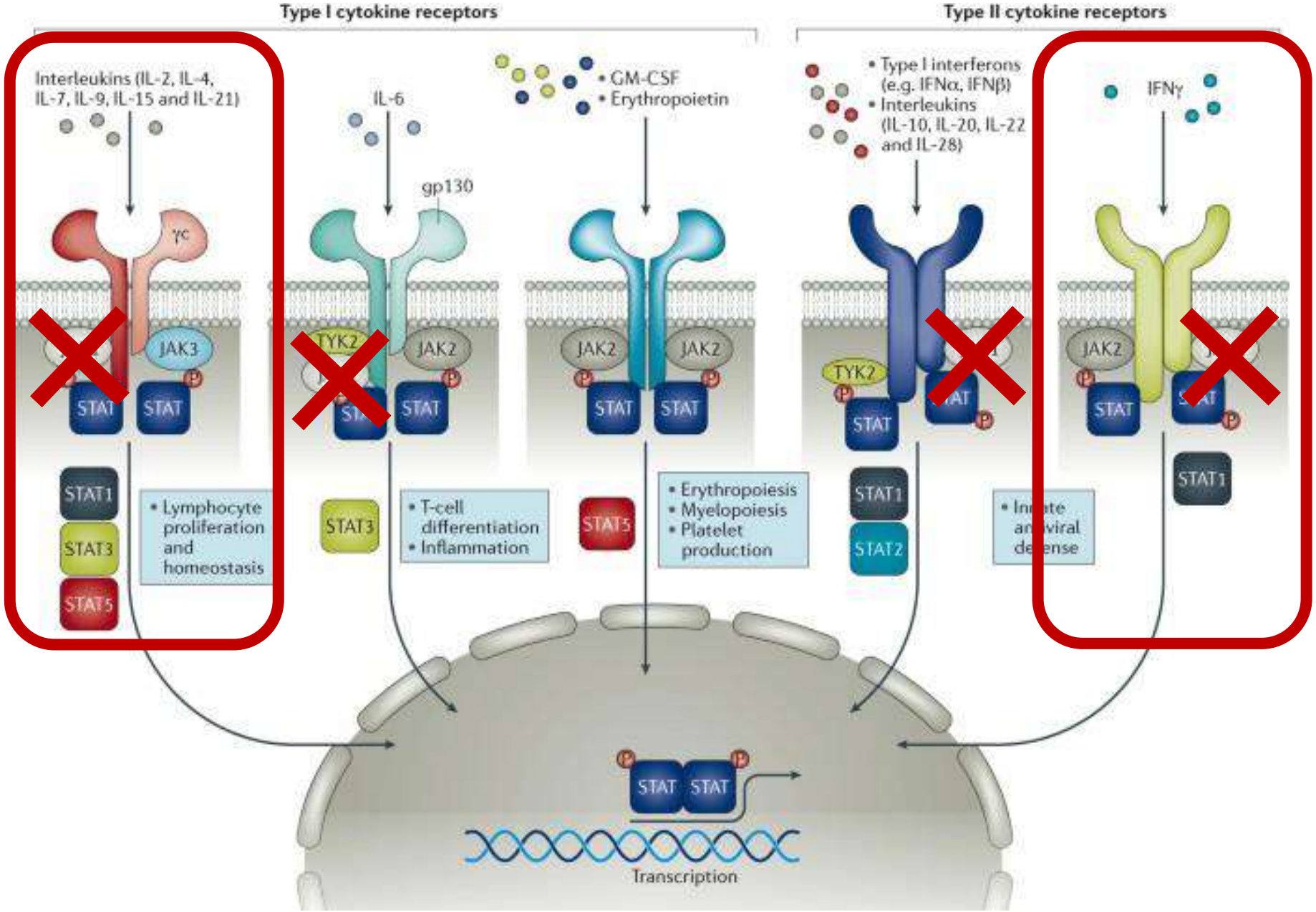
Divito SJ, Kupper TS. Nat Med. 2014 Sep;20(9):989-90

JAK Signaling



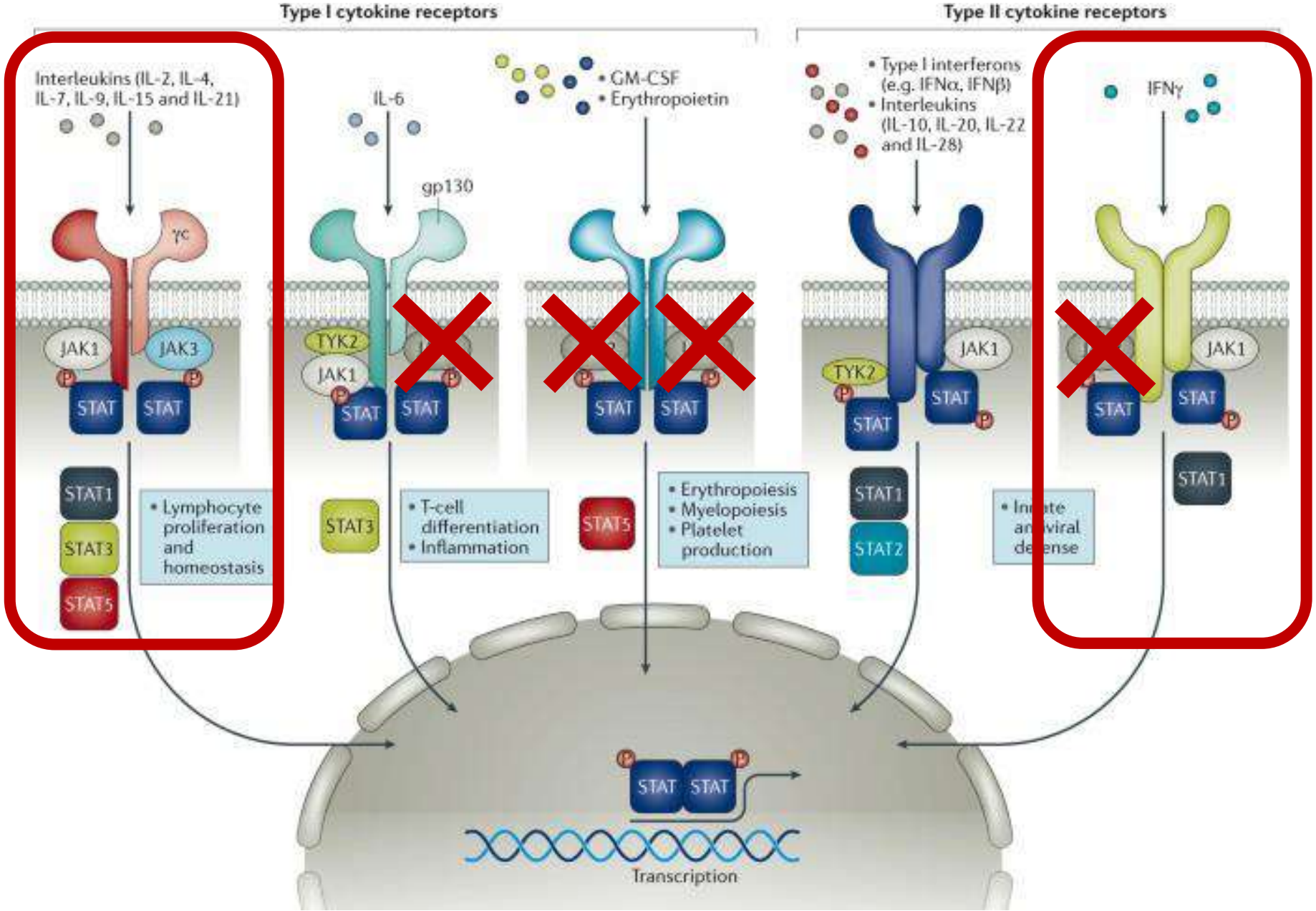
Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

JAK1 Inhibition



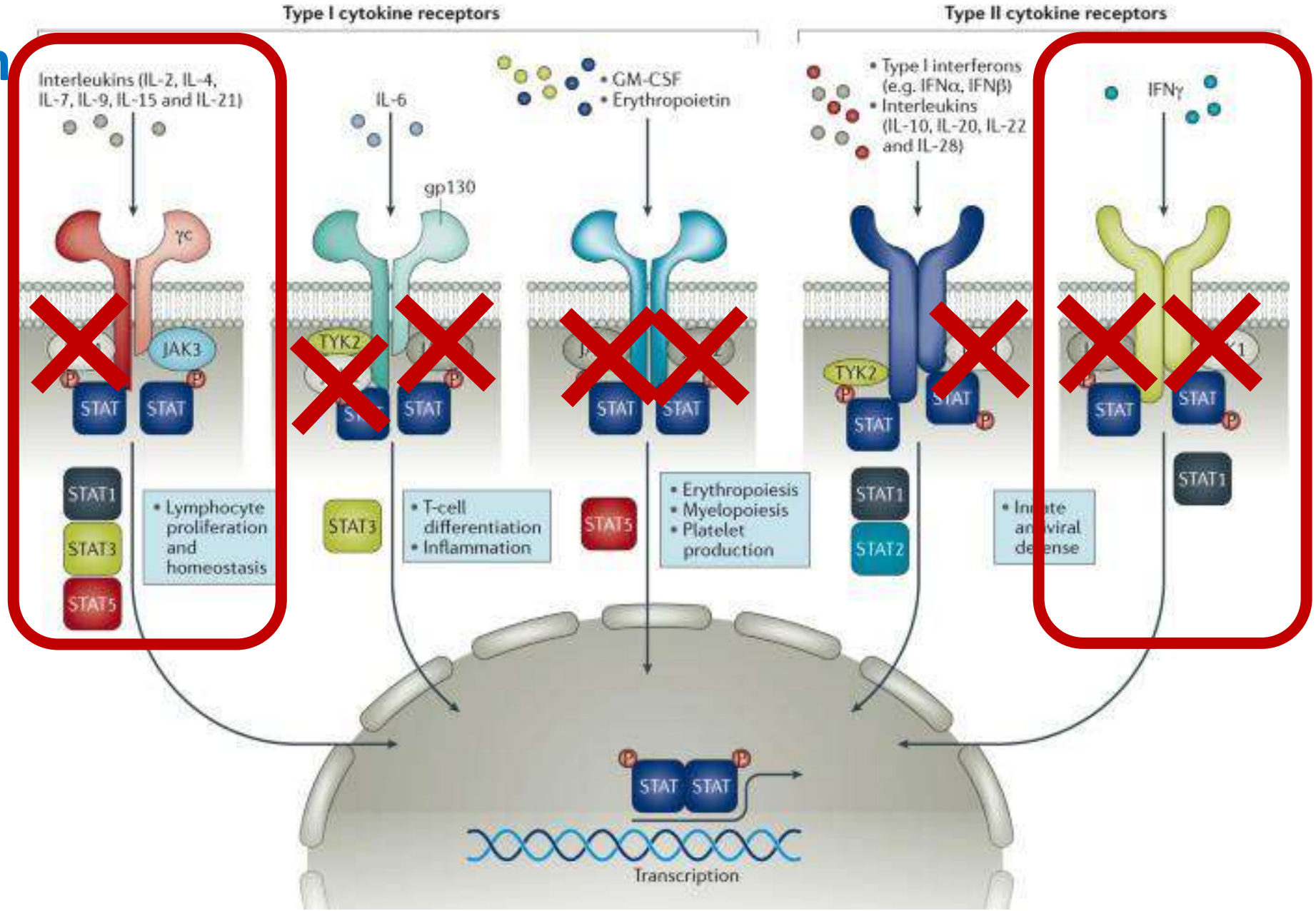
Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

JAK2 Inhibition



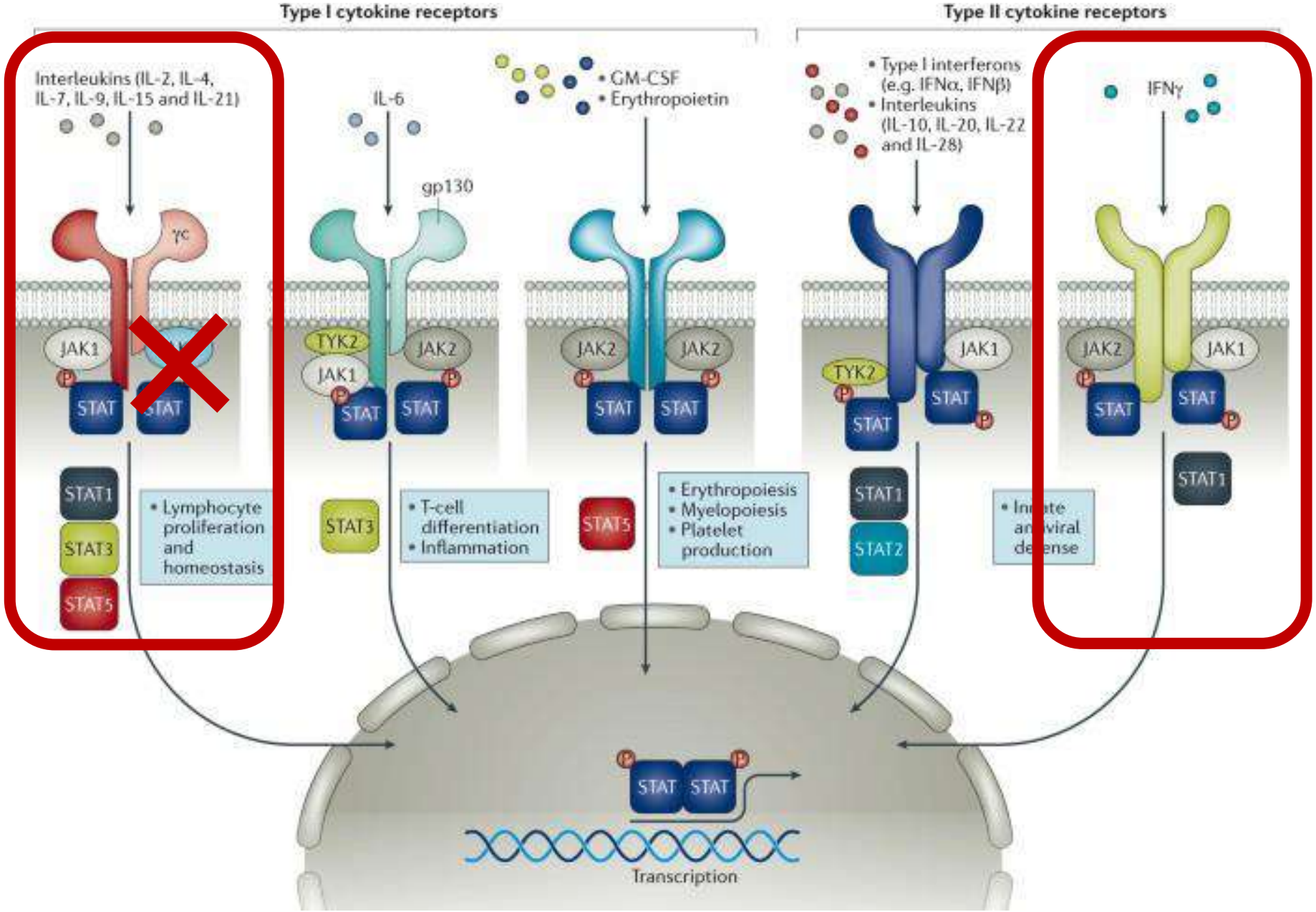
Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

JAK1/2 Inhibition



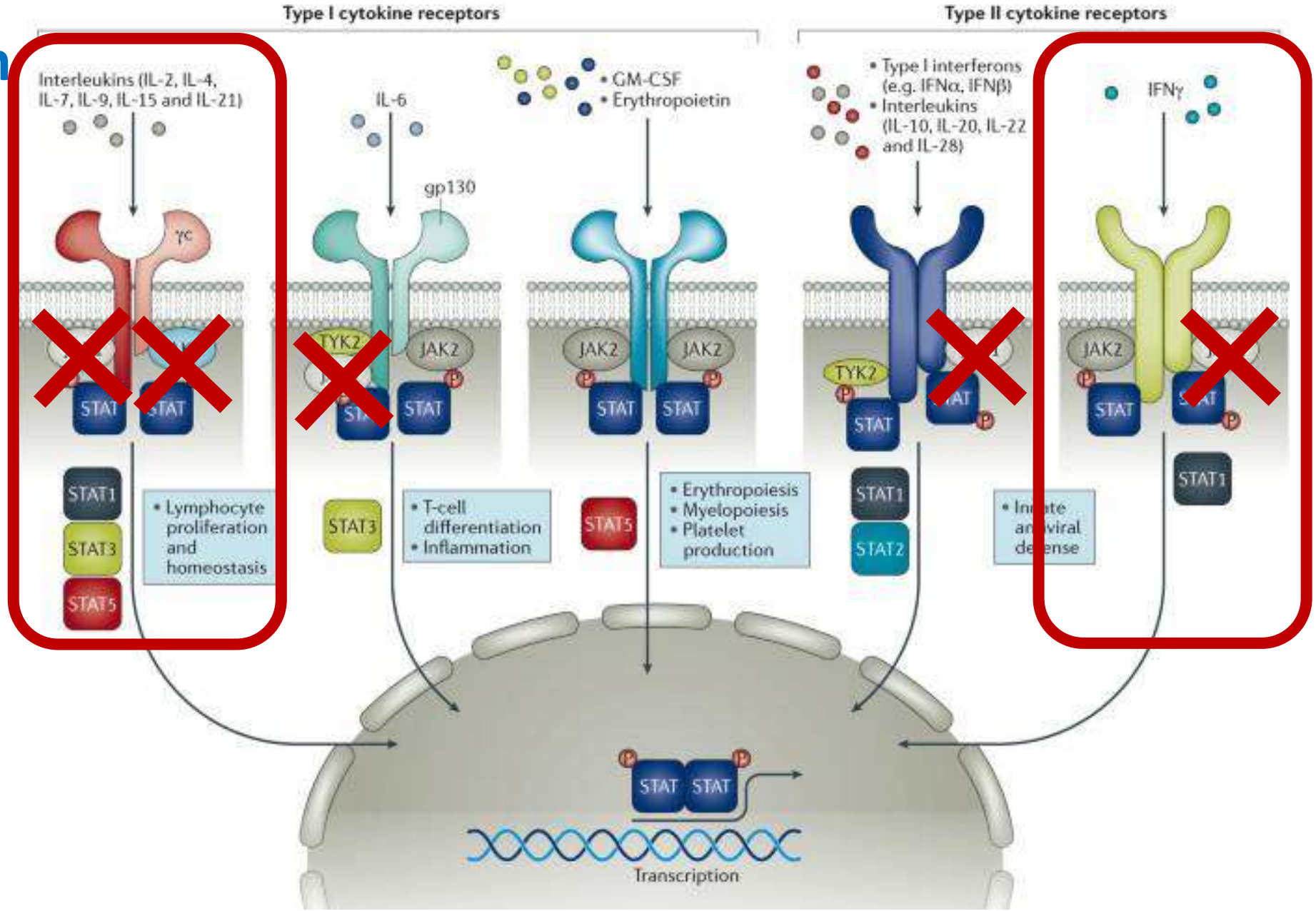
Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

JAK3 Inhibition



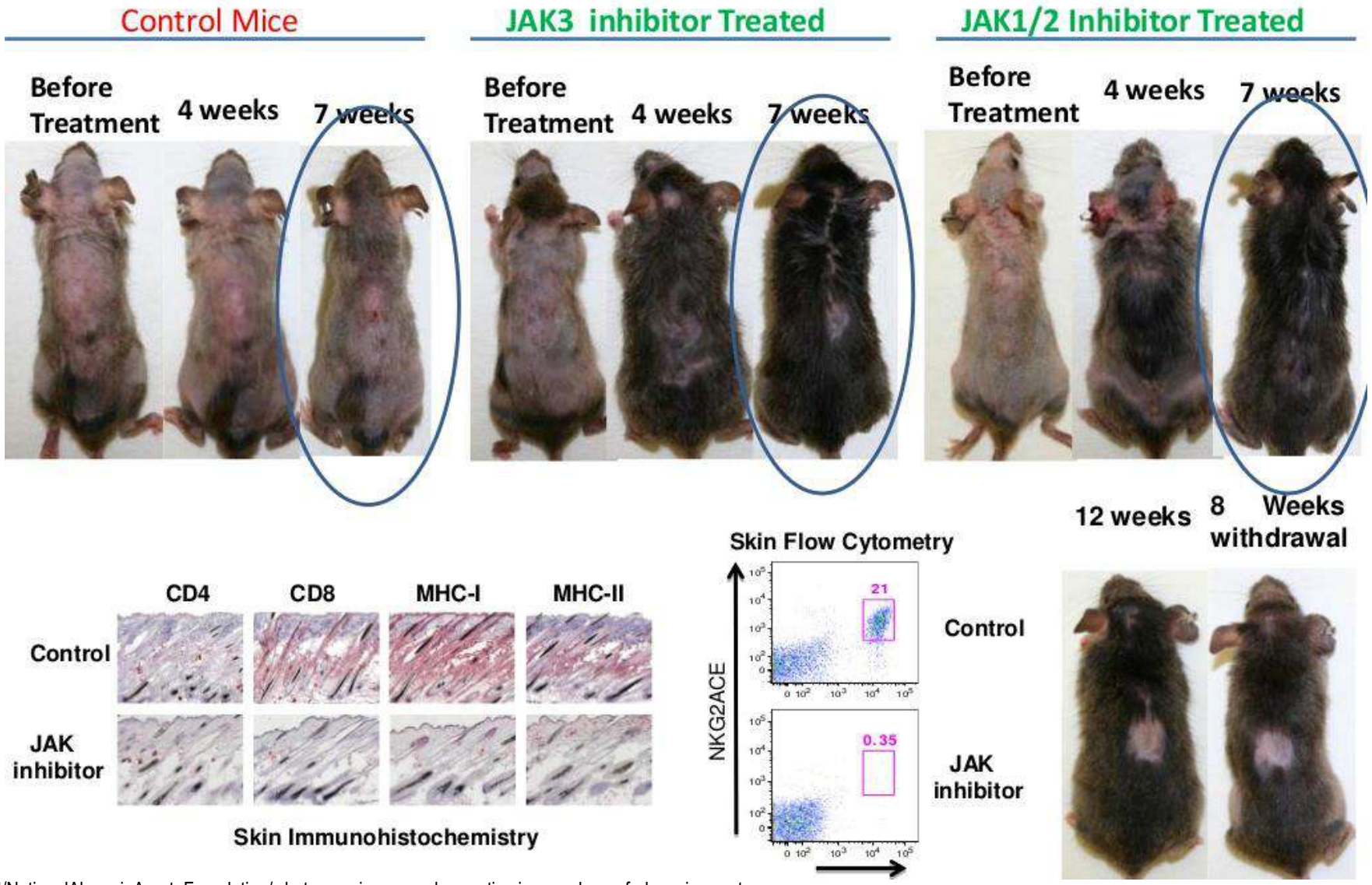
Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

