Initial Results From The SIGNAL-AA Study: Randomized Placebo Controlled Phase 2a Trial of a Bempikibart, Novel IL-7/TSLP Bifunctional Receptor Antagonist in Patients with Severe or Very Severe Alopecia Areata

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Dr. Brett King M.D., Ph.D.

American Academy of Dermatology
Late Breaker Session

March 8, 2025

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In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research may not have been verified by any independent source.

Alopecia Areata Has Life-Altering Impact and Current Treatment Options Are Limited

700K[1] people living with AA in the U.S.

- Often manifesting **before age 50**
- Up to **40% become chronic**, including complete loss of scalp and/or body hair
- Severity of disease and long duration of episode each associated with **lower rates of treatment response**

Olumiant approved in 2022, Litfulo approved in 2023, Leqselvi approved in 2024: all carry **class-wide Black Box Warning**[2]

Durable, long-term remission would be transformative

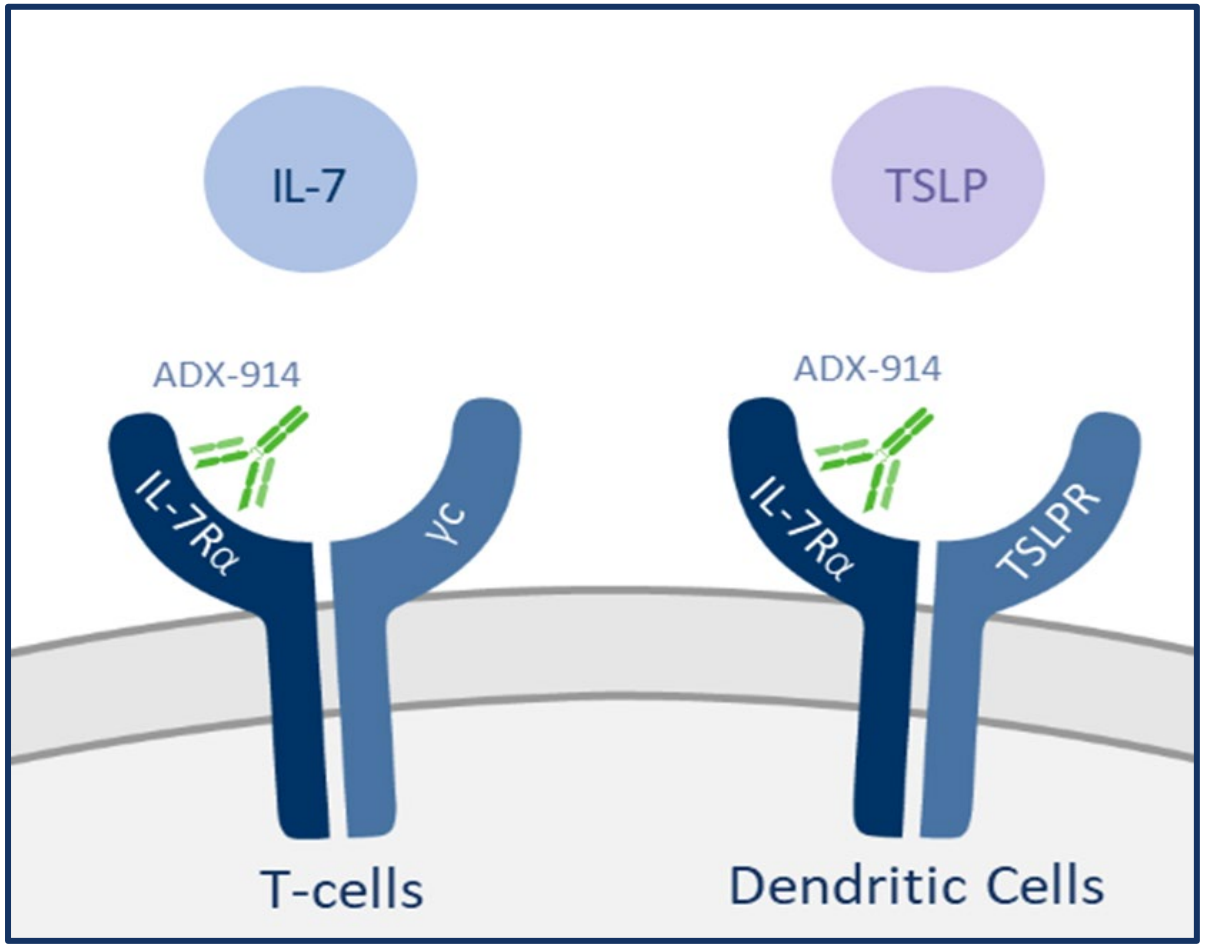
[1]Benigno M, et al. Clin Cosmet Investig Dermatol. 2020 Apr 1;13:259–266

[2]https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s006lbl.pdf, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215830s000lbl.pdf, https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217900s000lbl.pdf

Bempikibart: Bifunctional IL-7Rα Antagonist Antibody That Blocks IL-7 and TSLP Signaling

IL-7 receptor

Provides novel mechanism for rebalancing $T_{eff/mem}$ and T_{reg} function



TSLP receptor

Central regulator of dendritic cell differentiation, Th2 cytokine production

Favorable PK and Receptor Occupancy observed in Phase 2
Robust changes in clinical biomarkers indicative of potent IL-7 and TSLP inhibition

