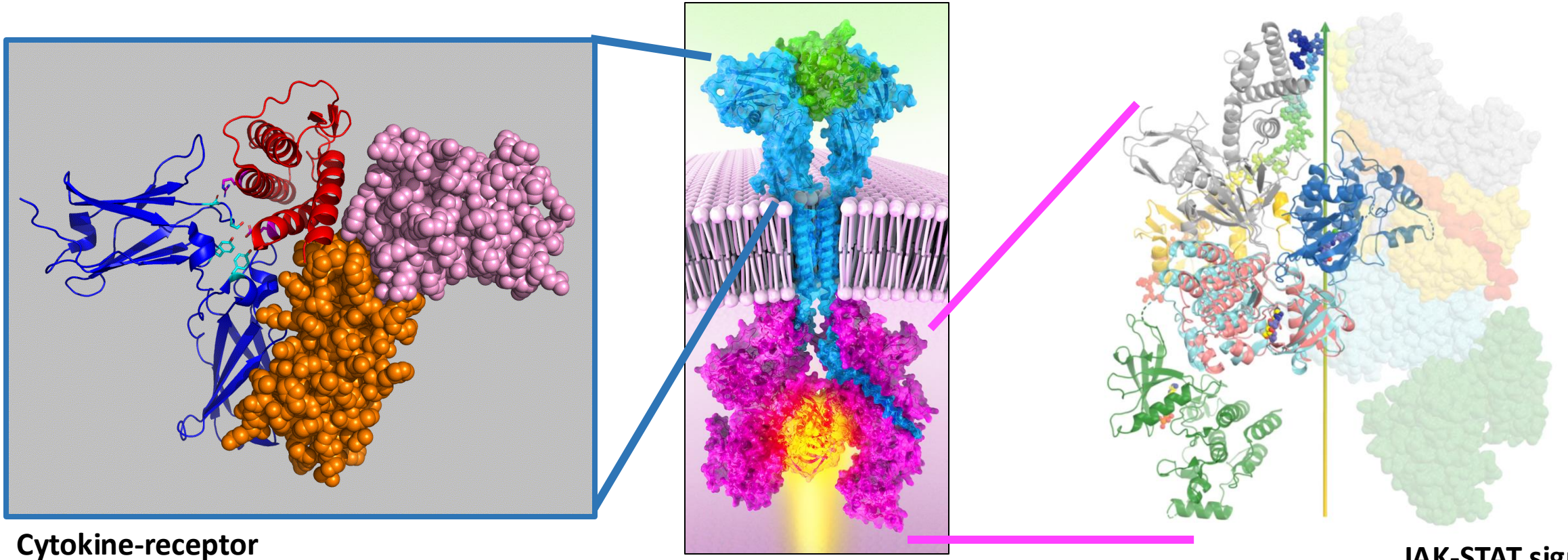
JAKi in Clinical Trials



Cytokine-receptor interactions outside the cell

JAK-STAT signaling inside the cell

Christopher G. Bunick, MD, PhD

Associate Professor of Yale Dermatology & Program in Translational Biomedicine

South Beach Symposium
medical + aesthetic dermatology

JAKi in Clinical Trials

Christopher G. Bunick, MD, PhD
Associate Professor of Dermatology & Program in Translational Biomedicine
Yale School of Medicine

DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Investigator

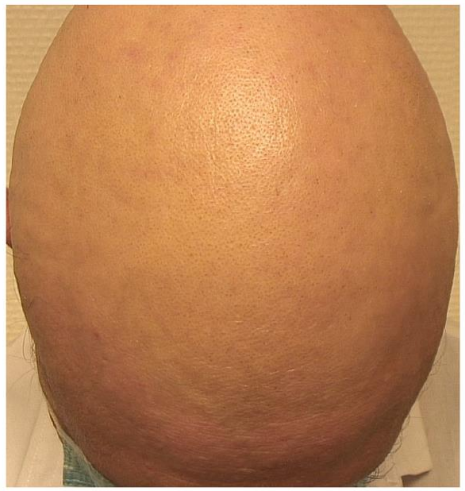
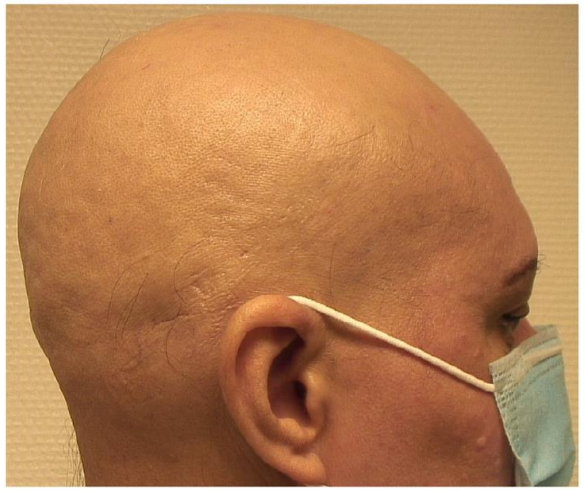
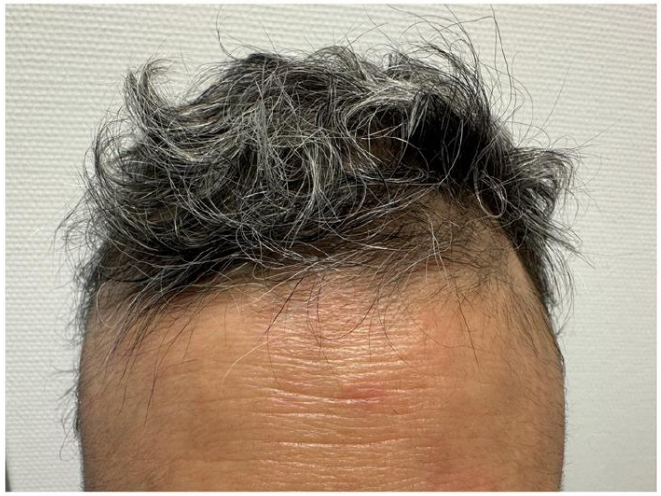
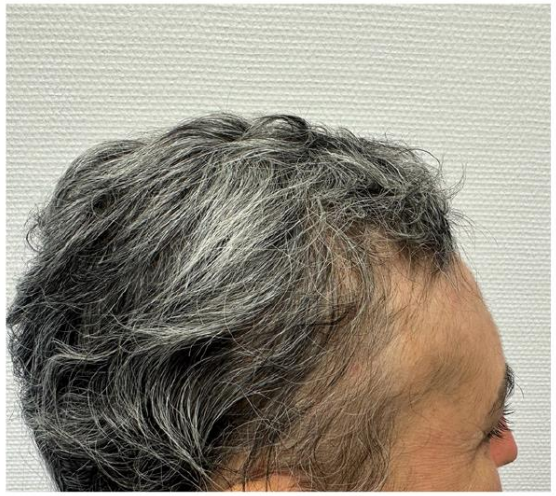
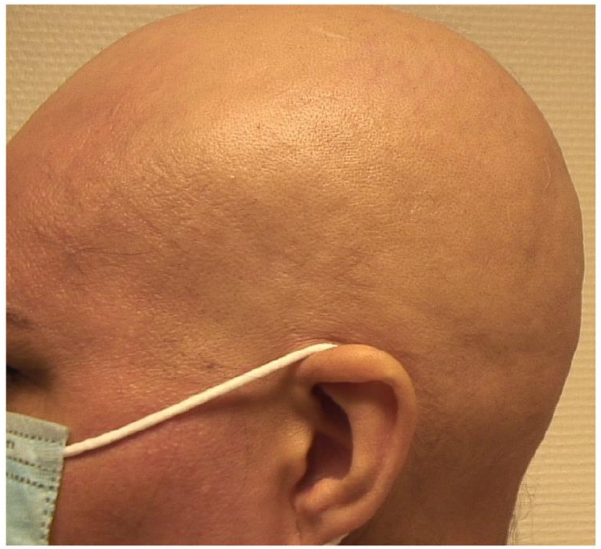
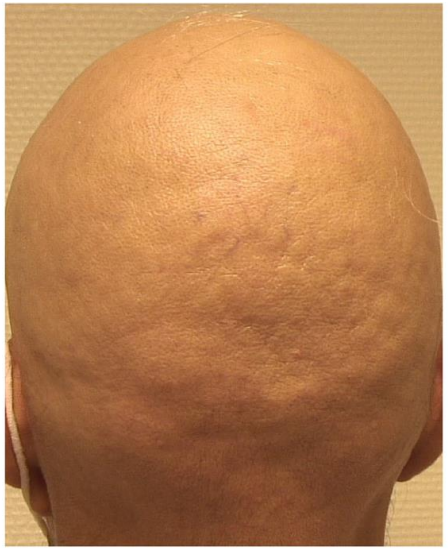
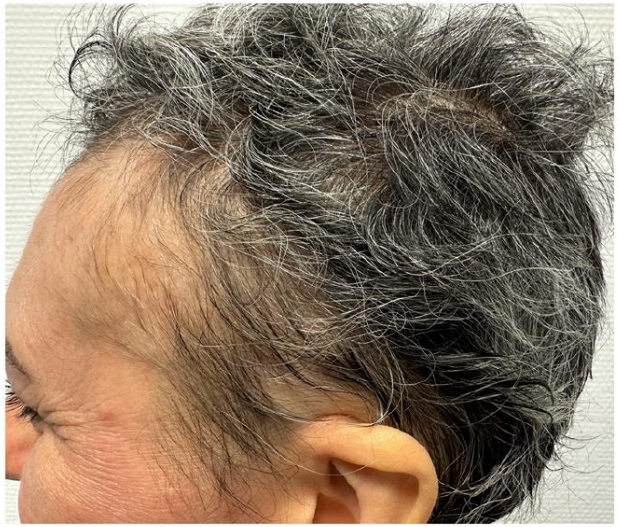
AbbVie
Almirall
Apogee
Daiichi Sankyo
LEO Pharma
Ortho Dermatologics
Sun Pharma
Takeda
Timber
Palvella

Consultant

AbbVie
Almirall
Amgen
Apogee
Arcutis
Botanix
Connect BioPharma
Dermavant
Eli Lilly
EPI Health/Novan
Incyte
LEO Pharma
Novartis
OrthoDermatologics
Pfizer
Regeneron
Sanofi
Sun Pharma
Takeda
Teladoc
Triveni
UCB
Veradermics

South Beach Symposium
medical + aesthetic dermatology

AD patients with AA show response to Upadacitinib


De la Torre-Gomar FJ, Velasco-Amador JP, Prados-Carmona Á, Ruiz-Villaverde R. Complete response of extensive alopecia areata refractory to baricitinib after five months of treatment with upadacitinib. J Dermatolog Treat. 2024 Dec;35(1):2304630.

JAK Inhibitors in Alopecia Areata Trials

FDA Approved for AA
Baricitinib
Ritlecitinib
Deuruxolitinib

Upadacitinib Phase 3 Trials in Alopecia Areata (12-63 yo), results at 24 weeks

	15 mg	30 mg	Placebo
Primary Endpoint (SALT ≤ 20): Percentage of patients achieving ≥80% scalp hair coverage.			
Study 1	44.6%	54.3%	3.4%
Study 2	45.2%	55.0%	1.5%
Secondary Endpoint (SALT ≤ 10): Percentage achieving ≥90% scalp hair coverage.			
Study 1	36.0%	47.1%	1.4%
Study 2	35.2%	45.8%	0.7%

https://www.prnewswire.com/news-releases/abbvie-announces-positive-topline-results-from-phase-3-up-aa-trial-evaluating-upadacitinib-rinvoq-for-alopecia-areata-302517362.html#:~:text=In%20Study%202%20of%20the,the%20third%20quarter%20of%202025;
https://plasticsurgerypractice.com/treatment-solutions/pharmaceuticals/abbvie-reports-positive-phase-3-results-alopecia-areata-drug/#:~:text=The%20second%20pivotal%20study%20shows,at%20AbbVie%2C%20in%20a%20release.

