Anti-OX40 monoclonal antibody IMG-007 exhibited clinical activity of hair regrowth, suppressed scalp inflammatory biomarkers in patients with severe alopecia areata in a Ph1b/2a study

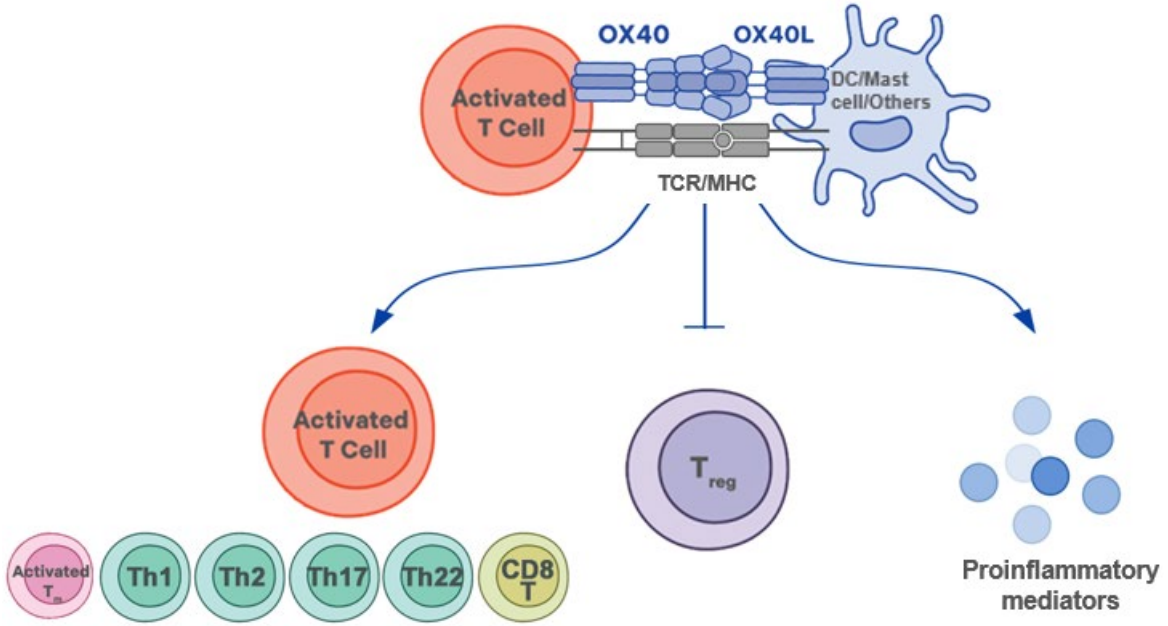
Emma Guttman[1], Maryanne Senna[2], Dusan Sajic[3], Catherine Maari[4], Megan Lau[1], Joseph Largen[1], Ester Del Duca[1], Juliana Pulsinelli[1], Joel Correa da Rosa[1], Chongtian Guo[5], Yancong Shen[5], Yufang Lu[5]

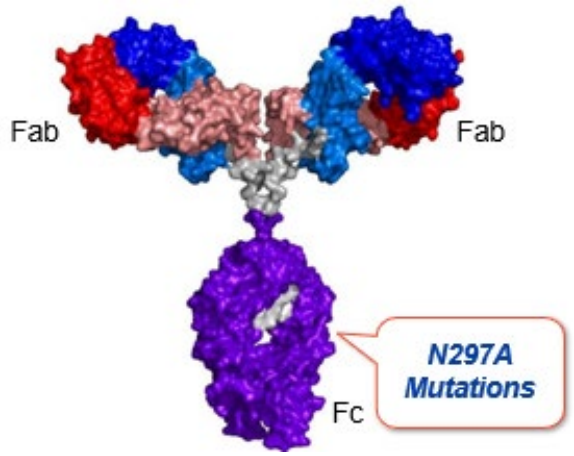
[1]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[2]Harvard Medical School, Boston, MA, USA
[3]Guelph Dermatology Research, Guelph ON, Canada
[4]Innovaderm Research, Montreal, QC, Canada
[5]ImageneBio, Inc, USA

Emma Guttman and Maryanne Senna are advisers for ImageneBio, the study sponsor.
Yufang Lu is an employee of ImageneBio; Chongtian Guo and Yancong Shen were employees of ImageneBio when the study was conducted.

