R&D Clinical Update

March 18, 2019

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Pipeline

Program	Indication(s)	Preclinical	Phase 1	Phase 2	Phase 3
A-101(45%) *Topical*	Common Warts				
ATI-502 JAK1/JAK3 Inhibitor *Topical*	Alopecia Areata				
	Vitiligo				
	Androgenetic Alopecia (exploratory)				
	Atopic Dermatitis (exploratory)				
ATI-501 JAK1/JAK3 Inhibitor *Oral*	Alopecia Areata				
ATI-450 MK-2 Pathway Inhibitor *Oral*	RA, Psoriasis, Hidradenitis Suppurativa, CAPS, Pyoderma Gangrenosum, Other				
ATI-1777 JAK1/JAK3 Inhibitor *Soft Topical*	Atopic dermatitis, Vitiligo, Alopecia Areata				
ITK/JAK3 Inhibitor *Soft Topical*	Psoriasis, Inflammatory Dermatoses				
ITK/JAK3 Inhibitor *Oral*	Psoriasis, Inflammatory Dermatoses				
MK-2 Pathway Inhibitor *Oral*	Oncology				
ITK/JAK3 Inhibitor *Oral, gut-restricted*	Ulcerative colitis / Crohn's disease				

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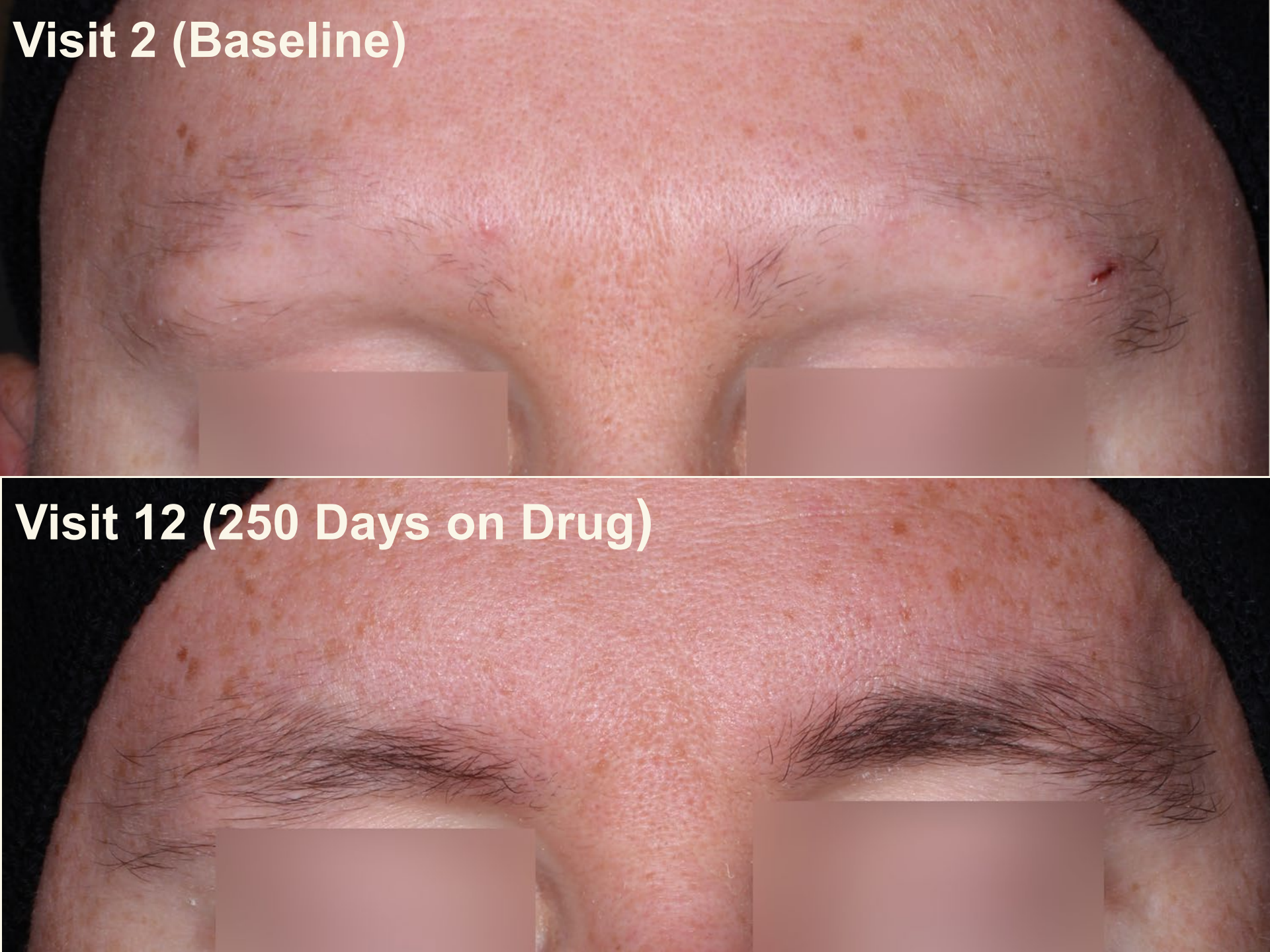
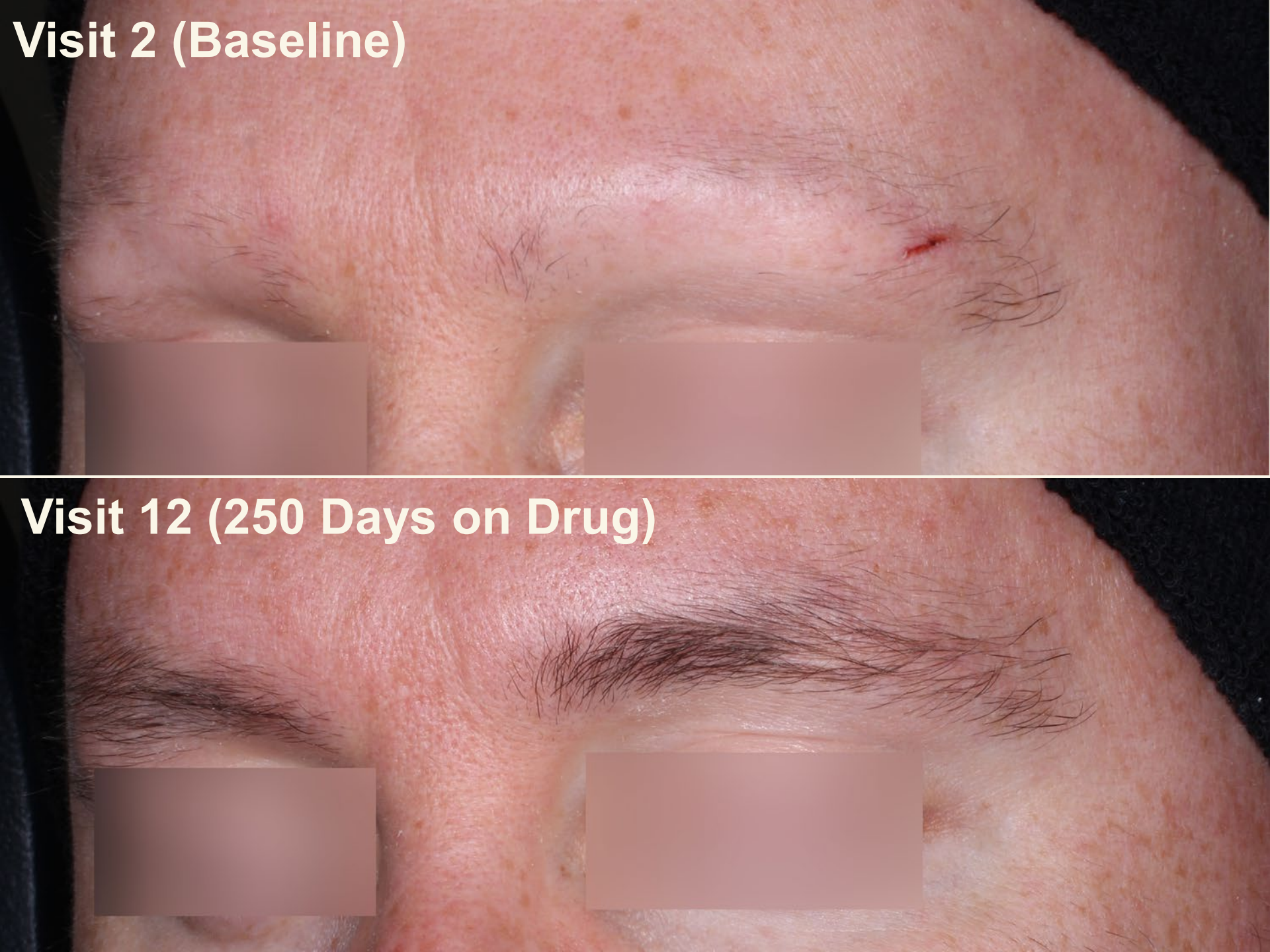
ATI-502-AUATB-201 - Australian Eyebrow