JAK Inhibitors in Alopecia Areata Trials

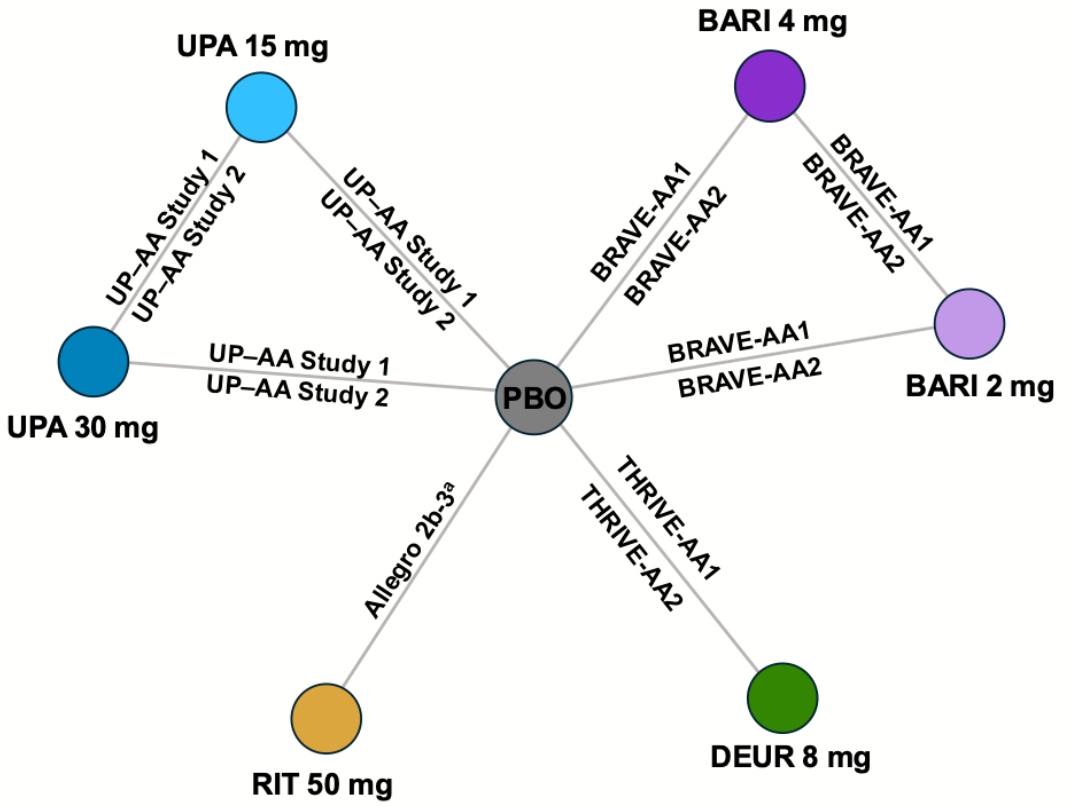
SALT < 20 Outcomes in Alopecia Areata Phase 3 Trials, results at 24 weeks

Drug/dose	Phase 3 Trial	Primary Endpoint
Upadacitinib 30 mg	UP-AA Study 1&2	54.3-55.0%
Upadacitinib 15 mg	UP-AA Study 1&2	44.6-45.2%
Baricitinib 4 mg	BRAVE-AA1 & AA2	35.9-38.8%
Deuruxolitinib 12 mg BID	THRIVE-AA1 & AA2	31.0-38.0%
Ritlecitinib 50 mg BID	ALLEGRO	23.0%

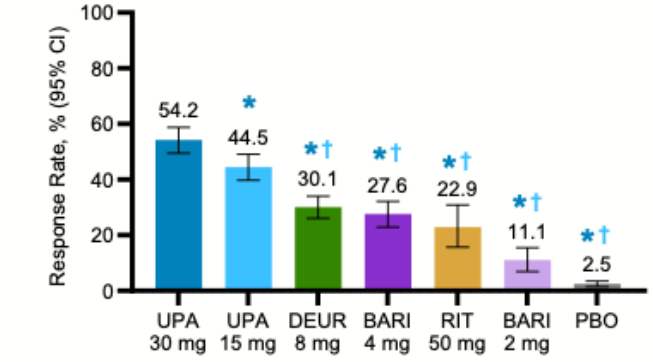
https://www.prnewswire.com/news-releases/abbvie-announces-positive-topline-results-from-phase-3-up-aa-trial-evaluating-upadacitinib-rinvoq-for-alopecia-areata-302517362.html#:~:text=In%20Study%202%20of%20the,the%20third%20quarter%20of%202025;
https://plasticsurgerypractice.com/treatment-solutions/pharmaceuticals/abbvie-reports-positive-phase-3-results-alopecia-areata-drug/#:~:text=The%20second%20pivotal%20study%20shows,at%20AbbVie%2C%20in%20a%20release.

Network Meta-Analysis Comparing Efficacy of Janus Kinase Inhibitors for Scalp Hair, Eyebrow, and Eyelash Regrowth in Adults and Adolescents With Alopecia Areata

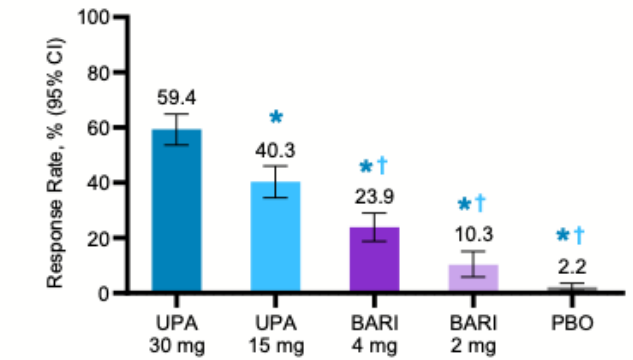
Figure 1. NMA Diagram of Included Studies



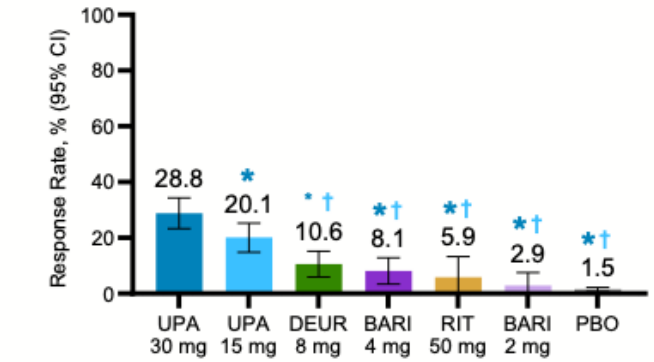
SALT Score ≤20 at Week 24[a]



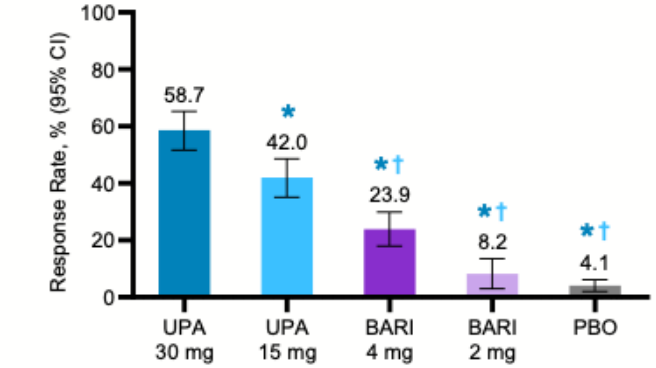
ClinRO Eyebrow Score 0/1 at Week 24[a]



SALT Score ≤20 at Week 12[b]



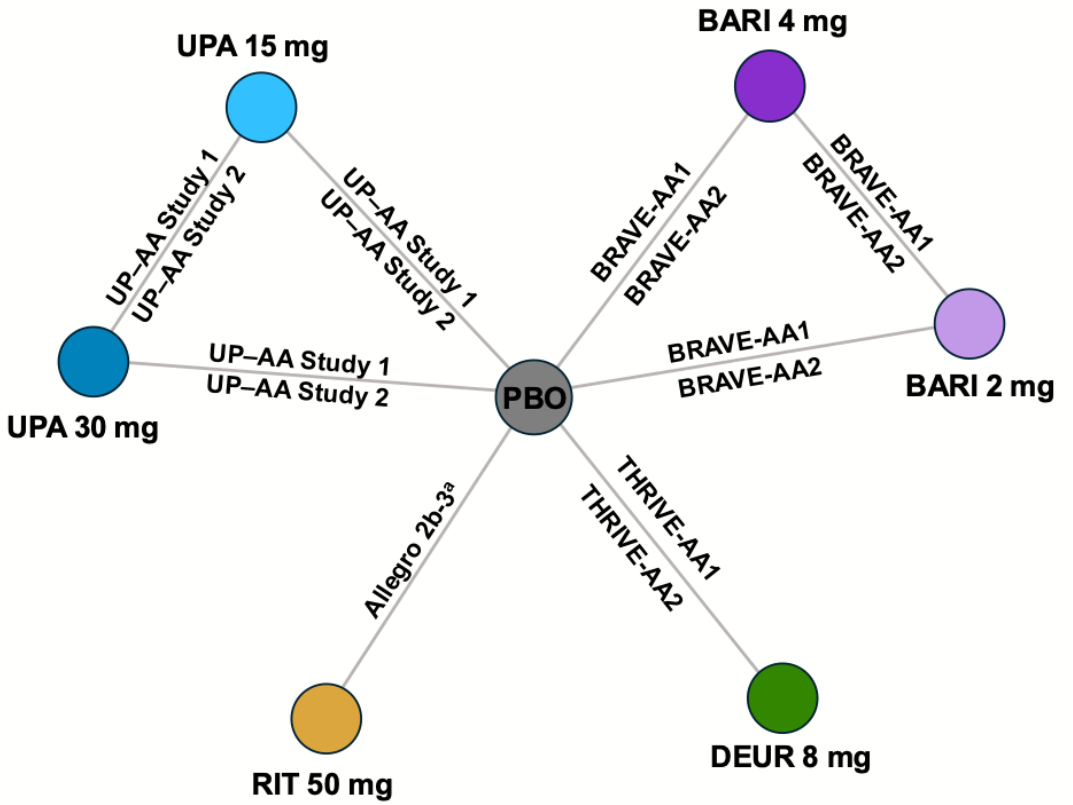
ClinRO Eyelash Score 0/1 at Week 24[a]



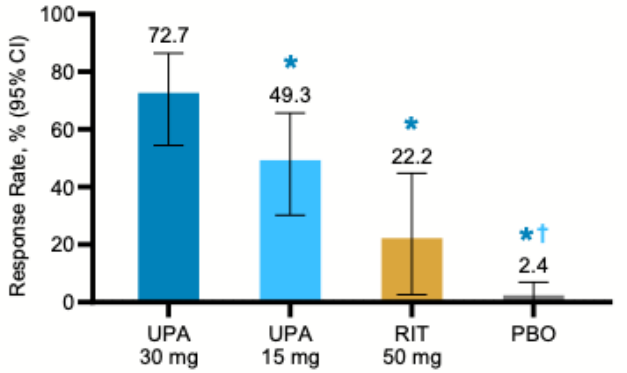
Arash Mostaghimi, Ahmed M. Soliman, Si-Tien Wang, Kristen Westerhoff, Jonathan J. Woolley, Andreas Lazar, Henrique D. Teixeira, Thierry Passeron. **Comparative Efficacy of Janus Kinase Inhibitors for Scalp Hair, Eyebrow, and Eyelash Regrowth in Adults and Adolescents With Alopecia Areata: A Systematic Literature Review and Network Meta-Analysis.** *Presented at the 2026 Maui Derm Conference, January 25–29, 2026; Maui, HI, USA.*

Network Meta-Analysis Comparing Efficacy of Janus Kinase Inhibitors for Scalp Hair, Eyebrow, and Eyelash Regrowth in Adolescents With Alopecia Areata

Figure 1. NMA Diagram of Included Studies

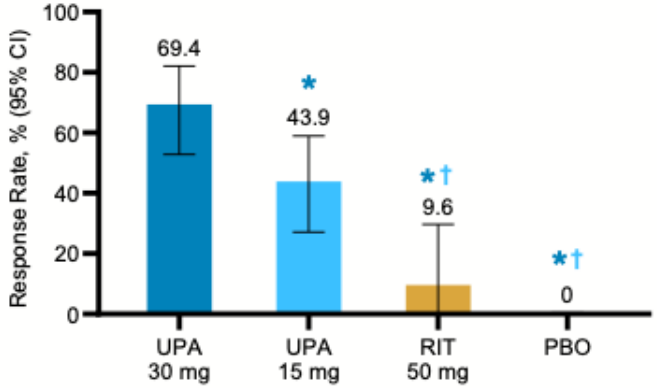


SALT Score ≤20 at Week 24[a] (Adolescents)



	UPA 30 mg	UPA 15 mg	RIT 50 mg	PBO
SUCRA (%) =	99.8	65.8	33.7	0.7
N =	47	48	18	42

SALT Score ≤10 at Week 24[a] (Adolescents)