IMG-007 is a non-depleting anti-OX40 mAb targeting various T cell subsets

OX40-OX40L signaling amplifies T cell responses by disrupting the balance between effector T cells and immunomodulatory Treg cells





- IMG-007 binds to OX40 and blocks OX40-OX40L signaling
- Fc N297A mutations to silence the ADCC function thereby minimizing T cell cytotoxicity[1]
- Extended half-life[2] supports the potential of extended dose regimens

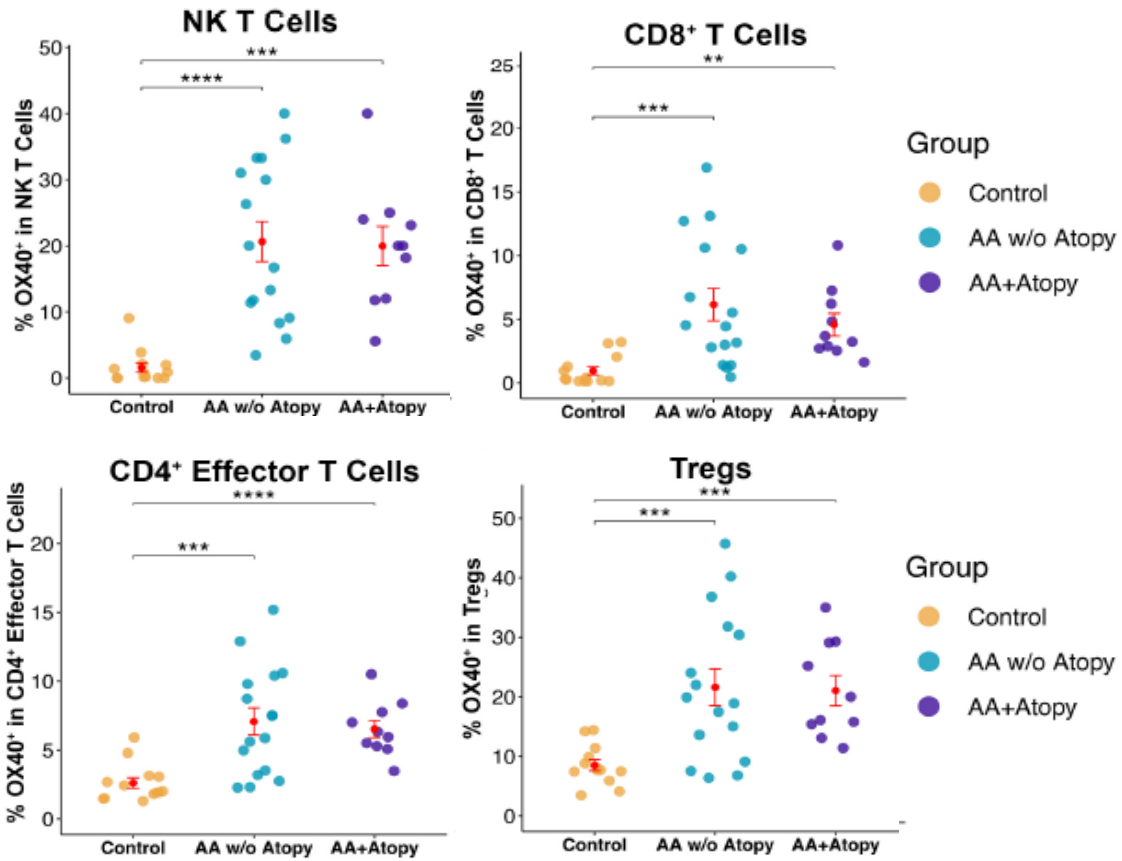
mAb: monoclonal antibody

1. ADCC: antibody-dependent cellular cytotoxicity. ADCC is a cytotoxic effector mechanism by which an antibody binds to and kills its antigen expressing cells through engaging its Fc region with immune effector cells, primarily natural killer (“NK”) cells. Based on nonclinical and clinical evaluations thus far, IMG-007 binds specifically to OX40 receptor on activated T cells to block their binding to OX40L without killing them
2. IMG-007 SC half-life is approximately 34.7 days for a single SC dose of IMG-007 600 mg based on a Phase 1 study in healthy adults (data on file).

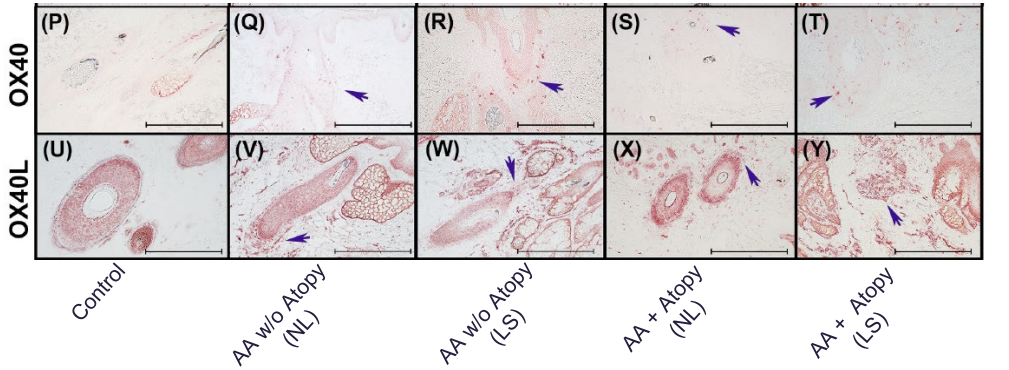
IMAGENE

Systemic and cutaneous OX40/OX40L upregulation in AA patients regardless of atopic background

