Advances in Clinical Study of Skin of Color: What Are We Learning?

MONA SHAHRIARI MD

ASSISTANT CLINICAL PROFESSOR OF DERMATOLOGY

YALE UNIVERSITY SCHOOL OF MEDICINE

ASSOCIATE DIRECTOR OF CLINICAL TRIALS

CCD RESEARCH PLLC

Objectives

- Discuss barriers to participation in clinical trial research and achieving clinical trial diversity
- Advance education on myths and misconceptions in dermatology clinical trials with a focus on pediatric patients
- Discuss progress in the clinical study of patients with skin of color

Myths and Misconceptions

“A drug that has been proven to be safe and effective in an adult, will be safe and effective in a child”

Are Children Just Little Adults?

- NO!
- It wasn't till the 1990s that a concerted effort to proactively study drugs in children began[1]
- Before this push, there was routine and widespread "off-label" use of medications in pediatric patients with the absence of safety, efficacy and dosing information[2]
- American Academy of Pediatrics[2]:

"There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents"

1. Kern SE et al. Expert Rev Clin Pharmacol. 2009 Nov 1;2(6):609-617
2. Ward RM et al, Clin. Pharmacol. Ther 2007;81:477–479

Legislative Efforts that Encourage Studying Therapeutics in Children

- 1997 US FDA Modernization Act (FDAMA)
  - Included provisions to incentivize drug developers to include children in clinical trials
  - Provided an extension of market exclusivity
- 2003 Pediatric Research Equity Act
  - Changed the statute from voluntary to mandatory
  - Extended the range of products that must be studied in children

1. Kern SE et al. Expert Rev Clin Pharmacol. 2009 Nov 1;2(6):609-617

“When developing a clinical trial program for the study of a therapy in both adult and pediatric patients, we can use the exact same clinical trial design and protocol regardless of patient age”

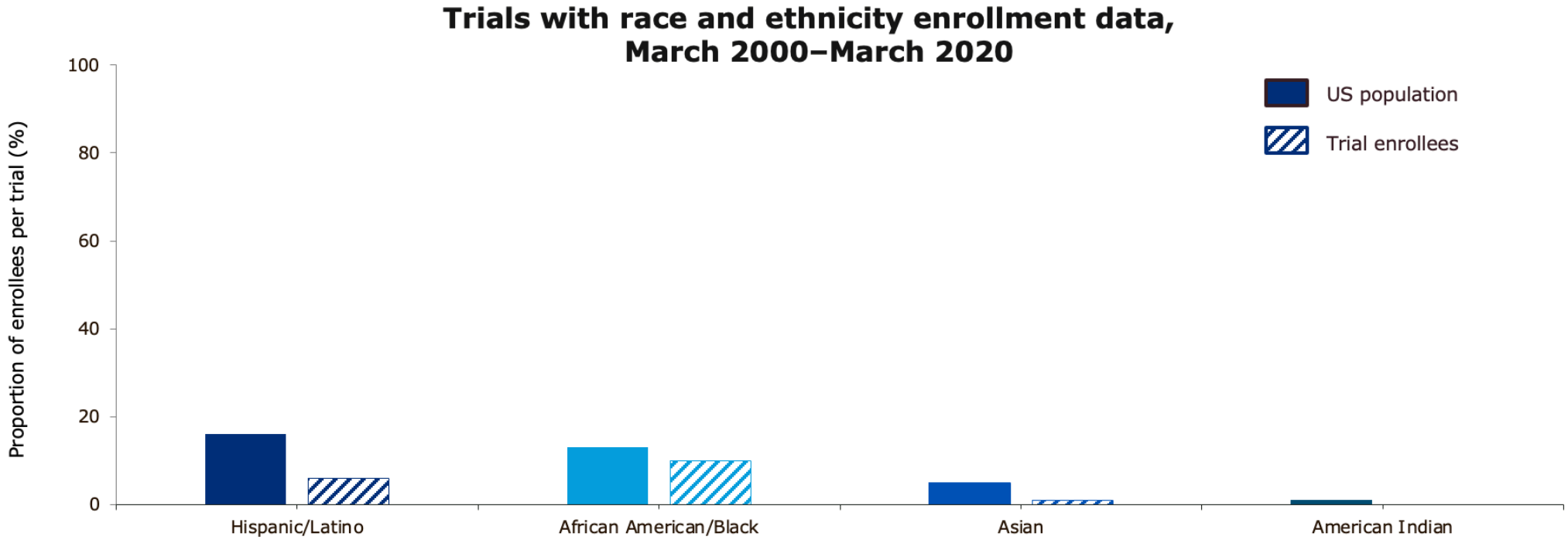
Challenges When Studying Children

- Ethical
  - Children can at best provide assent to participate in a trial while legal consent is from a parent or guardian
  - Depending on the child's age, relative risk, and IRB regulations, both parents may need to give consent
  - Risk of investigational drug should be similar to the non-research alternative for care
- Physiological
  - Differences in drug metabolism in children in comparison to adults
  - Differences in organ size and blood volume distribution can lead to variability in drug concentrations at target sites
- Formulations
  - Adult formulations aren't always feasible for children (e.g. pills vs liquids)