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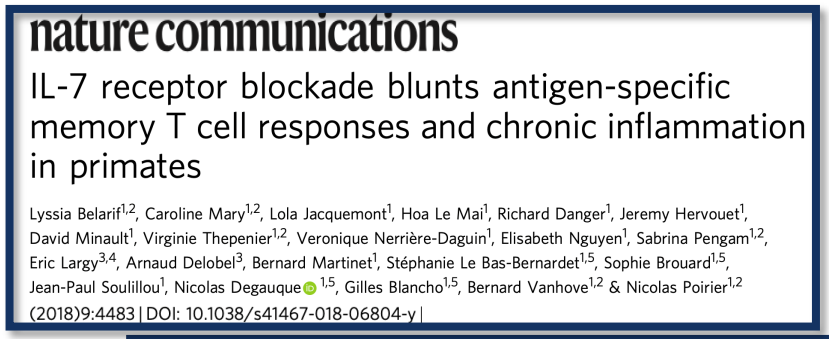
SIGNAL-AA First-in-Patient Observations of Durable Response Supported by Broad Literature Describing IL-7 Mechanistic Modulation of $T_{eff/mem}$ cells

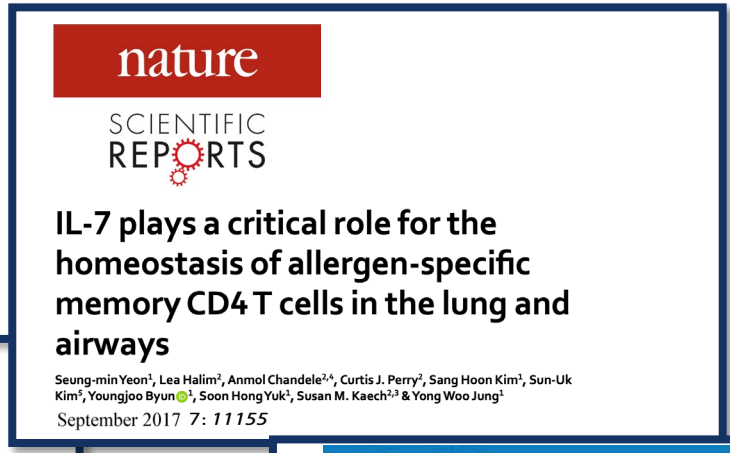


nature communications

IL-7 receptor blockade blunts antigen-specific memory T cell responses and chronic inflammation in primates

Lyssia Belarif[1,2], Caroline Mary[1,2], Lola Jacquemont[1], Hoa Le Mai[1], Richard Danger[1], Jeremy Hervouet[1], David Minault[1], Virginie Thepenier[1,2], Veronique Nerrière-Daguin[1], Elisabeth Nguyen[1], Sabrina Pengam[1,2], Eric Largy[3,4], Arnaud Delobel[3], Bernard Martinet[1], Stéphanie Le Bas-Bernardet[1,5], Sophie Brouard[1,5], Jean-Paul Soulillou[1], Nicolas Degauque[1,5], Gilles Blancho[1,5], Bernard Vanhove[1,2] & Nicolas Poirier[1,2]

(2018)9:4483 | DOI: 10.1038/s41467-018-06804-y |

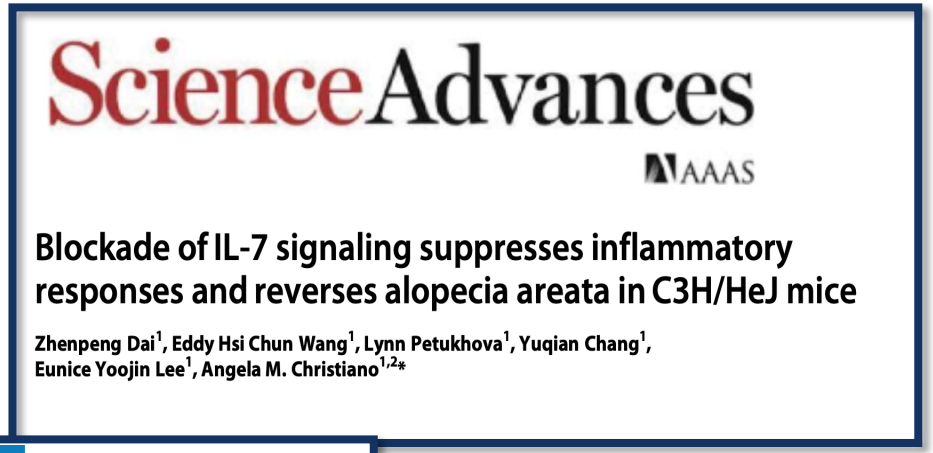


nature SCIENTIFIC REPORTS

IL-7 plays a critical role for the homeostasis of allergen-specific memory CD4 T cells in the lung and airways

Seung-min Yeon[1], Lea Halim[2], Anmol Chandele[2,4], Curtis J. Perry[2], Sang Hoon Kim[1], Sun-Uk Kim[5], Youngjoo Byun[1], Soon Hong Yuk[1], Susan M. Kaech[2,3] & Yong Woo Jung[1]