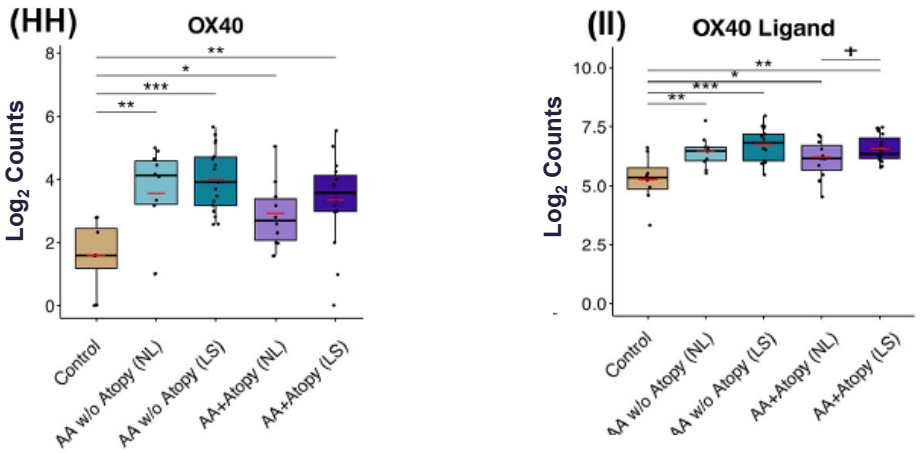
OX40+ cells are increased in blood



OX40 and OX40L expressions are increased in scalp



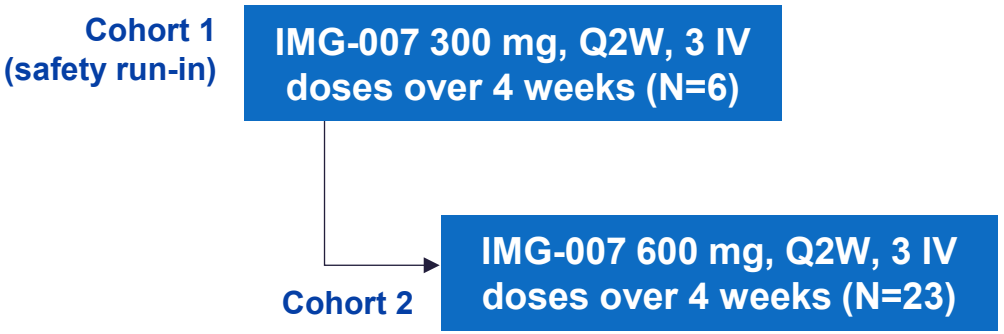
OX40+ and OX40L+ cellular infiltrates in hair follicles

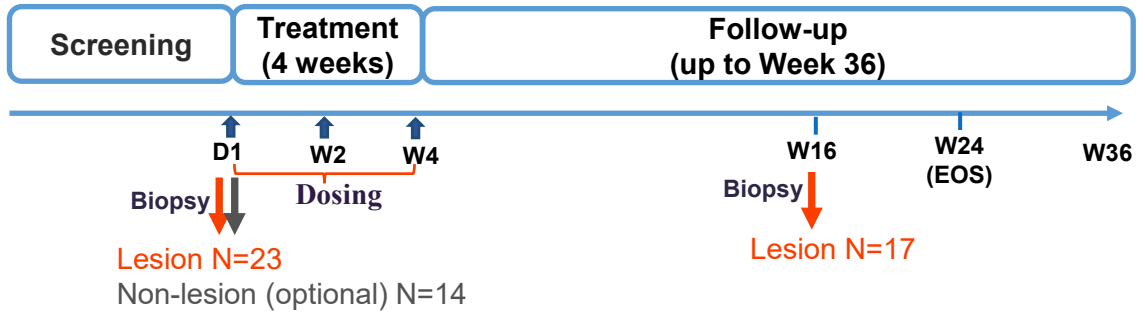


OX40/OX40L expression also correlates with proinflammatory cytokines, hair keratins in the scalp and AA disease severity

Kim M et al. Allergy, 2024;00:1–14
LS: lesional, NL: Nonlesional

Phase 1b/2a study evaluated the safety and clinical activity of IMG-007 in severe AA patients (with ≥ 50% scalp hair loss)





- Open-label[1] design
- Key endpoints:
  - Safety, tolerability
  - % changes from baseline in SALT score by visit

- 29 patients were enrolled from 11 centers in the U.S. and Canada
  - N=6 in the 300 mg cohort
  - N=23 in the 600 mg cohort
- 16 (of 23) patients in the 600 mg cohort also participated in an optional extended follow-up period up to Week 36
- Scalp biopsies
  - Biopsies were taken from a representative lesion at baseline and Week 16 visits
  - Biopsies were bisected for transcriptome sequencing and immunohistochemical (IHC) staining, respectively