Subject 01-008 (33/M)

- The onset date for the current episode of eyebrow loss was 2010, and the onset of Alopecia Areata was 2009.
- No previous therapies for eyebrow hair loss.
- As of 2/26/19, the subject has had 250 days of exposure to study drug.

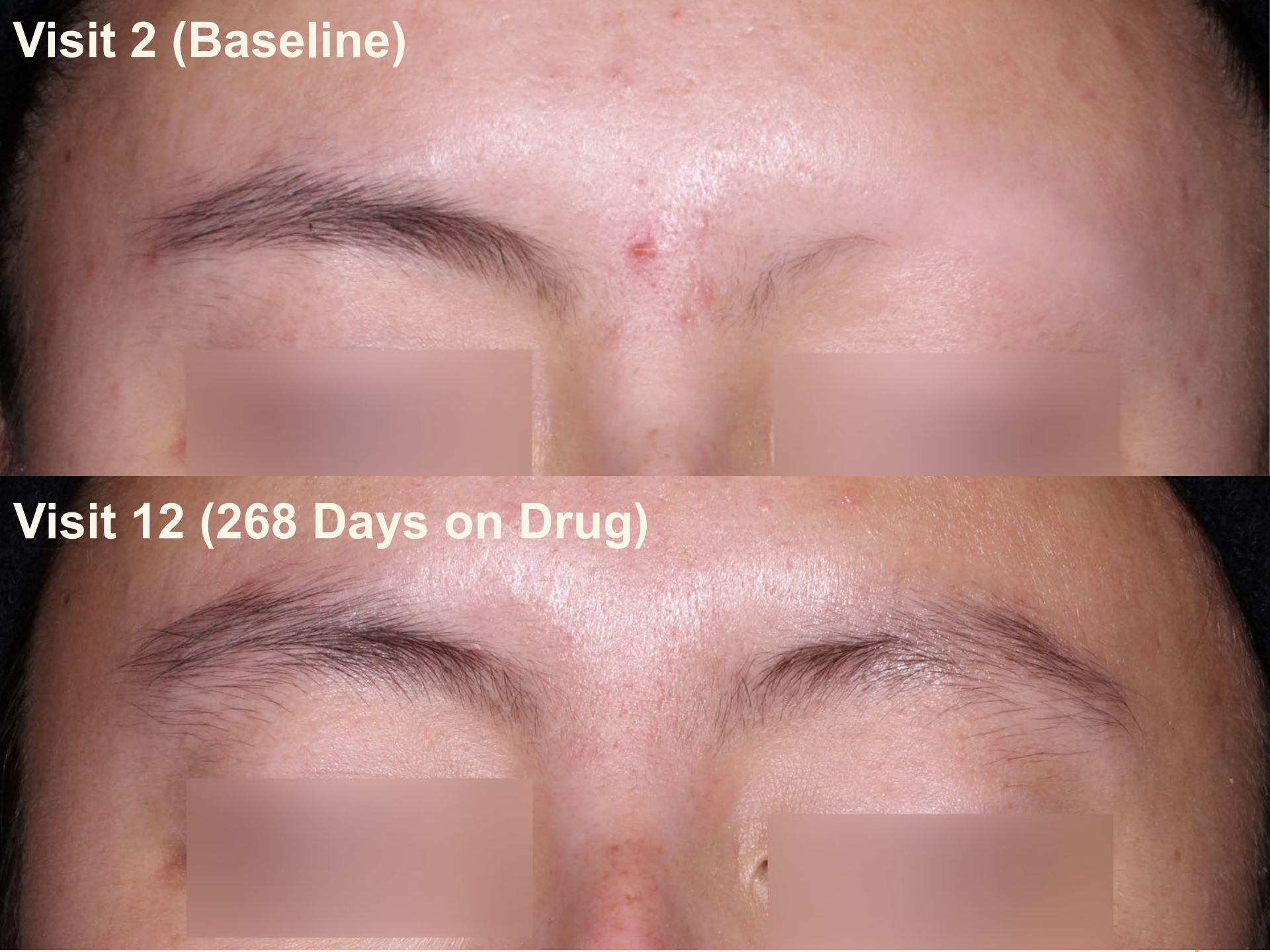

Visit 2 (Baseline)
Visit 12 (250 Days on Drug)


Visit 2 (Baseline)
Visit 12 (250 Days on Drug)


Visit 2 (Baseline)
Visit 12 (250 Days on Drug)

Subject 02-010 (23/F)

- The onset date for the current episode of eyebrow loss and the onset of Alopecia Areata was May 2017.
- The subject has previously used an undefined “other” treatment as therapy for eyebrow hair loss.
- As of 2/15/19, the subject has had 268 days of exposure to study drug.