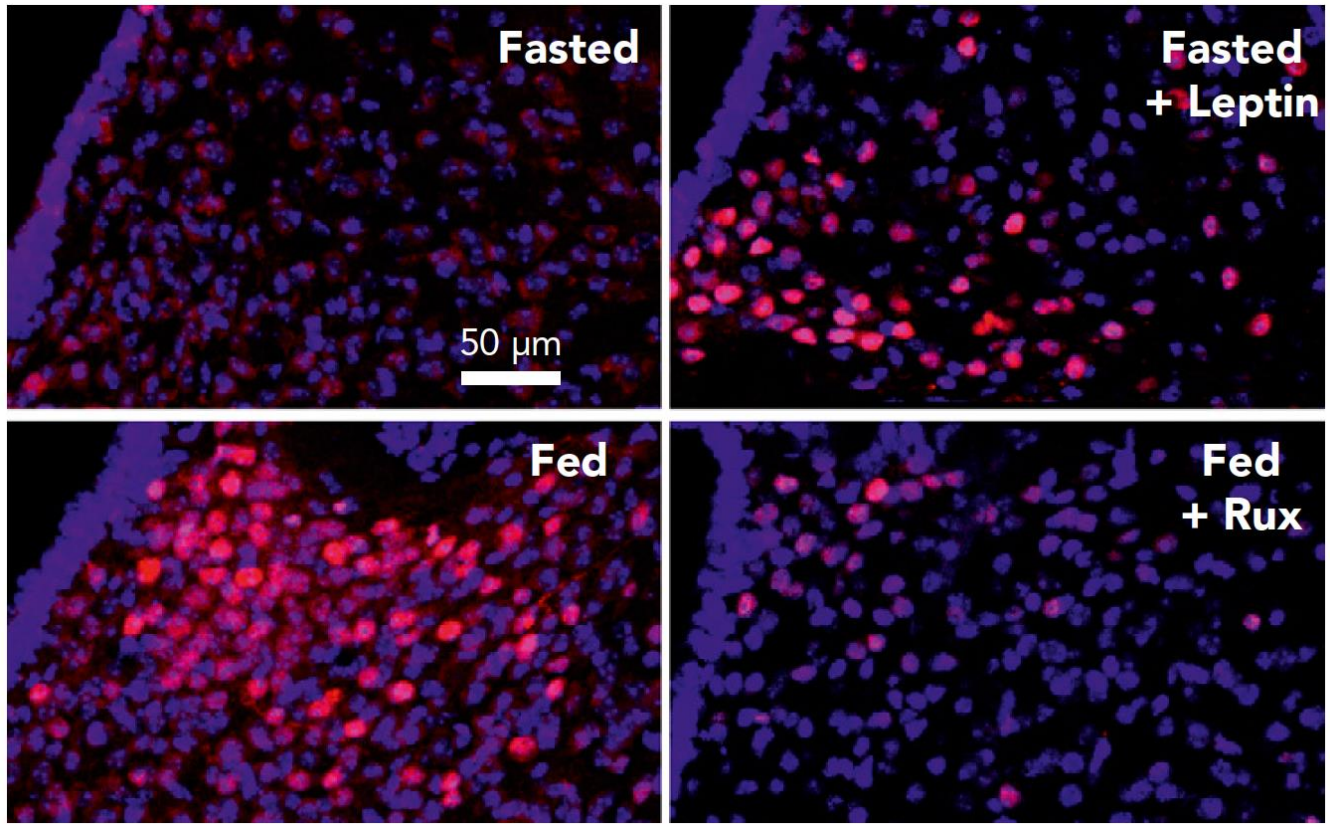


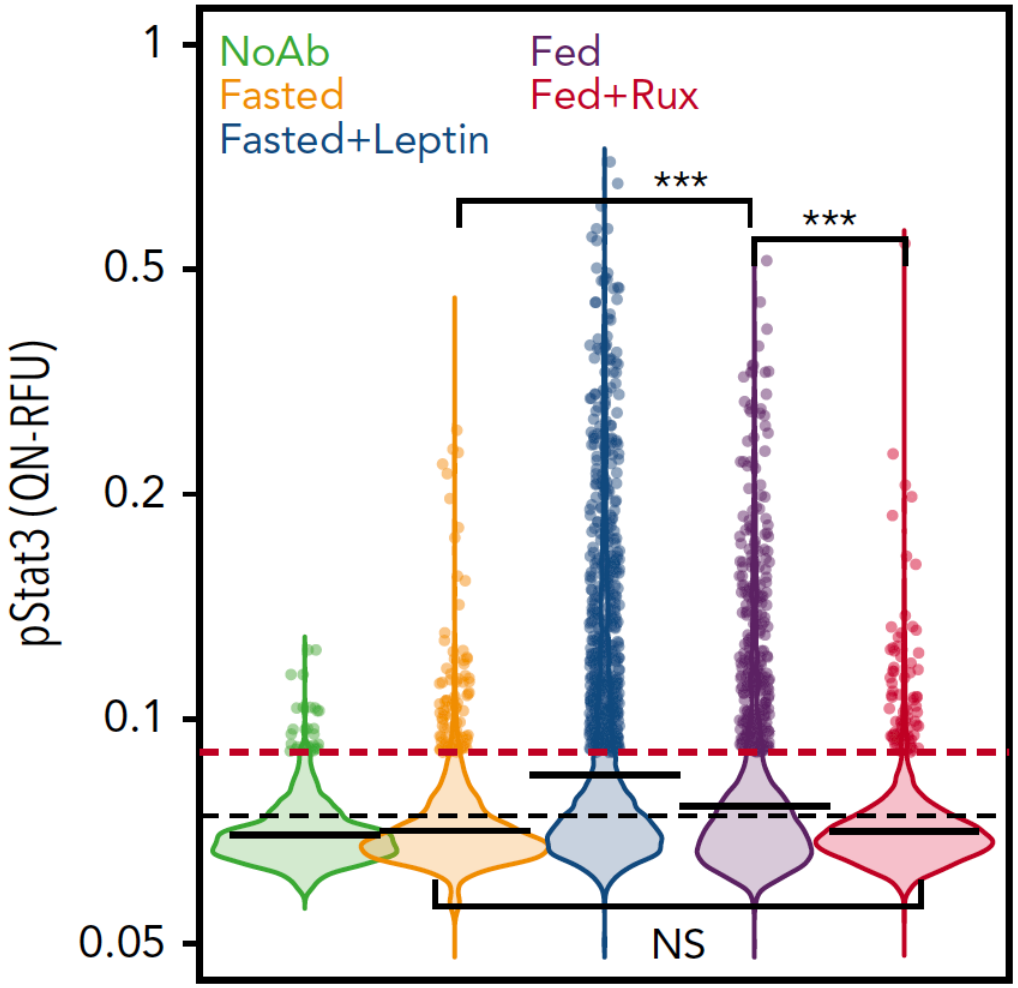
	UPA 30 mg	UPA 15 mg	RIT 50 mg	PBO
SUCRA (%) =	99.9	66.6	30.0	3.5
N =	47	48	18	42

Arash Mostaghimi, Ahmed M. Soliman, Si-Tien Wang, Kristen Westerhoff, Jonathan J. Woolley, Andreas Lazar, Henrique D. Teixeira, Thierry Passeron. **Comparative Efficacy of Janus Kinase Inhibitors for Scalp Hair, Eyebrow, and Eyelash Regrowth in Adults and Adolescents With Alopecia Areata: A Systematic Literature Review and Network Meta-Analysis.** *Presented at the 2026 Maui Derm Conference, January 25–29, 2026; Maui, HI, USA.*

Weight Gain with JAK2 Inhibition

JAK2 inhibitors can block postprandial leptin signaling in arcuate nucleus of hypothalamus because leptin receptor signaling largely occurs via JAK2/STAT3





Mollé N, Krichevsky S, Kermani P, Silver RT, Ritchie E, Scandura JM. Ruxolitinib can cause weight gain by blocking leptin signaling in the brain via JAK2/STAT3. Blood. 2020 Mar 26;135(13):1062-1066. doi: 10.1182/blood.2019003050. PMID: 32047890.

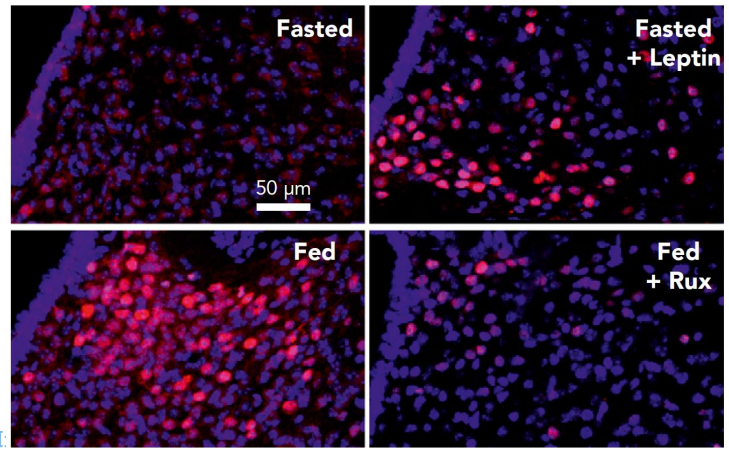
Weight Gain with JAK2 JH1 (kinase) Domain Inhibitors

BRAVE-AA1 & BRAVE-AA2 Trials

Baricitinib in AA (weight gain ≥7%)

2mg => 6/365 pts
4mg => 5/540 pts
PBO => 1/371 pts
E/100PY = 15-21

JAK2 inhibitors can block postprandial leptin signaling in arcuate nucleus of hypothalamus because leptin receptor signaling largely occurs via JAK2/STAT3

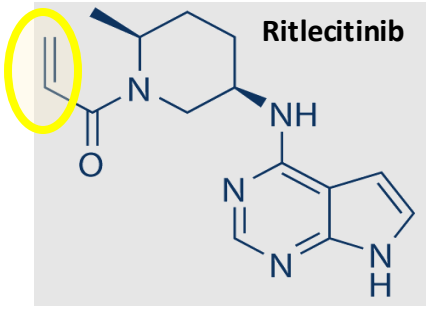


JAK Kinase Domain (JH1) Inhibitor Selectivity (IC_{50}, nM)

JAKi	JAK1	JAK2	JAK3	TYK2
Abrocitinib	29.0 nM	803 nM	>10,000 nM	1259 nM
Baricitinib	4.0 nM	6.6 nM	787.0 nM	61.0 nM
Deuruxolitinib	4.7 nM	20 nM	1335 nM	7 nM
Ritlecitinib	>10,000 nM	>10,000 nM	33.1 nM	>10,000 nM
Upadacitinib	14 nM	593 nM	1860 nM	2715 nM

Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A Comprehensive Overview of Globally Approved JAK Inhibitors. Pharmaceutics. 2022 May 6;14(5):1001.
Miot HA, Criado PR, de Castro CCS, Ianhez M, Talhari C, Ramos PM. JAK-STAT pathway inhibitors in dermatology. An Bras Dermatol. 2023 Sep-Oct;98(5):656-677.
Parmentier, J.M., Voss, J., Graff, C. *et al.* In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol* **2**, 23 (2018).
Ch'en PY, Ng J, Song EJ. Weight gain secondary to the use of Janus kinase inhibitors. Arch Dermatol Res. 2023 Dec;315(10):2773-2774.
Mollé N, Krichevsky S, Kermani P, Silver RT, Ritchie E, Scandura JM. Ruxolitinib can cause weight gain by blocking leptin signaling in the brain via JAK2/STAT3. Blood. 2020 Mar 26;135(13):1062-1066.

Ritlecitinib: mechanism of action & unique selectivity

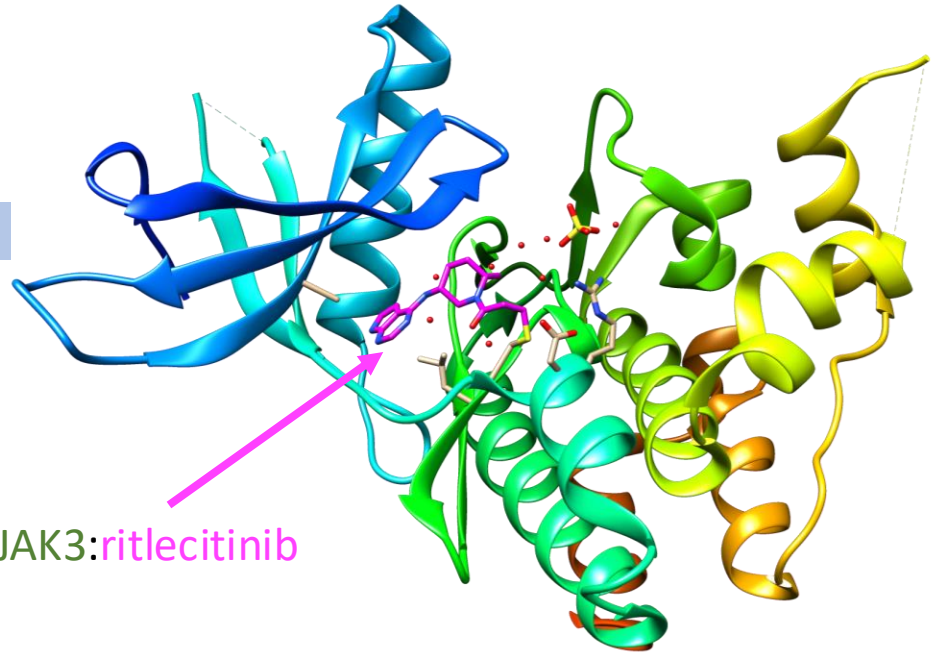


JAK 3 selective oral small molecule

Inhibits all 5 TEC kinases

	Tofacitinib	Ritlecitinib
BLK	NA	>10 000
BMX	>10 000	666
BTK	>10000	404
EGFR	NA	>10 000
HER2	NA	>10 000
HER4	NA	>10 000
ITK	>10 000	395[b,c]
JAK3	55[b]	33.1[b]
TEC	>10 000	403
RLK/TXK	>10 000	155
MAP2K7	NA	>10 000