JAK1/3 Inhibition



Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

Topical treatment with either JAK1/2 or JAK3 Inhibitor Results in Reversal of 2-3 Months' Duration Alopecia Areata



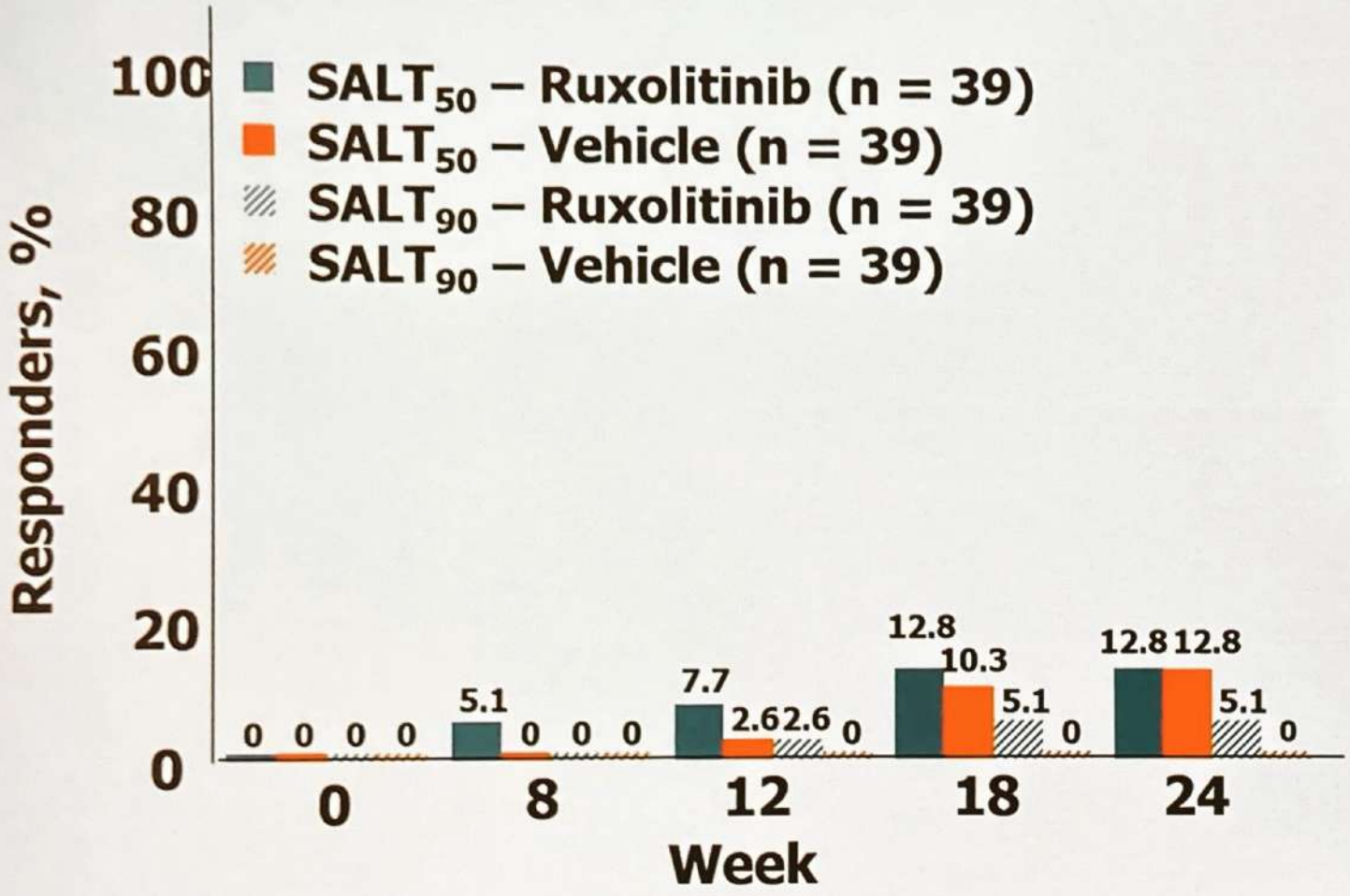
https://www.slideshare.net/NationalAlopeciaAreataFoundation/whats-new-in-research-genetics-immunology-of-alopecia-areata

Topical JAK inhibs

- Topical ruxolitinib 1.5% cream[a]
- Topical delgocitinib ointment[f]
- Ritlecitinib (PF-06651600)[b]
- Baricitinib[c,d]
- Deuruxolitinib (CTP-543)[e]

a. Olsen EA, et al. J Am Acad Dermatol. 2020;82:412-419; b. ClinicalTrials.gov. Accessed April 12, 2022. https://clinicaltrials.gov/ct2/show/NCT03732807; c. ClinicalTrials.gov. Accessed April 12, 2022. https://clinicaltrials.gov/ct2/show/NCT03570749; d. King B, et al. J Am Acad Dermatol. 2021;85:847-853; e. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04518995; f. Mikhaylov D, et al. Arch Dermatol Res. 2022 [Epub ahead of print]

Ruxolitinib 1.5% Cream: Phase 2 data

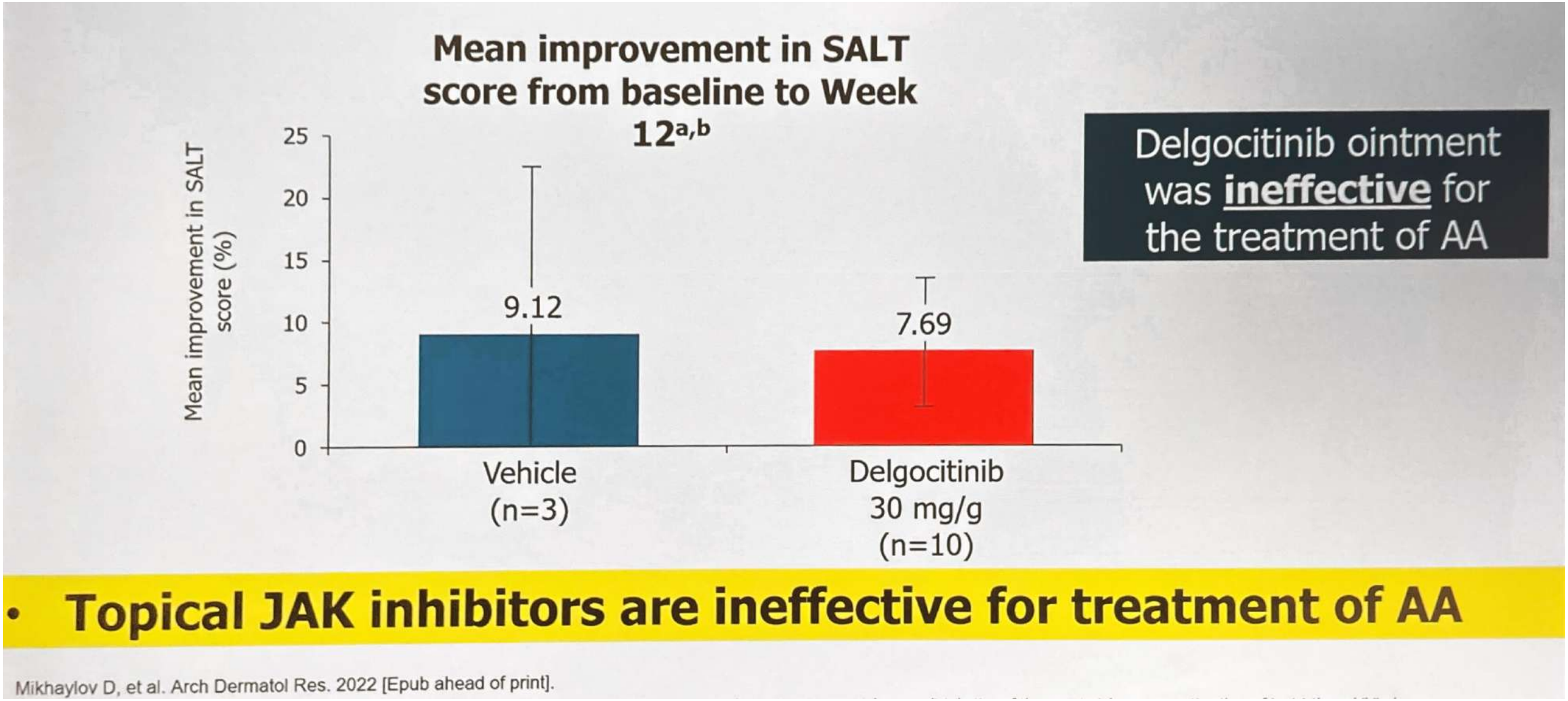


Ruxolitinib 1.5% cream was **ineffective** for the treatment of AA

* SALT50 = 50% improvement from baseline SALT score; SALT90 = 90% improvement from baseline SALT score.

Olsen EA, et al. J Am Acad Dermatol. 2020;82:412-419.

Delgocitinib Ointment: Phase 2 Data



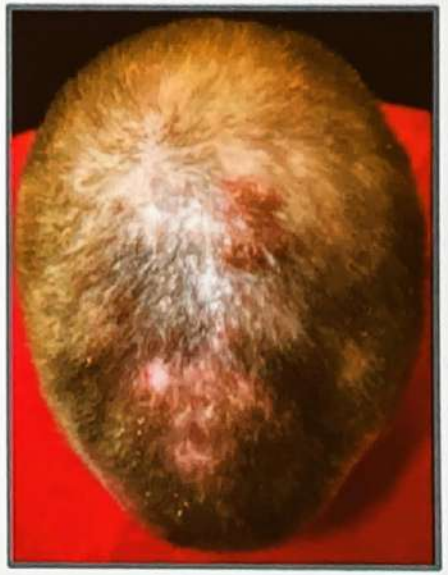
- **Topical JAK inhibitors are ineffective for treatment of AA**

Mikhaylov D, et al. Arch Dermatol Res. 2022 [Epub ahead of print].

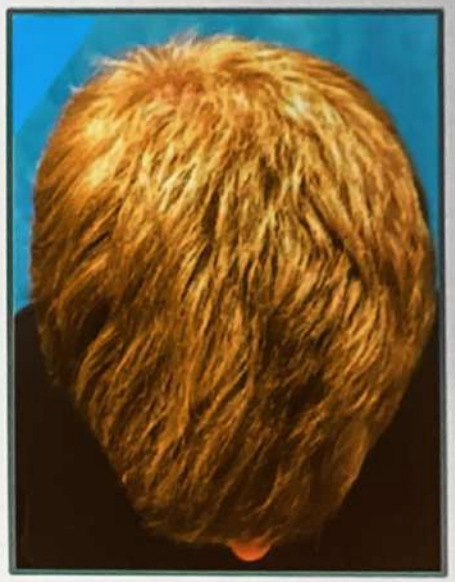
Two Birds with a Stone: Psoriasis + AA

Baseline

2 months
Tofacitinib 5 mg
twice daily



5 months
Tofacitinib
10 mg +
5 mg daily



8 months
Tofacitinib
10 mg +
5 mg daily

BID, twice daily.

Craiglow BG, King BA. J Invest Dermatol. 2014;134:2988-2990.

Reports of JAK Inhibitor Treatment in AA

Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata[a]

Oral ruxolitinib induces hair regrowth in patients with moderate to severe alopecia areata[b]

Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients[c]

Tofacitinib for the treatment of alopecia areata and variants in adolescents[d]

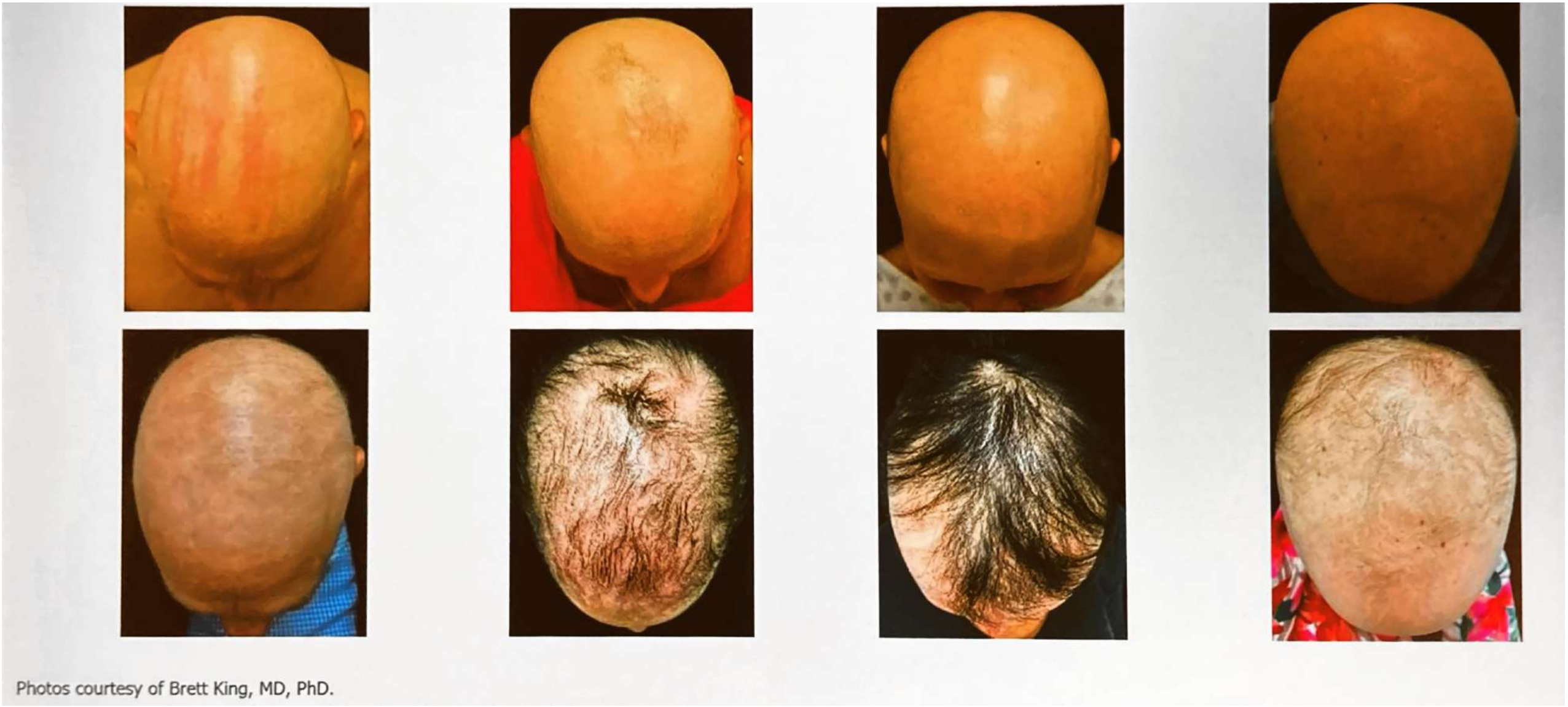
Tofacitinib for the treatment of alopecia areata in preadolescent children[e]

Ruxolitinib for the treatment of severe alopecia areata[f]

JAK, Janus kinase.

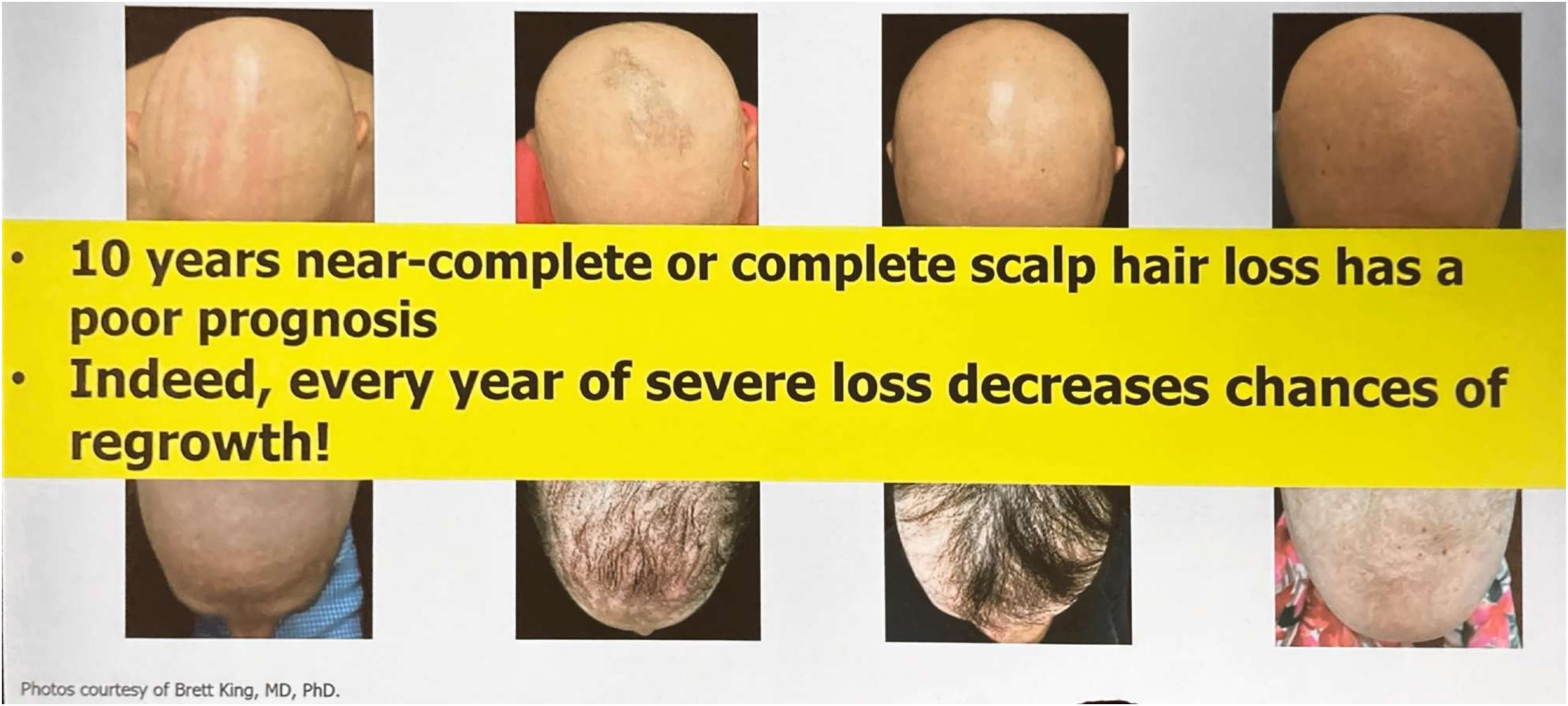
a. Crispin MK, et al. JCI Insight. 2016;1:e89776; b. Mackay-Wiggan J, et al. JCI Insight. 2016;1:e89790; c. Liu LY, et al. J Am Acad Dermatol. 2017;76:22-28;
d. Craiglow BG, et al. J Am Acad Dermatol. 2017;76:29-32; e. Craiglow BG, et al. J Am Acad Dermatol. 2019;80:568-569; f. Liu Y, et al. J Am Acad Dermatol. 2019;80:566-568.

Before and after tofacitinib

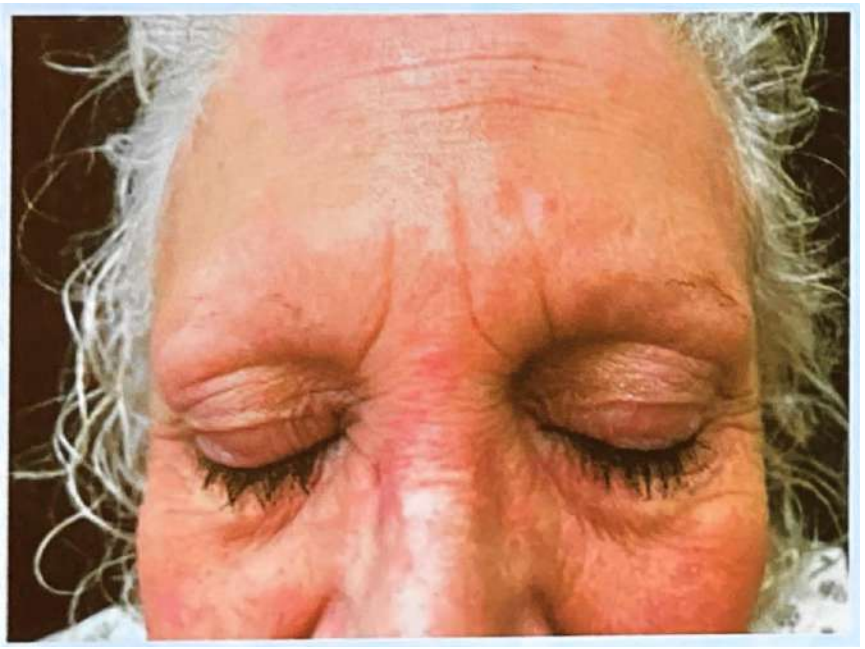


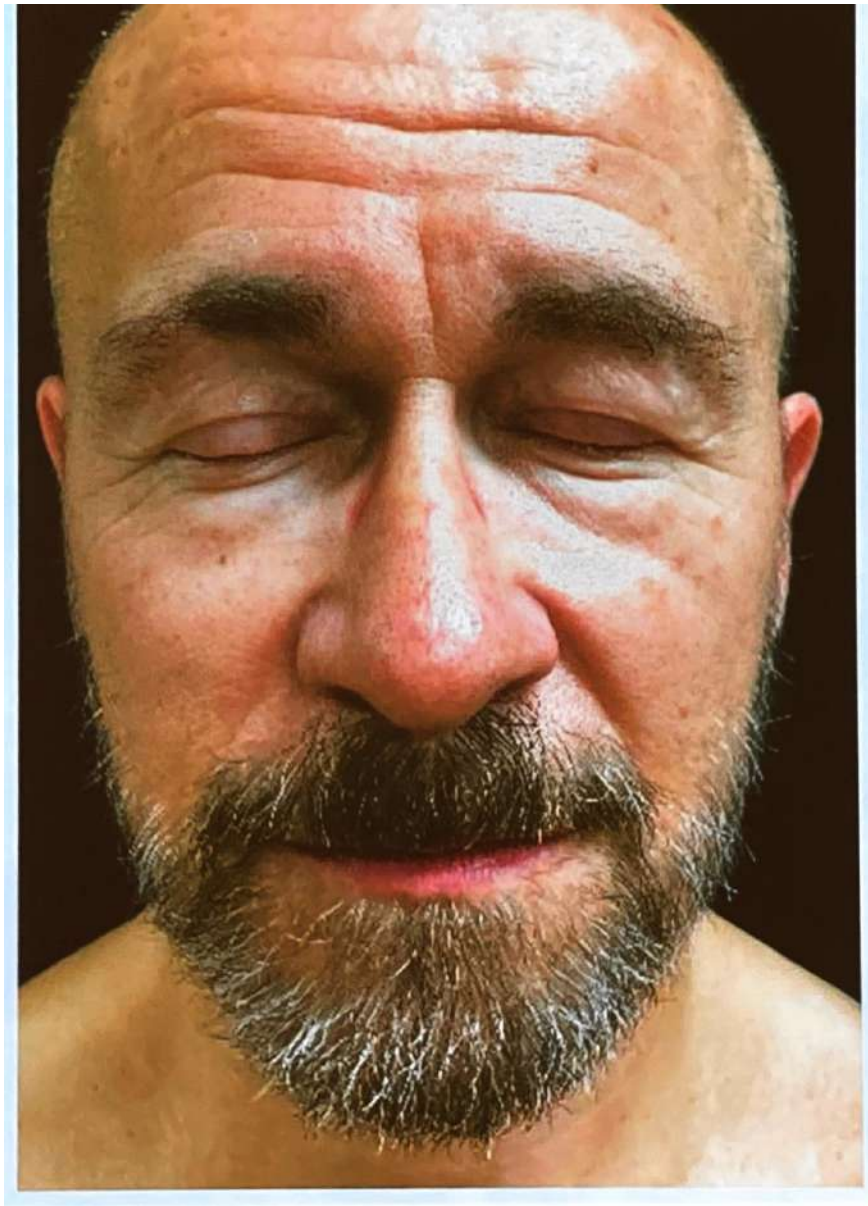
Photos courtesy of Brett King, MD, PhD.