1. In historical AA trials, the placebo effects were generally very low (<10%), making an open-label design adequate for an AA POC study
SALT: Severity of Alopecia Tool; EOS: End of study; L: lesional; NL: non-lesional

IMAGENE

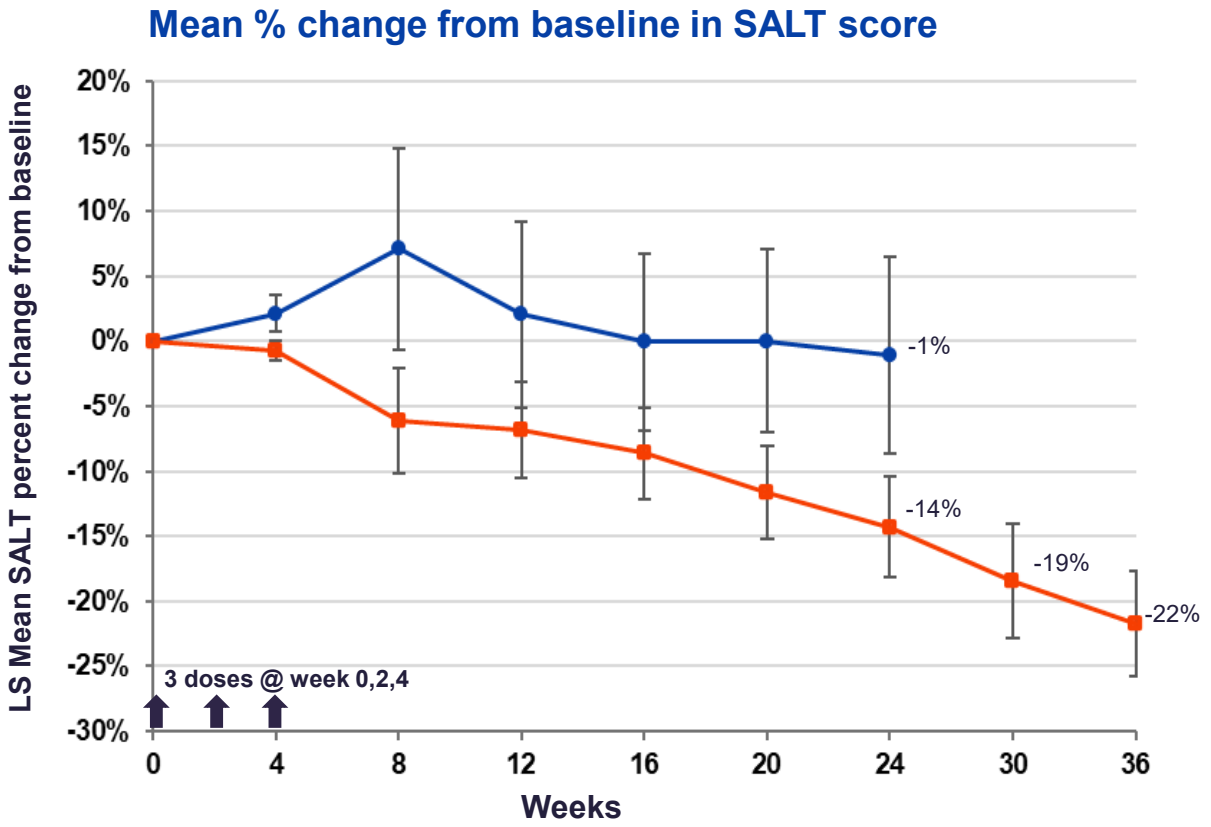
Demographics and key baseline characteristics

	IMG-007 300 mg N=6	IMG-007 600 mg N=23	Combined IMG-007 N=29
Age, yrs, mean (SD)	42.2 (15.5)	44.7 (15.1)	44.2 (14.9)
Female, n (%)	6 (100.0%)	16 (69.6%)	22 (75.9%)
Race, n (%)			
White	5 (83.3%)	14 (60.9%)	19 (65.5%)
Black	1 (16.6%)	6 (26.1%)	7 (24.1%)
Other	0 (0%)	3 (13.0%)	3 (10.3%)
BMI, kg/m^2, mean (SD)	28.8 (8.6)	31.6 (8.4)	31.0 (8.3)
Duration of AA, yrs, mean (SD)	7.8 (8.6)	14.2 (12.9)	12.9 (12.3)
Current Episode, yrs, mean (SD)	2.8 (2.7)	3.0 (2.2)	3.0 (2.3)
Baseline SALT, mean (SD)	87.2 (15.7)	78.6 (18.4)	80.4 (18.0)
SALT 50 to < 95, n (%)	3 (50%)	17 (74%)	20 (69%)
SALT ≥ 95, n (%)	3 (50%)	6 (26%)	9 (31%)
Affected areas, n (%)			
Scalp only	2 (33%)	4 (17%)	6 (21%)
Eyebrow involvement	4 (67%)	18 (78%)	22 (76%)
Eyelash involvement	3 (50%)	15 (65%)	18 (62%)