Irreversible covalent binding of JAK3 at a special Cys909 residue

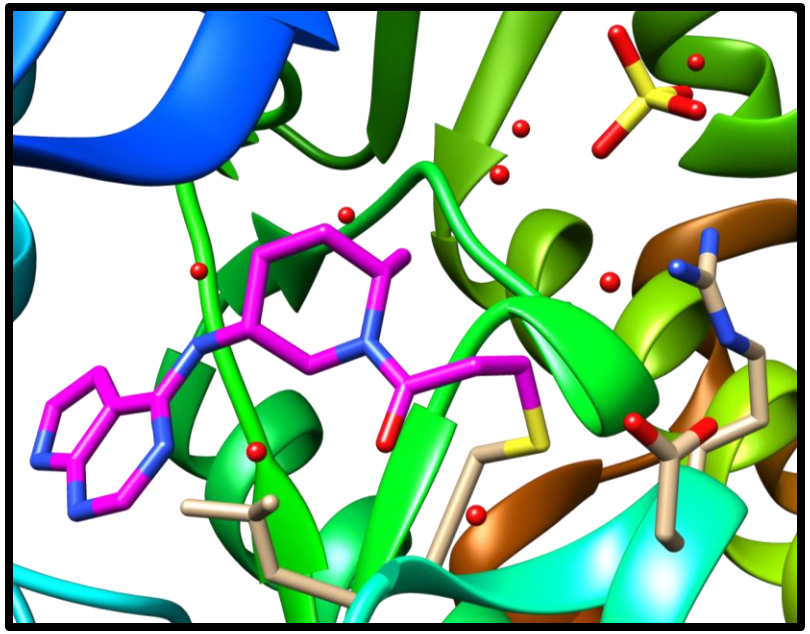


Protein Data Bank Code 5TOZ

Table 1. Kinases Amino Acid Sequence Alignment[a]

position (in JAK3)	904	905	906	907	908	909	912	940	945	947	948	953	954	956
JAK3	Y	L	P	S	G	C	D	L	C	H	R	R	N	L
JAK1	F	L	P	S	G	S	E	L	Y	H	R	R	N	L
JAK2	Y	L	P	Y	G	S	D	L	Y	H	R	R	N	L
TYK2	Y	V	P	L	G	S	D	L	Y	H	R	R	N	L
BLK	Y	M	A	R	G	C	D	I	S	H	R	A	N	L
BMX	Y	I	S	N	G	C	N	L	F	H	R	R	N	L
BTK	Y	M	A	N	G	C	N	L	F	H	R	R	N	L
EGFR	L	M	P	F	G	C	D	L	L	H	R	R	N	L
HER2	L	M	P	Y	G	C	D	L	L	H	R	R	N	L
HER4	L	M	P	H	G	C	E	L	L	H	R	R	N	L
ITK	F	M	E	H	G	C	D	L	V	H	R	R	N	L
TEC	F	M	E	R	G	C	N	L	F	H	R	R	N	L
RLK	F	M	E	N	G	C	N	L	Y	H	R	R	N	L
MAP2K7	L	M		G	T	C	K	L	V	H	R	S	N	L

[a]Amino acid sequence alignment of the four JAK isoforms and 10 other kinases containing a Cys residue at the equivalent position of Cys-909 in JAK3.



Xu H, et al. PF-06651600, a Dual JAK3/TEC Family Kinase Inhibitor. ACS Chem Biol. 2019 Jun 21;14(6):1235-1242.
Telliez JB, et al. Discovery of a JAK3-Selective Inhibitor: Functional Differentiation of JAK3-Selective Inhibition over pan-JAK or JAK1-Selective Inhibition. ACS Chem Biol. 2016 Dec 16;11(12):3442-3451.
Xu H, et al. PF-06651600, a Dual JAK3/TEC Family Kinase Inhibitor. ACS Chem Biol. 2019 Jun 21;14(6):1235-1242.

JAK Inhibitors in Hidradenitis Suppurativa Trials

FDA Approved for HS
Adalimumab (anti-TNF)
Secukinumab (anti-IL-17A)
Bimekizumab (anti-IL17A/F)

Povorcitinib Phase 3 Trials in HS (18y and older), results at 24 weeks

	45 mg	70 mg	Placebo
Primary Endpoint (HiSCR50 at Week 12): Percentage of patients achieving a ≥50% reduction in abscesses and inflammatory nodules.			
STOP-HS1	40.2%	40.6%	29.7%
STOP-HS2	42.3%	42.3%	28.6%
Responses at Week 24.			
HiSCR75	31.0%	40.3%	
HiSCR90	13.8%	27.7%	
HiSCR100	9.2%	21.3%	

- **Most Common Side Effects:** Acne, headache, nasopharyngitis, and upper respiratory tract infections.
- **Serious Events:** No deaths or major adverse cardiovascular events (MACE) were reported through Week 24.

https://incytecorp.gcs-web.com/news-releases/news-release-details/incyte-announces-new-24-week-phase-3-data-stop-hs-clinical-trial#:~:text=New%20data%20at%20Week%2024,no%20pain%20at%20Week%2024.

JAK Inhibitors in Hidradenitis Suppurativa Trials

FDA Approved for HS
Adalimumab
Secukinumab
Bimekizumab

Upadacitinib Phase 3 Trials in HS (STEP-UP, 12y and older): data not available yet

A Study to Assess Change in Disease Activity and Adverse Events of Oral Upadacitinib in Adult and Adolescent Participants With Moderate to Severe Hidradenitis Suppurativa Who Have Failed Anti-TNF Therapy (Step-Up HS).
ClinicalTrials.gov ID NCT05889182.

Upadacitinib Phase 2 Trials in HS (12y and older), results at 12 weeks

	15 mg	30 mg	Placebo
Primary Endpoint (HiSCR50 at Week 12): Percentage of patients achieving a ≥50% reduction in abscesses and inflammatory nodules.			
	n/a	38.3% (n=47)	23.8% (n=21)

Kimball AB, et al. Efficacy and safety of upadacitinib in moderate to severe hidradenitis suppurativa: A phase 2, randomized, placebo-controlled study. Presented at: American Academy of Dermatology Annual Meeting; March 17-21, 2023; New Orleans.

JAK Inhibitors in Hidradenitis Suppurativa Trials:

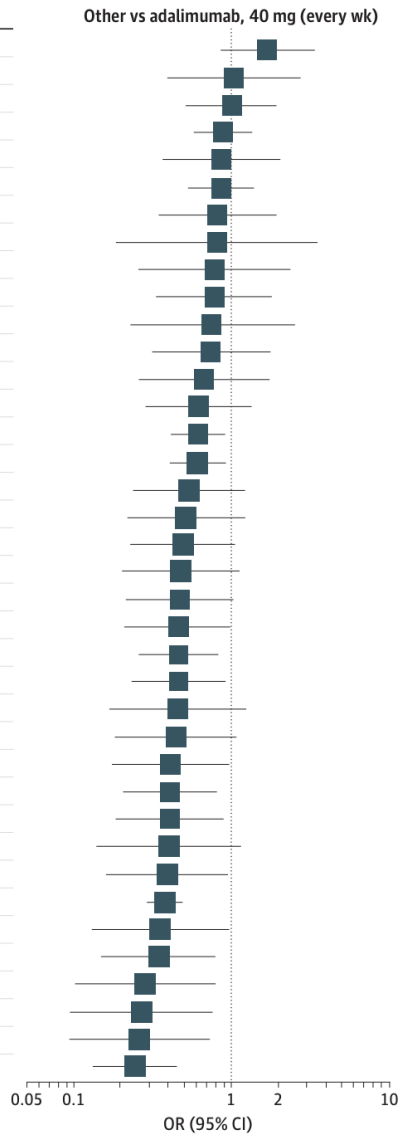
HiSCR50 comparison to adalimumab 40 mg weekly

JAKi study drug

FDA approved tx

Figure 3. Forest Plot of Hidradenitis Suppurativa Clinical Response (HiSCR)-50 Network Meta-Analysis Estimates for Each Treatment vs Adalimumab, 40 mg, Once per Week

Treatment	Direct evidence proportion	Direct comparisons	Total participants, No.	Confidence in findings	OR (95% CI)
Sonelokimab, 120 mg (every 4 wk)	0.62	1	67	Moderate	1.69 (0.86-3.31)
Lutikizumab, 300 mg (every 2 wk)	0	0	37	Very low	1.03 (0.40-2.69)
Sonelokimab, 240 mg (every 4 wk)	0.61	1	66	Low	1.00 (0.52-1.92)
Bimekizumab, 320 mg (every 2 wk)	0.15	1	624	Moderate	0.89 (0.58-1.35)
Povorcitinib, 15 mg (once daily)	0	0	52	Very low	0.87 (0.37-2.02)
Bimekizumab, 320 mg (every 4 wk)	0	0	288	Moderate	0.86 (0.54-1.37)
Brepocitinib, 45 mg (once daily)	0	0	52	Very low	0.82 (0.35-1.91)
Spesolimab, 1200 mg (every 2 wk)	0	0	35	Very low	0.81 (0.19-3.49)
LY3041658, 600 mg (every 2 wk)	0	0	45	Very low	0.78 (0.26-2.34)
Povorcitinib, 75 mg (once daily)	0	0	53	Very low	0.78 (0.33-1.80)
Upadacitinib, 30 mg (once daily)	0	0	47	Very low	0.75 (0.23-2.48)
Povorcitinib, 45 mg (once daily)	0	0	52	Very low	0.74 (0.32-1.74)
Lutikizumab, 300 mg (once weekly)	0	0	39	Very low	0.67 (0.26-1.71)
Guselkumab, 200 mg (every 4 wk)	0	0	59	Moderate	0.62 (0.29-1.33)
Secukinumab, 300 mg (every 4 wk)	0	0	360	High	0.62 (0.42-0.91)
Secukinumab, 300 mg (every 2 wk)	0	0	361	High	1.61 (0.41-0.90)
Bermekimab, 400 mg (once weekly)	0	0	51	Low	0.54 (0.24-1.22)
Imsidolimab, 200 mg (every 4 wk)	0	0	50	Low	0.52 (0.22-1.21)
Guselkumab, 1200 mg (wk 0, 4, 8)	0	0	60	Moderate	0.49 (0.23-1.05)
Imsidolimab, 100 mg (every 4 wk)	0	0	50	Low	0.48 (0.20-1.12)
Adalimumab, 40 mg (every 2 wk)	0.81	1	45	Low	0.47 (0.22-1.02)
Izokibep, 160 mg (once weekly)	0	0	57	Low	0.46 (0.21-1.01)
Avacopan, 30 mg (twice daily)	0	0	134	Moderate	0.46 (0.26-0.82)
Risankizumab, 180 mg (wk 0, 1, 2, 4, 12)	0	0	80	Moderate	0.46 (0.24-0.90)
IFX-1, 800 mg (every 4 wk)	0	0	33	Low	0.45 (0.17-1.22)
Ropsacitinib, 400 mg (once daily)	0	0	46	Low	0.45 (0.18-1.08)
Bermekimb, 1050 mg (once weekly)	0.78	1	35	Low	0.41 (0.18-0.96)
Risankizumab, 360 mg (wk 0, 1, 2, 4, 12)	0	0	81	Moderate	0.41 (0.21-0.80)
Izokibep, 160 mg (every 2 wk)	0	0	59	Moderate	0.41 (0.19-0.88)
CJM112, 300 mg (every 2 wk)	0	0	31	Moderate	0.40 (0.14-1.14)
Zimlovisertib, 400 mg (once daily)	0	0	47	Low	0.39 (0.16-0.95)
Placebo	0.98	7	1795	High	0.38 (0.30-0.49)
IFX-1, 1200 mg (every 2 wk)	0	0	33	Low	0.36 (0.13-0.96)
Bermekimab, 400 mg (every 2 wk)	0	0	50	Moderate	0.35 (0.15-0.79)
IFX-1, 400 mg (every 4 wk)	0	0	30	Moderate	0.28 (0.10-0.79)
IFX-1, 800 mg (every 2 wk)	0	0	31	Moderate	0.27 (0.10-0.75)
Lutikizumab, 100 mg (every 2 wk)	0	0	37	Low	0.26 (0.10-0.71)
Avacopan, 10 mg (twice daily)	0	0	134	Moderate	0.25 (0.13-0.45)



OR indicates odds ratio. The direct comparisons column refers to the number of studies (trials) in which each drug was directly compared with adalimumab, 40 mg, once per week. Direct evidence proportion quantifies the contribution of direct evidence to a particular network estimate. Number of participants refers to the total number of patients in each treatment arm across all studies, not for studies involving direct comparisons with adalimumab, 40 mg, once per week, specifically. ORs greater than 1 favor the other treatment, whereas ORs less than 1 favor adalimumab, 40 mg, once per week.

Garg A, Cohn E, Midgette B, Frasier K, Strunk A. Efficacy and Safety of Medical Interventions for Moderate to Severe Hidradenitis Suppurativa: A Living Systematic Review and Network Meta-Analysis. JAMA Dermatol. 2025 Sep 1;161(9):931-940. doi: 10.1001/jamadermatol.2025.1976. PMID: 40601333; PMCID: PMC12224058.