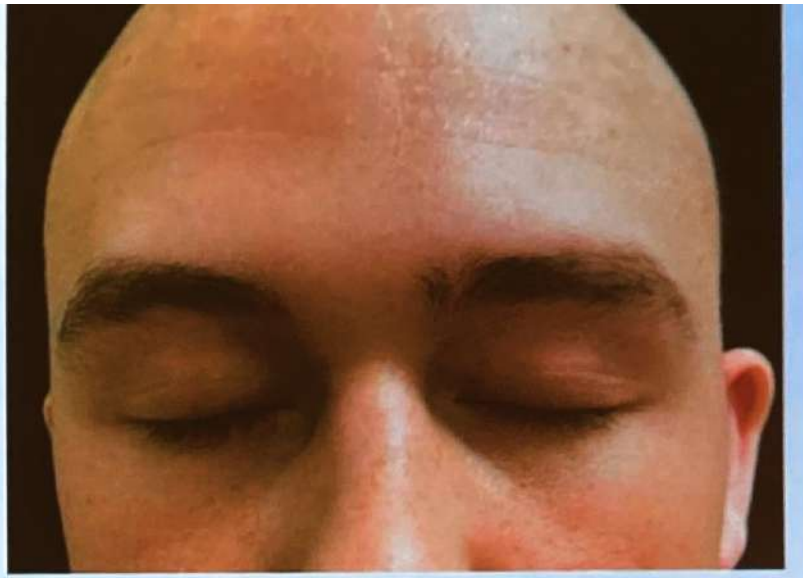
Before and after tofacitinib

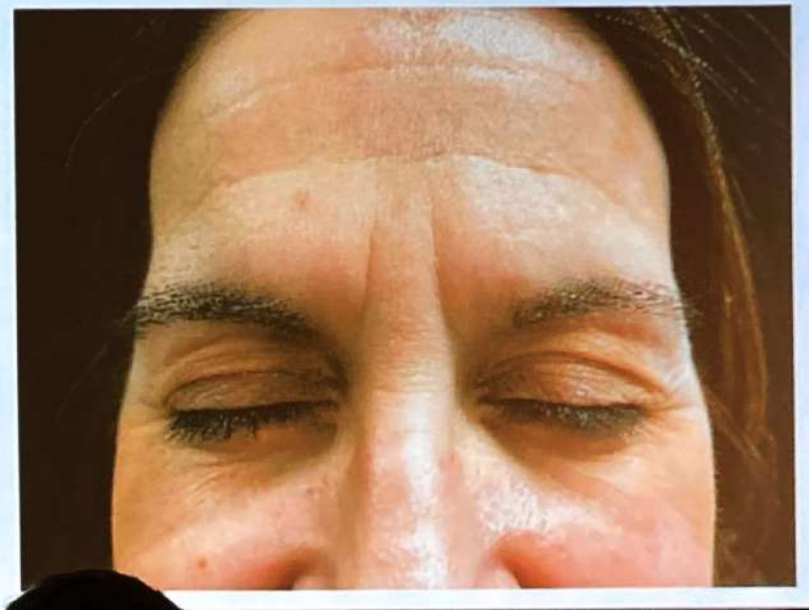


Response of Different Hair Bearing Sites is Unpredictable







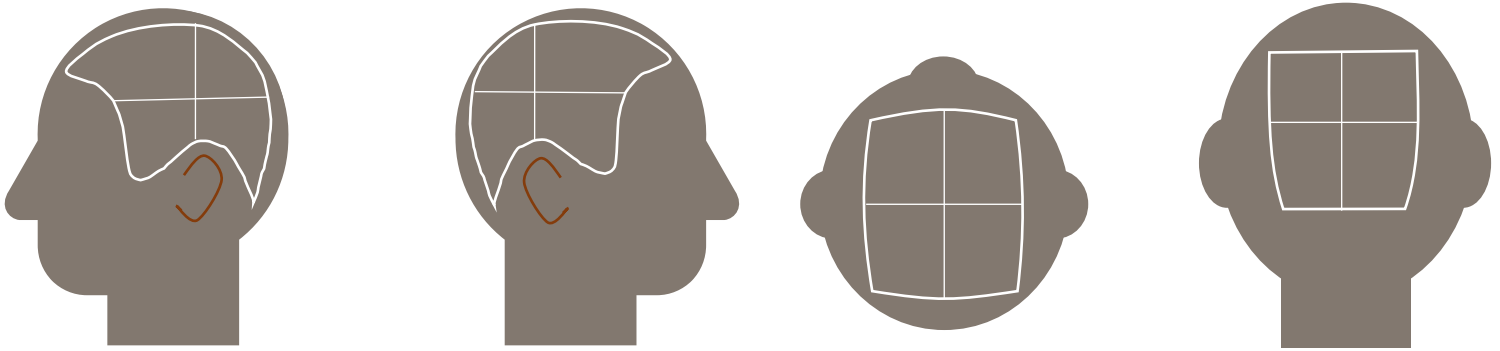


Severity of Alopecia Tool (SALT)

- SALT=0 full hair
- SALT=100 no hair

- The SALT is a visual aid designed to estimate percentage hair loss in AA[1]
  - The SALT score (0-100) corresponds to the % hair loss
- Only terminal hair areas are assessed, with non terminal hair considered as missing hair when using SALT[1]
- The SALT does not track individual lesions or small changes in density[2]

SALT visual aid



Left side (18%) | Right side (18%) | Top (40%) | Posterior (24%)

Calculating the SALT score[1]

1. % hair loss in each area X % of scalp covered by that area
2. Total sum of 4 products of each area = **SALT score**

AA=alopecia areata; SALT=Severity of Alopecia Tool
1. Data on file, Eli Lilly and Company; 2. https://www.slideshare.net/NationalAlopeciaAreataFoundation/standardizing-outcome-measures-in-alopecia-areata; 3. Olsen EA et al. *J Am Acad Dermatol* 2004;51(3):440-7

Selected alopecia areata clinical trials

- **Jaktinib (panJAK)** Suzhou Zelgen Biopharmaceuticals
- **Tofacitinib (JAK3/2/1)** Pfizer
- **ATI-501 (JAK1/3)** Aclaris
- **Ritlecitinib (JAK3/TEC)** Pfizer
- **Ivarmacitinib (JAK1)** Jiangsu Hengrui - Reistone Biopharma
- **Brepocitinib (JAK1/2/TYK2)** Pfizer-Priovant
- **Deucravacitinib (TYK2)** BMS

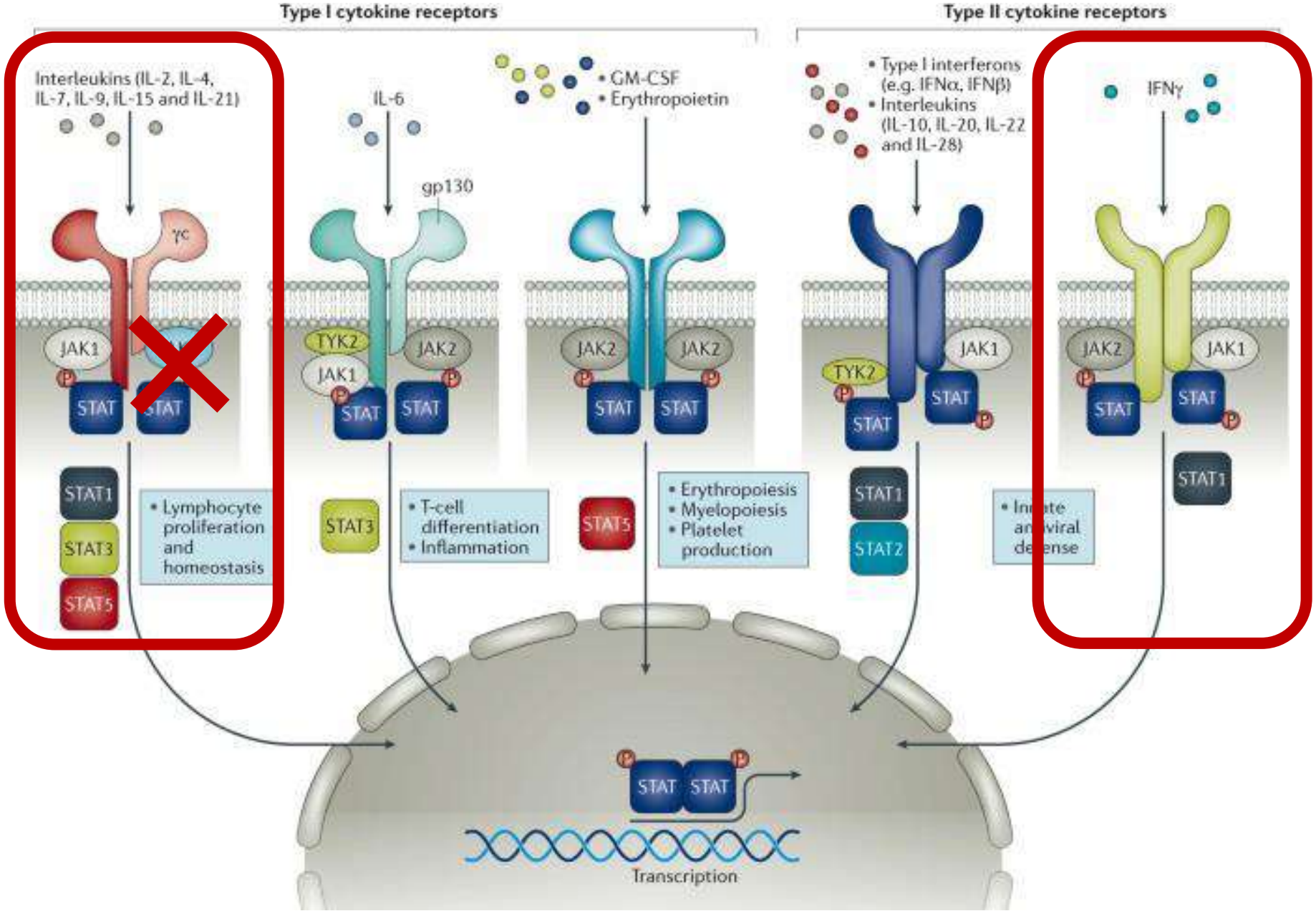
- **Baricitinib (JAK1/2/TYK2)** Lilly
- **Ruxolitinib (JAK1/2)** Incyte/Novartis
- **Deuruxolitinib CTP-543 (JAK1/2)** Concert Pharmaceuticals
- **KL130008 (JAK1/2)** Sichuan Kelun-Biotech Biopharmaceutical

- **Daxdilimab (IFN I)** Horizon Therapeutics
- **EQ101 (anti-IL-2/9/15 peptide)** Equillium

- **Fecal transplant** (Tel-Aviv Sourasky Medical Center) 2 years, not yet recruiting

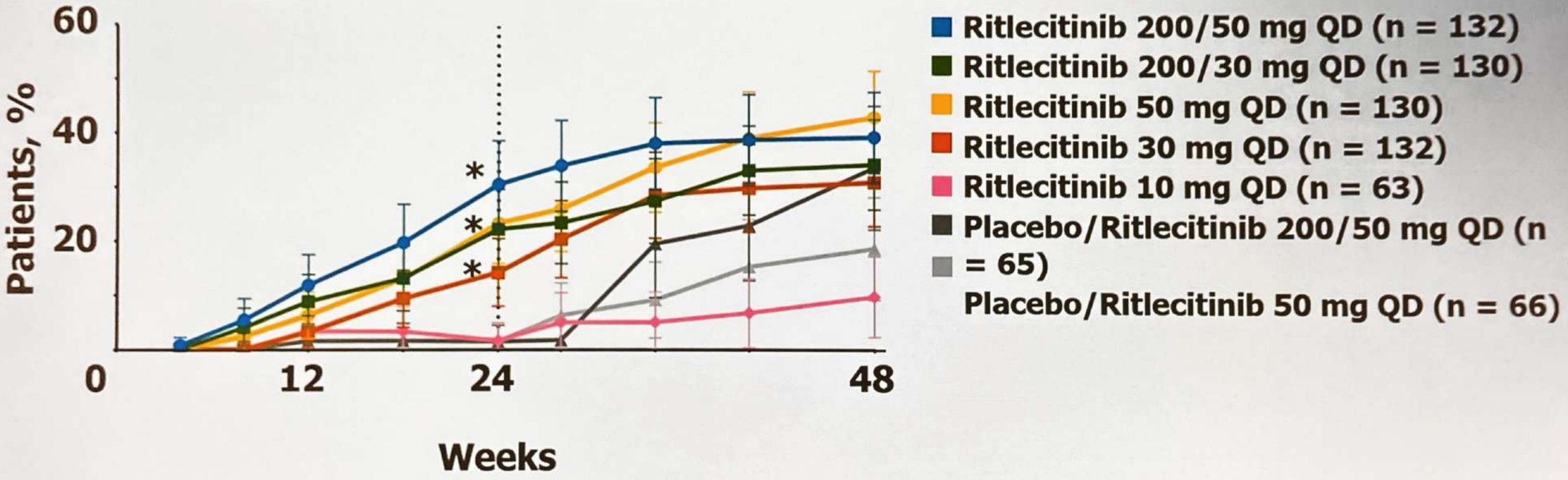
JAK3 inhibition

Ritlecitinib



Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

Ritlecitinib: Phase 3 Data

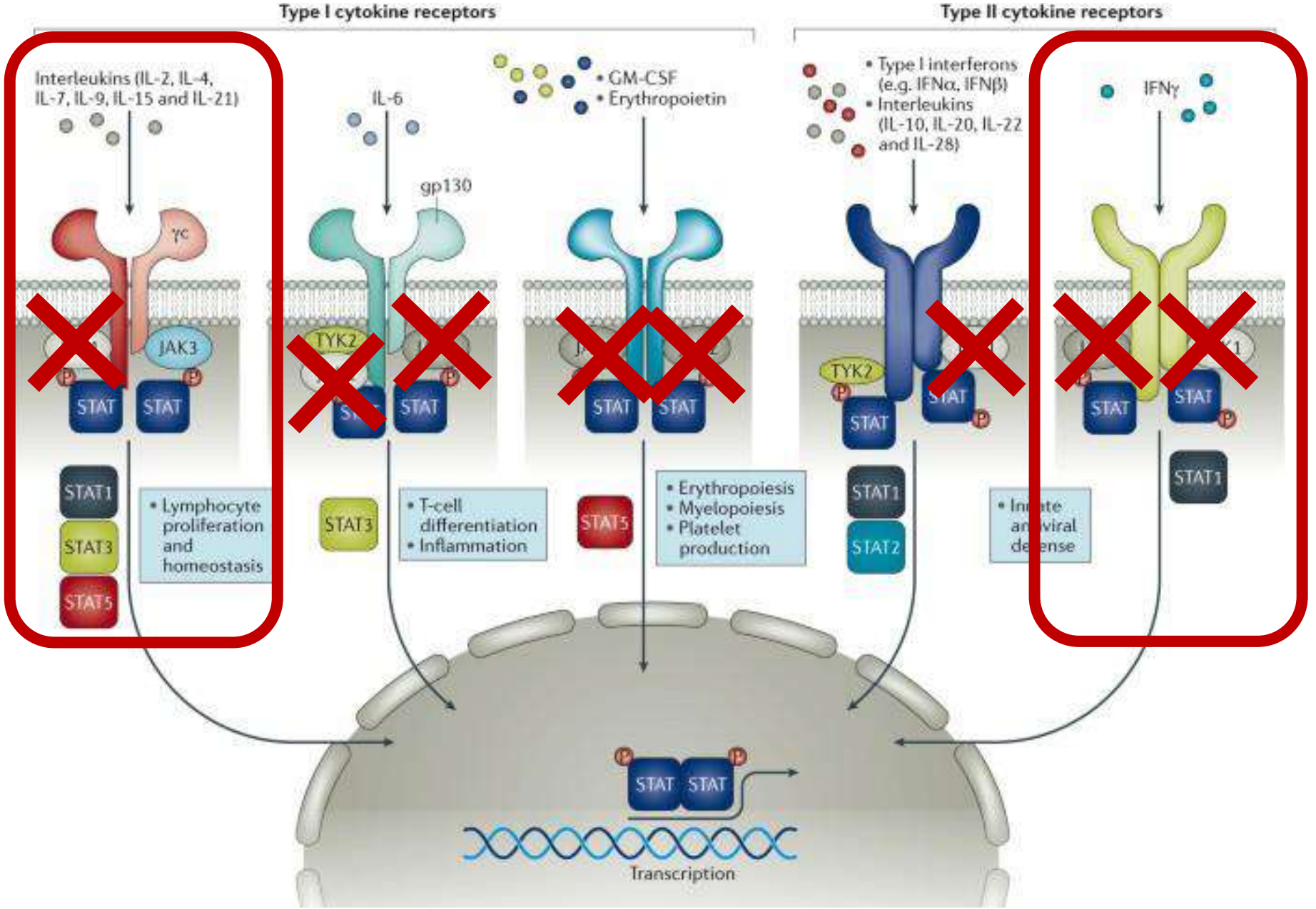


*Statistically significant compared to placebo for overall study ($P < .05$), EMA ($P < .01$) and FDA ($P < .00125$).

King B, et al. Presented at: European Academy of Dermatology and Venereology (EADV); September 29-October 2, 2021; Virtual. Presentation.

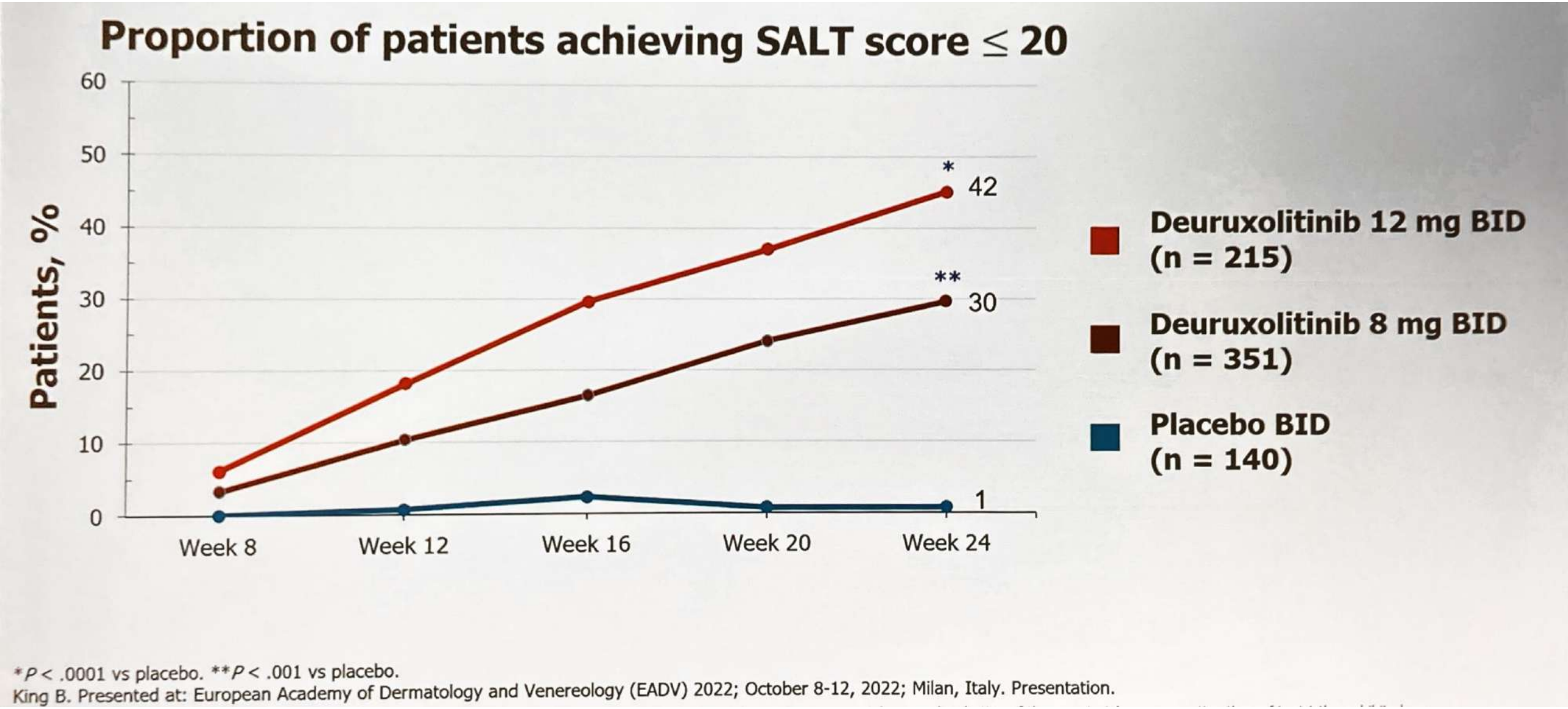
JAK1/2 inhibition

Baricitinib
Deruxolitinib
Ruxolitinib
KL 130008



Winthrop KL.. Nat Rev Rheumatol. 2017 May;13(5):320.