IMAGENE

4-wk treatment resulted in a dose-related trend in SALT score improvement

Patients in the 600 mg cohort showed greater improvement in SALT score than in the 300 mg cohort
(Allcomers: baseline SALT 50 - 100)



Progressive SALT reduction without plateauing by week 36, which is approximately 8 months after the last dose at Week 4

- At Week 36, 25% of patients in the 600 mg group achieved ≥ 30% reduction from baseline in SALT score

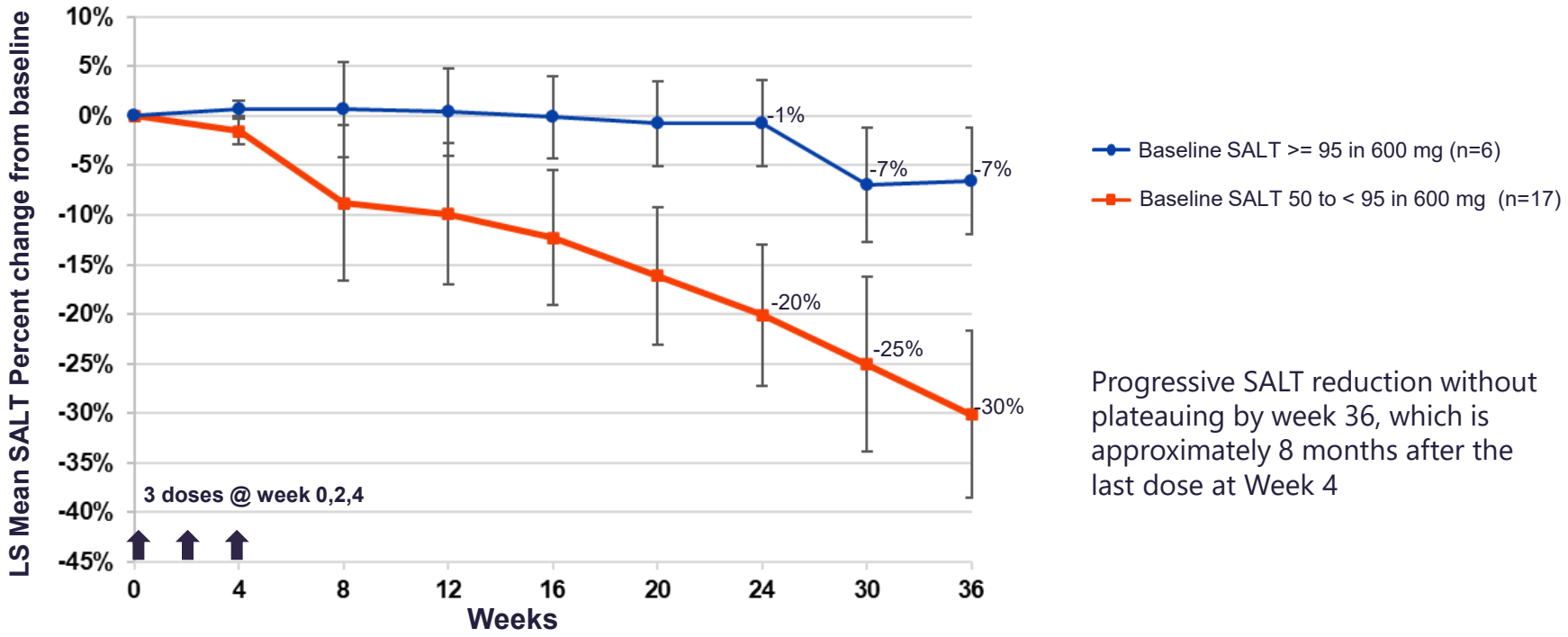
Least square (LS) mean percentage change from baseline in SALT is estimated from the mixed model repeated measure (MMRM).
All assessments after the start date of prohibited medication were set to missing.
All the collected data available after treatment discontinuation were included in the analysis.

IMAGENE

Marked improvement seen in patients with baseline SALT score 50 to < 95

Four-week (600 mg) treatment led to deeper improvement in patients with baseline SALT score 50 to < 95 than in patients with baseline SALT 95 - 100

Mean % change from baseline in SALT score



Progressive SALT reduction without plateauing by week 36, which is approximately 8 months after the last dose at Week 4

- At Week 36, approximately 36% of patients with baseline SALT score 50 to < 95 achieved ≥ 30% reduction from baseline in SALT score

Least square (LS) mean percentage change from baseline in SALT is estimated from the mixed model repeated measure (MMRM).
All assessments after the start date of prohibited medication were set to missing.
All the collected data available after treatment discontinuation were included in the analysis.