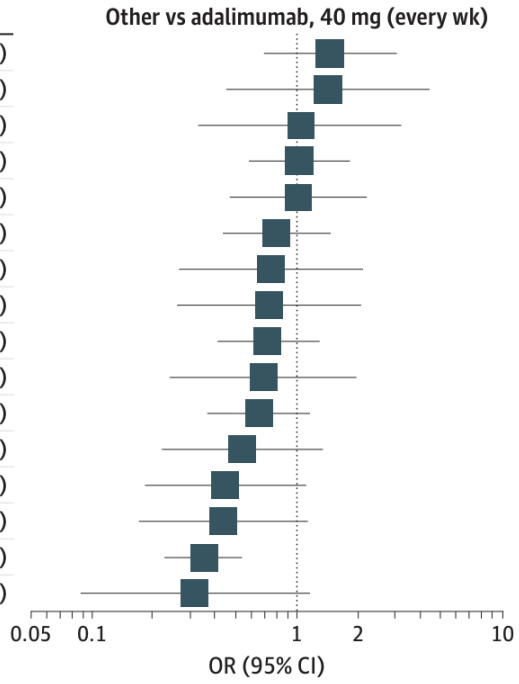
JAK Inhibitors in Hidradenitis Suppurativa Trials: HiSCR-75 comparison to adalimumab 40 mg weekly

JAKi study drug

FDA approved tx

Figure 5. Forest Plot of Hidradenitis Suppurativa Clinical Response (HiSCR)-75 Network Meta-Analysis Estimates For Each Treatment vs Adalimumab, 40 mg, Once Per Week

Treatment	Direct evidence proportion	Direct comparisons	Total participants, No.	Confidence in findings	OR (95% CI)
Sonelokimab, 120 mg (every 4 wk)	0.70	1	67	Low	1.45 (0.70-3.00)
Lutikizumab, 300 mg (every 2 wk)	0	0	37	Very low	1.41 (0.45-4.35)
Lutikizumab, 300 mg (once weekly)	0	0	39	Very low	1.03 (0.33-3.19)
Bimekizumab, 320 mg (every 2 wk)	0.25	1	624	Low	1.02 (0.59-1.78)
Sonelokimab, 240 mg (every 4 wk)	0.71	1	66	Low	1.01 (0.48-2.14)
Bimekizumab, 320 mg (every 4 wk)	0	0	288	Low	0.79 (0.43-1.45)
Povorcitinib, 15 mg (once daily)	0	0	52	Very low	0.74 (0.27-2.08)
Povorcitinib, 75 mg (once daily)	0	0	53	Very low	0.72 (0.26-2.02)
Secukinumab, 300 mg (every 4 wk)	0	0	360	Moderate	0.72 (0.41-1.26)
Povorcitinib, 45 mg (once daily)	0	0	52	Very low	0.68 (0.24-1.91)
Secukinumab, 300 mg (every 2 wk)	0	0	361	Moderate	0.65 (0.37-1.14)
Izokibep, 160 mg (once weekly)	0	0	57	Low	0.54 (0.22-1.33)
Izokibep, 160 mg (every 2 wk)	0	0	59	Low	0.44 (0.18-1.09)
Bermekimb, 1050 mg (once weekly)	0.83	1	35	Low	0.44 (0.17-1.11)
Placebo	0.93	4	946	High	0.35 (0.23-0.53)
Lutikizumab, 100 mg (every 2 wk)	0	0	37	Very low	0.32 (0.09-1.14)



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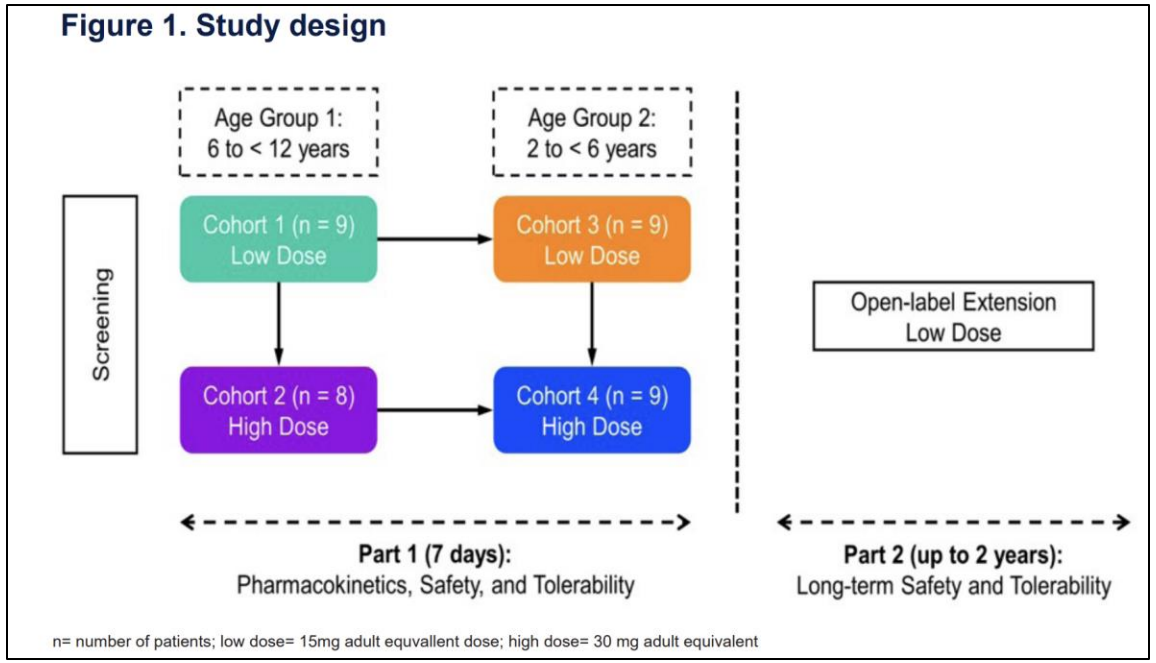
Garg A, Cohn E, Midgette B, Frasier K, Strunk A. Efficacy and Safety of Medical Interventions for Moderate to Severe Hidradenitis Suppurativa: A Living Systematic Review and Network Meta-Analysis. JAMA Dermatol. 2025 Sep 1;161(9):931-940. doi: 10.1001/jamadermatol.2025.1976. PMID: 40601333; PMCID: PMC12224058.

JAK Inhibitors in Pediatric Atopic Dermatitis Trials

A Phase 1 study was conducted to evaluate the PK, safety, and tolerability of low- and high-dose UPA over 7 days (Part 1) and the long-term safety and tolerability of low-dose UPA (Part 2) in pediatric patients with severe AD, with efficacy assessed as an exploratory objective.

Figure 1. Study design



n= number of patients; low dose= 15mg adult equvallent dose; high dose= 30 mg adult equivalent

Table 1. Baseline demographics and disease characteristics

Characteristics	All Participants (N = 35)
Age, years, median (range)	5.0 (2-11)
Female, n (%)	19 (54.3)
Race, n (%)	
White	21 (60.0)
Black or African American	10 (28.6)
Asian	3 (8.6)
American Indian/Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other	0
Multiple	1 (2.9)
Ethnicity, n (%)	
Hispanic or Latino	9 (25.7)
Not Hispanic or Latino	26 (74.3)
Weight, Kg, median (range)	20.7 (13.1-56.6)
BMI, Kg/m ^{2} ,median (range)	15.9 (14.2-32.7)
Baseline vIGA-AD, n (%)	
<4	0
4	35 (100)
EASI, median (range)	28.8 (21.6-59.7)
BSA, % median (range)	50.0 (20-100)

n= number of patients; BMI, body mass index;EASI= eczema area and severity index; vGIA-AD=validated investigator global asessment for atopic dermatitis

Amy S. Paller, Mercedes E. Gonzalez, Amal Assa'ad, Zachary A. Zinn, Shuai Hao, Kristina Unnebrink, Gweneth F. Levy, Henrique D. Teixeira, Alena Pechonkina, Yuli Qian, Mohamed-Eslam F. Mohamed, Shilpa Goel. Safety, Tolerability, and Exploratory Efficacy of Upadacitinib in Pediatric Patients With Severe Atopic Dermatitis. Presented at the Pediatric Dermatology Research Alliance (PeDRA) October 9-11, 2025, Minneapolis, MN, United States.

JAK Inhibitors in Pediatric Atopic Dermatitis Trials

A Phase 1 study was conducted to evaluate the PK, safety, and tolerability of low- and high-dose UPA over 7 days (Part 1) and the long-term safety and tolerability of low-dose UPA (Part 2) in pediatric patients with severe AD, with efficacy assessed as an exploratory objective.

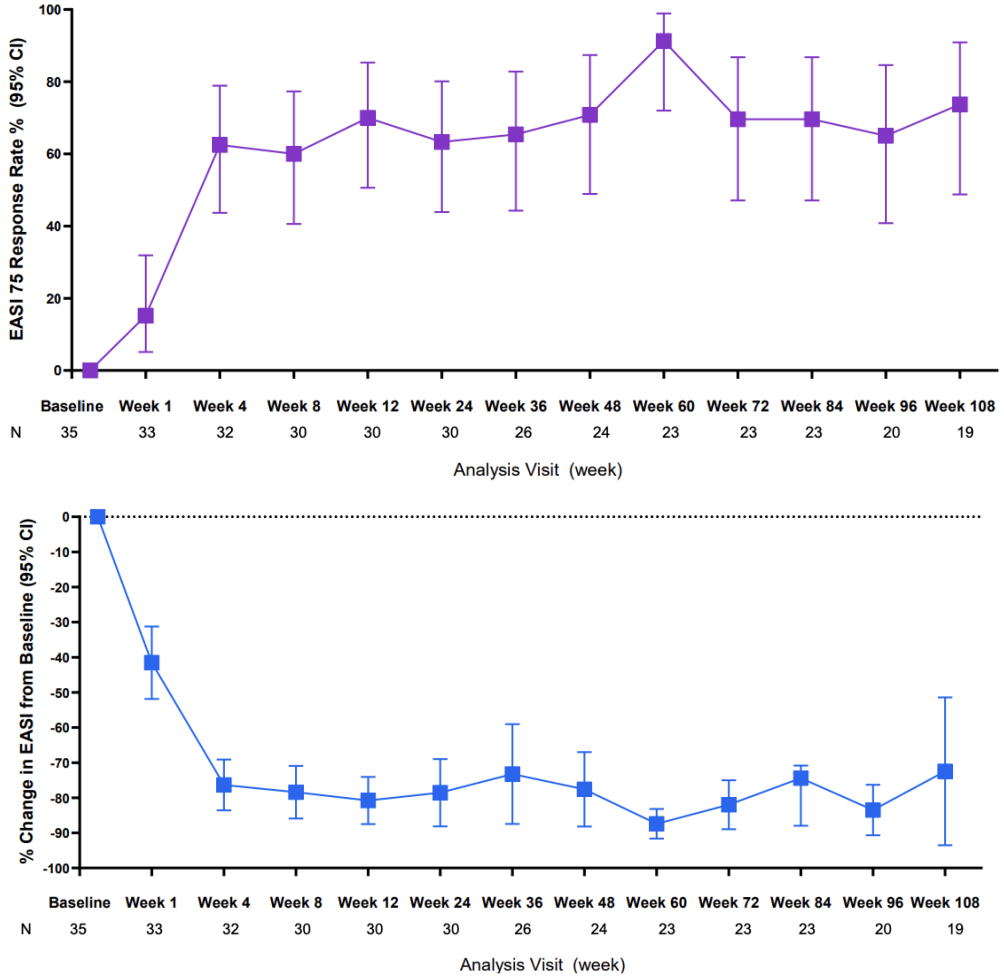


Table 3. Treatment-Emergent Adverse Events of Special Interest (AESI)

AESI	Patients with AESI n (%) Total N=33
Serious Infection	2 (6.1)
Opportunistic Infections excluding tuberculosis and herpes zoster	1 (3.0)
Malignancy	0
Confirmed malignancy	0
Malignancy	0
Non-melanoma skin cancer (NMSC)	0
Malignancy excluding NMSC	0
Lymphoma	0
Hepatic disoder	0
Gastrointestinal perforations	0
Anemia	0
Neutropenia	2 (6.1)
Lymphopenia	0
Herpes Zoster	2 (6.1)
Creatine phosphokinase (CPK) elevation	1 (3.0)
Renal dystfunction	0
Tuberculosis	0
Adjudicated MACE	0
Adjudicated VTE	0

n= number of patients; MACE, major adverse cardiac events ; VTE, venous thromboembolic event

Amy S. Paller, Mercedes E. Gonzalez, Amal Assa'ad, Zachary A. Zinn, Shuai Hao, Kristina Unnebrink, Gweneth F. Levy, Henrique D. Teixeira, Alena Pechonkina, Yuli Qian, Mohamed-Eslam F. Mohamed, Shilpa Goel. Safety, Tolerability, and Exploratory Efficacy of Upadacitinib in Pediatric Patients With Severe Atopic Dermatitis. Presented at the Pediatric Dermatology Research Alliance (PeDRA) October 9-11, 2025, Minneapolis, MN, United States.