September 2017 7: 11155

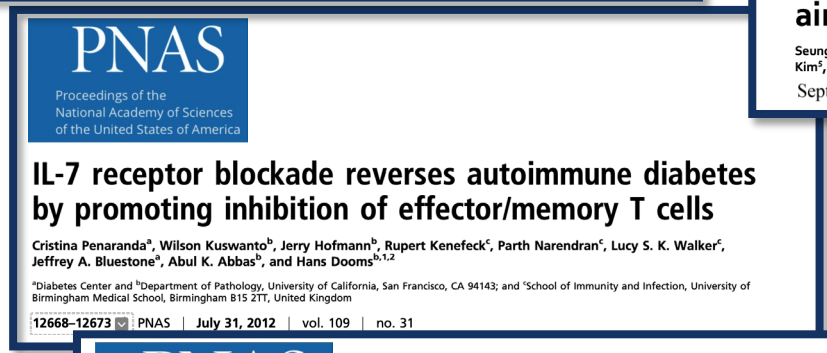


Science Advances

AAAS

Blockade of IL-7 signaling suppresses inflammatory responses and reverses alopecia areata in C3H/HeJ mice

Zhenpeng Dai[1], Eddy Hsi Chun Wang[1], Lynn Petukhova[1], Yuqian Chang[1], Eunice Yoojin Lee[1], Angela M. Christiano[1,2]*



PNAS

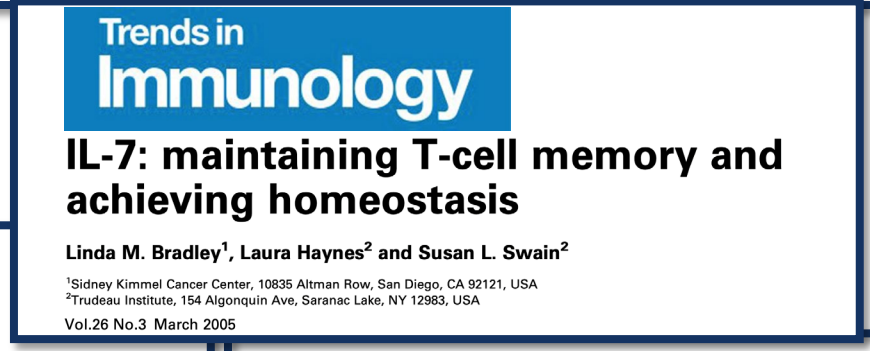
Proceedings of the National Academy of Sciences of the United States of America

IL-7 receptor blockade reverses autoimmune diabetes by promoting inhibition of effector/memory T cells

Cristina Penaranda[a], Wilson Kuswanto[b], Jerry Hofmann[b], Rupert Kenefeck[c], Parth Narendran[c], Lucy S. K. Walker[c], Jeffrey A. Bluestone[a], Abul K. Abbas[b], and Hans Dooms[b,1,2]

[a]Diabetes Center and [b]Department of Pathology, University of California, San Francisco, CA 94143; and [c]School of Immunity and Infection, University of Birmingham Medical School, Birmingham B15 2TT, United Kingdom

12668–12673 | PNAS | July 31, 2012 | vol. 109 | no. 31



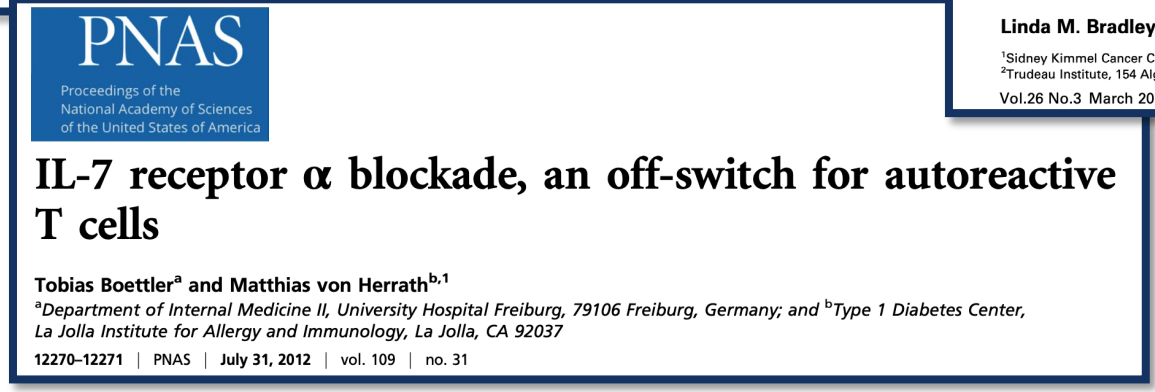
Trends in Immunology

IL-7: maintaining T-cell memory and achieving homeostasis

Linda M. Bradley[1], Laura Haynes[2] and Susan L. Swain[2]

[1]Sidney Kimmel Cancer Center, 10835 Altman Row, San Diego, CA 92121, USA
[2]Trudeau Institute, 154 Algonquin Ave, Saranac Lake, NY 12983, USA

Vol.26 No.3 March 2005



PNAS

Proceedings of the National Academy of Sciences of the United States of America

IL-7 receptor α blockade, an off-switch for autoreactive T cells

Tobias Boettler[a] and Matthias von Herrath[b,1]

[a]*Department of Internal Medicine II, University Hospital Freiburg, 79106 Freiburg, Germany; and* [b]*Type 1 Diabetes Center, La Jolla Institute for Allergy and Immunology, La Jolla, CA 92037*

12270–12271 | PNAS | July 31, 2012 | vol. 109 | no. 31

The Journal of Immunology

RESEARCH ARTICLE | DECEMBER 15 2012

IL-7 Abrogates Suppressive Activity of Human $CD4^+CD25^+FOXP3^+$ Regulatory T Cells and Allows Expansion of Alloreactive and Autoreactive T Cells FREE