Visit 2 (Baseline)
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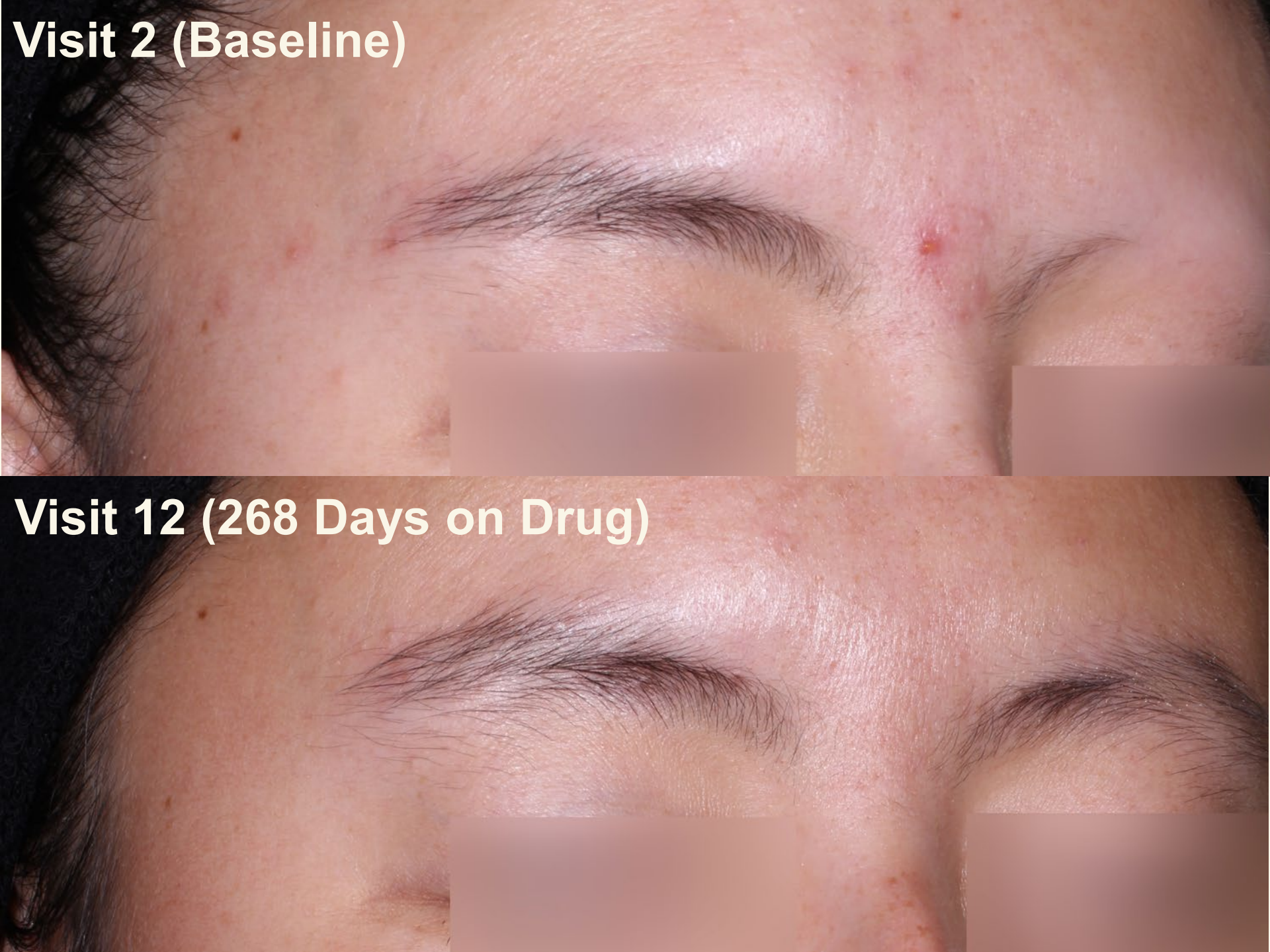
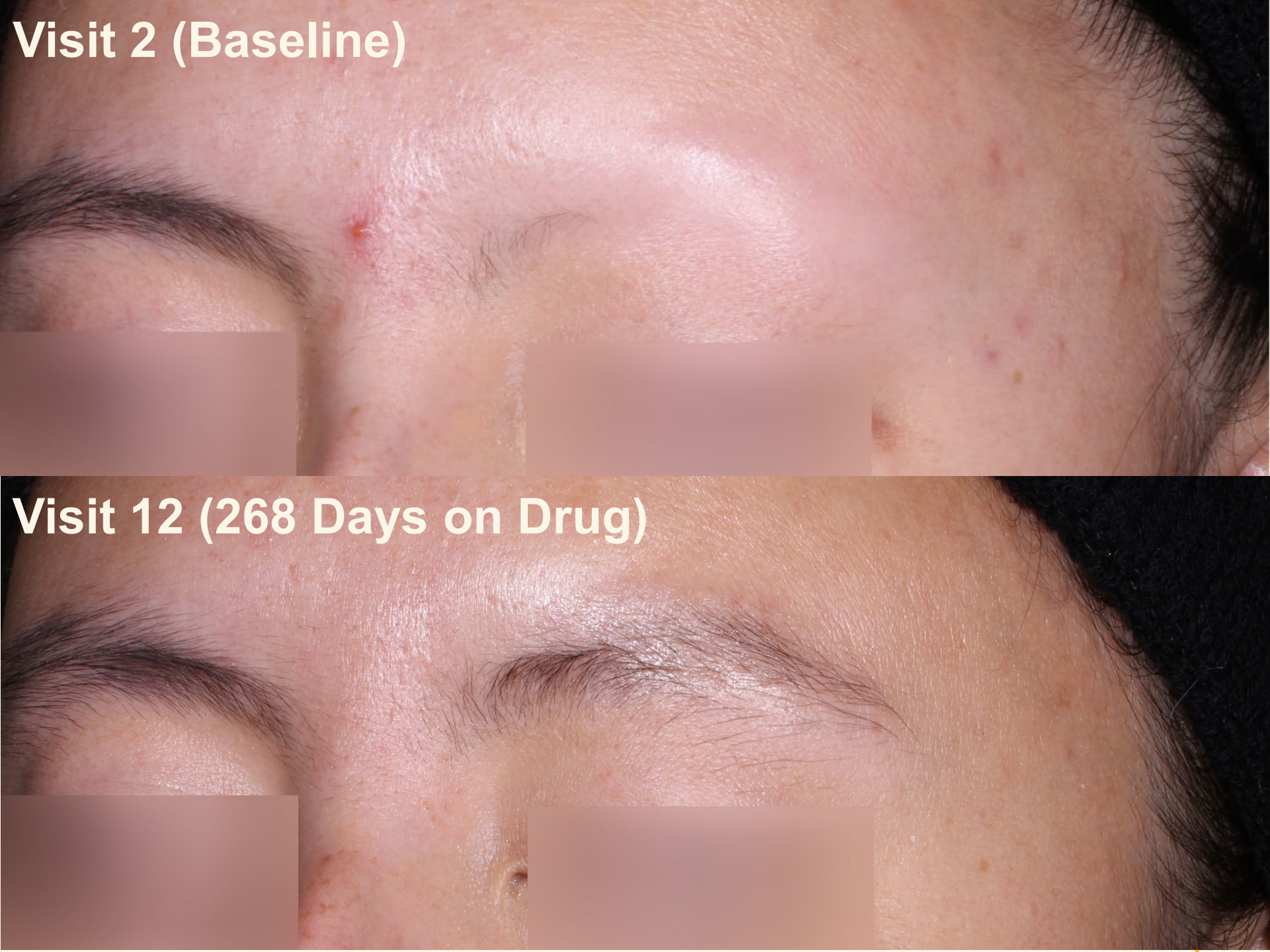
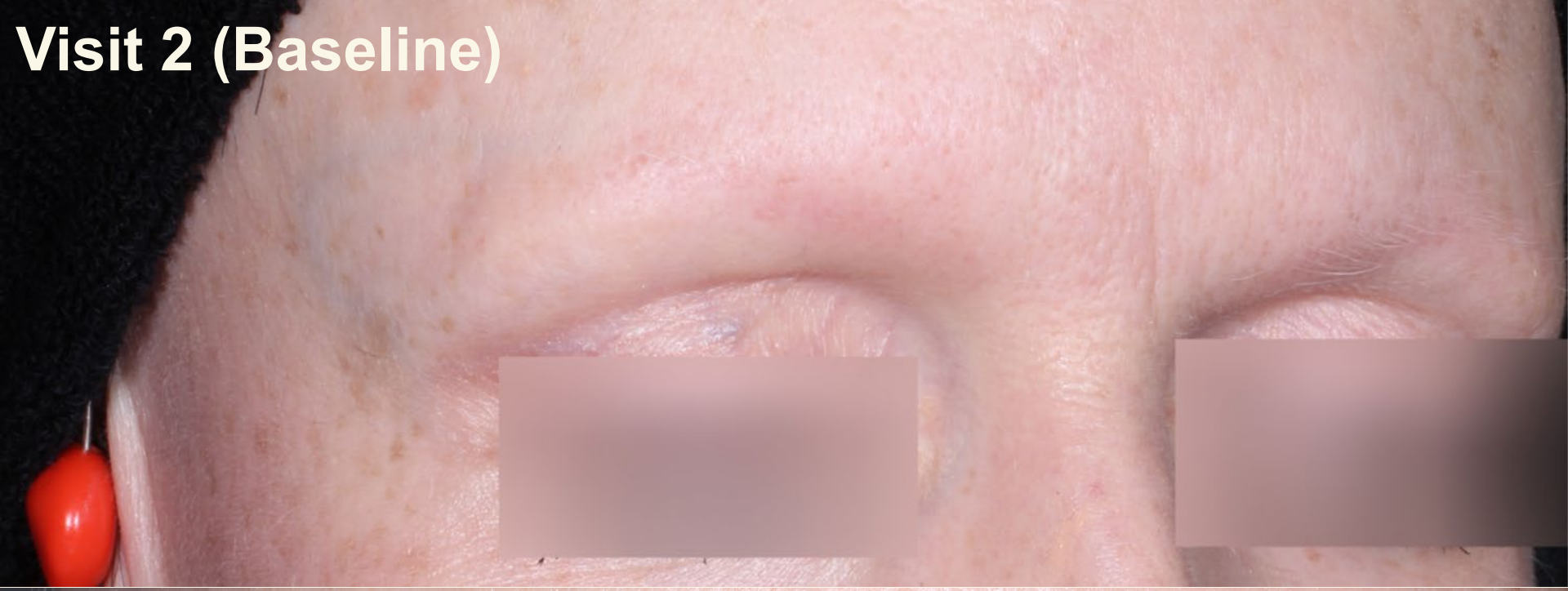