Deuruxolitinb: Phase 3 Data



*P < .0001 vs placebo. **P < .001 vs placebo.

King B. Presented at: European Academy of Dermatology and Venereology (EADV) 2022; October 8-12, 2022; Milan, Italy. Presentation.

AAD Annual Meeting, New Orleans
S042 Late Breaking Research Session
Mar 18, 2023, 1:30 PM–1:40 PM CDT

RESULTS FROM THRIVE-AA2: A DOUBLE BLIND, PLACEBO-CONTROLLED PHASE 3 CLINICAL TRIAL OF DEURUXOLITINIB (CTP-543), AN ORAL JAK INHIBITOR, IN ADULT PATIENTS WITH MODERATE TO SEVERE ALOPECIA AREATA

Brett King, MD, PhD
Yale University School of Medicine

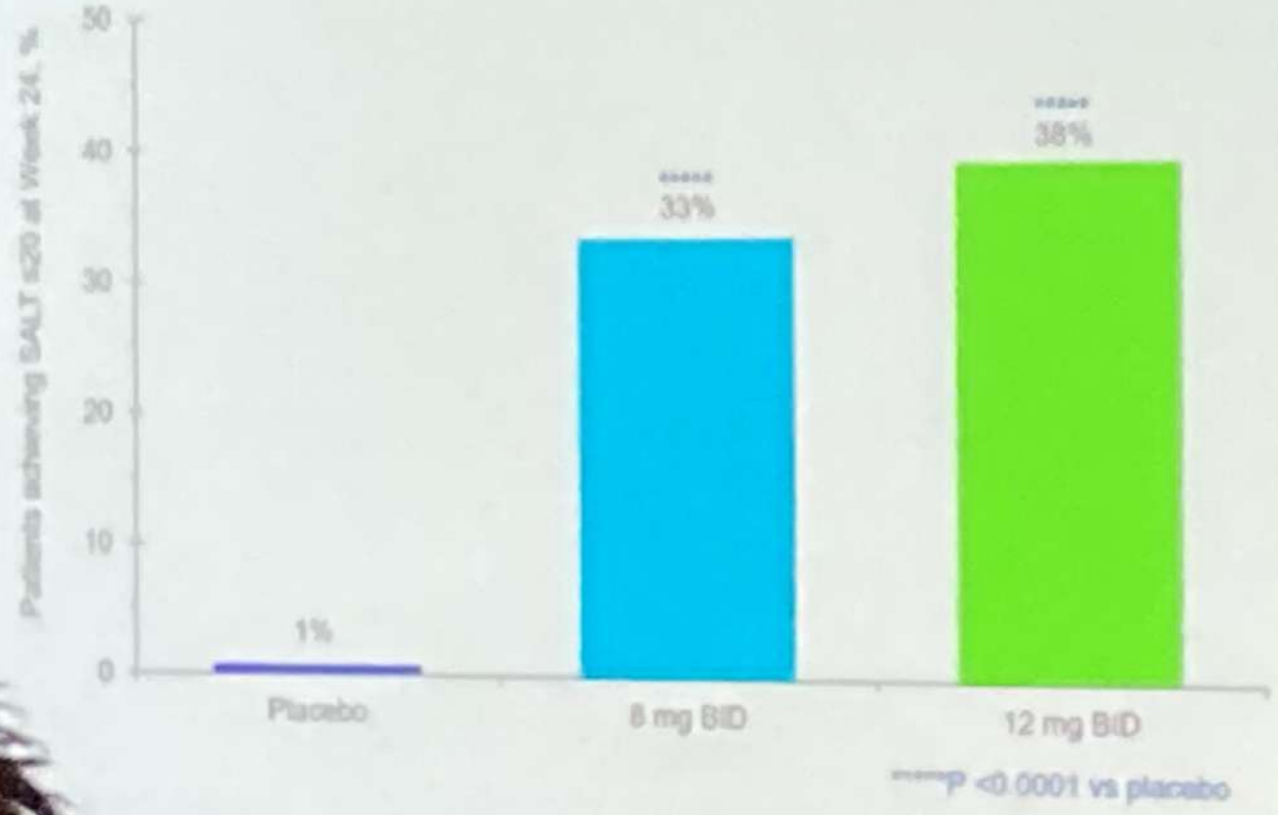
ClinicalTrials.gov Identifier: NCT04797650

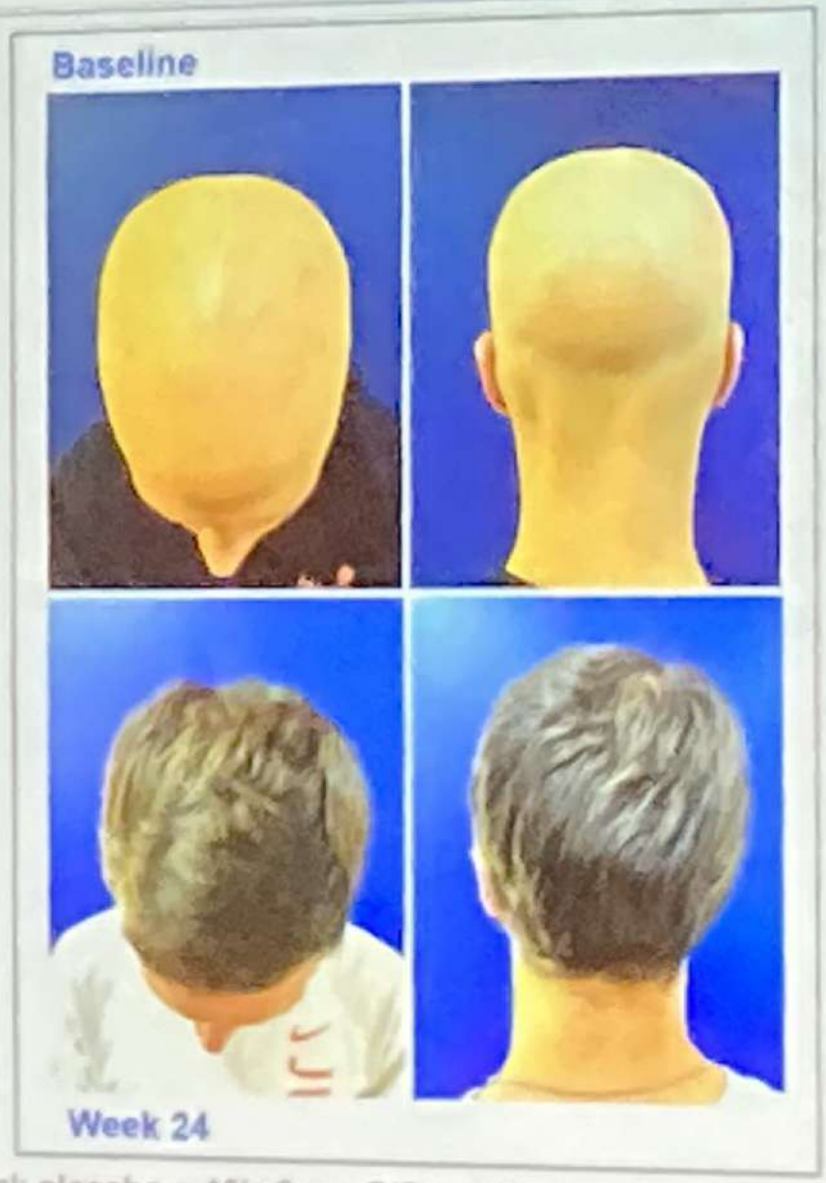
Both Doses of Deuruxolitinib Achieve Primary Efficacy Endpoint

THRIVE-AA2

Phase 3 study of deuruxolitinib in adults with moderate to severe alopecia areata

Proportion of Patients Achieving SALT Score ≤20 at Week 24



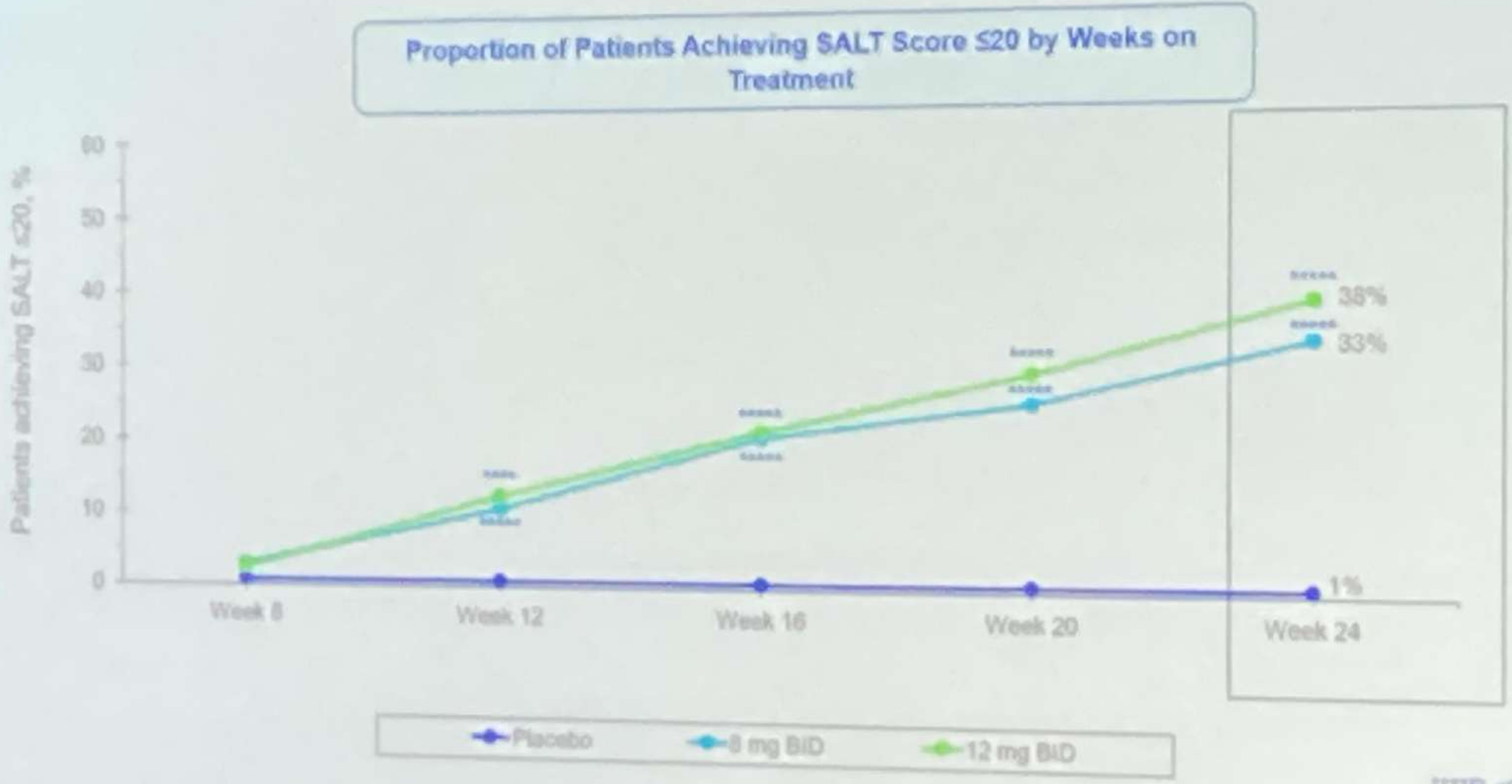


Proportion of patients achieving SALT score ≤20 at Week 24 from the THRIVE-AA1 trial: placebo = 1%; 8 mg BID = 30%; 12 mg BID = 42%

Proportion of Patients Achieving SALT Score ≤20 Over 24 Weeks of Deuruxolitinib Treatment

THRIVE-AA2

Phase 3 study of deuruxolitinib in adults with moderate to severe alopecia areata



****P <0.001 vs placebo

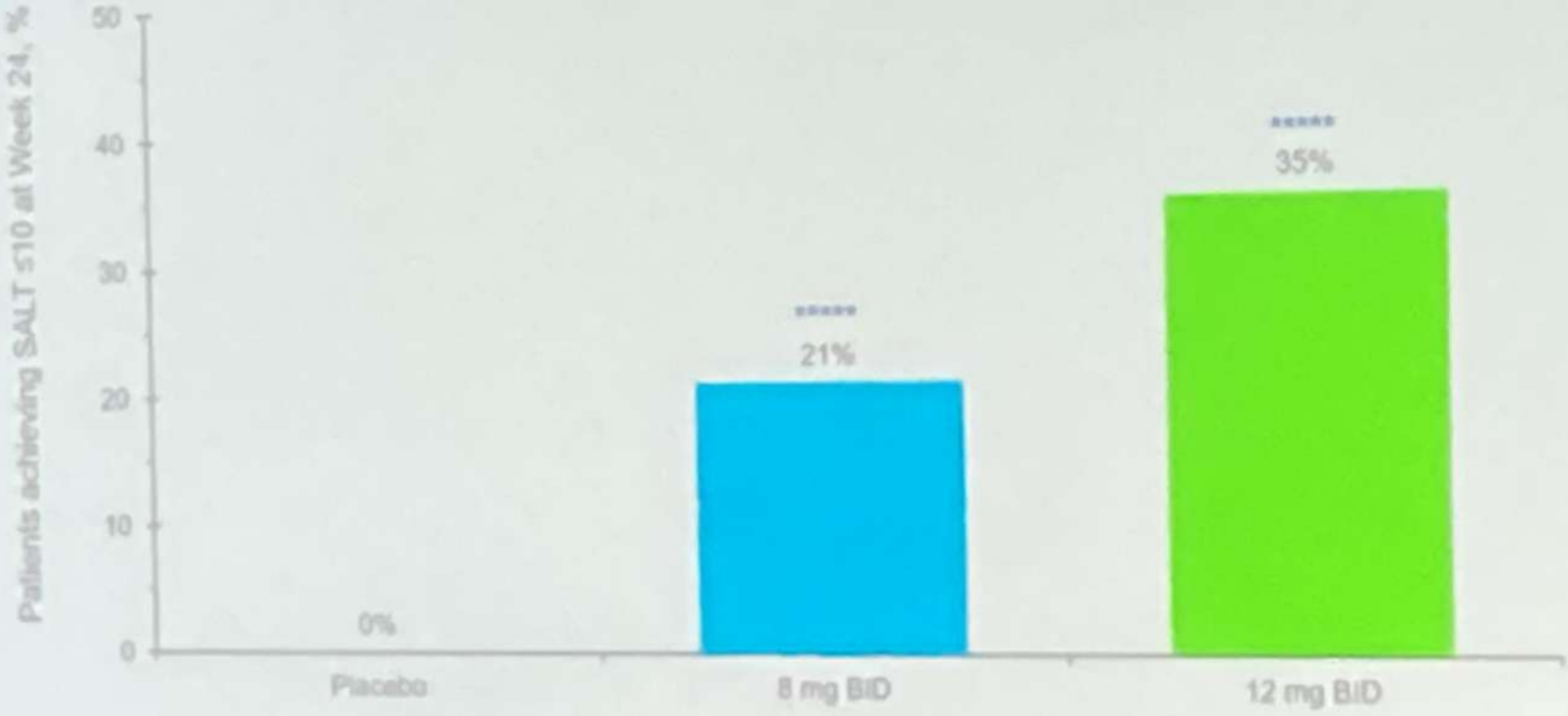
*****P <0.0001 vs placebo

Significant Effects on SALT Score ≤10

THRIVE-AA2

Phase 3 study of deuruxolitinib in adults with moderate to severe alopecia areata

Proportion of Patients Achieving SALT Score ≤10 at Week 24



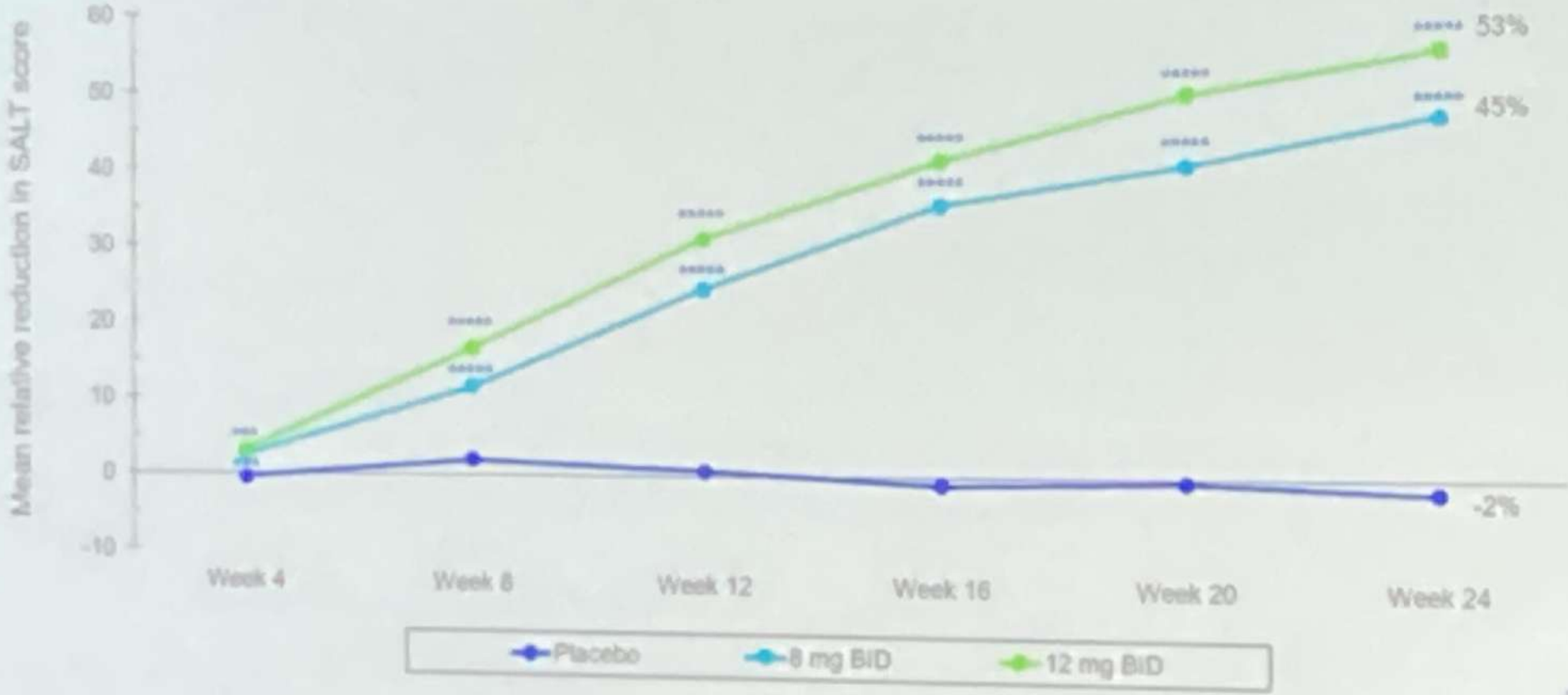
*****P <0.0001 vs placebo

Significant Changes in SALT Score as Early as Four Weeks

THRIVE-AA2

Phase 3 study of deuruxolitinib in adults with moderate to severe alopecia areata

Relative Change From Baseline SALT Score Over 24 Weeks



***P <0.01 vs placebo
***** P <0.0001 vs placebo

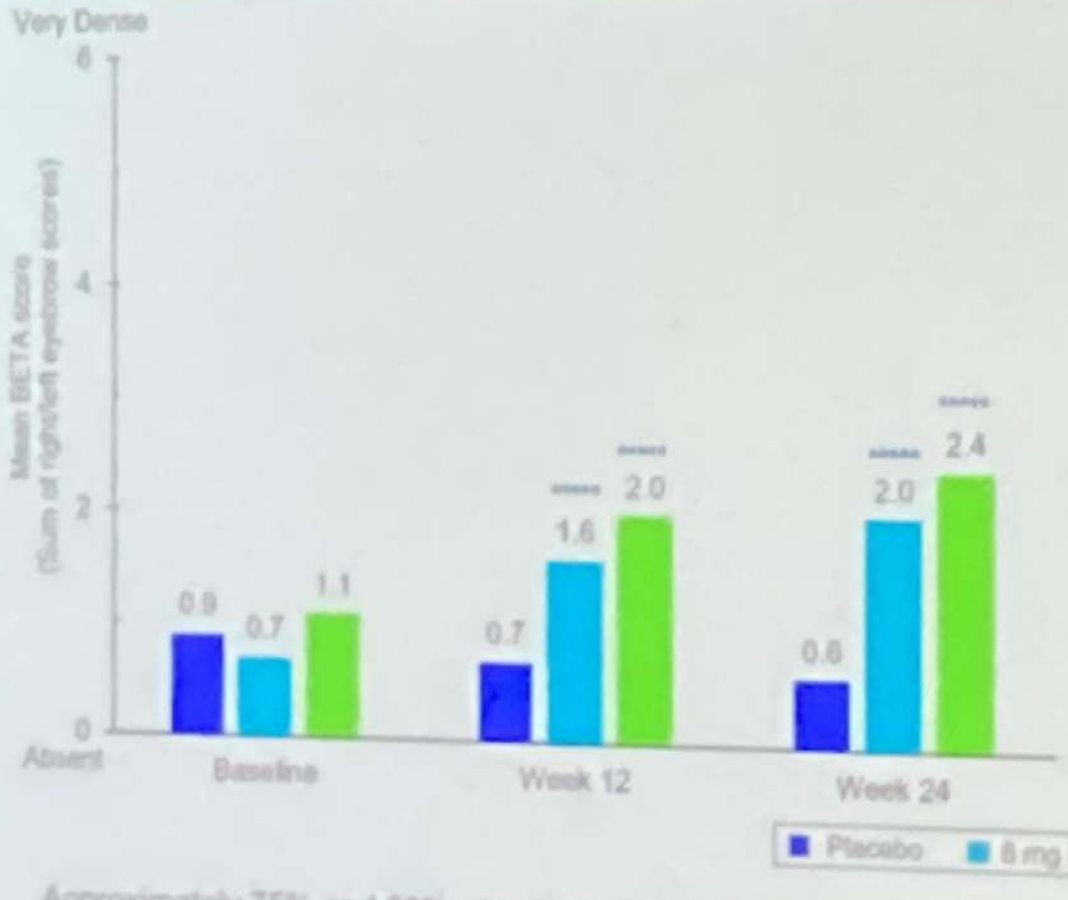
This graph represents a decrease (improvement) in SALT score relative to baseline