Anne-Kristin Heninger; ... et. al

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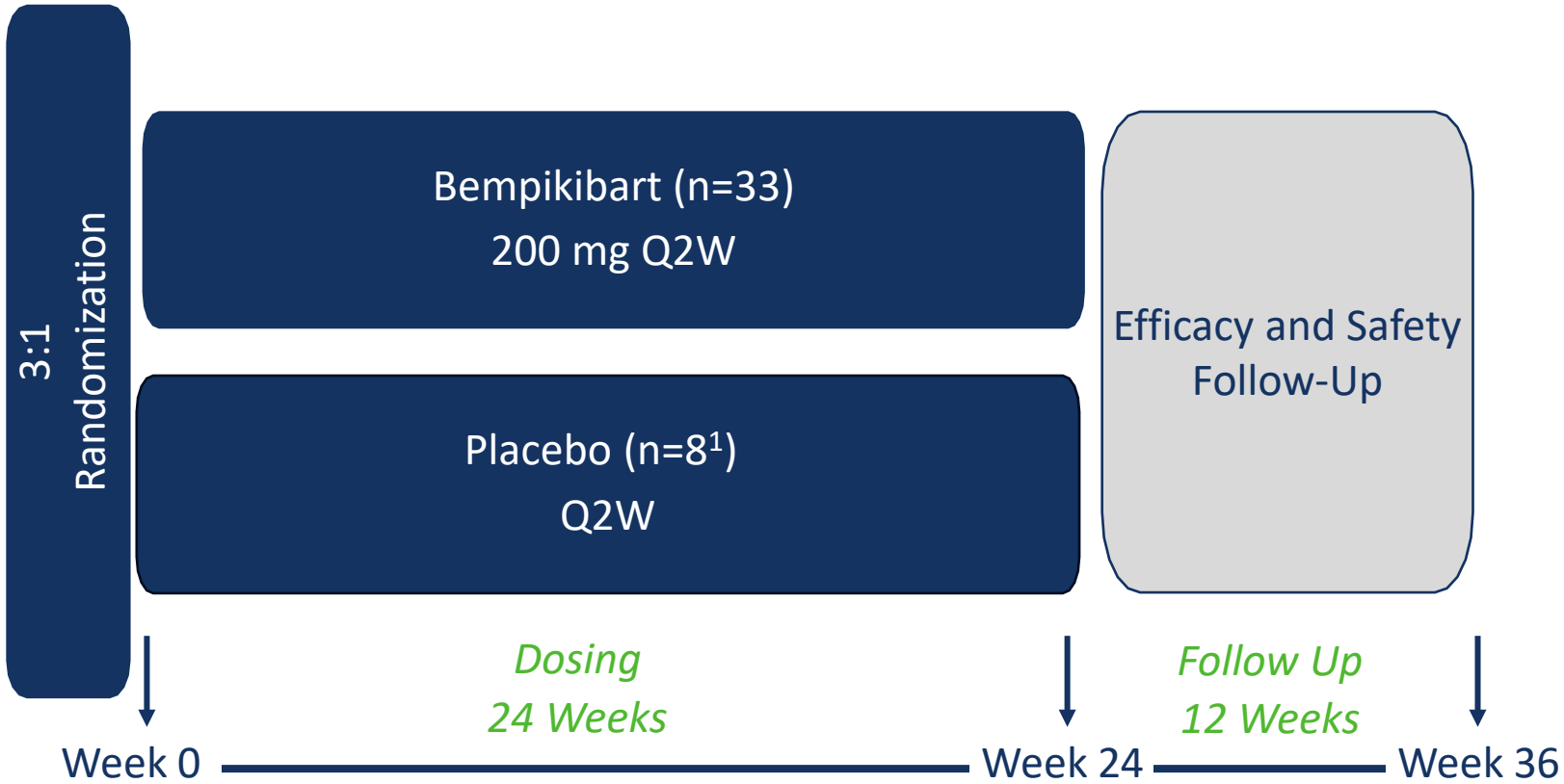
SIGNAL-AA Phase 2a "Part A": POC Study in Patients with Alopecia Areata Study Design

Part A



Design Elements

- First study in AA patients
- Key Inclusion/Exclusion Criteria
  - Severe/Very Severe Alopecia Areata (SALT 50-100)
  - No other forms of Alopecia
  - Duration of current episode >6 months and <10 years
  - Prior use of JAKi allowed with appropriate wash-out
- Primary endpoint: % change from baseline in SALT score at Week 24