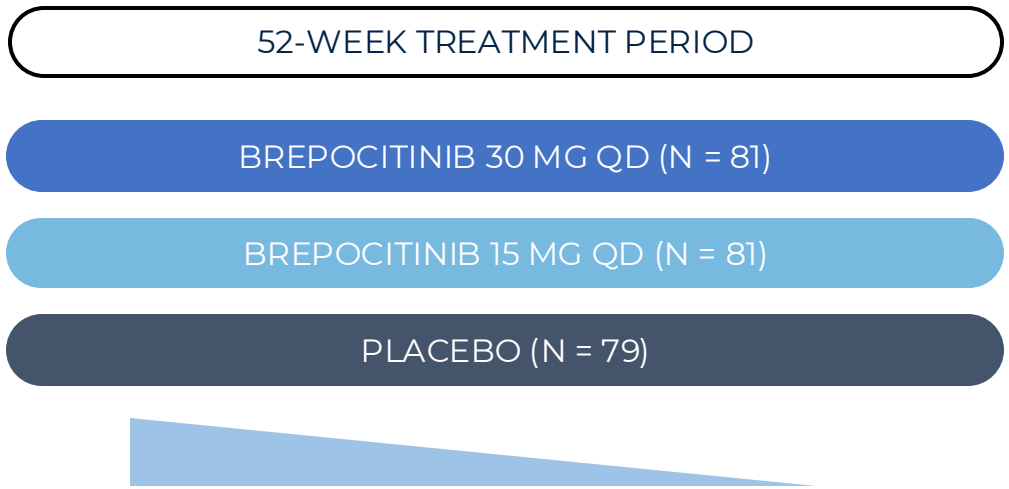
JAK1/TYK2 Inhibitor Brepocitinib in Dermatomyositis Trial

VALOR Phase 3 Study Design

- Distinguished by a 52-week endpoint, protocol-defined steroid taper, and inclusion of patients with active skin and muscle disease

N=241 adults with dermatomyositis

Randomized 1:1:1
by PhGA-VAS



Mandatory corticosteroid taper to ≤5 mg/day from week 12 to 36; recommended further tapering at investigator discretion

Primary Endpoint

Eligible Patients

- Definite or probable dermatomyositis (2017 EULAR/ACR criteria)
- Skin activity: CDASI-A ≥6
- Muscle activity: MMT-8 ≤142
- Refractory or intolerant to SOC therapy

Permitted Background Therapy

Oral IST, antimalarial, and/or OCS

Primary Endpoint

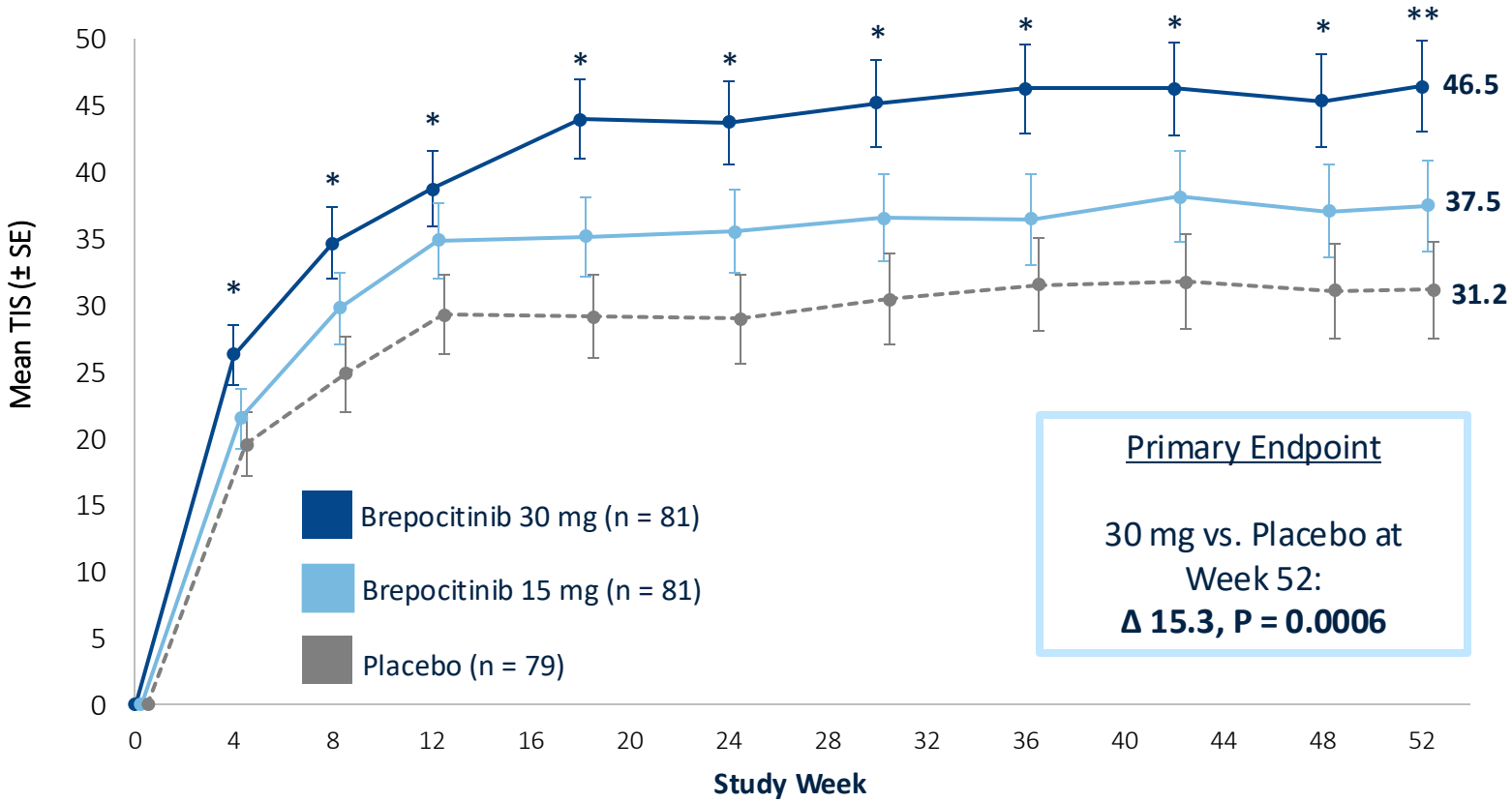
30 mg vs. placebo mean Total Improvement Score at Week 52

IST: Immunosuppressive therapy
OCS: Oral corticosteroids
CDASI-A: Cutaneous Dermatomyositis Activity and Severity Index - Activity Subscore
MMT-8: Manual testing of 8 muscle groups
SOC: Standard of care
PhGA-VAS: Physician's Global Assessment – Visual Analog Scale

JAK1/TYK2 Inhibitor Brepocitinib in Dermatomyositis Trial

Primary Endpoint: Mean TIS at Week 52

Primary endpoint met with clinically-meaningful and consistent efficacy despite greater steroid tapering



Primary Endpoint

30 mg vs. Placebo at Week 52:
Δ 15.3, P = 0.0006

Steroid reduction among subjects on background OCS

	Brepocitinib 30mg	Placebo
Mean dose at baseline (mg)	12.2	11.3
≤2.5 mg at month 12	**62%**	**34%**
Off steroids at month 12	**42%**	**23%**

*Nominal P < 0.05
** P < 0.001

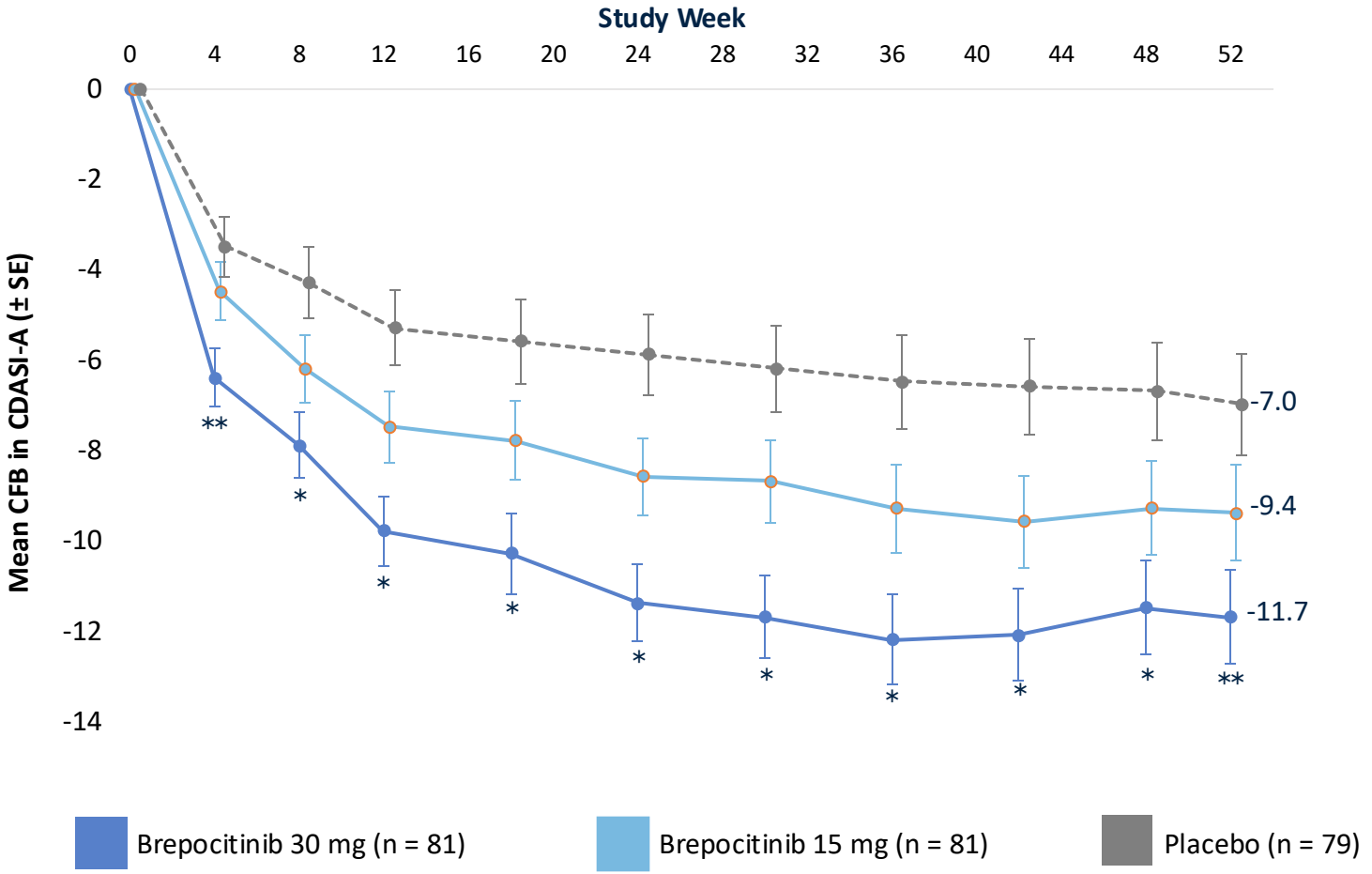
1) The definition of rescue medication was prespecified. This included initiation or clinically-meaningful increase in intensity of one or more systemic therapies given for treatment of DM.

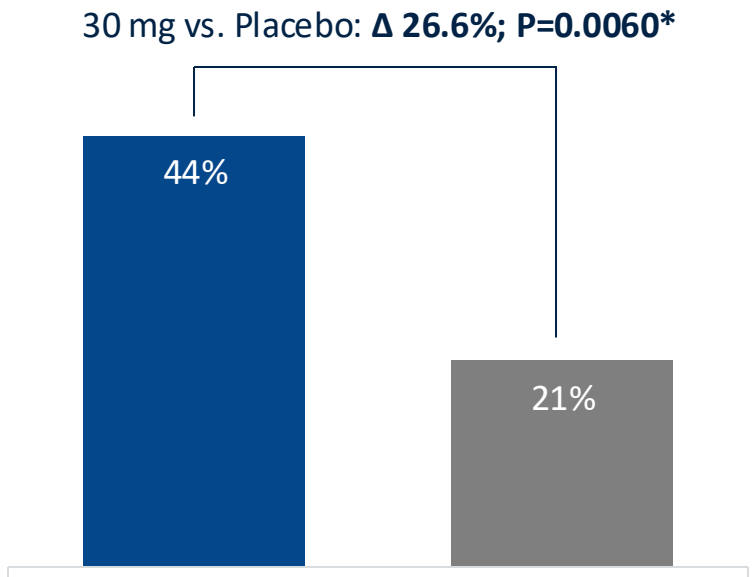
2) The robustness of the primary endpoint result with brepocitinib 30 mg was confirmed with multiple prespecified sensitivity analyses, including a treatment policy analysis and tipping point analysis.