Significant Improvement in Eyebrow and Eyelash Regrowth

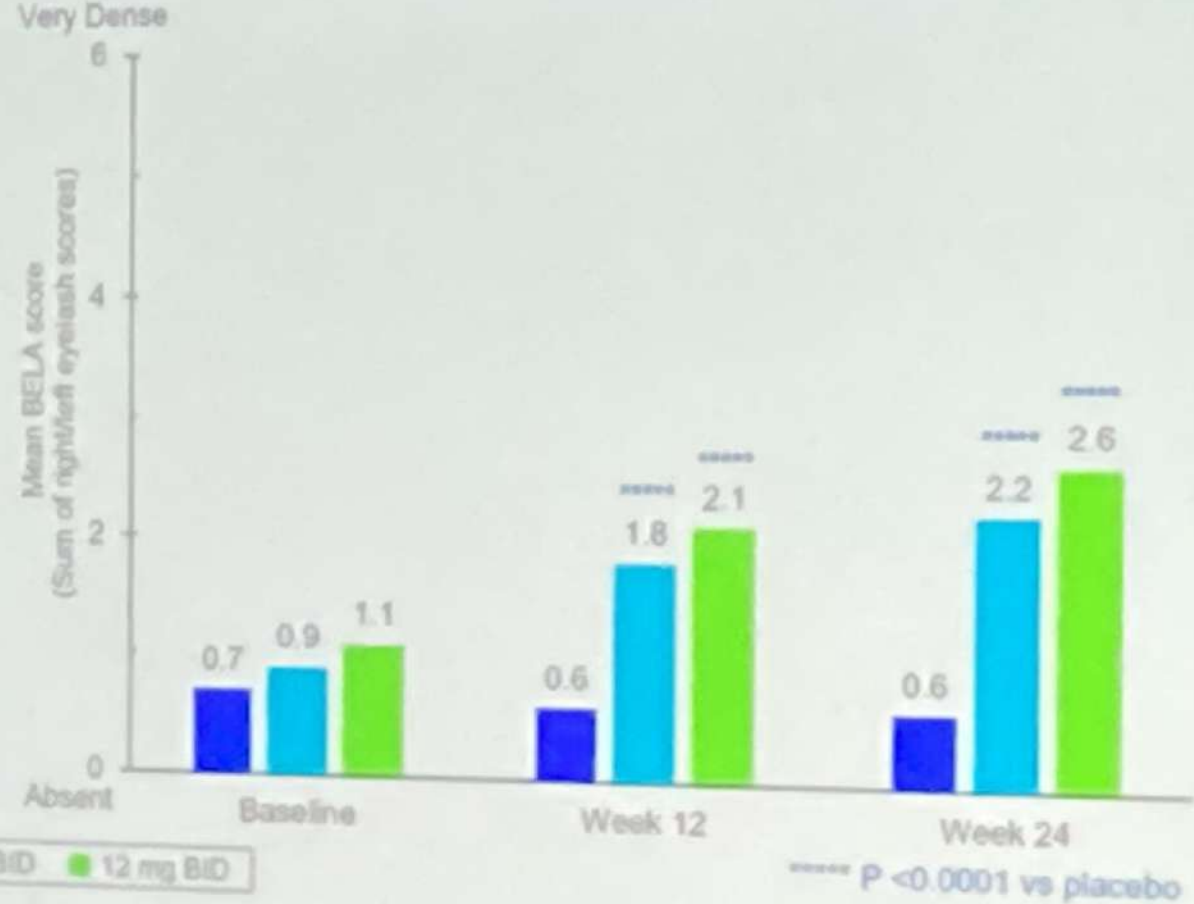
THRIVE-AA2

Phase 3 study of deuruxolitinib in adults with moderate to severe alopecia areata

BETA Score for Patients With Eyebrow Involvement at Baseline Only



BELA Score for Patients With Eyelash Involvement at Baseline Only

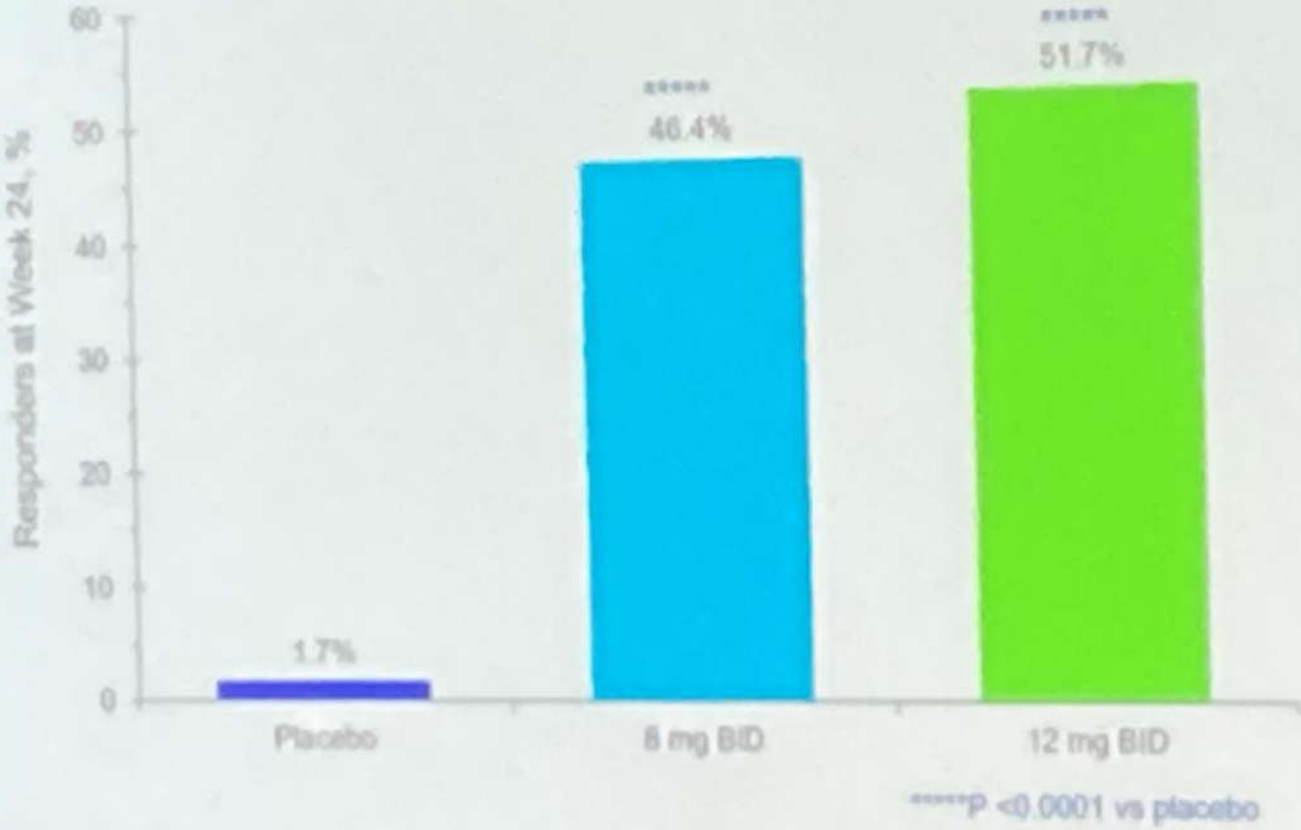


***** P <0.0001 vs placebo

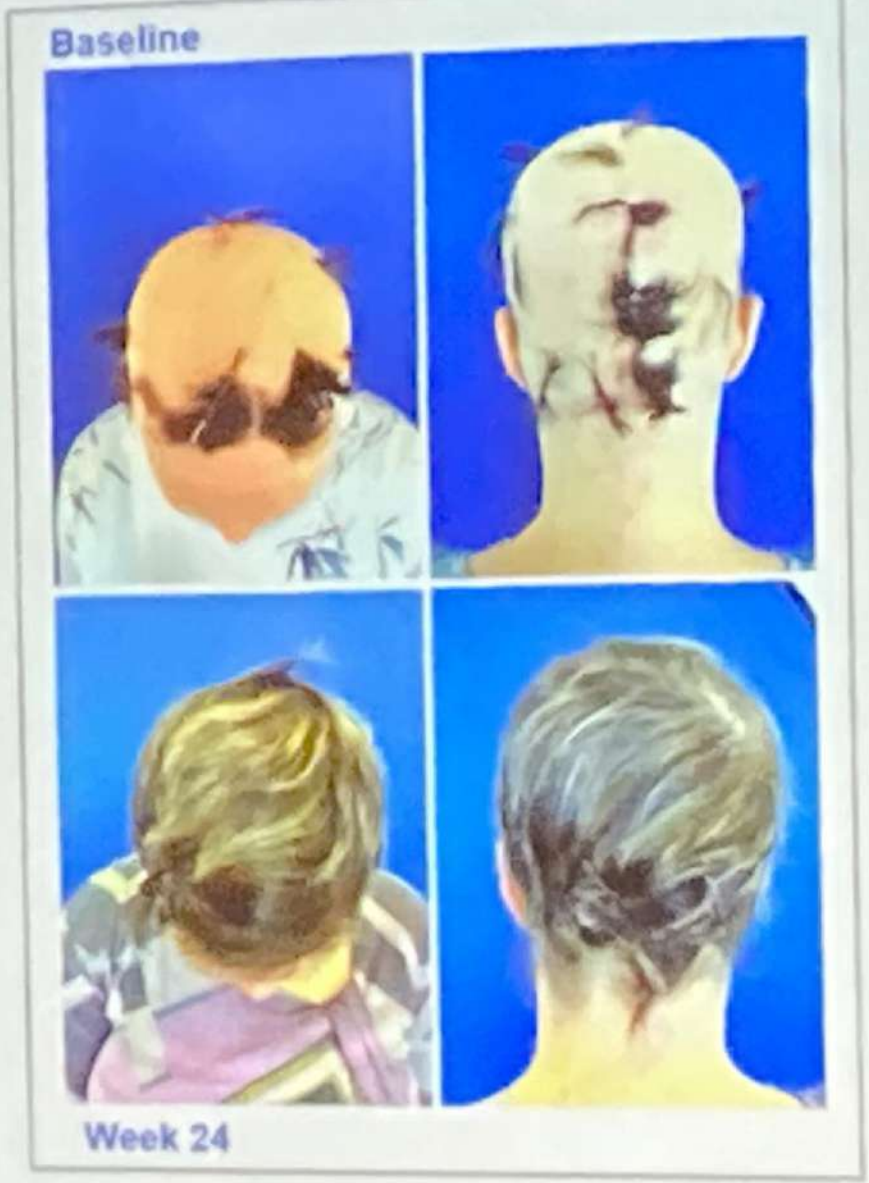
Approximately 75% and 69% of patients had eyebrow and eyelash involvement at Baseline, respectively

High Degree of Patient Satisfaction With Scalp Hair

Patient Response of 'Very Satisfied' or 'Satisfied' on SPRO at Week 24



*****P <0.0001 vs placebo



Responder: Patient responding as 'very satisfied' or 'satisfied' on SPRO

Serious Adverse Events

THRIVE-AA2
Phase 3 study of deuruxolitinib in adults with moderate to severe alopecia areata

	Placebo (n = 130)	Deuruxolitinib 8 mg BID (n = 256)	Deuruxolitinib 12 mg BID (n = 129)	Total (n = 515)
Total Serious TEAEs, n	0	3	2	5
Number of patients with any serious TEAEs, n %	0	3 (1.2)	2 (1.6)	5 (1.0)
Number of patients with related serious TEAEs, n %	0	1 (0.4)	0	1 (0.2)
Number of patients with not related serious TEAEs, n %	0	2 (0.8)	2 (1.6)	4 (0.8)

Summary of treatment-related SAEs

Placebo (n = 130)	Deuruxolitinib 8 mg BID (n = 256)	Deuruxolitinib 12 mg BID (n = 129)
	Pneumonia influenza	

Summary of unrelated SAEs by preferred term

Placebo (n = 130)	Deuruxolitinib 8 mg BID (n = 256)	Deuruxolitinib 12 mg BID (n = 129)
	Appendicitis	Radius fracture
	Migraine with aura	Osteoarthritis

There were no deaths or thromboembolic events reported in THRIVE-AA2.

FDA NEWS RELEASE

FDA Approves First Systemic Treatment for Alopecia Areata

Share | Tweet | Linkedin | Email | Print

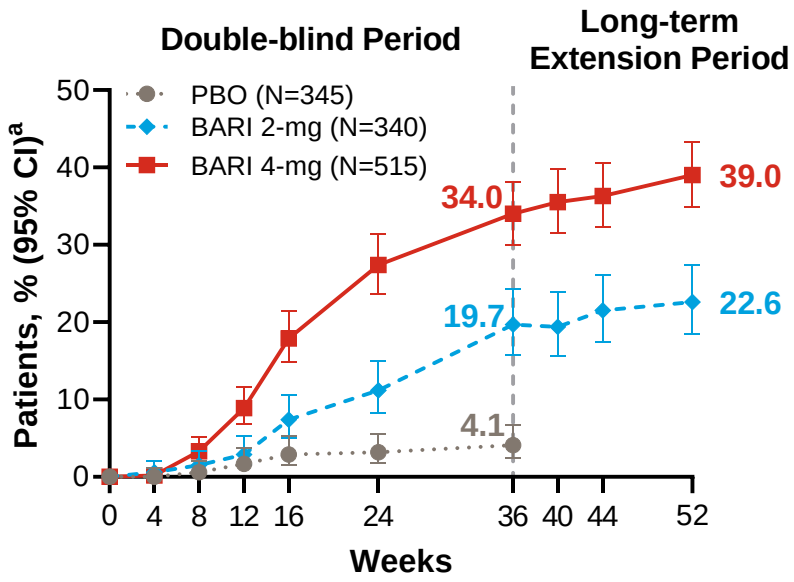
For Immediate Release: June 13, 2022

[a]CIs are constructed using the Wilson method, without continuity correction.
BARI = baricitinib; CI = confidence interval; PBO = placebo; SALT = Severity of Alopecia Tool.
Kwon O, et al. Presented at: AAD Annual Meeting; March 25-29, 2022; Boston, MA. Late-breaking abstract SO26.

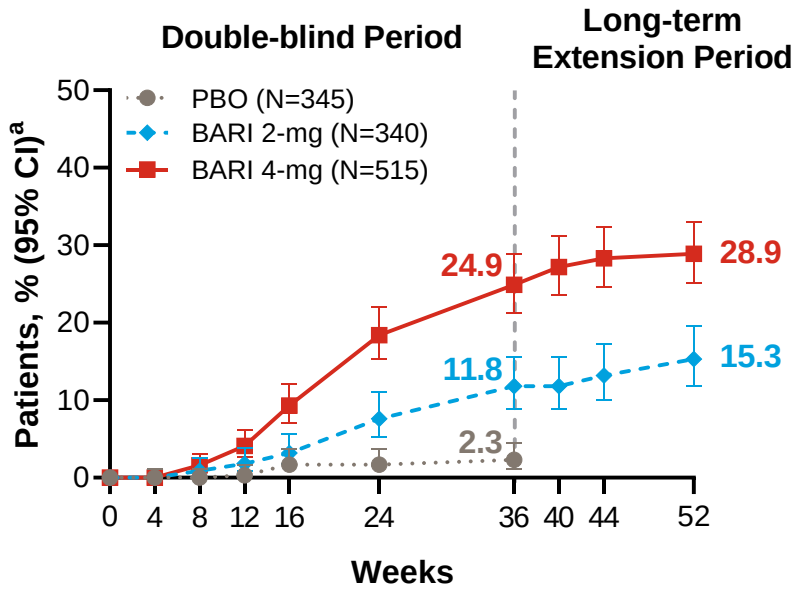
Proportion of Patients Achieving SALT Score ≤20 and SALT Score ≤10 Increased Over 52 Weeks of BARI Treatment, NRI – BRAVEE- AA1 y BRAVE-AA2

- SALT=0 full hair
- SALT = 100 no hair

SALT Score ≤20



SALT Score ≤10



- Proportions of patients achieving SALT score ≤20 and SALT score ≤10 were higher for patients treated with BARI 4-mg vs. BARI 2-mg

Non-responder imputation used for missing data

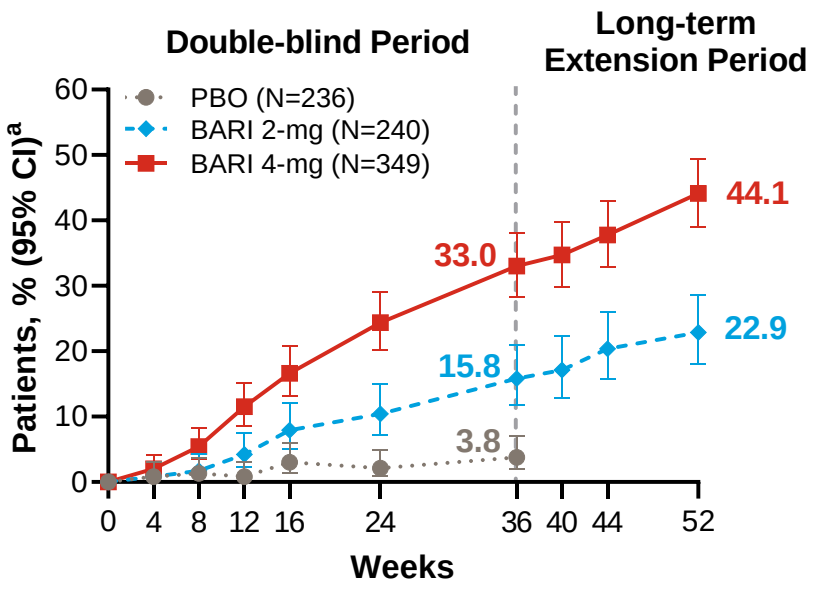
Patients randomized to BARI (4-mg or 2-mg QD) at baseline retained their treatment allocation through W52, whereas PBO non-responders were rescued at W36

[a] CIs are constructed using the Wilson method, without continuity correction

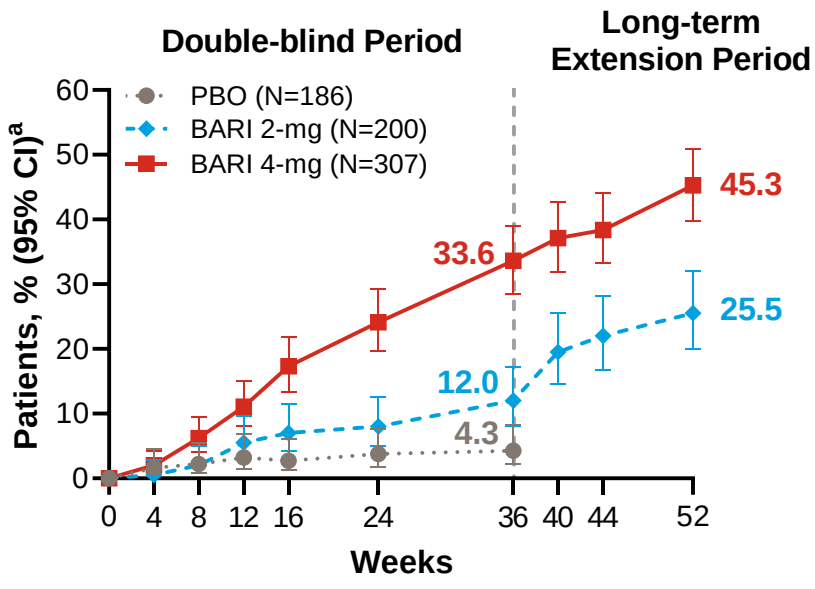
BARI=baricitinib; CI=confidence interval; PBO=placebo; SALT=Severity of Alopecia Tool

Continued Improvements in Eyebrow and Eyelash Hair Regrowth Were Observed Over 52 Weeks of BARI Treatment

ClinRO Measure for EB Hair Loss 0-1 With ≥2-Point Improvement From Baseline Among Patients With ClinRO EB ≥2 at Baseline



ClinRO Measure for EL Hair Loss 0-1 With ≥2-Point Improvement From Baseline Among Patients With ClinRO EL ≥2 at Baseline



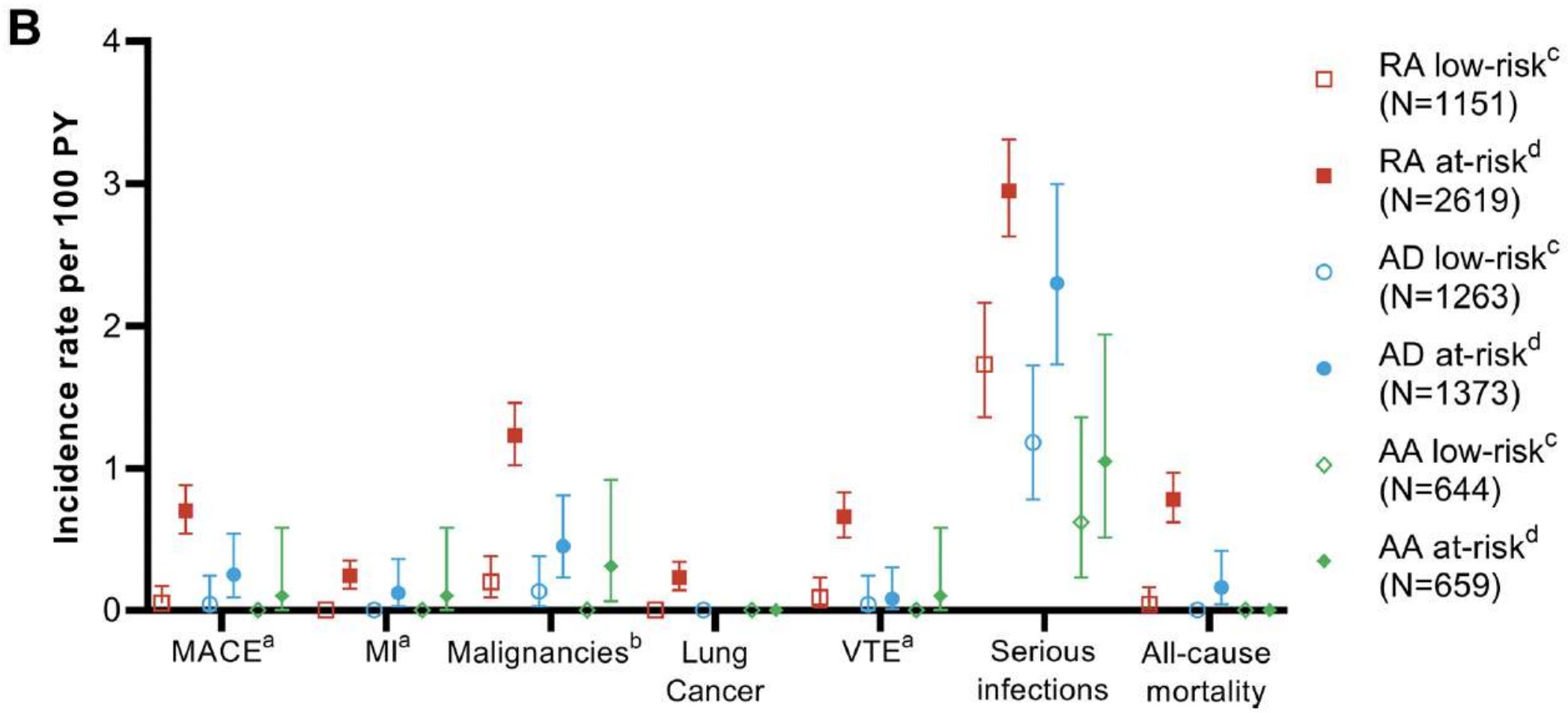
Non-responder imputation used for missing data. A score of 0 or 1 indicates full coverage or minimal gaps in eyebrows and eyelashes

Patients randomized to BARI (4-mg or 2-mg QD) at baseline retained their treatment allocation through W52, whereas PBO non-responders were rescued at W36

[a] CIs are constructed using the Wilson method, without continuity correction

BARI=baricitinib; CI=confidence interval; ClinRO=clinician-reported outcome; EB=eyebrow; EL=eyelash; PBO=placebo

Baricitinib Safety for Events of Special Interest in Populations at Risk



Taylor PC, et al. Adv Ther. 2023 Feb 20:1–17.