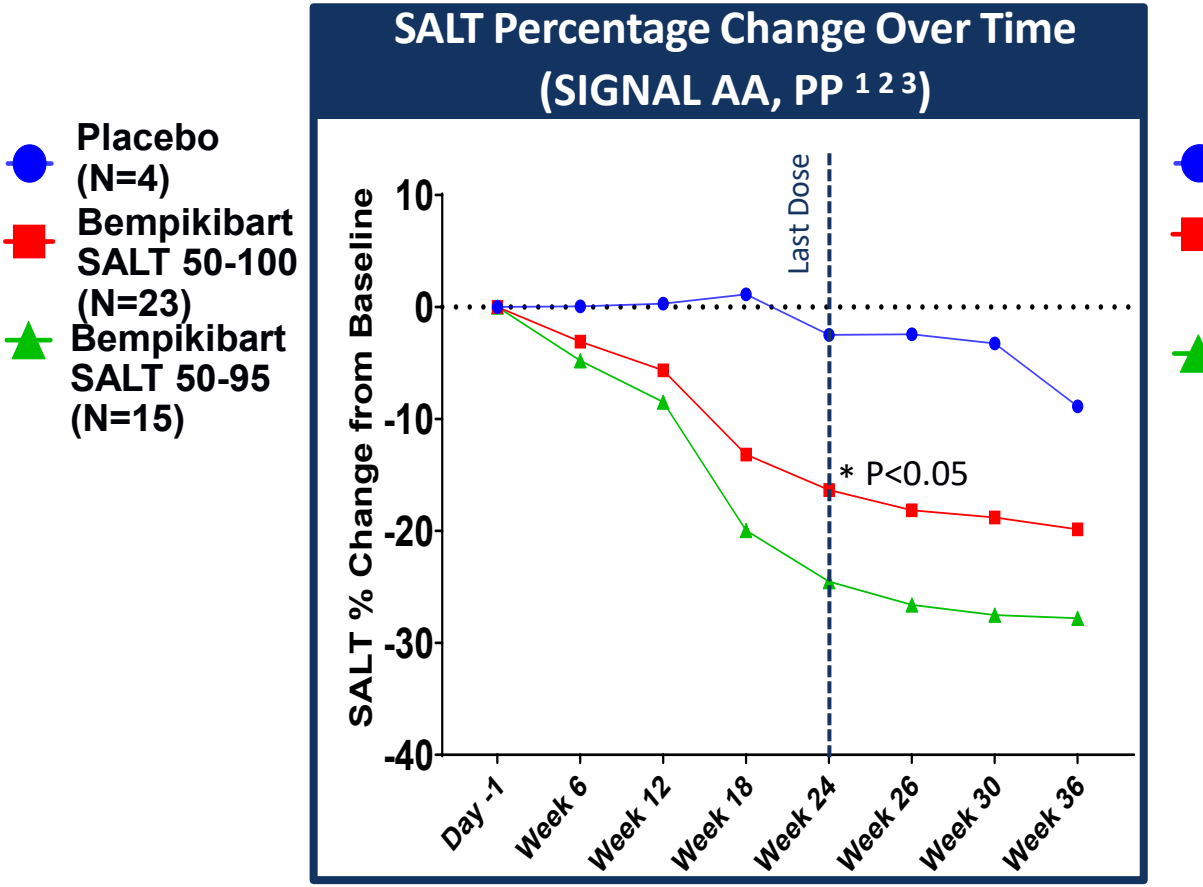
1. Analysis excludes 3 placebo subjects from a single site who were in major violations of inclusion criteria.