JAK1/TYK2 Inhibitor Brepocitinib in Dermatomyositis Trial

Time Course of CDASI-Activity Change from Baseline

Statistically significant reduction in CDASI-A observed as early as Week 4 and maintained through Week 52, even with substantial corticosteroid tapering





Portion of Patients Achieving Cutaneous Clinical Remission by Week 52 (CDASI-A ≤ 5)

Subjects with baseline CDASI-A > 14

CDASI-A: Cutaneous Dermatomyositis Activity and Severity Index - Activity Subscore
*Nominal P < 0.05
** P < 0.001

JAK1/TYK2 Inhibitor Brepocitinib in Dermatomyositis Trial

AESIs Occurred at Similar Frequencies Across Groups

Only two malignancies were observed, both in placebo group; only one thromboembolic event was observed, also in placebo group; other AESIs were observed in both brepocitinib 30mg and placebo groups at similar frequencies

	Brepocitinib 30 mg QD (N=81)	Brepocitinib 15 mg QD (N=81)	Placebo (N=79)
Participants with:			
AEs	73 (90%)	70 (86%)	72 (91%)
Death	0	0	0
SAEs	13 (16%)	7 (9%)	10 (13%)
Infection SAEs	8 (10%)	2 (3%)	1 (1%)
AEs leading to treatment discontinuation	5 (6%)	6 (7%)	9 (11%)
AEs leading to study discontinuation	3 (4%)	4 (5%)	3 (4%)
Adverse Events of Special Interest:			
Cardiovascular events	1 (1%)	0	2 (3%)
Thromboembolic events	0	0	1 (1%)
Viral reactivation	4 (5%)	2 (2%)	4 (5%)
Opportunistic infections	0	0	0
New or recurrent diagnoses of malignancy	0	0	2 (3%)
Increase in ALT or AST	1 (1%)	2 (2%)	1 (1%)

Abbreviations: AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, SAE=serious adverse event.
Note: Percentages are based on the number of unique participants with an event out of the column total. Treatment-emergent AEs are reported.
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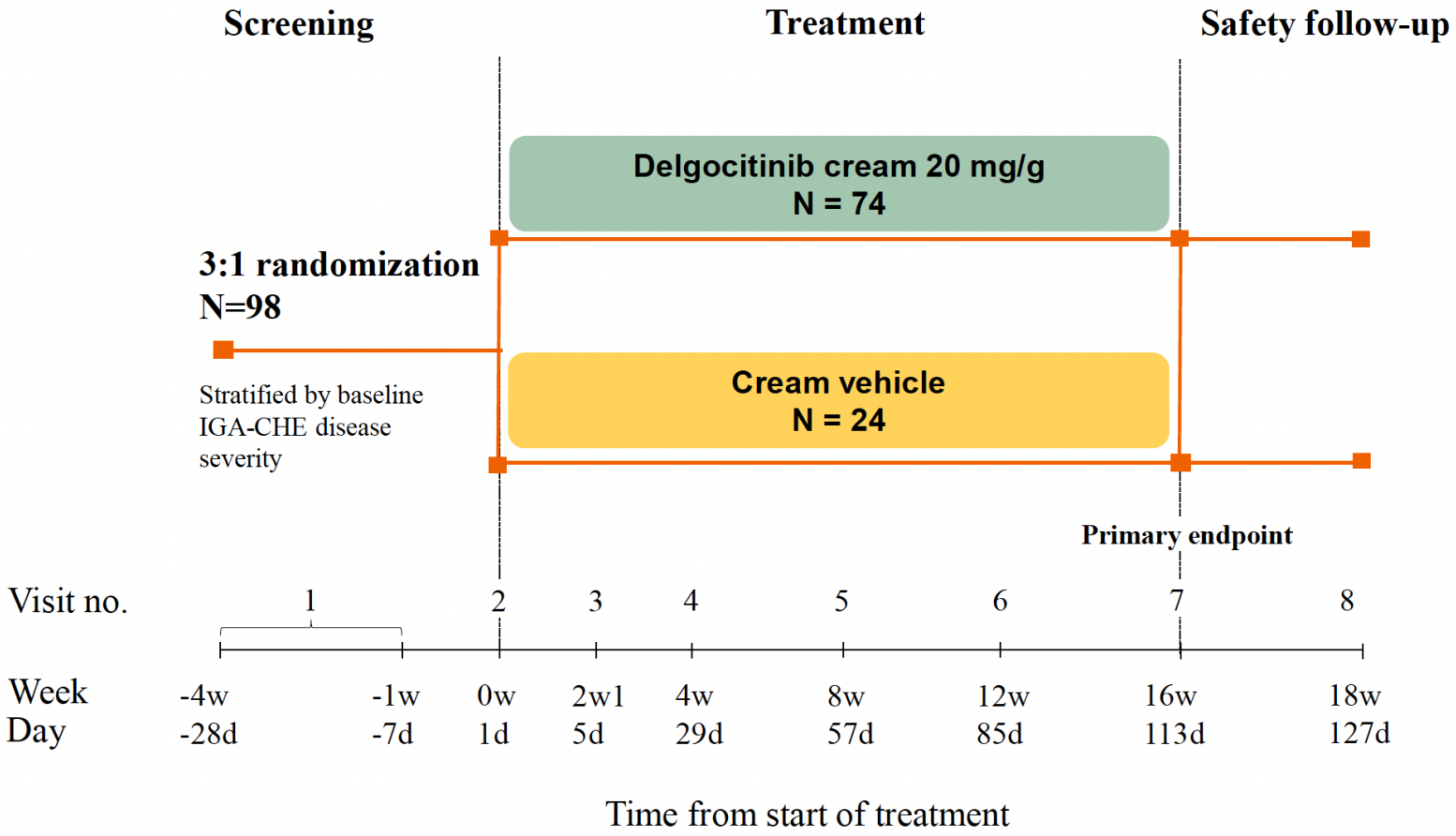
Pan-JAK Inhibitor Delgocitinib in Chronic Hand Eczema Trial – DELTA TEEN

Goal: To evaluate the efficacy and safety of twice-daily applications of delgocitinib cream compared with cream vehicle for a 16-week treatment period in adolescents with moderate to severe CHE



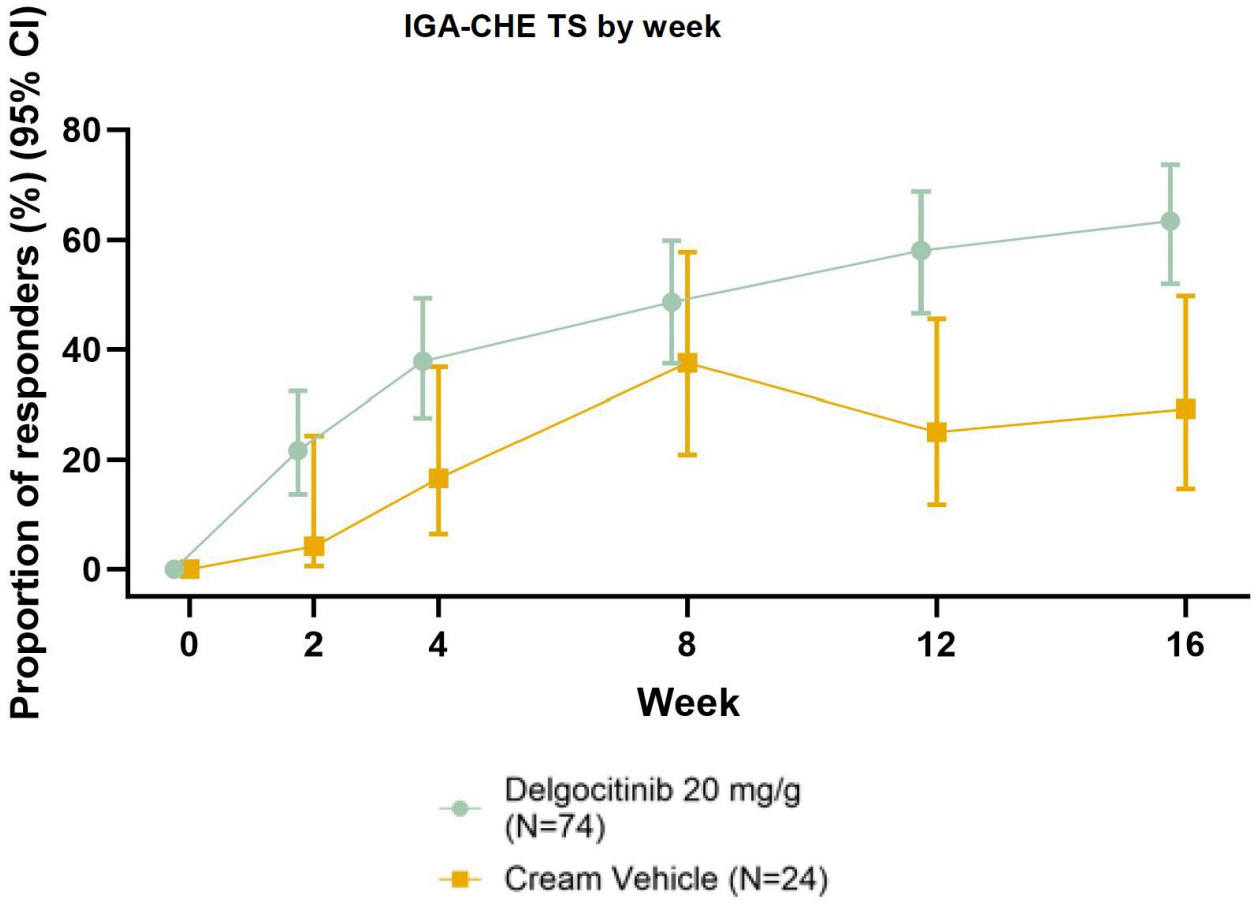
Key inclusion criteria

- Age 12 to 17 years at screening and baseline.
- Disease severity graded as moderate to severe (i.e. an IGA-CHE score of 3 or 4).
- Inadequate response to TCS, or TCS medically inadvisable.

Sonja Molin, Eulalia Baselga, J. Navarro-Triviño, Ziad Reguiai, Sofie De Schepper, James Halpern, Danielle Marcoux, John Su, Paweł Brzewski, Stine Dalsbø Antonsen, Line Conradsen Hiort, Anders Søhoel, Patrick Thøgersen, Diana Rubel. DELTA TEEN Phase 3 trial: Efficacy and Safety of Delgocitinib Cream in Adolescents with Moderate to Severe Chronic Hand Eczema. Late breaker presentation at the 34th Annual Congress of the European Academy of Dermatology and Venereology (EADV), 17th – 20th of September 2025.

Pan-JAK Inhibitor Delgocitinib in Chronic Hand Eczema Trial – DELTA TEEN

Delgocitinib cream is superior to cream vehicle for the primary endpoint (IGA-CHE TS at Week 16): IGA-CHE score of 0/1 (clear/almost clear) with a ≥2 step improvement from baseline).



Delgocitinib cream N=74 Responders (%)	Cream vehicle N=24 Responders (%)	Difference (95% credibility interval)[a]	Probability[b]
47 (63.5%)	7 (29.2%)	37.9% (13.5% to 58.2%)	0.999

a = The 95% credibility interval is generated as the 2.5% and 97.5% quantiles of the difference in posterior distributions. Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥0.

b = Probability that the difference in posterior distributions between delgocitinib cream 20 mg/g minus cream vehicle is larger than zero.

Go to next p

Sonja Molin, Eulalia Baselga, J. Navarro-Triviño, Ziad Reguiai, Sofie De Schepper, James Halpern, Danielle Marcoux, John Su, Paweł Brzewski, Stine Dalsbø Antonsen, Line Conradsen Hiort, Anders Søhoel, Patrick Thøgersen, Diana Rubel. DELTA TEEN Phase 3 trial: Efficacy and Safety of Delgocitinib Cream in Adolescents with Moderate to Severe Chronic Hand Eczema. Late breaker presentation at the 34th Annual Congress of the European Academy of Dermatology and Venereology (EADV), 17th – 20th of September 2025.