Long-Term Efficacy of Baricitinib in Alopecia Areata: 104-Week Results From BRAVE-AA1 and BRAVE-AA2

Maryanne M. Senna,[1] Arash Mostaghimi,[2] Manabu Ohyama,[3] Rodney Sinclair,[4] Yves Dutronc,[5] Wen-Shuo Wu,[5] Guanglei Yu,[5] Chiara Chiasserini,[5] Najwa Somani,[5] Brett King[6]

[1]Lahey Hospital and Medical Center and Harvard Medical School, Boston, USA; [2]Brigham and Women's Hospital, Boston, USA; [3]Kyorin University Faculty of Medicine, Tokyo, Japan; [4]Sinclair Dermatology, Melbourne, Australia; [5]Eli Lilly and Company, Indianapolis, USA; [6]Yale School of Medicine, New Haven, USA

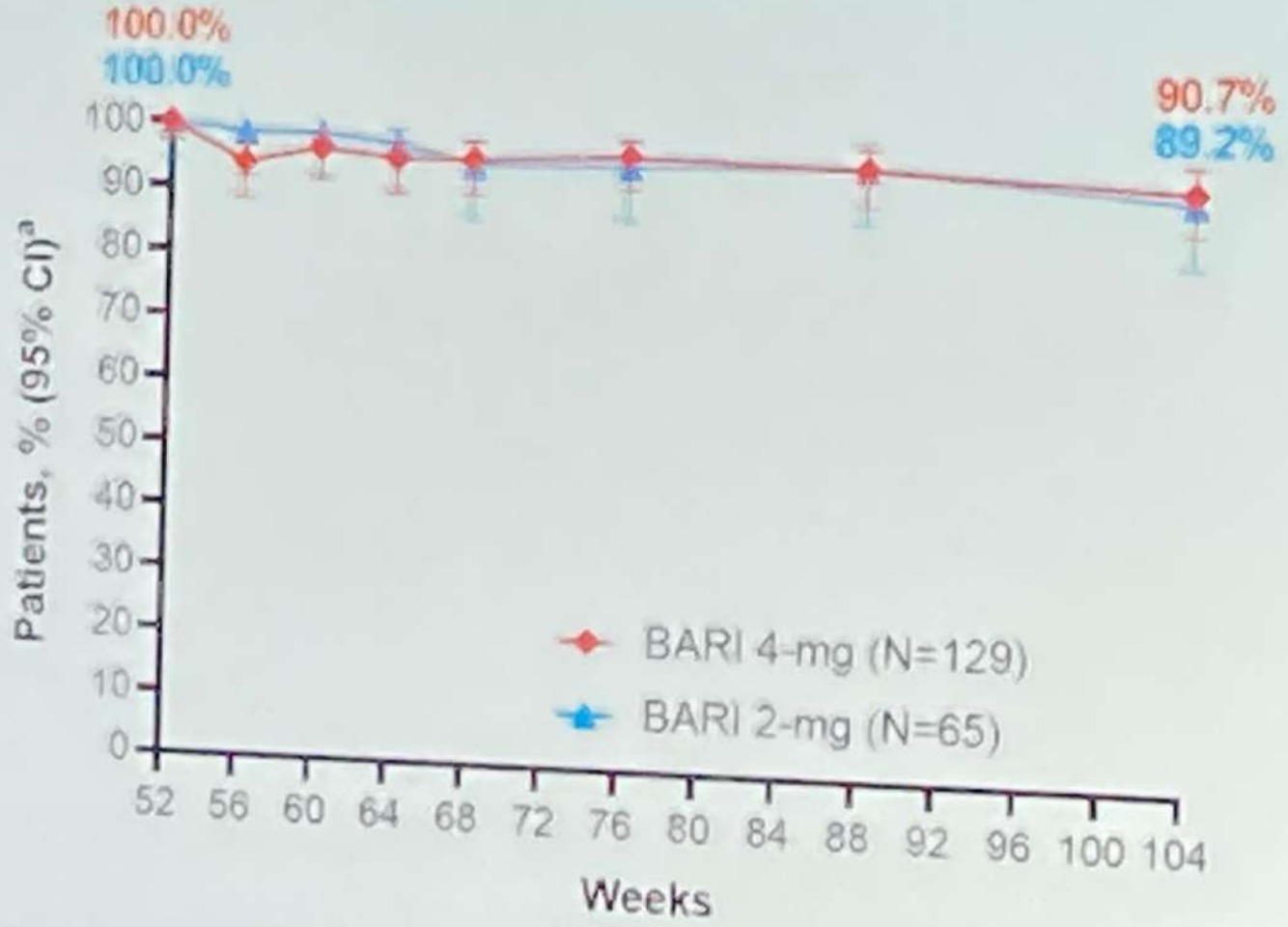
DISCLOSURES: **M. M. Senna** has served on advisory boards and/or has been a consultant for: Arena Pharmaceuticals, Concert Pharmaceuticals, Eli Lilly and Company, and Pfizer; and is a clinical trial investigator for: Concert Pharmaceuticals and Eli Lilly and Company; **A. Mostaghimi** has been a consultant for: AbbVie, Concert Pharmaceuticals, Digital Diagnostics, Eli Lilly and Company, and Pfizer; **M. Ohyama** has received lecture and advisory fees from: Eli Lilly Japan K.K., Janssen, Pfizer Japan, Rohto Pharmaceutical, and Taisho Pharmaceutical; and has received research grants from: Advantest Corporations, Maruho, Shiseido, and Sun Pharma Japan; **R. Sinclair** has been an investigator for and/or provided professional services to: AbbVie, Aarotek Scientific, Akeso Biopharma, Amgen, Arcutis, Arena Pharmaceuticals, Ascend Laboratories, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Coherus BioSciences, Connect Biopharma, Cutanea, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Janssen, LEO Pharma, Medimmune, Merck Sharp & Dohme, Novartis, Oncobiologics, Pfizer, Regeneron, Reistone Biopharma, Roche, Samson Medical Technologies, Sanofi, Sun Pharma, and UCB Pharma; **Y. Dutronc**, **W. Wu**, **G. Yu**, **C. Chiasserini**, and **N. Somani** are employees and shareholders of: Eli Lilly and Company; **B. King** has served on advisory boards and/or is a consultant and/or clinical trial investigator for: AbbVie, Almirall, AltruBio, AnaptysBio, Arena Pharmaceuticals, Bioniz Therapeutics, Bristol Myers Squibb, Concert Pharmaceuticals, Eli Lilly and Company, Horizon Therapeutics, Incyte Corporation, LEO Pharma, Otsuka/Visterra, Pfizer, Regeneron, Sanofi Genzyme, TWi Biotechnology, and Viela Bio; and is on speaker's bureaus for: AbbVie, Incyte Corporation, LEO Pharma, Pfizer, Regeneron, and Sanofi Genzyme

Medical writing assistance was provided by Loredana Sporni, PhD, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company

Sponsored by Eli Lilly and Company, under license from Incyte Corporation

Clinically Meaningful Scalp Hair Regrowth Was Maintained Through Week 104 in ~90% of Patients Treated With BARI 4-mg or 2-mg Who Responded at Week 52

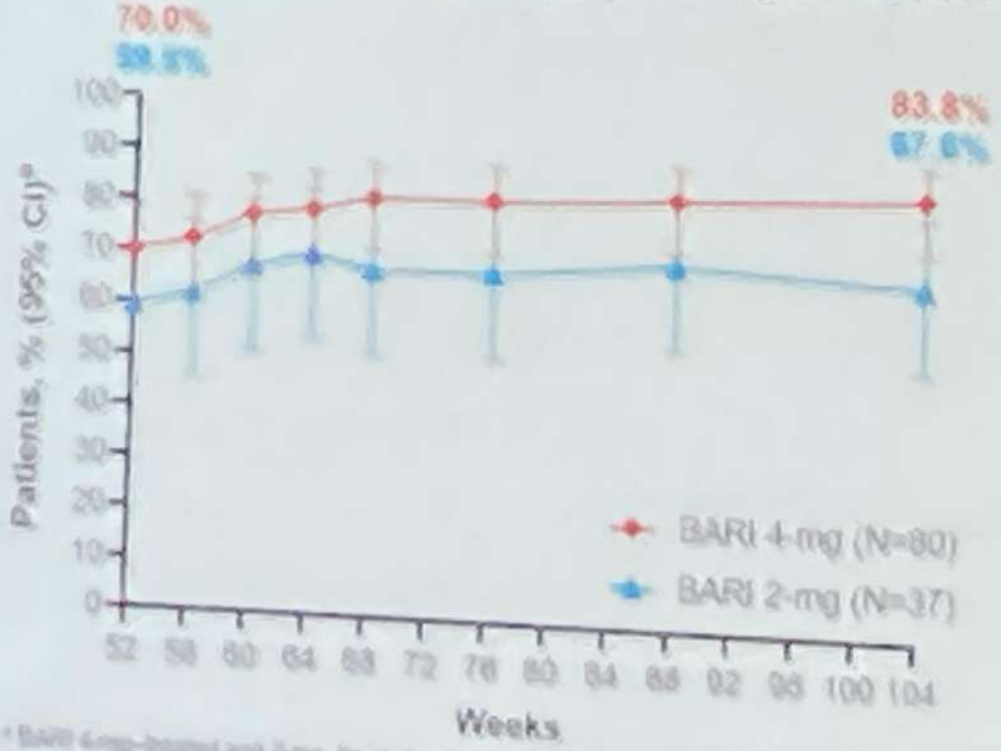
Proportion of Week 52 Responders[a] Who Achieved SALT Score ≤20 Through Week 104



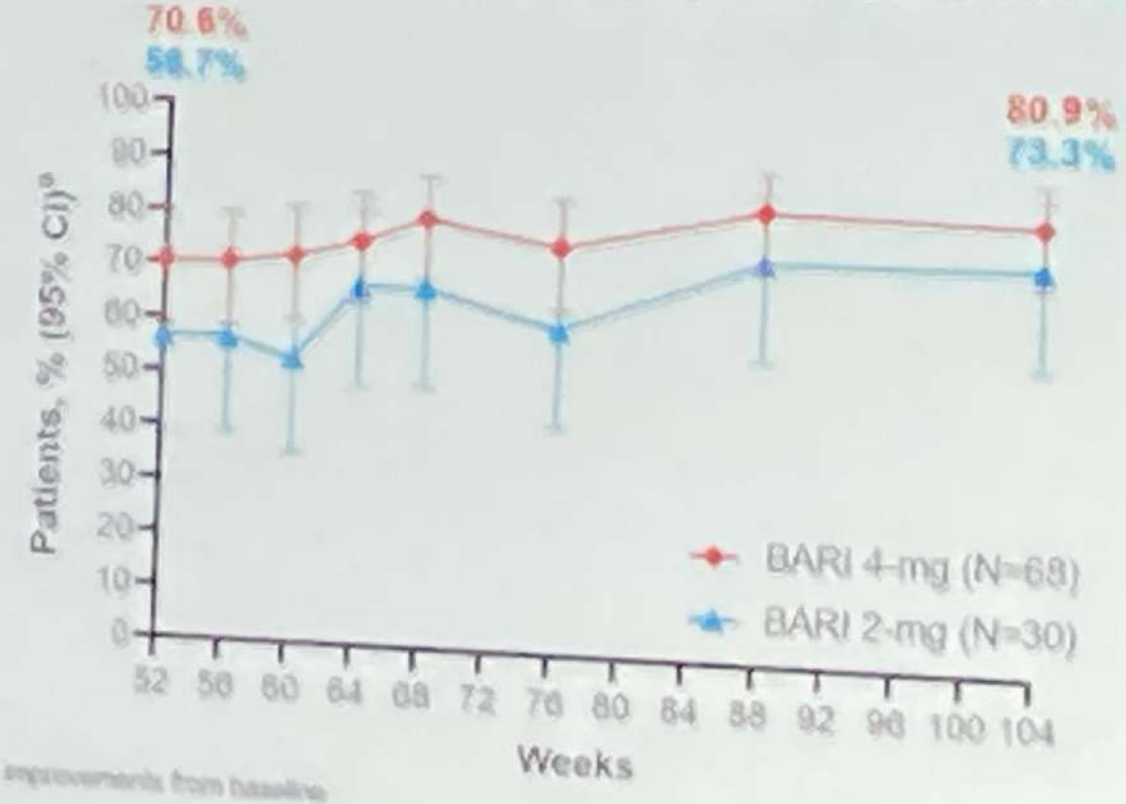
[a]Patients who achieved SALT score ≤20 at Week 52.
Note: Data were summarized with mLOCF imputation.
BARI=baricitinib; CI=confidence interval; mLOCF=modified last observation carried forward; SALT=Severity of Alopecia Tool

Proportion of Patients Achieving Complete or Nearly Complete Regrowth of Eyebrows and Eyelashes Increased From Week 52 Through Week 104 Among Week 52 Responders[a]

Proportion of Week 52 Responders[a]
With ClinRO EB ≥2 at Baseline
Who Achieved ClinRO EB (0,1)[b] Through Week 104



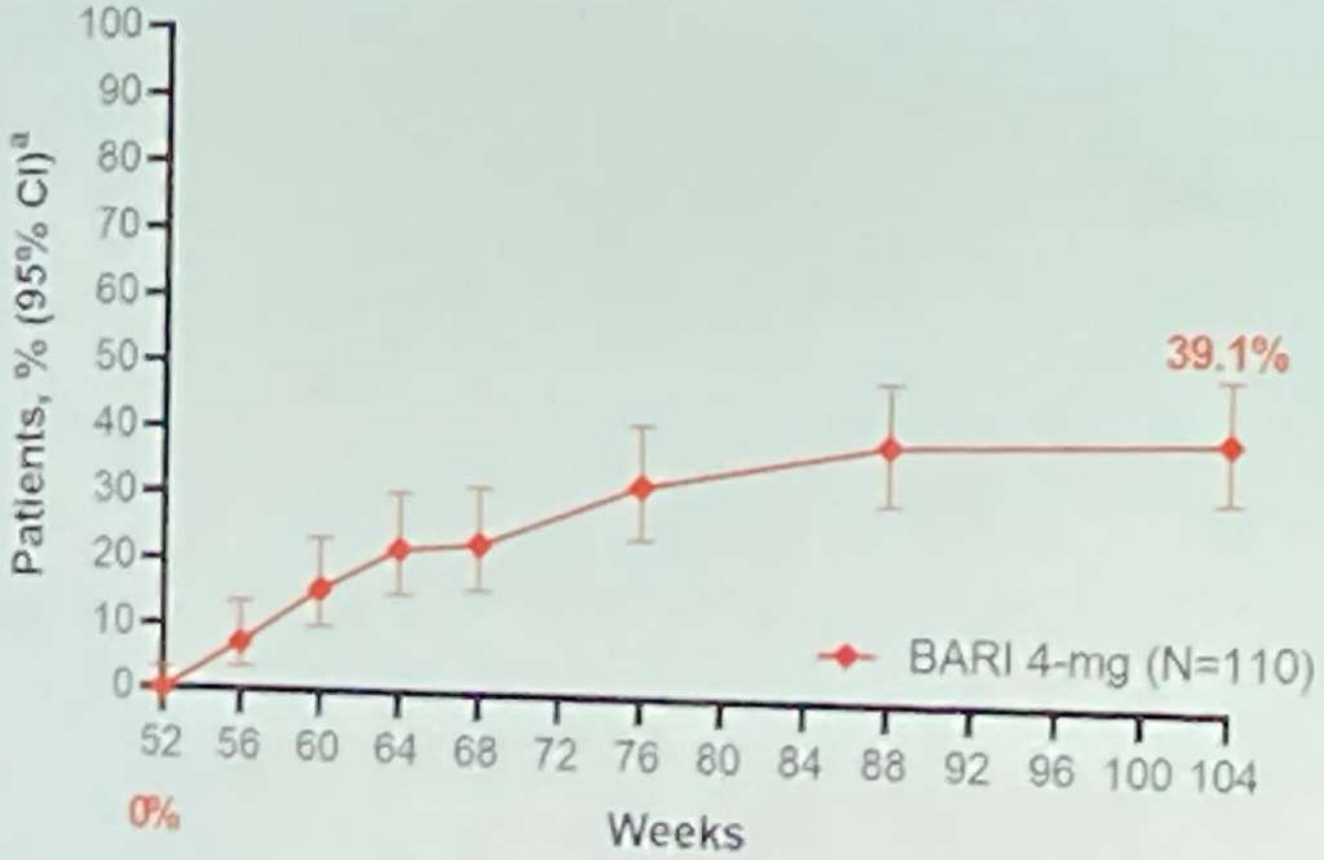
Proportion of Week 52 Responders[a]
With ClinRO EL ≥2 at Baseline
Who Achieved ClinRO EL (0,1)[b] Through Week 104



[a] BARI 4-mg–treated and 2-mg–treated patients with SALT score ≤20 at Week 52. [b] With ≥2-point improvements from baseline.
Note: Data were normalized with mLOCF imputation.
BARI=baricitinib; CI=confidence interval; ClinRO=clinician-reported outcome; ClinRO EB=ClinRO Measure for Eyebrow Hair Loss; ClinRO EL=ClinRO Measure for Eyelash Hair Loss; mLOCF=modified last observation carried forward; SALT=Severity of Alopecia Tool.