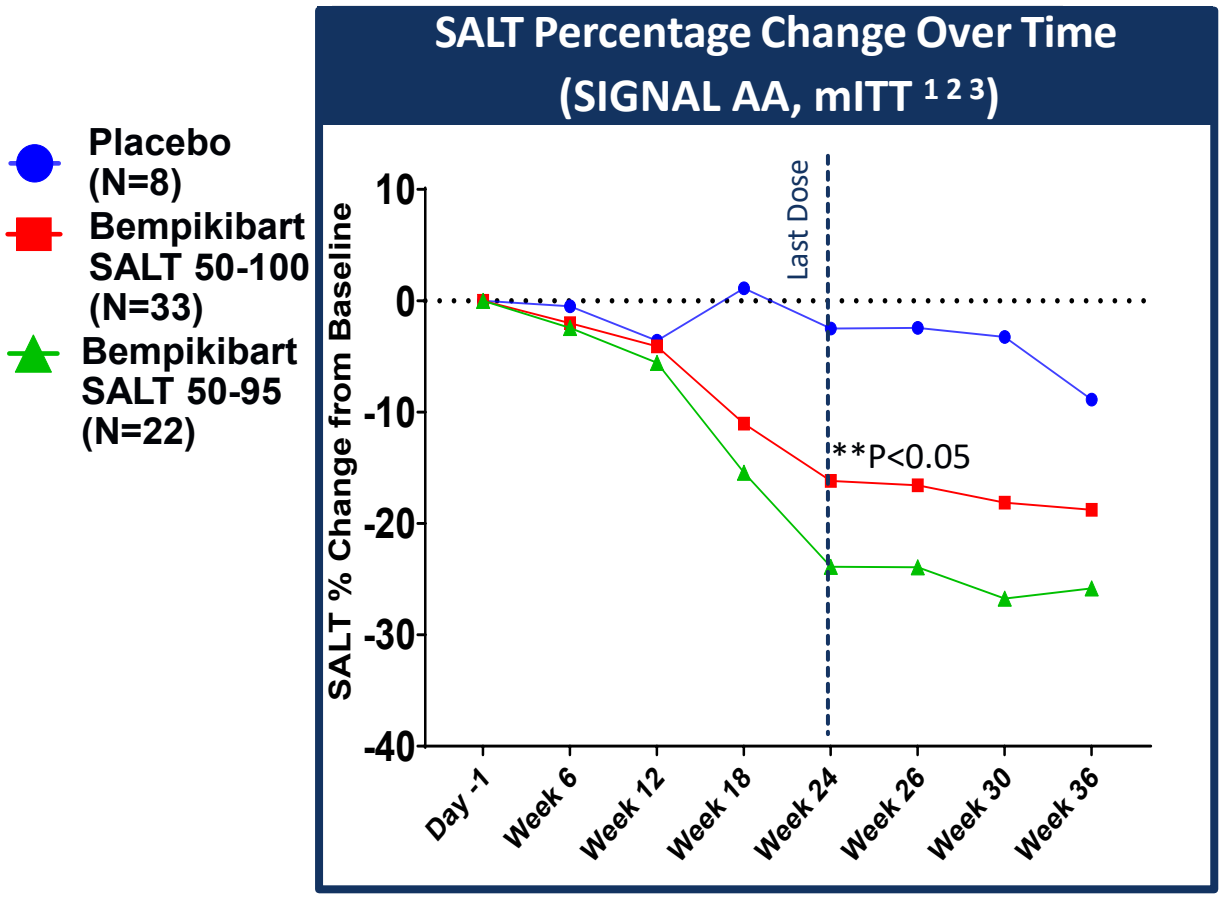
SIGNAL-AA Part A: Demographics

Characteristics	Per Protocol Population (PP)			Modified Intent To Treat Population (mITT)		
	Bempikibart 200 mg (N=23)	Placebo (N=4)	Total (N=27)	Bempikibart 200 mg (N=33)	Placebo (N=8[1])	Total (N=41)
Age (years), Mean (SD)	47.7 (11.3)	59.8 (11.9)	49.5 (12.0)	48.8 (10.2)	46.9 (11.1)	48.5 (11.4)
Sex, n (%) Female	19 (82.6)	2 (50)	21 (75.6)	27 (81.8)	4 (50)	31 (75.6)
Race, n (%) Asian Black or African American White Others	1 (4.3) 7 (30.4) 13 (56.5) 2 (8.6)	0 (0.0) 1 (25.0) 3 (75.0) 0 (0.0)	1 (3.7) 8 (29.6) 16 (59.2) 2 (7.4)	1 (3.0) 10 (30.3) 19 (57.6) 3 (9.0)	1 (12.5) 3 (37.5) 4 (50) 0 (0.0)	2 (4.8) 13 (31.7) 23 (56.0) 3 (7.2)
Baseline SALT Score Mean (SD)	75.8 (20.4)	88.4 (22.5)	77.7 (20.7)	74.9 (20.3)	81.9 (21.0)	76.3 (20.4)
Baseline SALT score, n (%) ≥50 to <95 ≥95 to 100	15 (65.3) 8 (34.7)	1 (25) 3 (75)	16 (59.3) 11 (40.7)	22 (66.7) 11 (33.3)	4 (50) 4 (50)	26 (63.4) 15 (36.6)
Duration (months) current episode Mean (SD)	62 (36.7)	39.3 (20.5)	58.7 (35.4)	65.8 (34.8)	61.9 (30.5)	65.0 (33.7)

1. Analysis excludes 3 placebo subjects from a single site who were in major violations of inclusion criteria.

SIGNAL-AA: Part A SALT Data Through Week 36 Showed Continued Benefit Over Time Supporting Potential for Durable Effect Following Dosing Cessation





Mean SALT reduction continues after dosing cessation, consistent with predicted MOA

[1]Analysis excludes 3 placebo subjects from a single site who were in major violations of inclusion criteria. Step down between mITT to Per Protocol: 10 early terminations, 2 missed week 24 visit, 1 missed multiple doses, 1 major hairstyle change. [2] 2 discontinued or LTFU by wk26, 3 discontinued or LTFU by wk36. [3] Data as of database lock date 02/05/2025

*p < 0.05 vs placebo on primary end point of percentage change from baseline at 24 weeks by Wilcoxon Rank Sum test, 1-sided

**P < 0.05 vs placebo at 24 weeks by Mann-Whitney Rank Sum Test, 1-sided, with missing values included as collected

Bempikibart Demonstrated Impressive Improvement on SALT Reduction at Week 24 Shows Continued Effects After Dosing Cessation through Week 36

Patients with baseline SALT 50-100, PP[1]	Week 24 Plasma PK > Threshold N=23	Dosing Cessation	Week 26[2] Plasma PK > Threshold N=21	Week 36[3] Plasma PK < Threshold N=19[4]
Mean SALT Score % Δ	16.3%		18.2%	19.9%
$SALT_{30}$ (% pts)[5]	17.4%		19.0%	36.8%
SALT Score ≤20 (% pts)[5]	9.0%		14.3%	5.3%

Patients with baseline SALT 50-95, PP[1]	Week 24 N=15	Dosing Cessation	Week 26 N=14[6]	Week 36 N=13[7]
Mean SALT Score % Δ	24.5%		26.6%	27.8%
$SALT_{30}$ (% pts)[5]	26.7%		28.6%	53.8%
SALT Score ≤20 (% pts)[5]	13.3%		21.4%	7.7%

Patients assigned to Placebo (baseline SALT 50-100), PP[1]	Week 24 N=4	Dosing Cessation	Week 26 N=4	Week 36 N=3[8]
Mean SALT Score % Δ	2.5%		2.4%	8.9%
$SALT_{30}$ (% pts)[5]	0.0%		0.0%	0.0%
SALT Score ≤20 (% pts)[5]	0.0%		0.0%	0.0%

PK: pharmacokinetics; pts: patients; SALT: Severity of Alopecia Tool.

[1] Analysis excludes 3 placebo subjects from a single site who were in major violations of inclusion criteria.