Visit 2 (Baseline)
Visit 12 (268 Days on Drug)


Visit 2 (Baseline)
Visit 12 (268 Days on Drug)

Subject 02-007 (45/F)

- The onset date for the current episode of eyebrow loss was 2013, and the onset of Alopecia Areata was 1986.
- Prior therapies for eyebrow hair loss include glucocorticosteroids and JAK inhibitors.
- As of 2/22/19, the subject has had 289 days of exposure to study drug with a 47 day gap.


Visit 2 (Baseline)
Visit 12 (289 Days on Drug*)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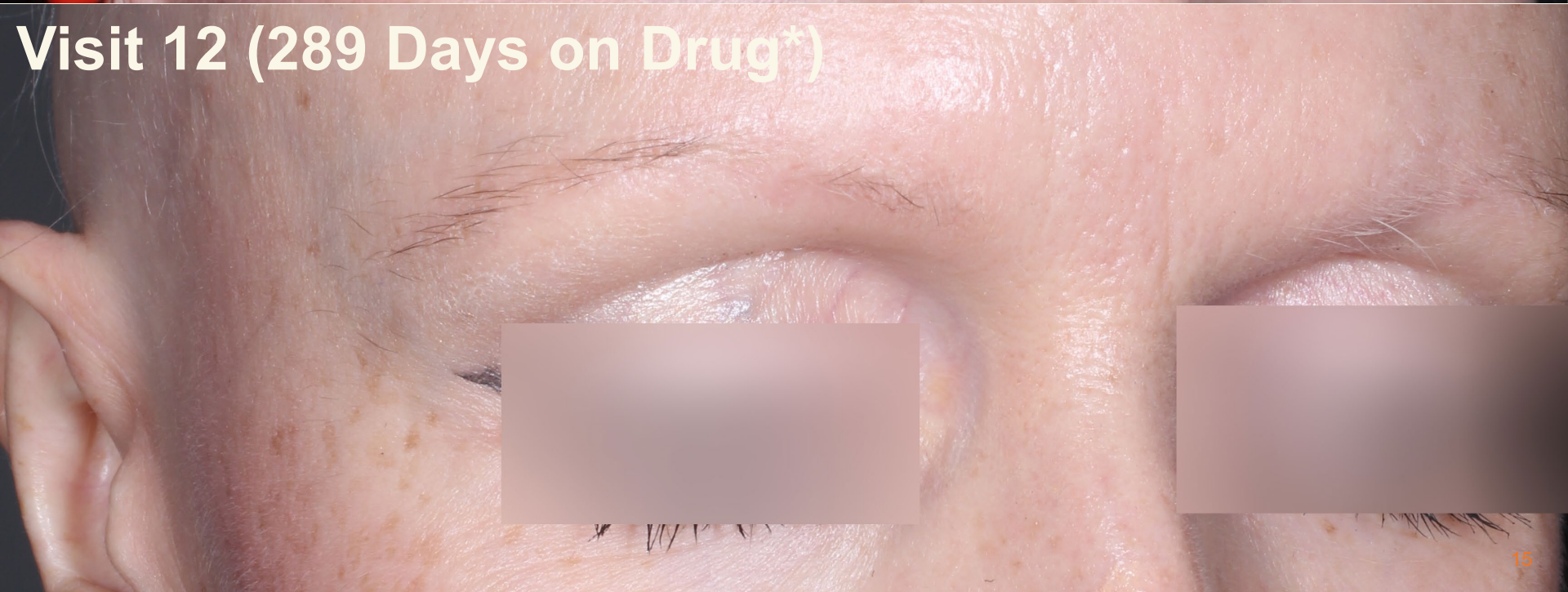
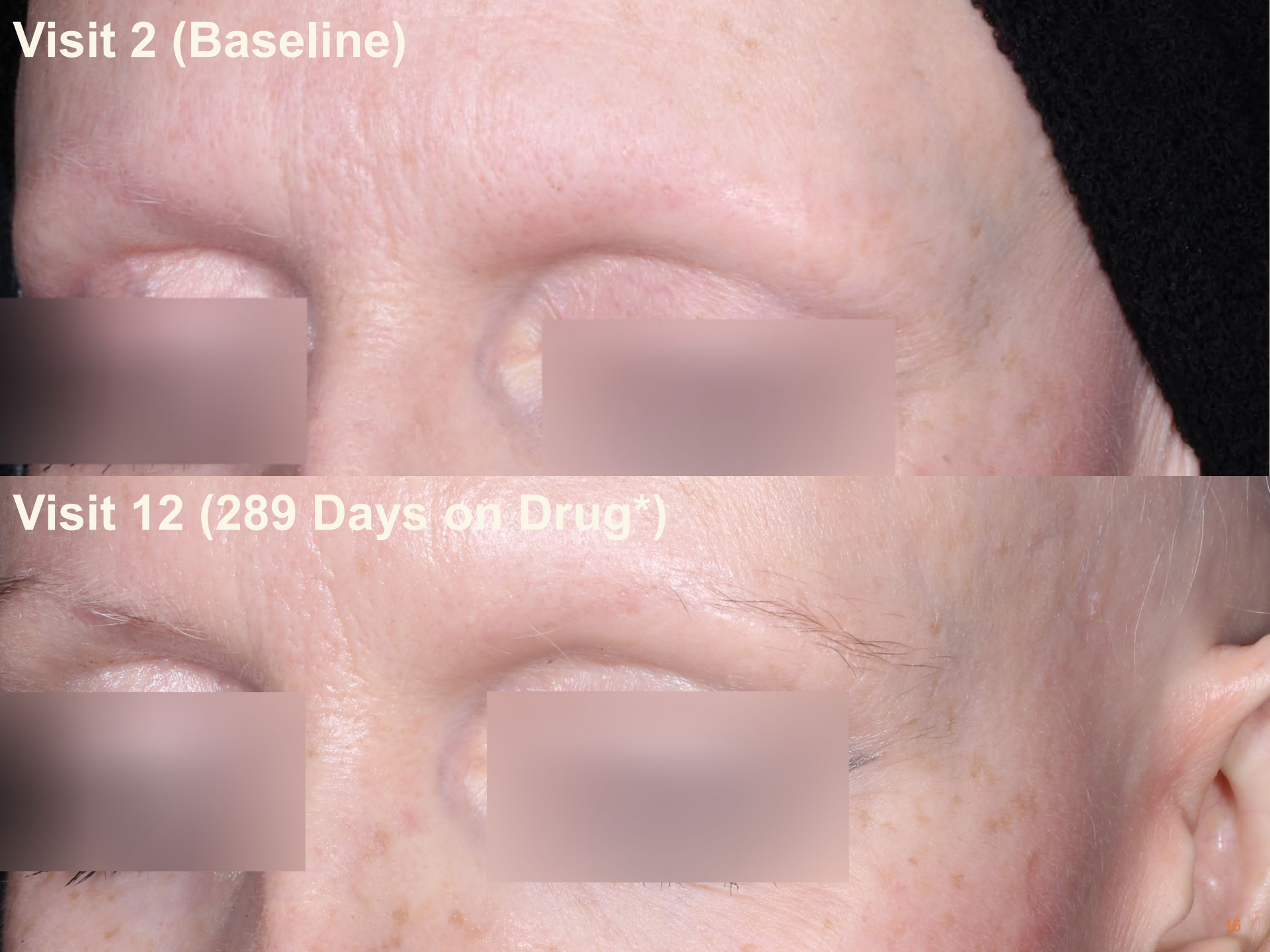
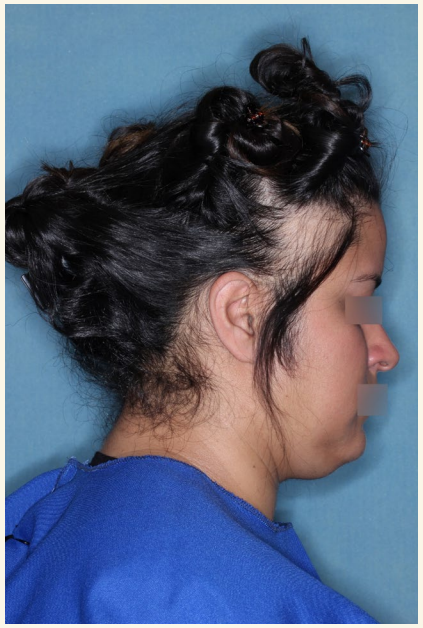