Almost 40% of Week 52 Mixed Responders Achieved Clinically Meaningful Scalp Hair Regrowth at Week 104

Proportion of Week 52 Mixed Responders Who Achieved SALT Score ≤20 Through Week 104

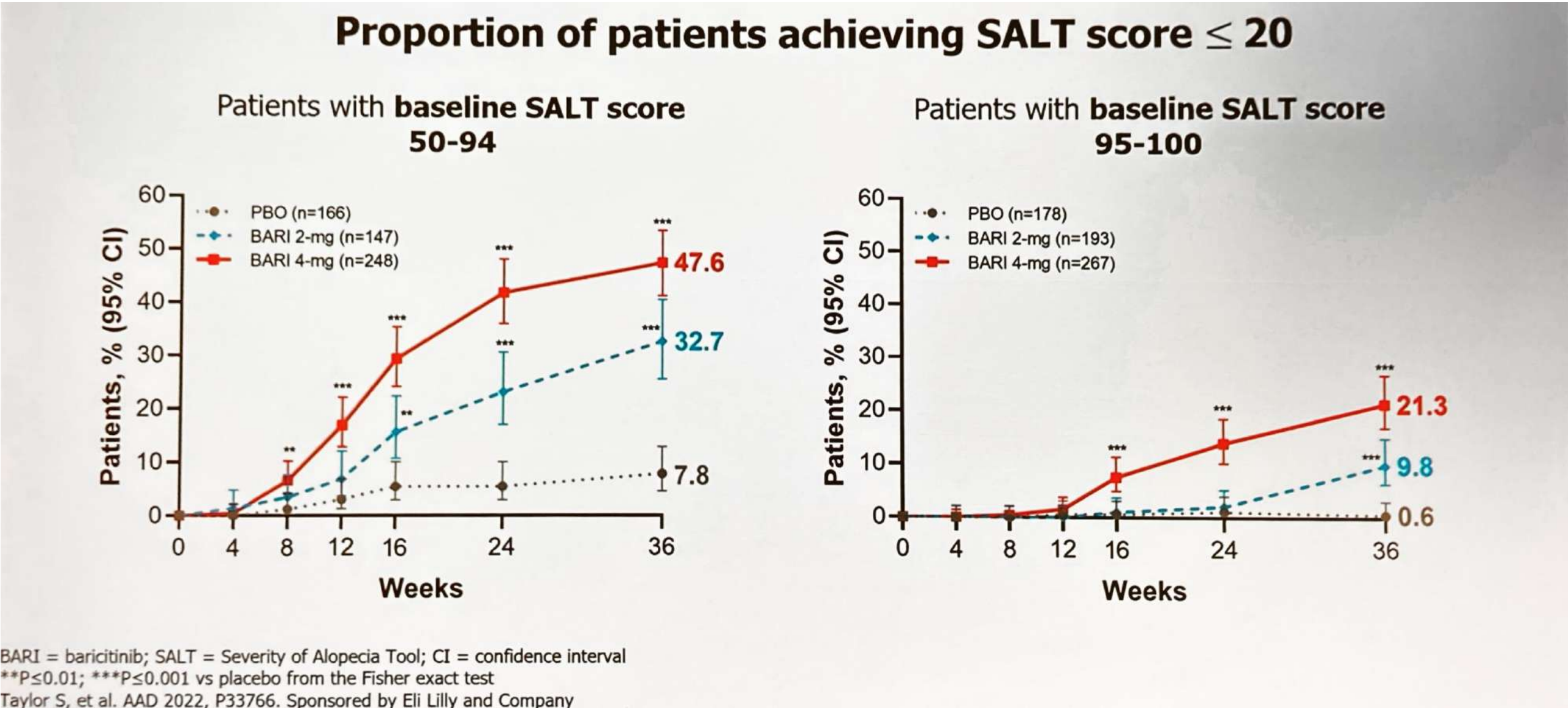


[a] BARI 4-mg–treated patients who had SALT score >20 at Week 52 but had reached SALT score ≤20 at prior visit(s) and/or patients with ClinRO EB/EL scores ≥2 at baseline who had achieved a ClinRO EB/EL improvement from baseline of ≥2 points at Week 52

BARI=baricitinib; CI=confidence interval; ClinRO=clinician-reported outcome; ClinRO EB=ClinRO Measure for Eyebrow Hair Loss; ClinRO EL=ClinRO Measure for Eyelash Hair Loss; SALT=Severity of Alopecia Tool

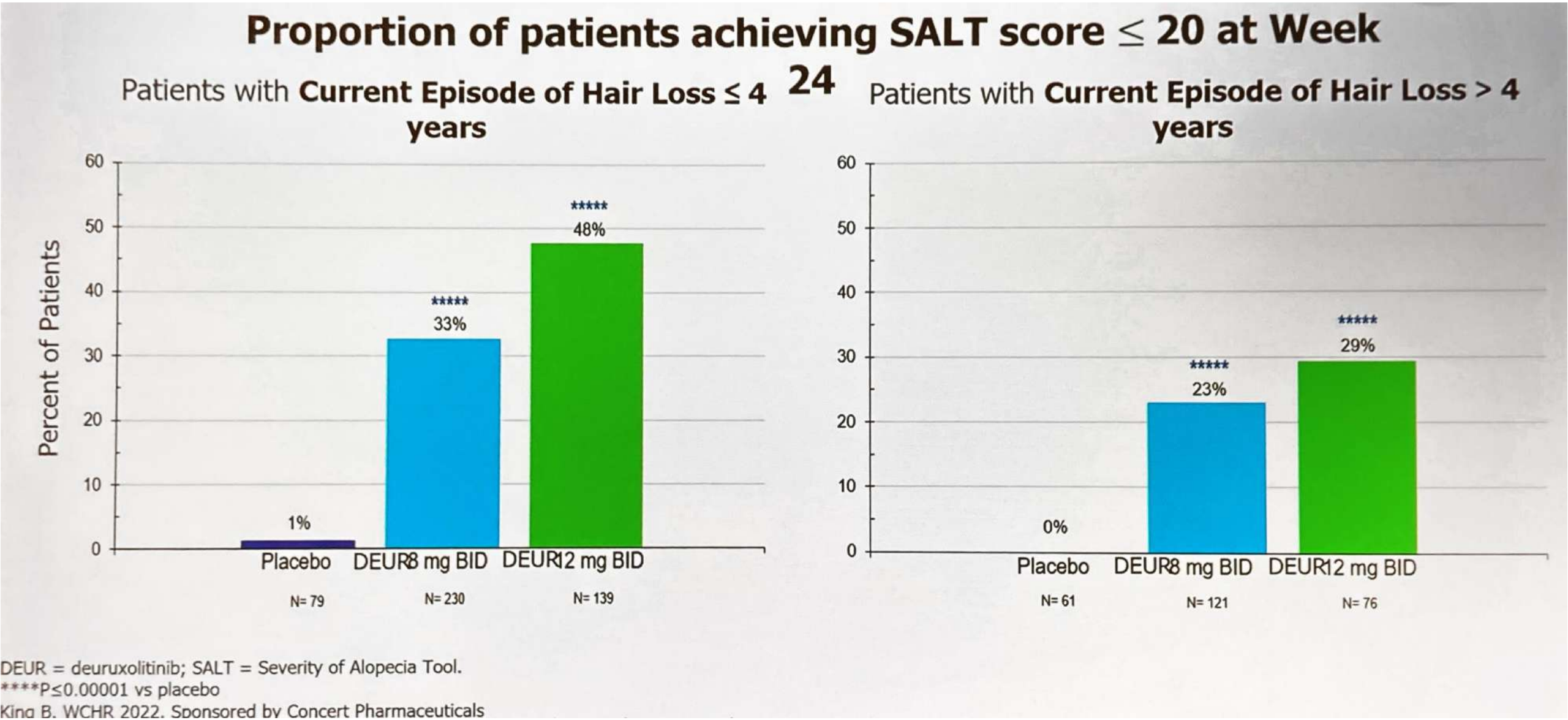
Practical Considerations

Factors that Impact Efficacy: Baseline SALT Score



BARI = baricitinib; SALT = Severity of Alopecia Tool; CI = confidence interval
**P≤0.01; ***P≤0.001 vs placebo from the Fisher exact test
Taylor S, et al. AAD 2022. P33766. Sponsored by Eli Lilly and Company

Factors that Impact Efficacy: Duration of Current Episode of Severe Disease

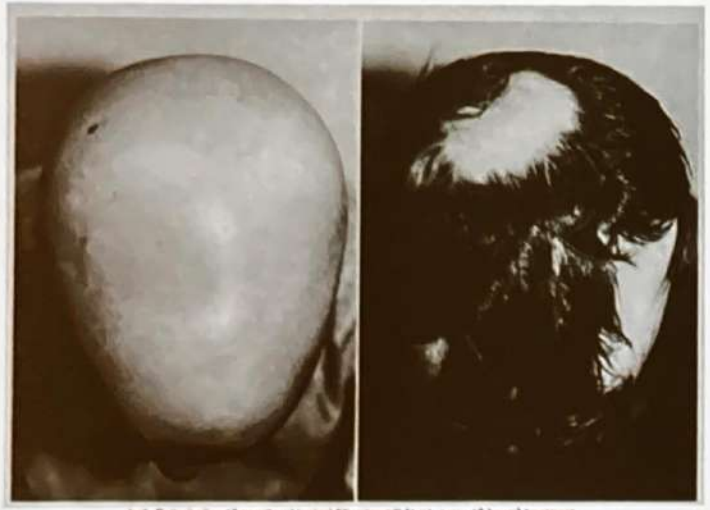


DEUR = deuruxolitinib; SALT = Severity of Alopecia Tool.
****P≤0.00001 vs placebo
King B. WCHR 2022. Sponsored by Concert Pharmaceuticals

Repurposing of Oral Minoxidil for Alopecia Areata

Evaluation of Oral Minoxidil in the Treatment of Alopecia Areata

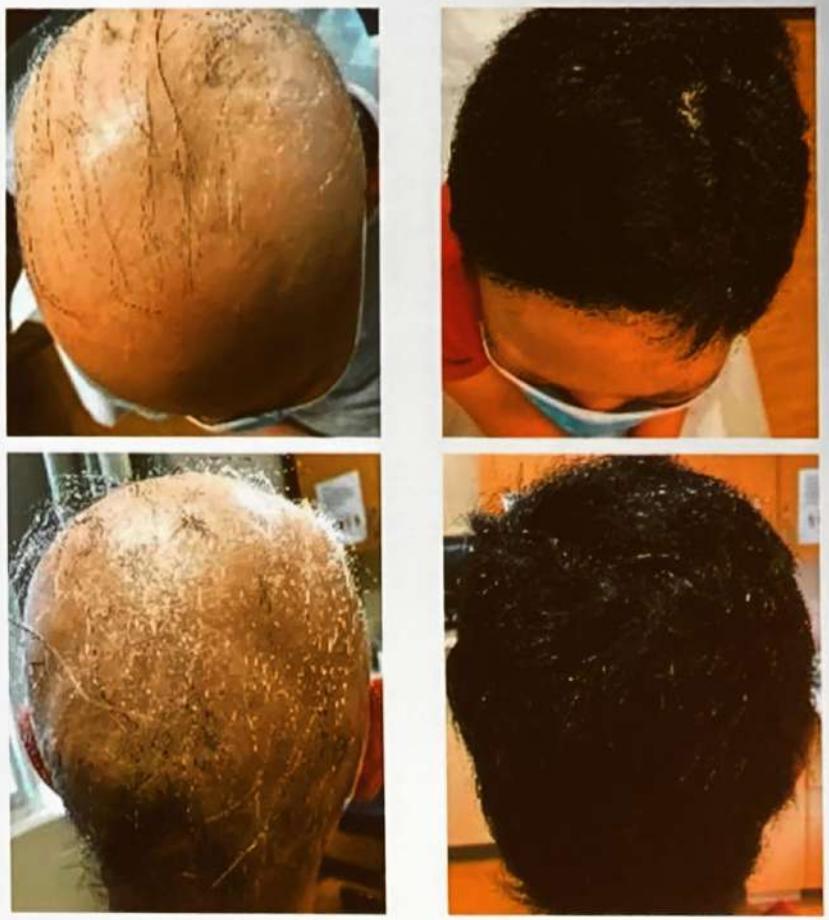
- Minoxidil 5 mg twice daily
- Cosmetic response in 12/65 patients (18%)
  - In 8/21 patients (38%) with < 75% scalp hair loss
  - In 4/44 patients (9%) with ≥ 75% scalp hair loss



Left, Patient after 15 months of topical 5% minoxidil (1 mL every 12 hours) treatment. Right, Same patient after four months of oral minoxidil (5 mg every 12 hours) treatment.

Fiedler-Weiss VC, et al. Arch Derm. 1987;123:1488-1490
Photos courtesy of Brett King, MD, PhD.

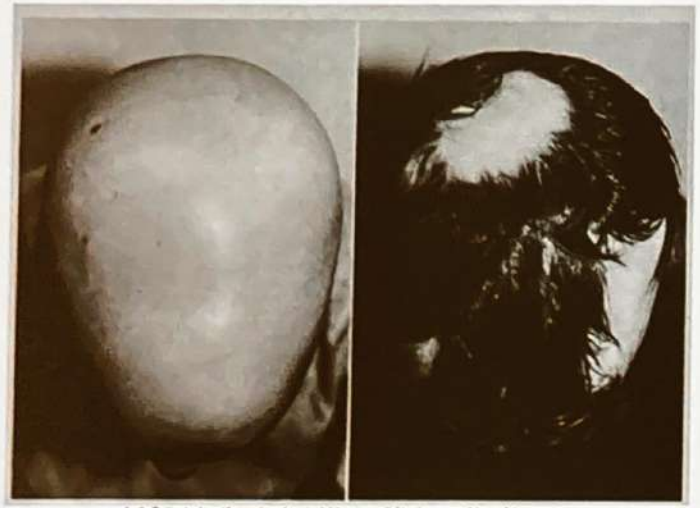
Before and After Minoxidil 2.5 mg BID + Spironolactone 25 mg BID for 4 months



Repurposing of Oral Minoxidil for Alopecia Areata

Evaluation of Oral Minoxidil in the Treatment of Alopecia Areata

- Minoxidil 5 mg twice daily
- Cosmetic response in 12/65 patients (18%)
  - In 8/21 patients (38%) with < 75% scalp hair loss
  - In 4/44 patients (9%) with ≥ 75% scalp hair loss



Left, Patient after 15 months of topical 5% minoxidil (1 mL every 12 hours) treatment. Right, Same patient after four months of oral minoxidil (5 mg every 12 hours) treatment.

Combination tofacitinib and oral minoxidil treatment for severe alopecia areata

8/12 patients (67%) achieved $SALT_{75}$ (≥ 75% scalp hair regrowth), 7 of whom (58% of all the patients) achieved hair regrowth taking tofacitinib 5 mg twice daily over 3 to 9 months

Adjuvant oral minoxidil for the treatment of alopecia areata refractory to Janus kinase inhibitors

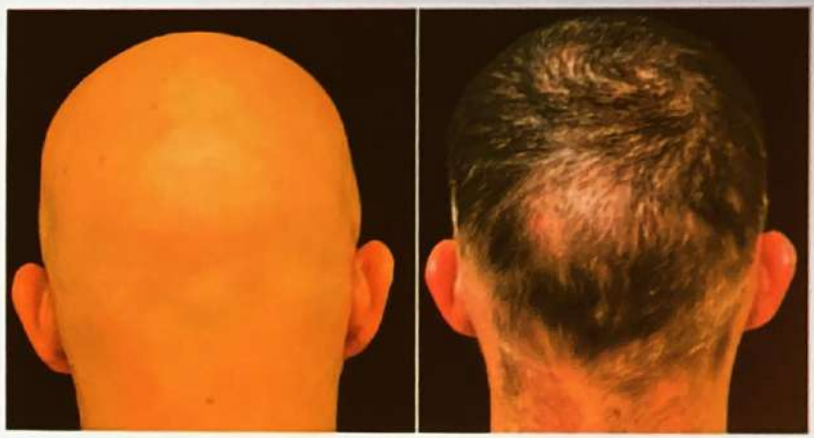
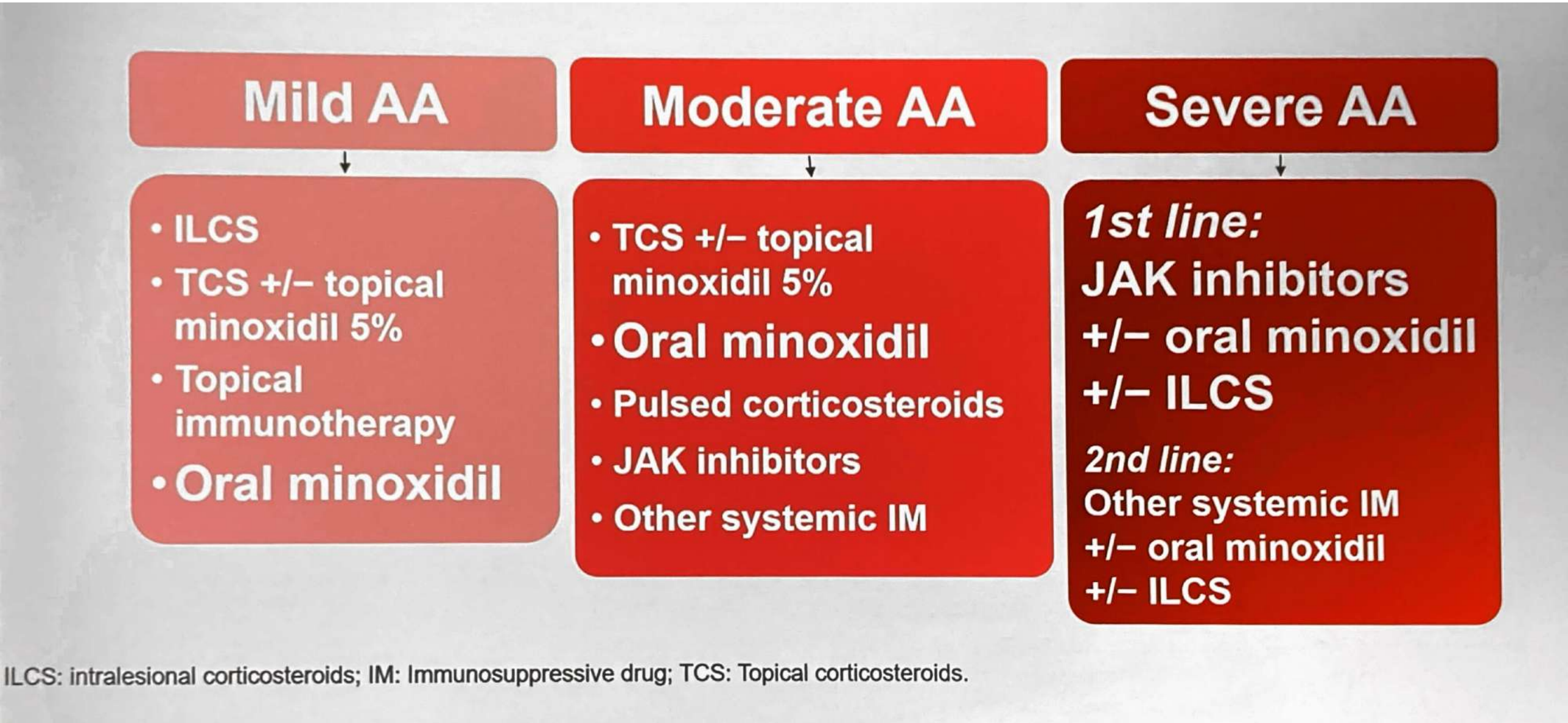


FIGURE 2: Alopecia areata unresponsive to JAK inhibitor monotherapy. Left: After 6 months of ruxolitinib 25 mg twice daily, Severity of Alopecia Tool (SALT) score was 100% (same as prior to starting ruxolitinib). Right: Nine months after starting adjuvant oral minoxidil (AOM), SALT score was 23%.

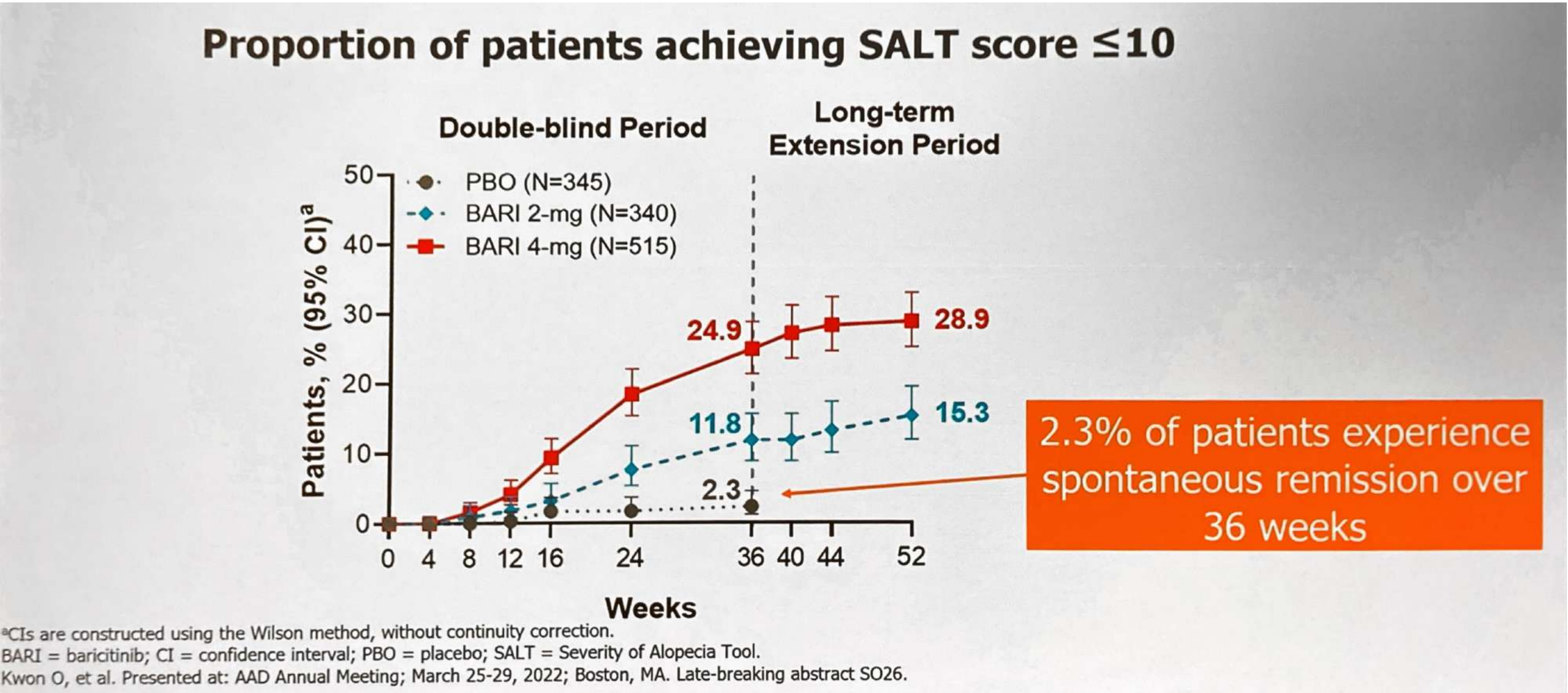
Fiedler-Weiss VC, et al. Arch Derm. 1987;123:1488-1490; Wambier CG, et al. J Am Acad Dermatol. 2021;85:743-745; Wambier CG, et al. Surg Cosmet Dermatol. Rio de Janeiro. 2020;12:74-75.

Alopecia Areata Treatment Algorithm



ILCS: intralesional corticosteroids; IM: Immunosuppressive drug; TCS: Topical corticosteroids.