Pan-JAK Inhibitor Delgocitinib in Chronic Hand Eczema Trial – DELTA TEEN

Delgocitinib cream is superior to cream vehicle for all key secondary endpoints

	Key secondary endpoint	Delgocitinib cream N=74 Responders (%)	Cream vehicle N=24 Responders (%)	Difference (95% credibility interval)[a]	Probability[b]
	HECSI-90 at Week 16	**53 (71.6%)**	**9 (37.5%)**	36.4% (12.3% to 59.9%)	0.999
ITCH	≥4 points reduction of HESD itch score at Week 16[c]	**35 (64.8%)**	**7 (36.8%)**	31.7% (5.6% to 51.1%)	0.989
PAIN	≥4 points reduction of HESD pain score at Week 16[c]	**31 (63.3%)**	**5 (33.3%)**	31.2% (8.7% to 49.4%)	0.994
	≥4 points reduction of HESD score at Week 16[c]	**30 (55.6%)**	**5 (31.3%)**	25.1% (3.9% to 42.3%)	0.986

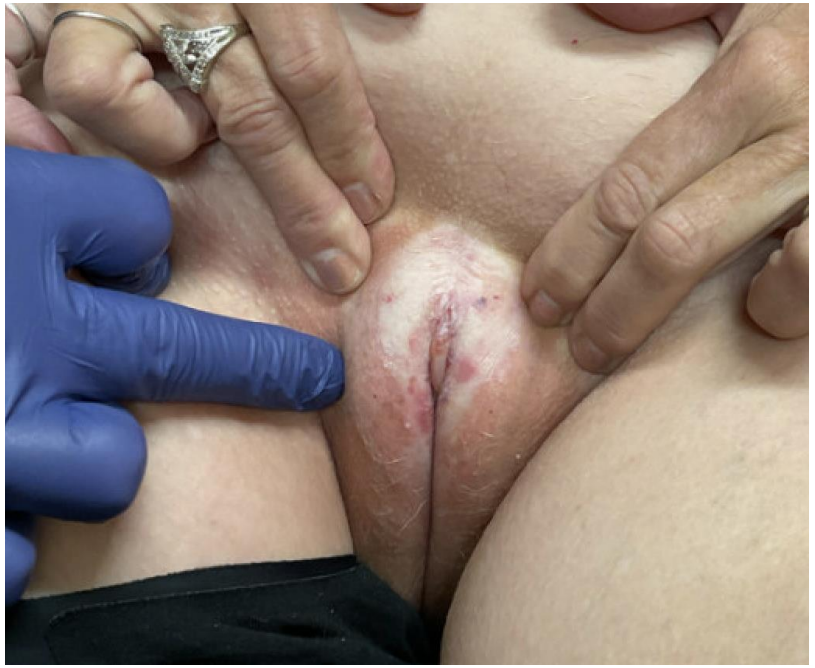
a = The 95% credibility interval is generated as the 2.5% and 97.5% quantiles of the difference in posterior distributions. Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥0. **b** = Probability that the difference in posterior distributions between delgocitinib cream 20 mg/g minus cream vehicle is larger than zero. **c** = Reduction of the score (weekly average) of ≥4 points from baseline to Week 16 among subjects with a baseline score (weekly average) ≥4 points.

Sonja Molin, Eulalia Baselga, J. Navarro-Triviño, Ziad Reguiai, Sofie De Schepper, James Halpern, Danielle Marcoux, John Su, Paweł Brzewski, Stine Dalsbø Antonsen, Line Conradsen Hiort, Anders Søhoel, Patrick Thøgersen, Diana Rubel. DELTA TEEN Phase 3 trial: Efficacy and Safety of Delgocitinib Cream in Adolescents with Moderate to Severe Chronic Hand Eczema. Late breaker presentation at the 34th Annual Congress of the European Academy of Dermatology and Venereology (EADV), 17th – 20th of September 2025.

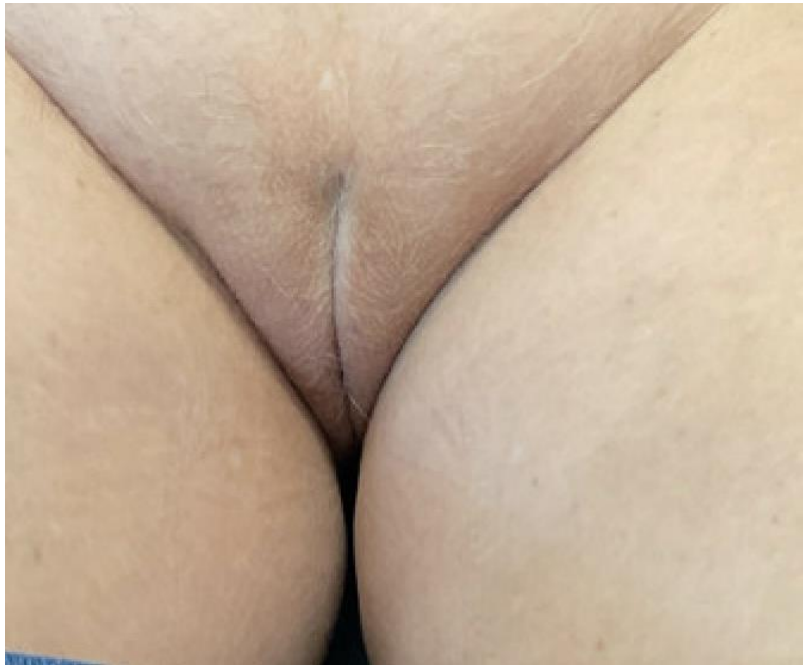
Pan-JAK Inhibitor Delgocitinib in Phase 3 Lichen Sclerosus Trial

New Phase 3 Trial Launched – Lichen Sclerosus

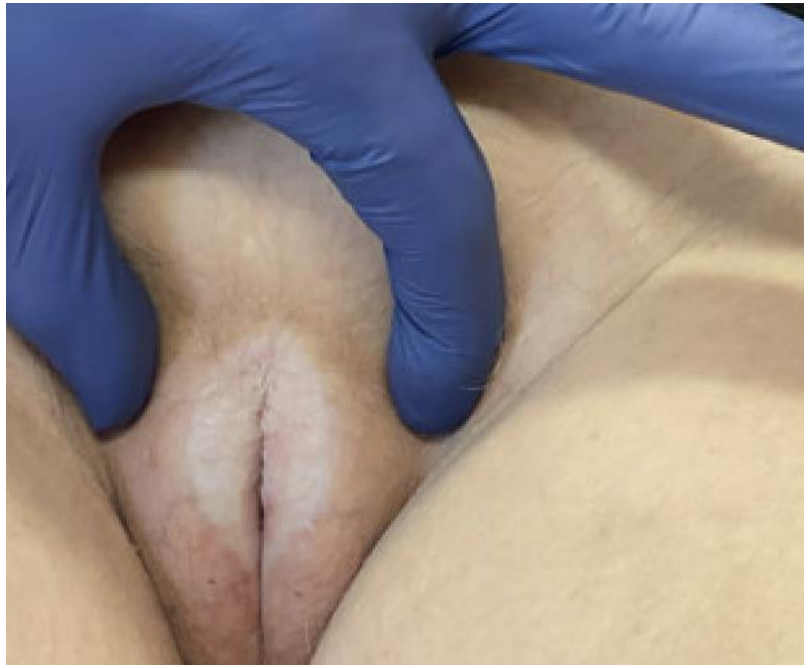
9/22/25
Itch NRS 9/10
Failed Protopic, TCS



10/16/25
Itch NRS 1/10
Delgocitinib 2.5% cream BID



10/16/25
Itch NRS 1/10
Delgocitinib 2.5% cream BID



74 yo WF with history of vulvar lichen sclerosus, chronic pruritus.
Photos courtesy Dr. Christopher Bunick, MD, PhD, with patient permission.

Oral JAK Inhibitors in Vitiligo Trials: Phase 2 completed, Phase 3 ongoing

Parameter	**Upadacitinib (Selective JAK1 inhibitor)**	**Ritlecitinib (JAK3/TEC family kinase inhibitor)**	References
Trial Design	Phase 2, multicentre, randomized, double-blind, placebo-controlled, dose-ranging (NCT04927975)	Phase 2b, randomized, double-blind, placebo-controlled (NCT03715829)	[1-2]
Patient Population	Adults (18-65 years) with extensive non-segmental vitiligo; F-VASI ≥0.5, T-VASI ≥5 (n=185)	Adults with active non-segmental vitiligo (n=364)	[1-2]
Dosing Regimens Studied	6 mg, 11 mg, 22 mg once daily vs placebo (2:2:2:1:1 randomization)	10 mg, 30 mg, 50 mg (±loading dose), 200/50 mg (with loading dose) once daily vs placebo	[1-2]
Study Duration	24 weeks (period 1) + 28 weeks extension (period 2); total 52 weeks	24 weeks (dose-ranging) + 24 weeks extension; total 48 weeks	[1-2]
Primary Endpoint	Percent change from baseline in F-VASI at week 24	Percent change from baseline in F-VASI at week 24	[1-2]
F-VASI Week 24 Results (vs Placebo)	**UPA 11 mg: -21.27% (95% CI -36.02 to -6.52; p=0.0051)** **UPA 22 mg: -19.60% (95% CI -35.04 to -4.16; p=0.0132)** UPA 6 mg: -7.60% (95% CI -22.18 to 6.97; p=0.3037)	**Ritlecitinib 50 mg with loading: -21.2% vs 2.1% placebo (p<0.001)** **Ritlecitinib 50 mg without loading: -18.5% vs 2.1% placebo (p<0.001)** Ritlecitinib 30 mg: -14.6% vs 2.1% placebo (p=0.01)	[1-2]
T-VASI Week 24 Results (vs Placebo)	**UPA 22 mg: -14.27% (95% CI -24.24 to -4.30; p=0.0053)** **UPA 11 mg: -10.84% (95% CI -20.37 to -1.32; p=0.0259)** UPA 6 mg: -7.45% (95% CI -16.86 to 1.96; p=0.1198)	**Did not demonstrate statistically significant superiority over placebo on T-VASI at week 24**	[1-2]
Long-term Efficacy	**Continuous, progressive repigmentation through week 52 without reaching a plateau**	Accelerated improvement observed after treatment with ritlecitinib 200/50 mg in extension period (n=187)	[1-2]
Combination with nbUVB Phototherapy	Not studied in Phase 2 trial	**Week 24 F-VASI: -69.6% (ritlecitinib + nbUVB) vs -55.1% (monotherapy); p=0.009 (OC)** **Week 24 T-VASI: -46.8% (ritlecitinib + nbUVB) vs -24.5% (monotherapy); p<0.001 (OC)**	[1, 3]

1. Once-Daily Upadacitinib Versus Placebo in Adults With Extensive Non-Segmental Vitiligo: A Phase 2, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Dose-Ranging Study. EClinicalMedicine. 2024. Passeron T, Ezzedine K, Hamzavi I, et al.

2. Efficacy and Safety of Oral Ritlecitinib for the Treatment of Active Nonsegmental Vitiligo: A Randomized Phase 2b Clinical Trial. Journal of the American Academy of Dermatology. 2023. Ezzedine K, Peeva E, Yamaguchi Y, et al.

3. Response to Ritlecitinib With or Without Narrow-Band Ultraviolet B Add-on Therapy in Patients With Active Nonsegmental Vitiligo: Results From a Phase 2b Extension Study. Journal of the American Academy of Dermatology. 2025. Yamaguchi Y, Peeva E, Adiri R, et al.

Oral JAK Inhibitors in Vitiligo Trials: Phase 2 completed, Phase 3 ongoing

Parameter	**Upadacitinib (Selective JAK1 inhibitor)**	**Ritlecitinib (JAK3/TEC family kinase inhibitor)**	References
Most Common TEAEs	COVID-19, headache, acne, fatigue	No dose-dependent trends in TEAEs or SAEs across 48 weeks	[1-2]
Serious TEAEs Through Study Period	8 serious TEAEs through 52 weeks, including: - 1 death (unknown cause, deemed unrelated) - 1 breast cancer (deemed unrelated) - 1 coronary artery arteriosclerosis (UPA 6 mg, possibly related) - 1 non-fatal ischemic stroke (UPA 11 mg, possibly related)	Well tolerated; no dose-dependent trends in serious AEs	[1-2]
Discontinuation Rates	Higher in UPA 22 mg group than UPA 11 mg and UPA 6 mg groups	Not specifically reported	[1-2]
Biomarker Effects	Decreased CXCL9 levels in peripheral blood; decreased CD4+CD3+/CD8+CD3+ T cell ratio; downregulated Th1-like Tregs (CD4+Foxp3+IFN-γ+ Tregs)	**Significant reductions in CD3/CD8 T-cell infiltrates** **Significant increases in melanocyte markers (tyrosinase, Melan-A) in lesions (50 mg groups; p<0.05)** Dose-dependent downregulation of T-cell activation, NK, cytotoxic markers (IL-2, IL2-RA, IL-15, CCR7, CD5, CRTAM, NCR1, XCL1, KIR3DL1, FASLG, KLRD; p<0.05) Changes correlated with clinical response	[4-5]
Active vs Stable Lesion Response	Not specifically studied	**Ritlecitinib 50 mg significantly stabilized depigmentation in both active and stable lesions vs placebo** Stable lesions showed greater repigmentation; active lesions required stabilization of inflammation first	[6]
Response Across Fitzpatrick Skin Types	Not specifically reported in Phase 2 trial	**Light skin (FST I-III): -15.2 F-VASI improvement vs placebo (p=0.004)** **Dark skin (FST IV-VI): -37.4 F-VASI improvement vs placebo (p<0.0001)** Patients with dark skin responded earlier than those with light skin	[7]
New Safety Signals	No new safety signals observed	No new safety signals; well tolerated with nbUVB addition	[1-2][3]
Current Development Status	**Phase 3 trial ongoing (Viti-Up; NCT06118411) evaluating upadacitinib 15 mg in adults and adolescents with non-segmental vitiligo**	Phase 2b completed; further development status not specified in available literature	[1, 8]

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5. Improvements in Immune/Melanocyte Biomarkers With JAK3/TEC Family Kinase Inhibitor Ritlecitinib in Vitiligo. The Journal of Allergy and Clinical Immunology. 2023. Guttman-Yassky E, Del Duca E, Da Rosa JC, et al.

6. Ritlecitinib, a JAK3/TEC Family Kinase Inhibitor, Stabilizes Active Lesions and Repigments Stable Lesions in Vitiligo. Archives of Dermatological Research. 2024. Yamaguchi Y, Peeva E, Duca ED, et al.

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JAKi in Clinical Trials

Thank you!

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