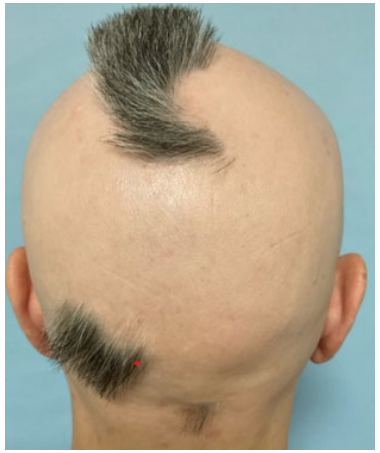
IMAGENE

Photos showing improvement after 4-week treatment with IMG-007

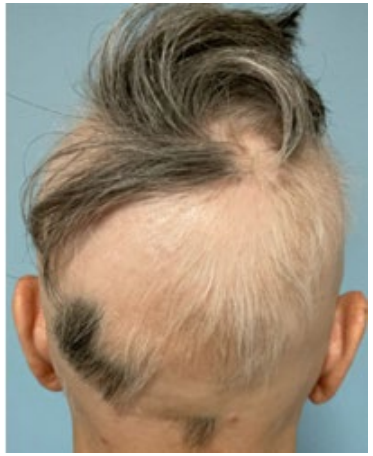
Patients after 3 IV 600 mg doses at Week 0, 2 and 4