1. Kern SE et al. Expert Rev Clin Pharmacol. 2009 Nov 1;2(6):609-617

“Our clinical trial populations in dermatology represent the racial and ethnic diversity of the patients we see in real world clinical practice”

Underrepresentation of Minority Racial and Ethnic Groups in U.S. Clinical Trials



Turner BE, Steinberg JR, Weeks BT, Rodriguez F, Cullen MR. Race/ethnicity reporting and representation in US clinical trials: a cohort study. Lancet Reg Health Am. 2022 Jul;11:100252

Table IV. Racial and ethnic representation as a percent of total participants per dermatologic disease category

Racial data from 215 clinical trials

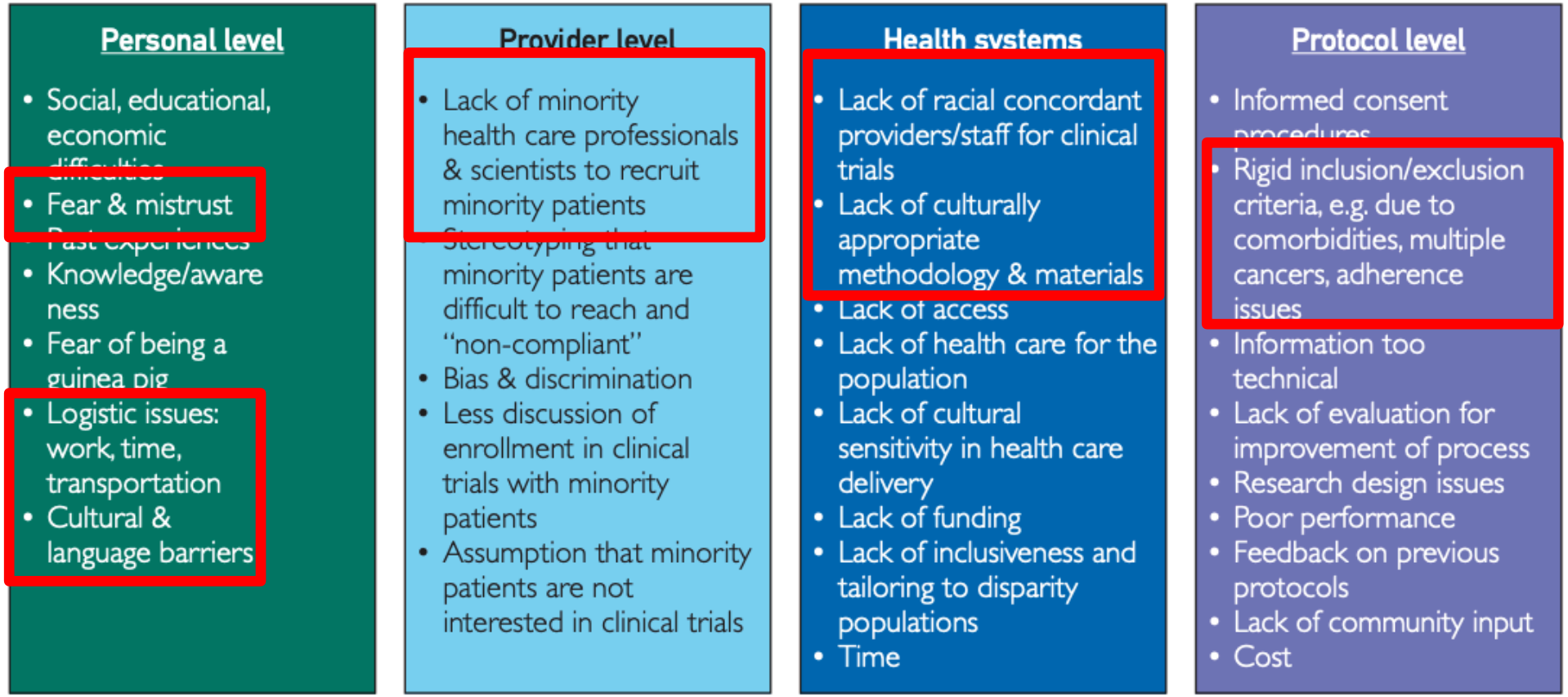
Demographic	Psoriasis (n = 18,741)	Eczema/atopic dermatitis (n = 9992)	Acne (n = 7076)	Nonmelanoma skin cancer (n = 2232)	Aesthetics (n = 1890)	Melanoma (n = 1855)	Alopecia (n = 1381)	Rosacea (n = 1201)	Tinea (n = 788)	Papillomavirus (warts) (n = 688)
White	84.9% (15,917)	66.5% (6649)	77.5% (5487)	91.5% (2043)	75.1% (1420)	89.1% (1653)	73.0% (1008)	97.0% (1165)	51.9% (409)	89.5% (616)
Black/African American	2.9% (536)	11.6% (1163)	12.6% (893)	2.2% (50)	8.1% (154)	4.4% (82)	7.9% (109)	0.6% (7)	47.5% (374)	6.8% (47)
American Indian/ Alaskan Native	1.6% (292)	0.5% (47)	0.5% (32)	0.2% (4)	0.7% (13)	0.0% (0)	0.4% (6)	0.4% (5)	0.0% (0)	0.1% (1)
Asian	8.0% (1492)	18.6% (1163)	4.1% (293)	0.4% (10)	5.3% (100)	1.7% (32)	15.9% (220)	1.2% (14)	0.0% (0)	1.0% (7)
Native Hawaiian and other Pacific Islander	0.3% (61)	0.4% (35)	0.4% (30)	0.0% (0)	0.5% (10)	0.1% (2)	0.4% (5)	0.0% (0)	0.0% (0)	0.0% (0)
Two or more races	0.8% (141)	1.0% (99)	2.3% (160)	0.0% (0)	0.7% (14)	0.8% (15)	0.6% (8)	0.1% (1)	0.6% (5)	0.3% (2)
Other	0.2% (39)	1.0% (101)	0.0% (0)	3.0% (68)	0.2% (3)	0.0% (0)	1.2% (16)	0.0% (0)	0.0% (0)	1.2% (8)
Unknown or not reported	1.4% (263)	0.4% (43)	1.4% (99)	2.6% (57)	1.1% (20)	3.8% (71)	0.7% (9)	0.7% (9)	0.0% (0)	1.0% (7)