Visit 12 (289 Days on Drug*)

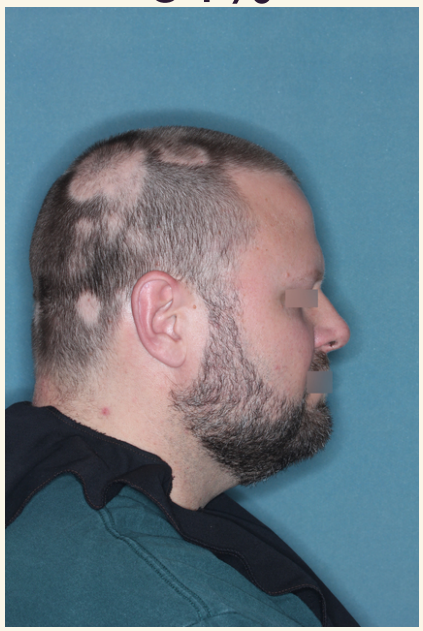

Visit 2 (Baseline)
Visit 12 (289 Days on Drug*)

Spectrum of Hair Loss

24%



34%



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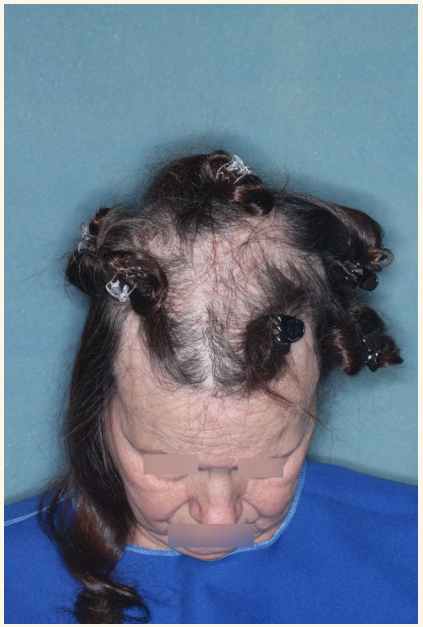

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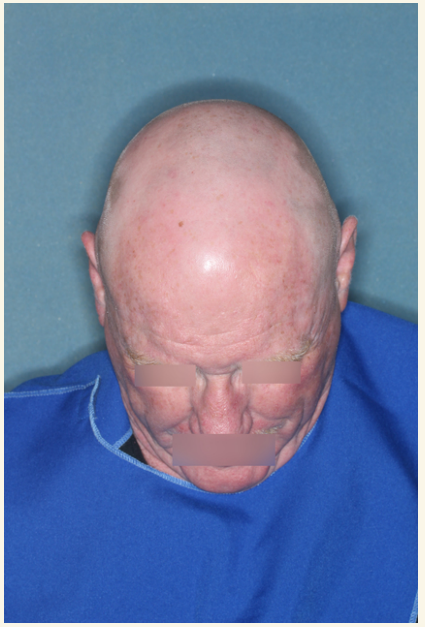

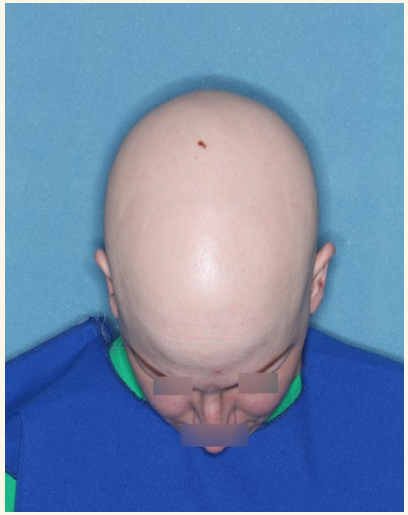

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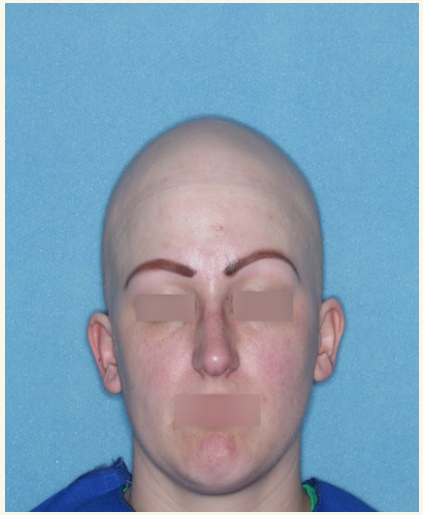