[2] Mean trough concentration of bempikibart above 5 µg/ml; [3] Mean trough concentration of bempikibart below 5 µg/ml

[4] 2 discontinued or Lost to follow-up (LTFU) by Week 26, 2 discontinued or LTFU by Week 36

[5] Placebo-adjusted [6] 1 withdraw from the study by week 26 [7] 2 discontinued or LTFU by Week 36 ; [8]1 LTFU by week 30

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SIGNAL-AA Case Study - Severe AA with 4.5 Year Episode: Response through Week 42 Supports Potential for Durable Hair Regrowth with Bempikibart Treatment

- 52-year-old female
- Duration of episode: 4.5 years
- Baseline SALT: 56 (Severe)
- SALT (Week 24): 10.5
- **SALT (Week 36): 4**
- **SALT (Week 42): 2**

Durable Response and Additional Growth at Week 42

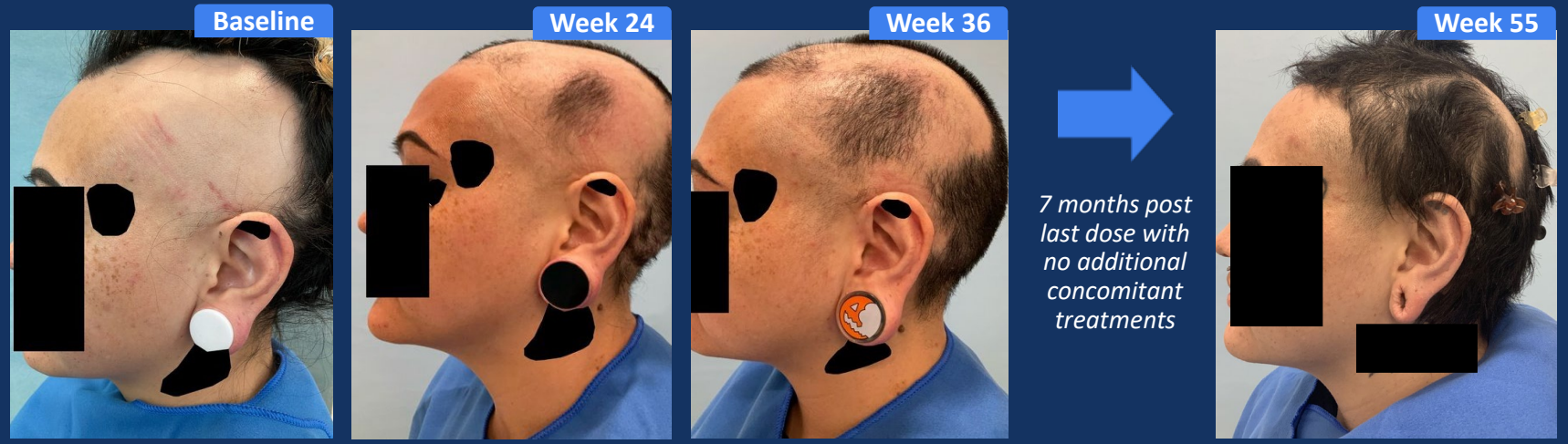
SIGNAL-AA Examples of Continued Response 7 Months Post Dosing Cessation: Supports Potential for Remittive Effect with Bempikibart Treatment

Case 1

- 61-year-old female
- Duration of Episode: 3.1 years
- Baseline SALT: 98.2 (Very Severe)
- **SALT (Week 36): 88.4**
- **SALT (Week 54): 8**

Case 2

- 32-year-old female
- Duration of episode: 9 months
- Baseline SALT: 61.1 (Severe)
- **SALT (Wk 36): 35.3**
- **SALT (Wk 55): 23.6**



Patients with significant hair regrowth after dosing with maintenance of effect ~7 months after last dose support potential for paradigm changing approach

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Potential for Bempikibart to Induce Durable Responses Supported by Longer-Term Follow-Up

- **A patient contacted sponsor with post-study hair growth requesting expanded access**
- **Sponsor contacted all site investigators regarding patient follow-up**
- **Of patients who responded that completed the treatment period and showed a SALT response during the trial (n=12), all achieved maintenance of response or further hair growth in the post treatment period**
  - For these 12 subjects, median follow-up to date 41 weeks; 17 weeks post last treatment
  - 7/12 achieved additional hair growth by SALT assessment post treatment
- **Data collection ongoing and Open Label Extension expected to begin 1H'25**

SIGNAL AA: Overall Summary of Treatment Emergent Adverse Events Through Week 36

	Bempikibart[1] (N = 33) n (%) [# Events]	Placebo (N = 8) n (%) [# Events]
Participants with at least 1 TEAE	23 (70%) [108]	3 (38%) [9]
Participants with at least 1 TEAE by greatest reported relationship with study treatment		
Not related	6 (18%) [12]	0 [0]
Related	17 (52%) [51]	3 (38%) [4]
Participants with at least 1 TEAE by worst reported severity CTCAE grade[2]		
Grade 1 - Mild	10 (30%) [24]	2 (25%) [6]
Grade 2 - Moderate	11 (33%) [25]	1 (13%) [1]
Grade 3 – Severe (1 patient acute myocardial infarction – not related)	1 (3.0%) [3]	0 [0]
Grade 4 - Life threatening (1 patient nut allergy - not related)	1 (3.0%) [1]	0 [0]
Grade 5 - Death	0 [0]	0 [0]

Bempikibart Demonstrated Favorable Safety and Tolerability Profiles with No Grade 3 or Higher Related Adverse Events