Patient 1

Baseline

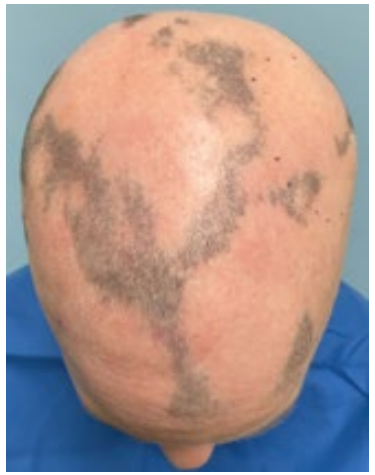


Week 24

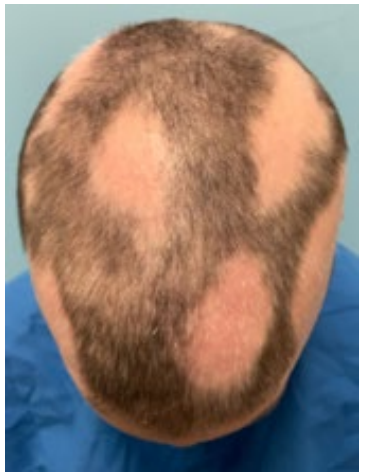


Patient 2

Baseline

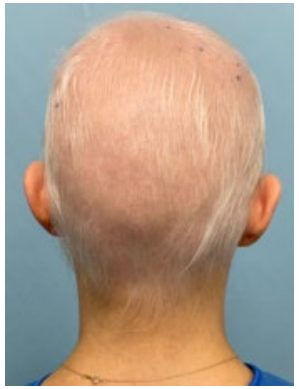


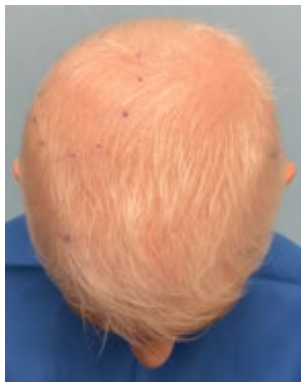
Week 24



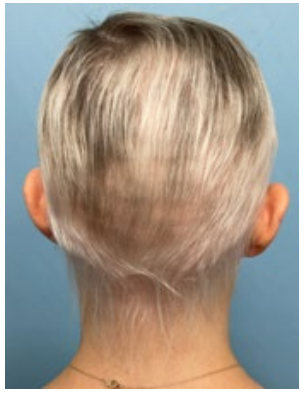
Patient 3

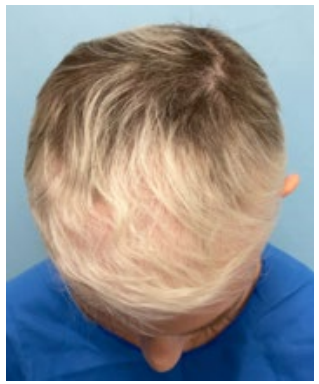
Baseline



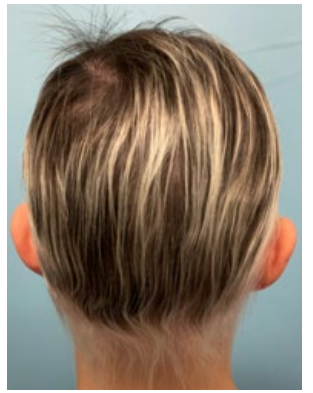


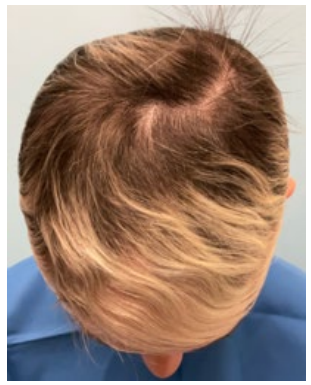
Week 16





Week 24



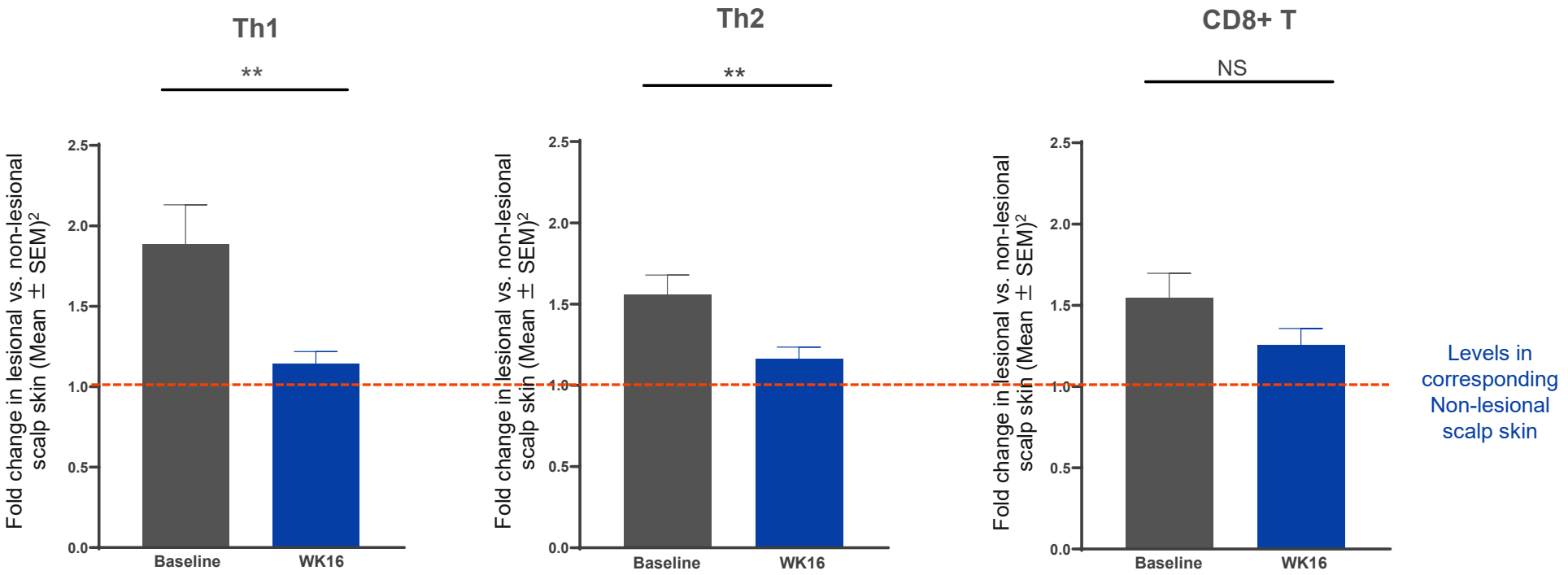


Week 36

IMAGENE

Durable suppression of inflammatory markers of Th1, Th2, and CD8+ T cells at Week 16 after 4-week treatment

At baseline, patients showed activations of inflammatory markers of Th1, Th2, and CD8+ T cells in the AA lesional scalp, compared to the non-lesional scalp, which has been shown previously[1]



1. Kim M, et al. Allergy, 2024, 79(12): 3401-3414; Guttman-Yassky E, et al. JACI, 2022, 149(4): 1318-1328; Fuentes-Duculan J, et al. Experimental Dermatology, 2016, 25(4): 282-286.
2. Data from 4 participants who used prohibited medications have been censored (after the start of the prohibited use).