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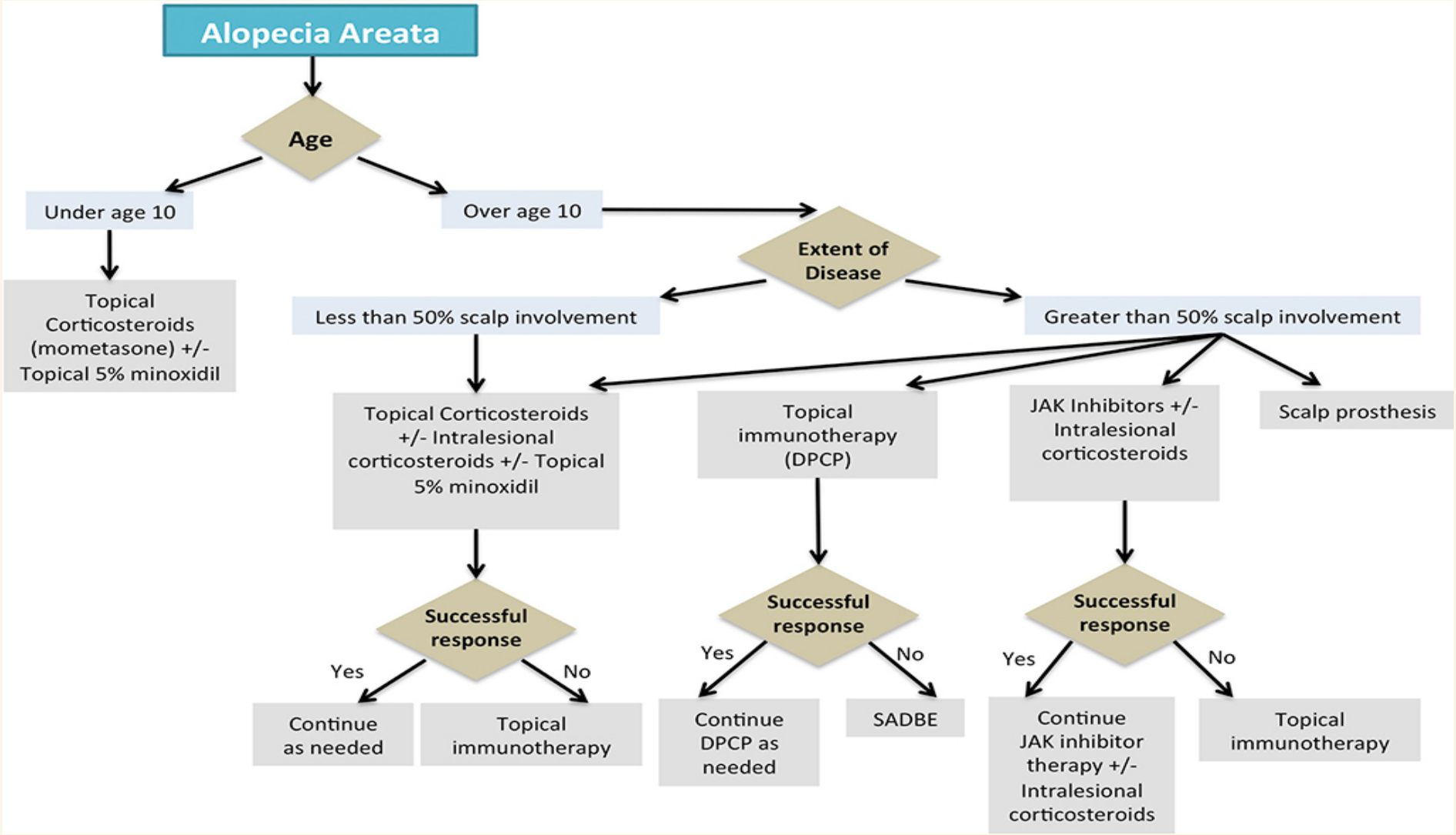
Current treatment paradigm



https://www.naaf.org/alopecia-areata/alopecia-areata-treatments - Last accessed 3-14-19

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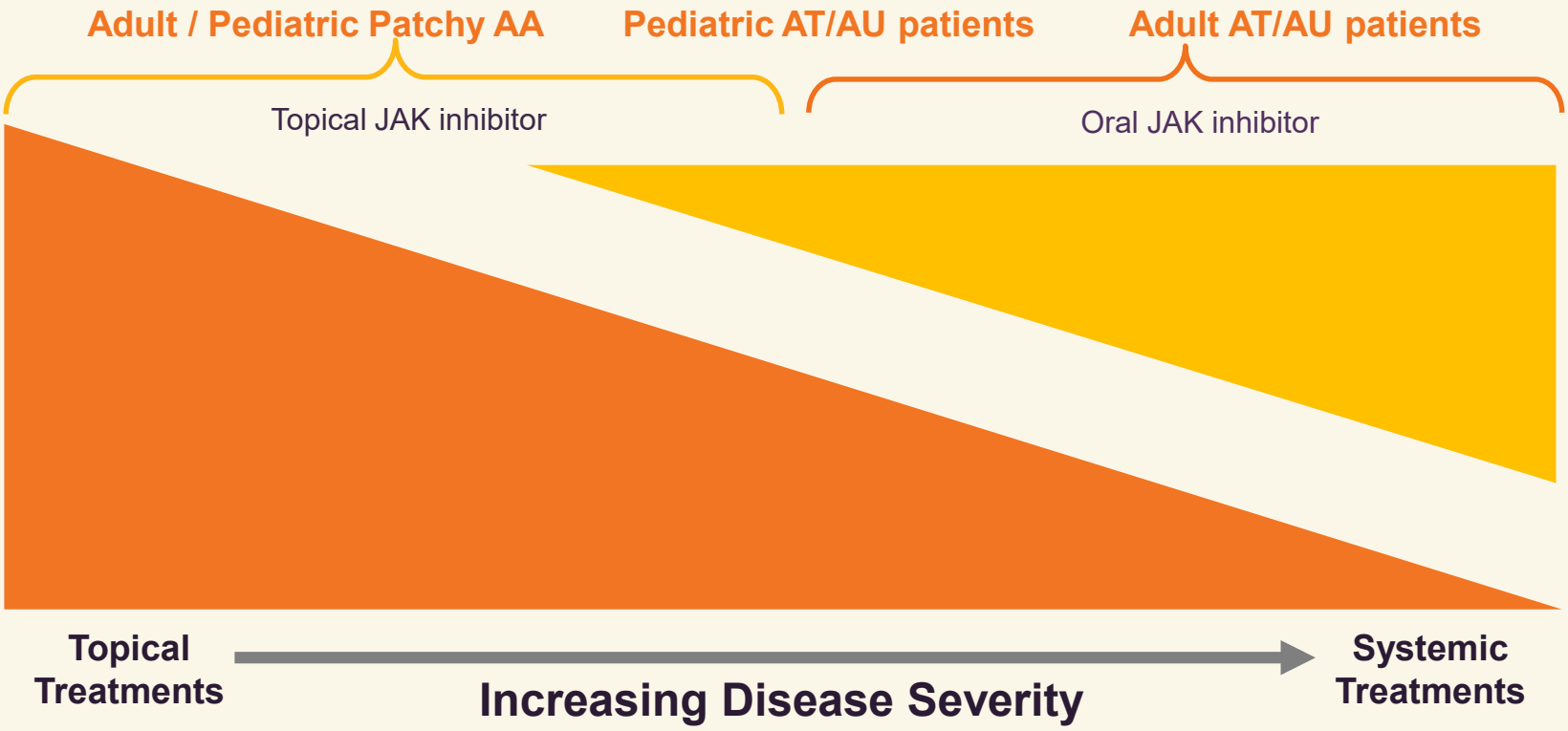
Alopecia Areata: Potential Treatment Paradigms



INDUCTION:

Topical JAK inhibitor may be efficacious in patients with less severe patchy AA

Oral JAK inhibitor may be best option in patients with more severe AT/AU phenotypes

MAINTENANCE:

AT/AU patients may be able to maintain hair with topical JAK inhibitor

Concomitant topical therapy may decrease reliance on longer term oral therapy in some patients

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ATI-450 (MK-2 Inhibitor)

MK-2 Pathway Inhibitor (MK-2 PI) ATI-450

- Pharmacologically unique MOA
- MK-2 pathway inhibitors target the production and activity of key inflammatory cytokines including TNFα, IL-1α, IL-1β and IL-6
- ATI-450 inhibits the cytokine targets of established biologics:
  - Anti-TNFs: Humira®, Enbrel®, Remicade®
    - *RA, psoriasis, psoriatic arthritis, IBD, ankylosing spondylitis*
  - Anti-IL1s: Kineret®, Ilaris®, Arcalyst®
    - *CAPS, Still's disease, SJIA, cardiovascular disease*
  - Anti-IL6: Kevzara®, Actemra®
    - *RA, Castleman's disease*
- Aclaris is developing MK-2 pathway inhibitors for chronic inflammatory disease and autoimmune disease