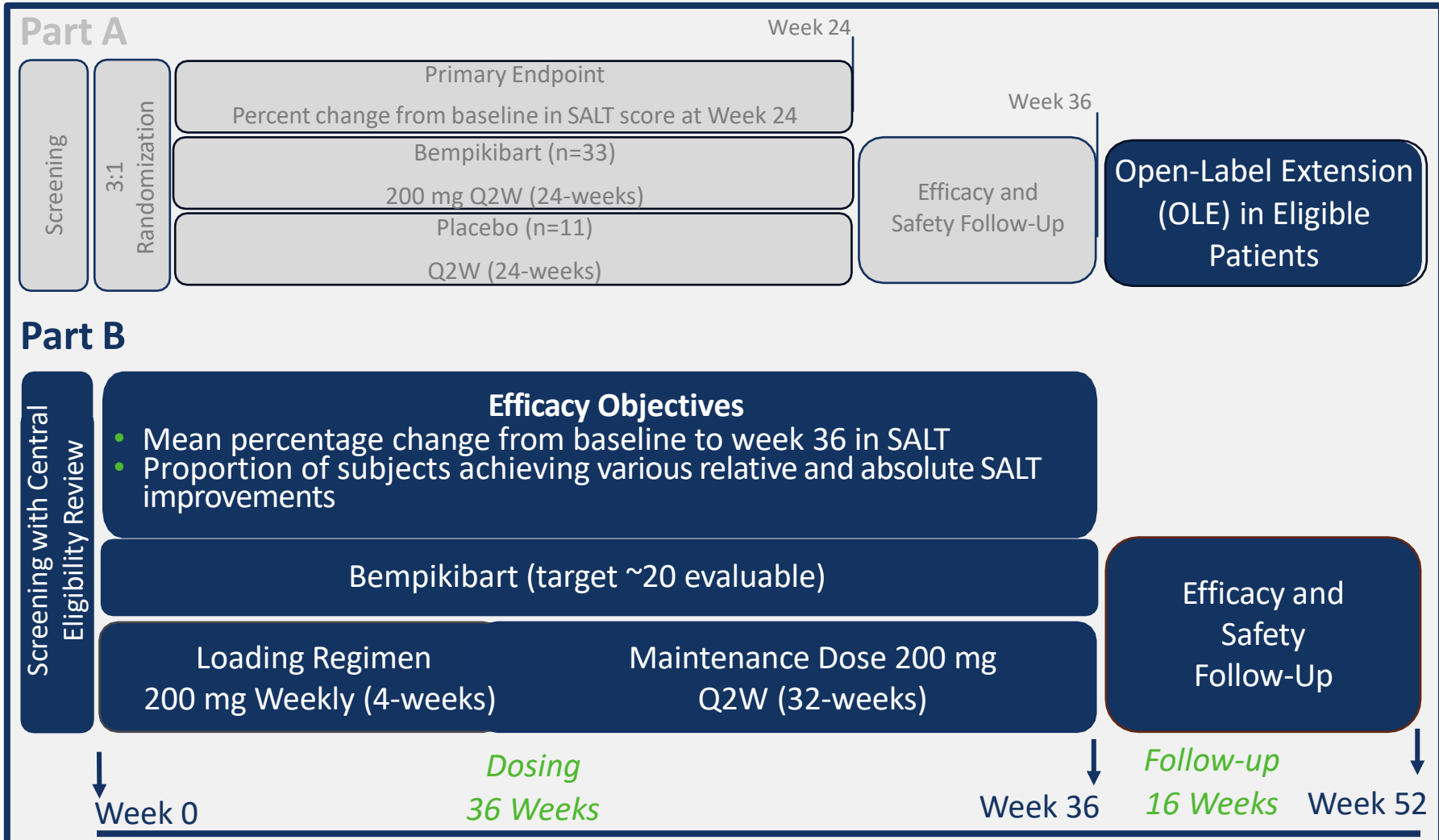
Abbreviations: AA: alopecia areata; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event.

[1] Participants experiencing multiple AEs were counted only once under the greatest reported relationship with study treatment.

[2] Participants experiencing multiple AEs were counted only once under the worst reported severity for each treatment group.

- 1 Grade 1 Mild Lymphopenia is reported in Bempikibart
- No related viral infections are reported in Bempikibart

SIGNAL-AA Phase 2a: Part A and Part B Study Designs



Design Elements

Part B

- **Key Inclusion/Exclusion Criteria**
  - Severe/Very Severe (SALT 50-100)
  - Duration of current episode >6 months and <4 yrs
  - Exclusion of JAK inhibitors same as Part A
- **Design Modifications from Part A**
  - Loading regimen: designed to accelerate PK/PD dynamics to maximize clinical activity
  - Longer dosing: 36-weeks
  - Longer follow-up: 52-weeks

Summary: Maturing SIGNAL-AA Data Supports Potentially Differentiated Profile in Alopecia Areata

- **Hair regrowth with durable response supports potential for transformative paradigm; extensive MOA literature supports potential long-term durability of effect post-dosing cessation**

- **Response to bempikibart observed in severe and very severe populations**
  - Response in patients with long current episode duration
    - Mean current episode duration in SIGNAL-AA: 5-6 years, substantially longer than prior JAK trials (2.5-4 years)[1,2,3]
    - Literature suggests response rates drop by 50% or more in patients with a current episode >4 years[4,5]

- **All treatment-related events were mild or moderate**
  - No new safety signals
  - No safety findings related to expected, on-mechanism lymphocyte reduction
  - No related infections

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[1]King, B. Br J Dermatol 2023; 189:666–673, [2]https://labeling.pfizer.com/ShowLabeling.aspx?id=19638, [3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217900s000lbl.pdf, [4]Peeva E, et al. AAD 2019, S034 Late-breaking Research: Clinical Trials Sponsored by Pfizer, [5]King B. World Congress of Dermatology 2023. Sponsored by Eli Lilly and Company

Thank you to all the clinical trial investigators and patients in the SIGNAL-AA trial

Thank you to the American Academy of Dermatology for the opportunity to share these data today