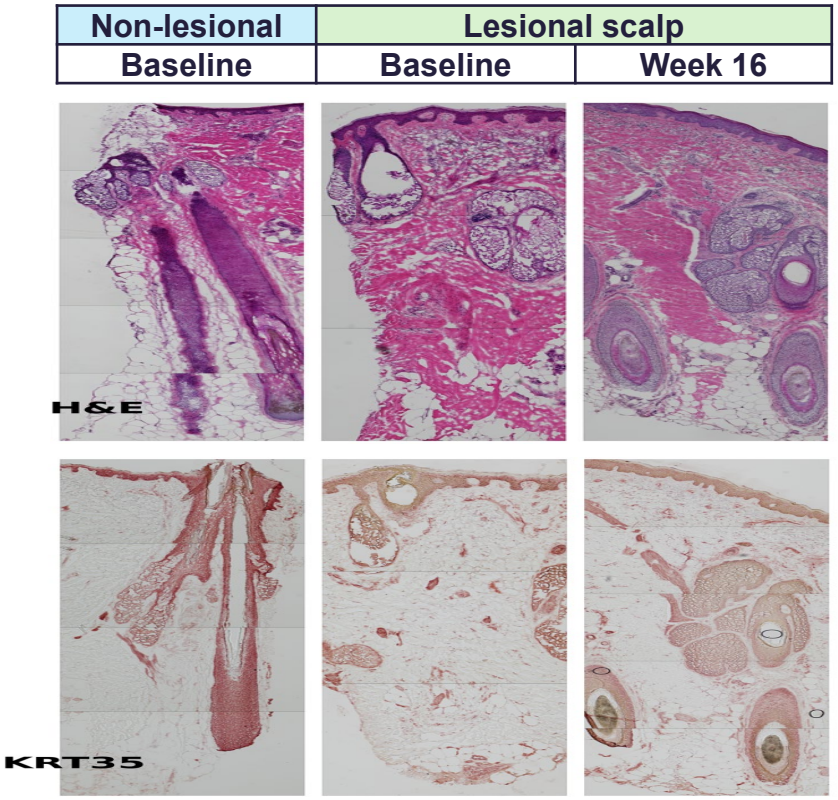
* p<0.05, ** p<0.01, unpaired T-test; SEM: standard error of the mean

For lesional scalp expression results (600mg), Ns at Baseline and wk16 were 23 and 17, respectively. Non-lesional scalp gene expression levels were measured in the corresponding non-lesional tissues, n=14.

Bulk RNAseq was used to measure gene expression levels in Th1 (CXCL9, CXCL10, CXCL11, CXCR3, IFNG, IL12RB1, CCL3, CCL4), Th2 (IL13, CCL13, CCL26, CCL17, IL4, CCL19, CCL8, CCL2, OSM, IL13RA2) and CD8+ T cells (GZMB, GZMA, CD8A, PRF1, KLRC1, CCL5, CXCR6)

Th: T helper

A trend of increased KRT35 IHC expression in lesions at Week 16



KRT35 staining intensity in the cortex of the hair shaft within the hair follicle

n (%)	**BL-NL** N=14	**BL-LS** N=22	**WK16-LS** N=16
POS	10 (71%)	5 (23%)	10 (63%)
POS/NEG	2 (14%)	7 (32%)	2 (13%)
NEG	0 (0%)	4 (18%)	2 (13%)
NA	2 (14%)	6 (27%)	2 (13%)

POS: intense signal
POS/NEG: intermediate signal
NEG : barely detectable signal
NA: no hair follicle

- Lesional expression of hair-associated keratin genes at baseline were downregulated.
- A trend of increased KRT35 IHC expression in lesions were noted at week 16

KRT35: Keratin35; KRT35 expression is an indicator of early stage of hair differentiation
For IHC data, staining positive cell counts or staining intensity were analyzed. Unpaired T-test was used for evaluation of statistical significance between groups
BL-NL: baseline-non-lesional scalp; BL-LA: baseline lesional scalp, WK16-LS: WK16-lesional scalp
POS: Positive; NEG: negative

IMG-007 was overall well-tolerated in patients with severe alopecia areata

TEAEs occurring in two or more patients during 24-Week Period

Preferred term	IMG-007 300 mg (N=6) n (%)	IMG-007 600 mg (N=23) n (%)	IMG-007 combined (N=29) n (%)
Headache	2 (33.3)	2 (8.7)	4 (13.8)
Nasopharyngitis	0 (0.0)	3 (13.0)	3 (10.3)
Hypertension	0 (0.0)	2 (8.7)	2 (6.9)
Streptococcal infection	0 (0.0)	2 (8.7)	2 (6.9)

TEAE incidence was generally similar between the 24-week and extended 36-week periods

- There were no SAEs or severe TEAEs
- All TEAES were mild or moderate in severity
- There were no TEAEs of pyrexia or chills

PT: preferred term; TEAE, treatment-emergent adverse event;

Key takeaways

- Treatment with three doses of IMG-007 300 mg and 600 mg over four weeks resulted in dose-related clinical activity signal of hair regrowth
- Patients in the 600 mg group showed a progressive SALT score reduction without plateauing by week 36, which is approximately 8 months after the last dose at Week 4
- Four-week treatment with IMG-007 600 mg resulted in a broad and durable suppression of activated T cell expressions and partial restoration of hair keratins in the scalp biopsies
- IMG-007 was overall well-tolerated in patients with severe AA
- These results suggest that blocking OX40-OX40L signaling with IMG-007 could be a potential therapeutic strategy for treating AA patients.