MK-2 = mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2)
RA = rheumatoid arthritis; IBD = inflammatory bowel disease; SJIA = systemic juvenile idiopathic arthritis

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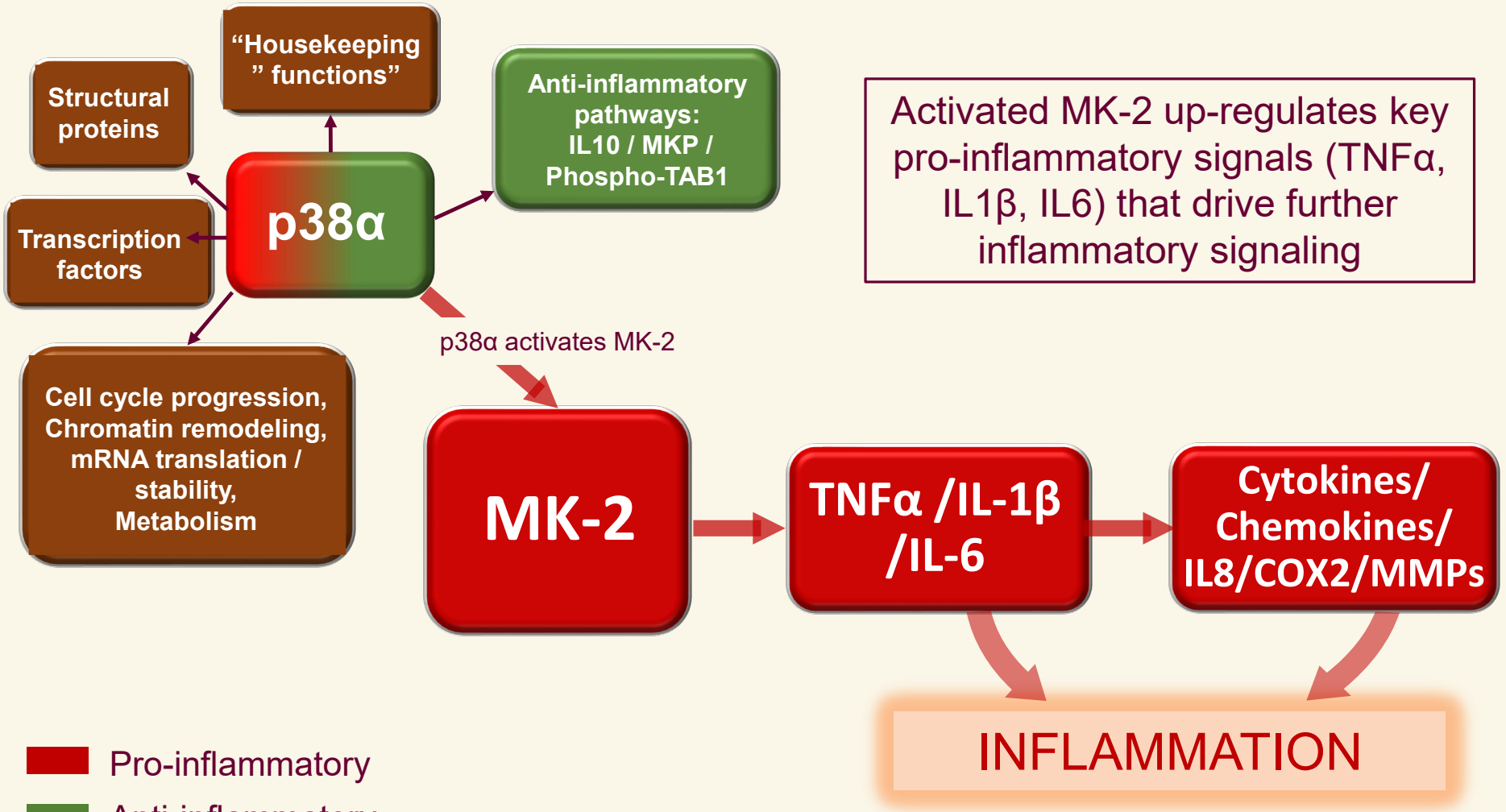
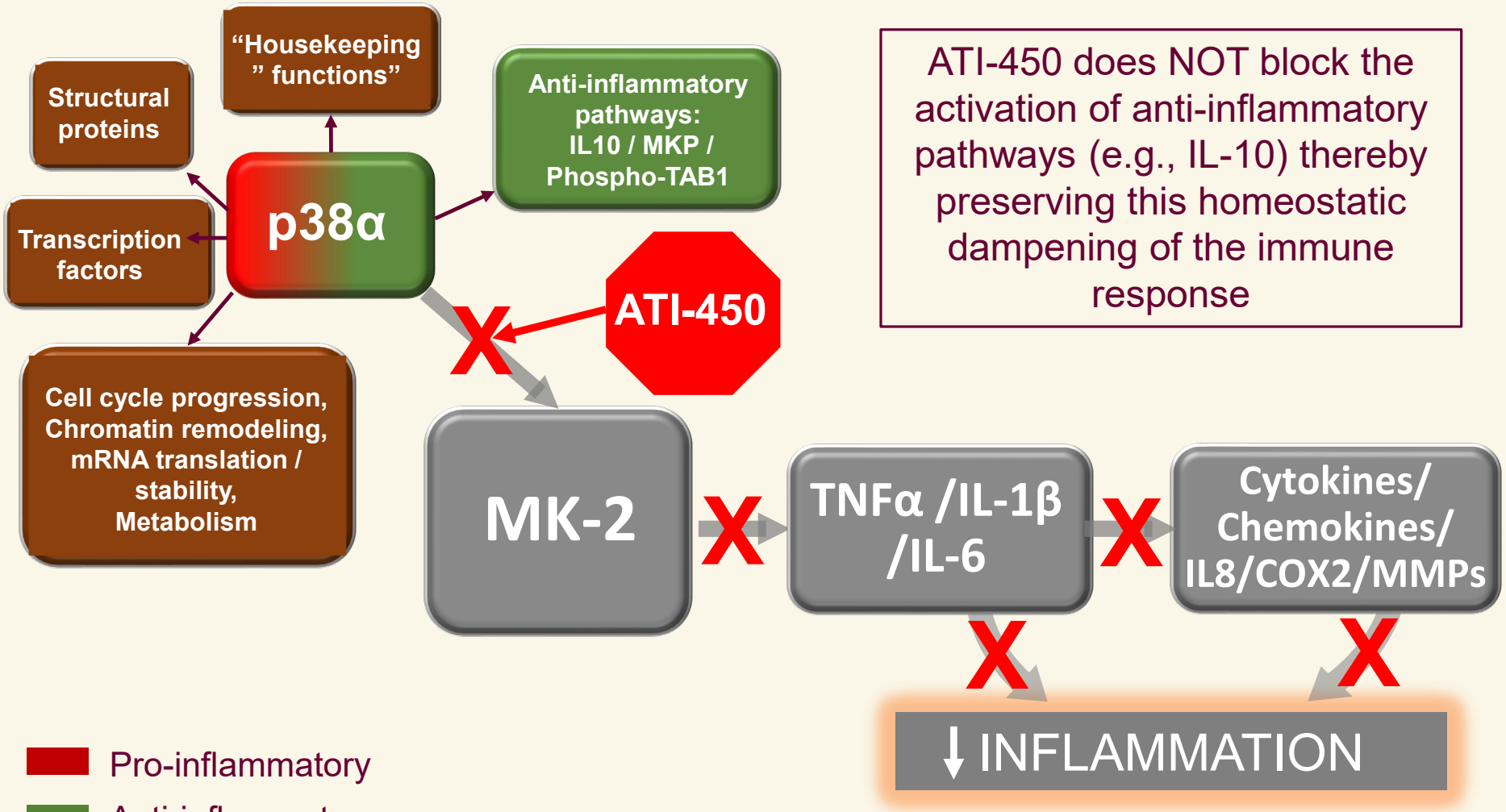
The MK2 Pathway Drives Key Inflammatory Cytokines: TNFα, IL-1β and IL-6