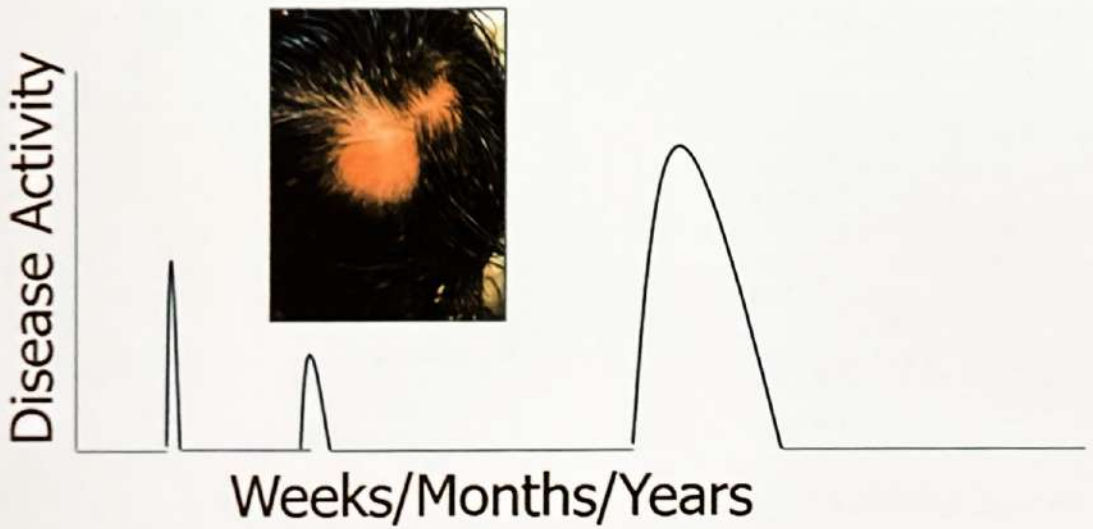
Spontaneous Remission of Alopecia Areata: 2.3% at 36 Weeks



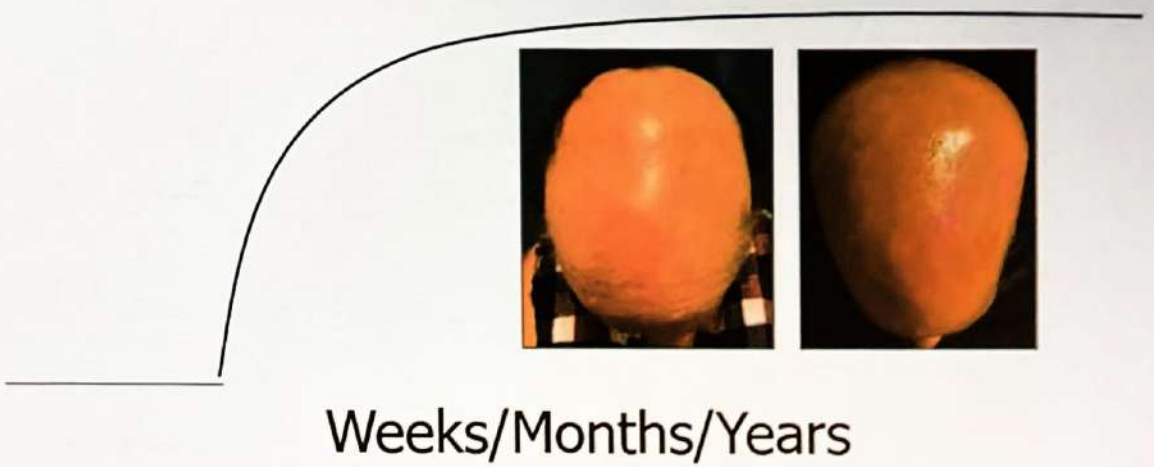
[a]CIs are constructed using the Wilson method, without continuity correction.
BARI = baricitinib; CI = confidence interval; PBO = placebo; SALT = Severity of Alopecia Tool.
Kwon O, et al. Presented at: AAD Annual Meeting; March 25-29, 2022; Boston, MA. Late-breaking abstract SO26.

Natural History of Alopecia Areata

In cases of ***limited hair loss***, spontaneous remission is not uncommon, though many patients will have **unpredictable, relapsing and remitting disease**



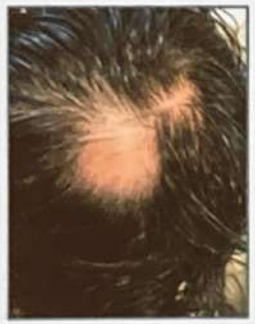
In cases of ***severe hair loss***, hair loss is **chronic** and **spontaneous remission is *rare***



Photos courtesy of Brett King, MD, PhD.

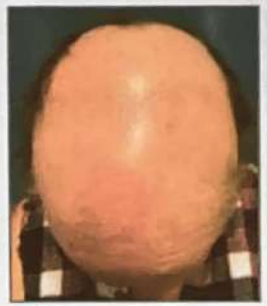
Natural History of Alopecia Areata

In cases of ***limited hair loss***, spontaneous remission is not uncommon, though many patients will have **unpredictable, relapsing and remitting disease**



In cases of ***severe hair loss***, hair loss is **chronic** and **spontaneous remission is**

Everybody asks "When to stop JAK inhibitor treatment?"



The answer: "As long as the person wants to have hair."

Photos courtesy of Brett King, MD, PhD.

Long-Term Treatment of Alopecia Areata with Baricitinib

EMA

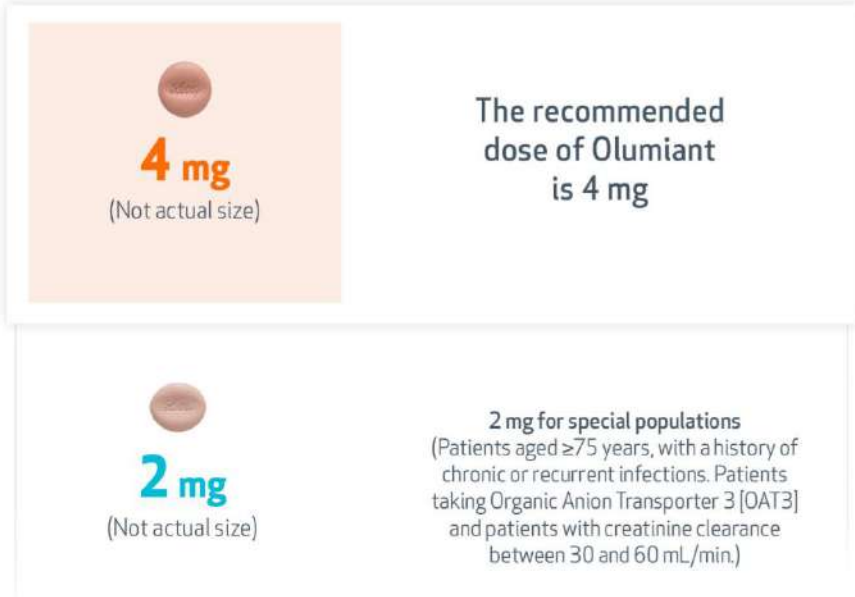
Alopecia areata

La dosis recomendada de baricitinib es de 4 mg una vez al día. Una dosis de 2 mg una vez al día puede ser apropiada para pacientes como los de edad ≥ 75 años y para pacientes con antecedentes de infecciones crónicas o recurrentes. También puede considerarse una dosis de 2 mg una vez al día para los pacientes que hayan logrado un control sostenido de la actividad de la enfermedad con 4 mg una vez al día y sean aptos para reducción de dosis (ver sección 5.1).

Una vez alcanzada una respuesta estable, se recomienda continuar el tratamiento durante al menos varios meses, para evitar recaídas. El balance beneficio-riesgo del tratamiento se debe reevaluar a intervalos regulares de forma individual.

Se debe considerar la interrupción del tratamiento en pacientes que no muestren evidencia de beneficio terapéutico después de 36 semanas de tratamiento.

https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf



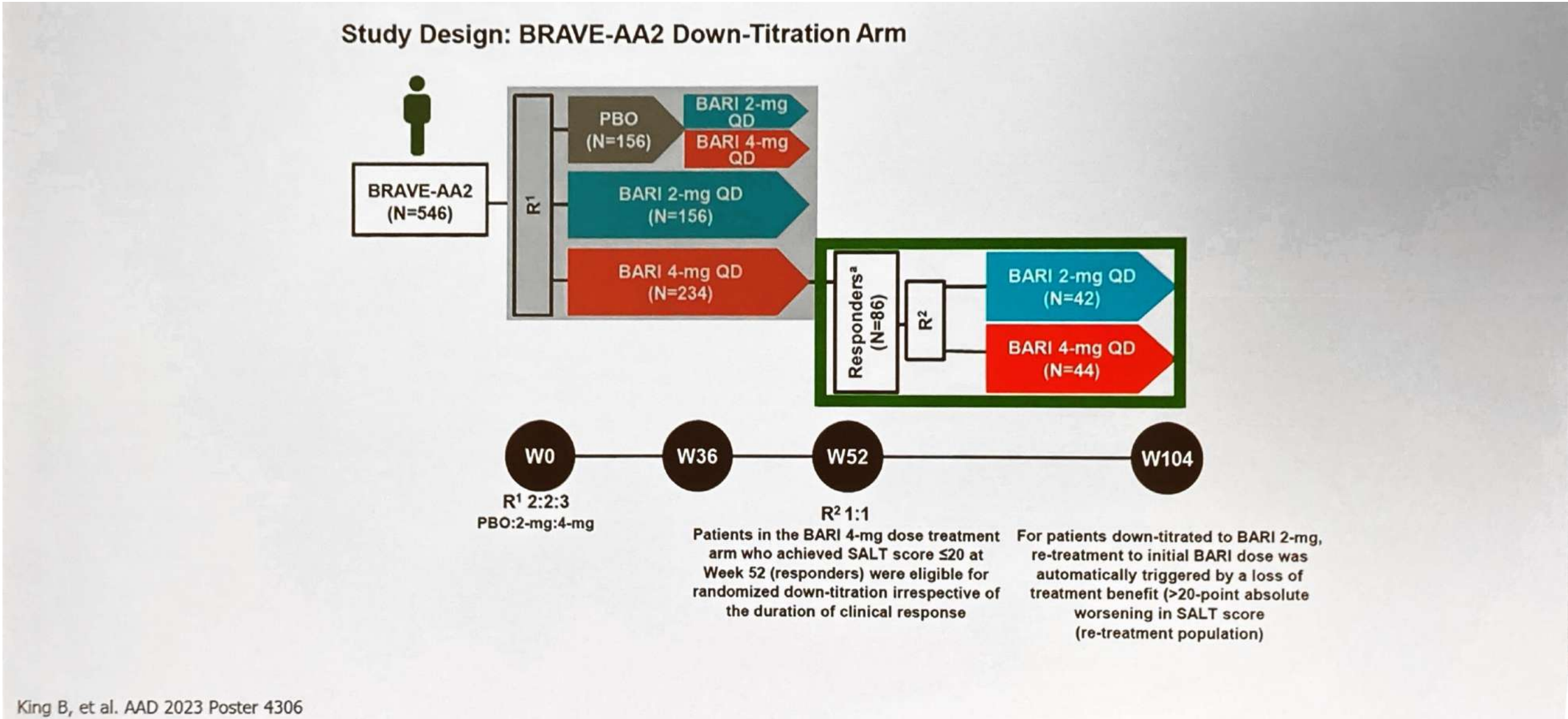
FDA

Alopecia Areata:

- 2 mg once daily. Increase to 4 mg once daily, if the response to treatment is not adequate. (2.4)
- For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, consider treating with 4 mg once daily. (2.4)
- Reduce the dose to 2 mg once daily when an adequate response has been achieved. (2.4)

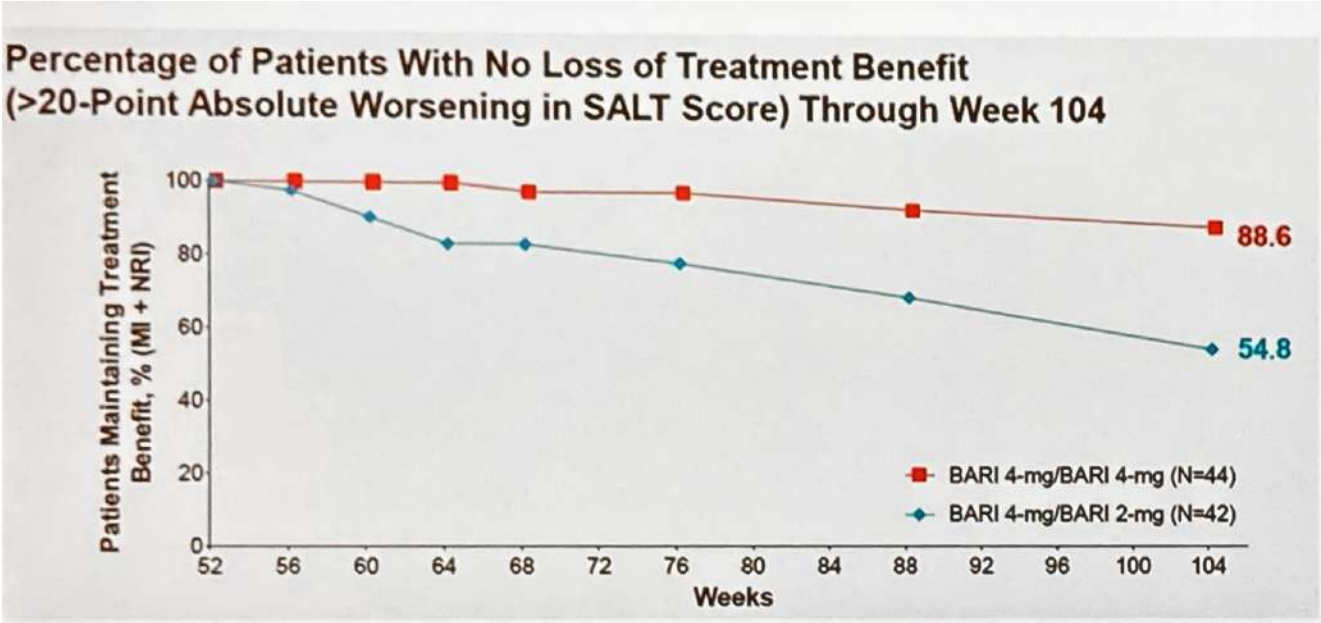
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf

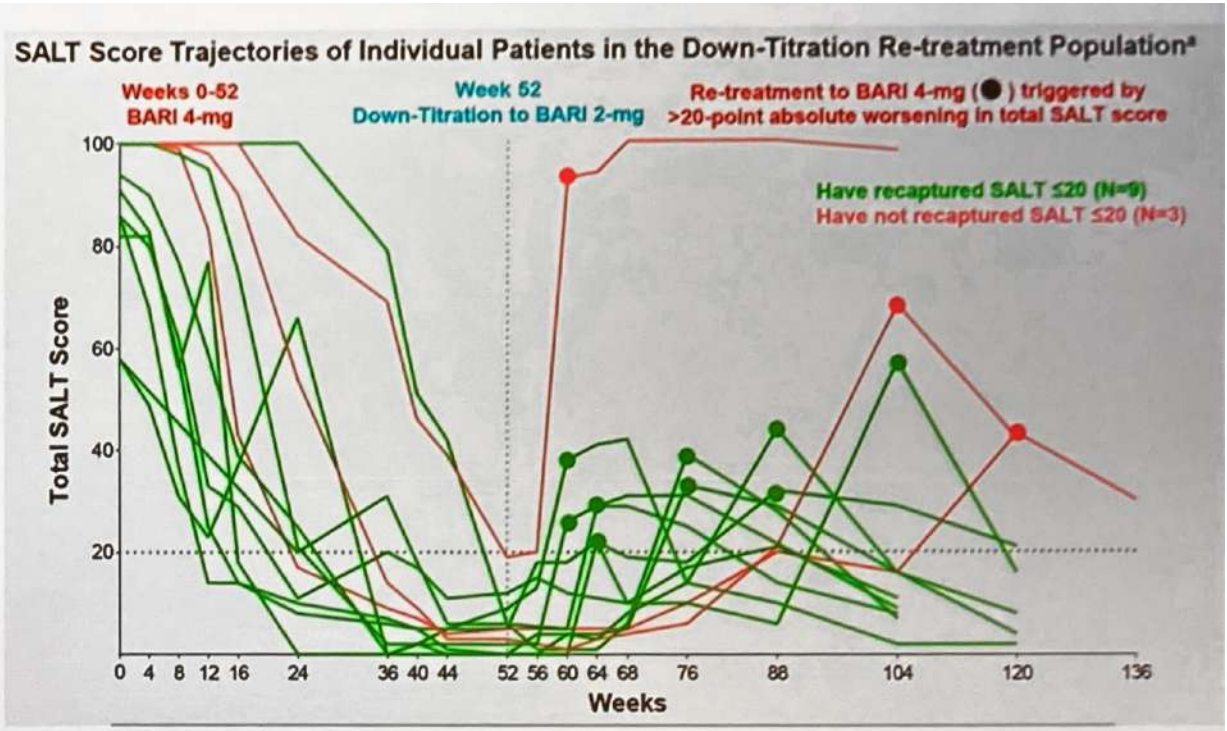
Long Term Treatment with JAK inhibitors and Dose Reduction



King B, et al. AAD 2023 Poster 4306

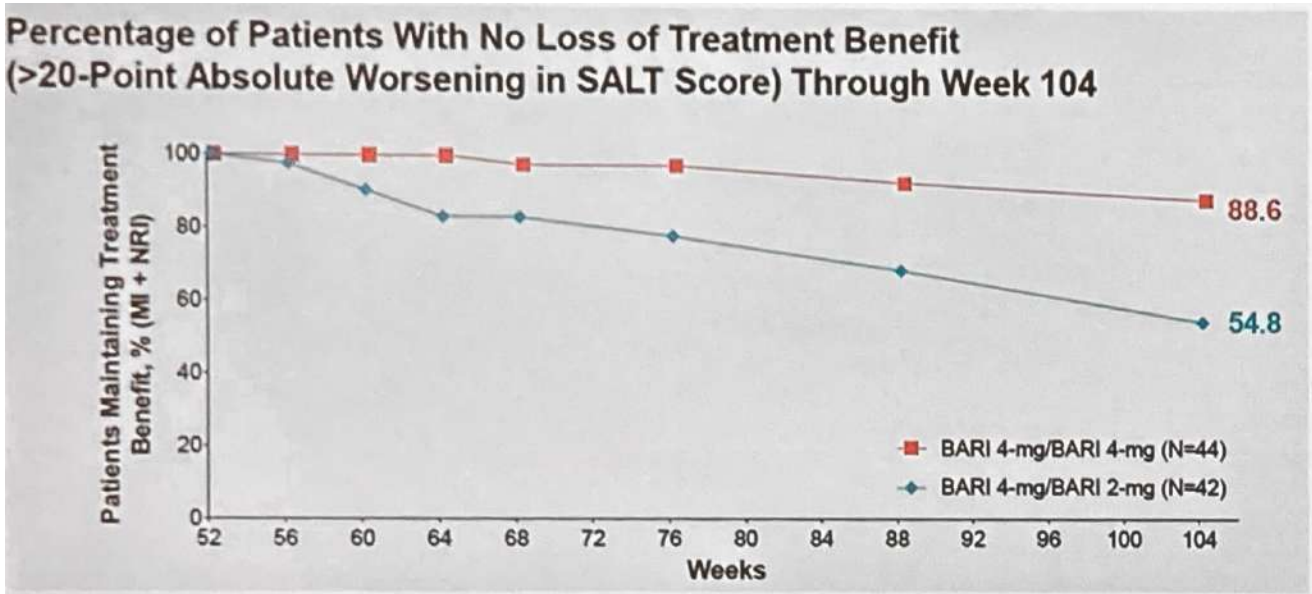
Abrupt Tapering of Baricitinib from 4 mg to 2 mg leads to relapse

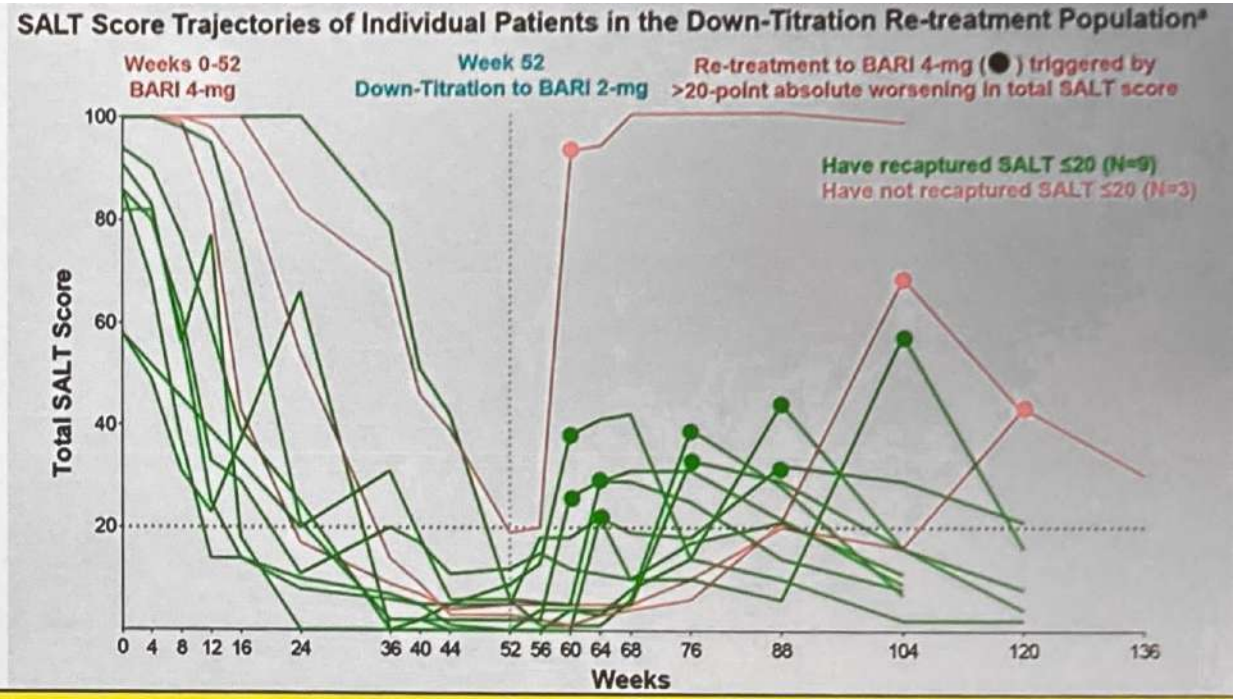




King B, et al. AAD 2023 Poster 4306

Abrupt Tapering of Baricitinib from 4 mg to 2 mg leads to relapse





- ***ABRUPT BIG DOSE DECREASES*** **will lead to disease flare in many patients**
- **Worsening of AA may be seen in weeks but usually occurs many months after *ABRUPT BIG DOSE DECREASES***
- **Worsening of AA after *ABRUPT BIG DOSE DECREASES* may be precipitous**
- **Regrowth of hair after resuming prior dose of JAK inhibitor takes many, many weeks**

Abrupt Tapering of Baricitinib from 4 mg to 2 mg leads to relapse

- After regrowth, continue the dose that the patient is taking…

– YOU DON'T HAVE TO TAPER!

- ***When*** **tapering the dose of JAK inhibitor, GO SLOW!**
- **Make SMALL CHANGES/DECREASES IN THE DOSE and continue that dose for at least 4 months before even considering another small change in the dose**

King B, et al. AAD 2023 Poster 4306

Conclusions (1/2)

- AA is a complex polygenic autoimmune disease
- Little data to support use of methotrexate, cyclosporine and systemic steroids for treatment of AA
- **Topical JAK inhibitors do not work** in AA
- **Oral minoxidil may be as effective** as monotherapy for some patients **and** may be **synergistic** in combination with JAK inhibitors
- **Baricitinib has been approved**; **ritlecitinib and deuruxolitinib** show promise in clinical trials (applications submitted)

Conclusions (2/2)

- **Early treatment improves prognosis**
- **Long duration** of current episode of severe AA carries **poor prognosis**
- **Spontaneous remission is rare** with severe disease
- Long term **continuous treatment required**
- **Dose tapering of JAK inhibitors should be slow**