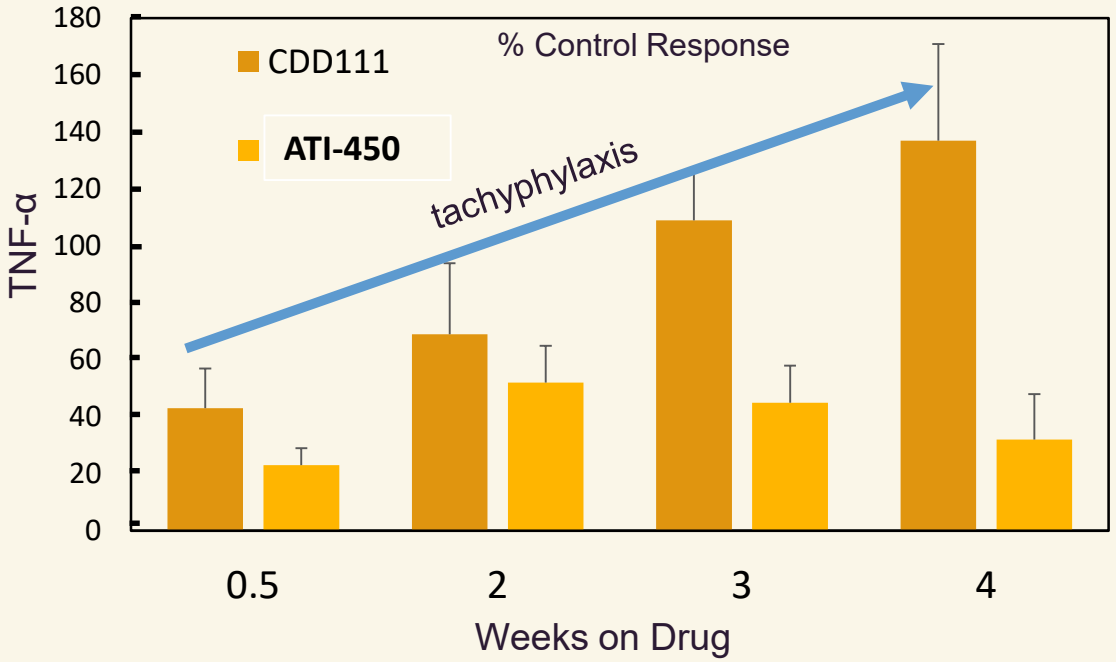
ATI-450 Inhibits the Expression of Key Inflammatory Cytokines: TNFα, IL-1β and IL-6



ATI-450 does NOT block the activation of anti-inflammatory pathways (e.g., IL-10) thereby preserving this homeostatic dampening of the immune response

Mouse LPS-Induced TNFα Production
ATI-450 demonstrated durable response (no tachyphylaxis)

- Global p38 inhibitor CDD-111 lost inhibition over time
- **This investigational MK-2 pathway inhibitor ATI-450 demonstrated durable responses in this model (no tachyphylaxis)**



- Conventional p38 (CDD-111) and MK-2PI (ATI-450) administered to mice in feed starting day 1 and continuing through day 28
- At the time point indicated, mice were LPS challenged and blood TNFα levels determined

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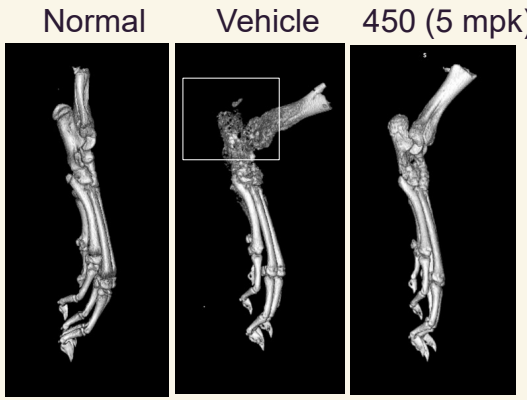
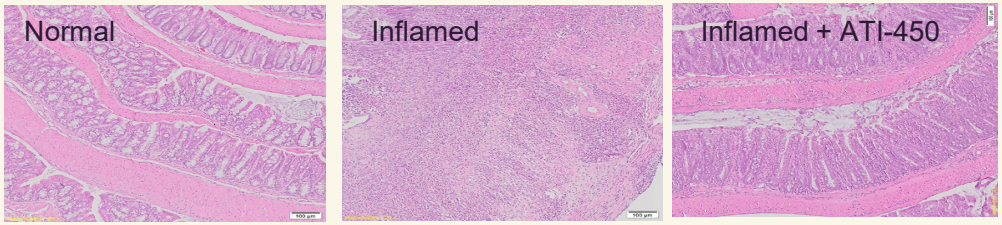
In vivo Results of MK-2 Pathway Inhibitor ATI-450

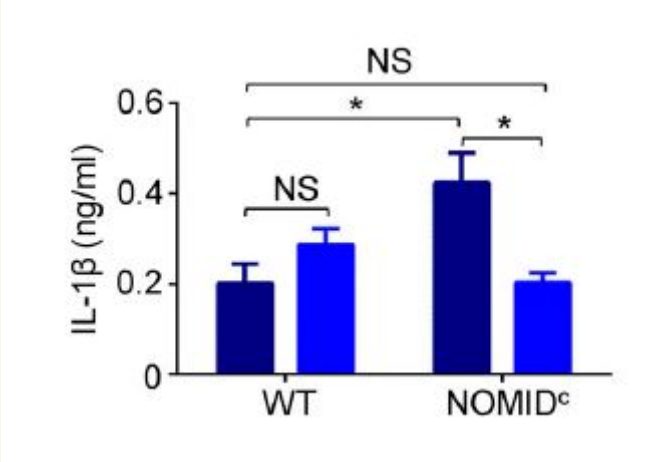
Joint Protection in Rat Arthritis Model[1]



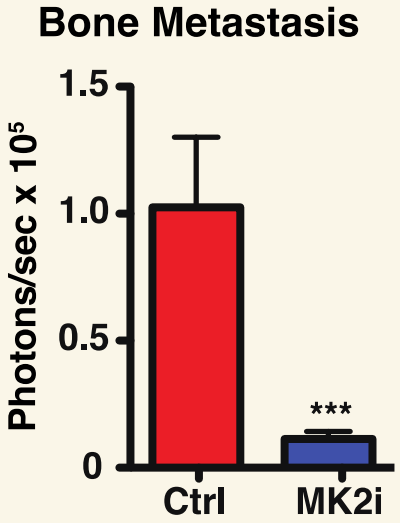
Blockade of Gut Inflammatory Infiltrate in Murine Adoptive Transfer Ulcerative Colitis Model[3]



Cytokine (IL-1 Beta) Modulation in Orphan Autoinflammatory Disease (CAPS)[1]



Reduction in Breast Cancer Bone Metastasis in Mice[2]



[1] Wang C, et al. J Exp Med. 2019;215(5):1315-1325.
[2] Murali B, et al. Cancer Res. 2019;78(19)5618-5630.
[3] Data on File. Aclaris Therapeutics Inc.

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THANK YOU

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