Ethnic data from 152 clinical trials

	Psoriasis (n = 14,315)	Eczema/atopic dermatitis (n = 7716)	Acne (n = 6234)	Nonmelanoma skin cancer (n = 1740)	Aesthetics (n = 1202)	Melanoma (n = 1290)	Alopecia (n = 1381)	Rosacea (n = 765)	Tinea (n = 407)	Papillomavirus (warts) (n = 688)
Hispanic or Latino	10.7% (1530)	10.3% (794)	22.1% (1375)	3.0% (52)	17.3% (208)	7.1% (132)	12.5% (161)	25.0% (191)	0.0% (0)	16.3% (112)

Mineroff J et al., J Am Acad Dermatol, 2023.

Challenges in achieving diversity in clinical trials



Odedina FT, Wieland ML, Barbel-Johnson K, Crook JM. Community Engagement Strategies for Underrepresented Racial and Ethnic Populations. Mayo Clin Proc. 2024 Jan;99(1):159-171

Why is Diversity in Clinical Trials Important?

Contains Nonbinding Recommendations

Draft — Not for Implementation

Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry[1]

- Intended to increase enrollment of participants who are members of historically underrepresented populations in clinical studies
  - Age, race, ethnicity, sex
- This will help improve the strength and generalizability of the evidence for the intended use population

FDA Guidance

- Broaden eligibility criteria and avoid unnecessary exclusions
- Design trials in ways that achieve participant diversity
  - Initiate studies in sites with diverse populations
  - Consider transportation barriers for those that live in rural or remote locations
    - Flexibility in visit times and frequency of in person visits (consider televisits)
    - Instead of visiting the trial site, include options such as mobile medical professionals, blood collection workers to visit participant homes or have participants visit a local lab
  - Consider participation challenges for older adults, children, people with disabilities and those with cognitive impairments
- Improve practices for recruiting participants to clinical trials
  - Consider diverse investigators and study coordinators to assist with trial recruitment
  - Trial related resources in multiple languages
  - Sponsor's can engage with the target participants' community and build trust

FDA.gov

Pediatric Focus: Bridging the Gap for Equitable Care

- Social determinants of health (SDOH) impact health equity
  - Where the children live, parental income, parental education, access to health insurance, access to health care, support systems, etc.
- In the US, race is often a surrogate of SDOH for pediatric disease
- SDOH and race impact clinical trial participation and outcomes
  - When not considered, uptake of newer therapies in some communities may be limited:
    - Ineffective
    - Impractical in a low resource area
    - Not utilized due to cultural concerns

Nwankwo C et al. Int J Womens Dermatol. 2024 Aug 19;10(3):e173

PROGRESS-Used at the Inception of a Trial

- P: Place of residence
- R: Race/Ethnicity/Culture/Language
- O: Occupation
- G: Gender
- R: Religion
- E: Education
- S: Socioeconomic status
- S: Social capital

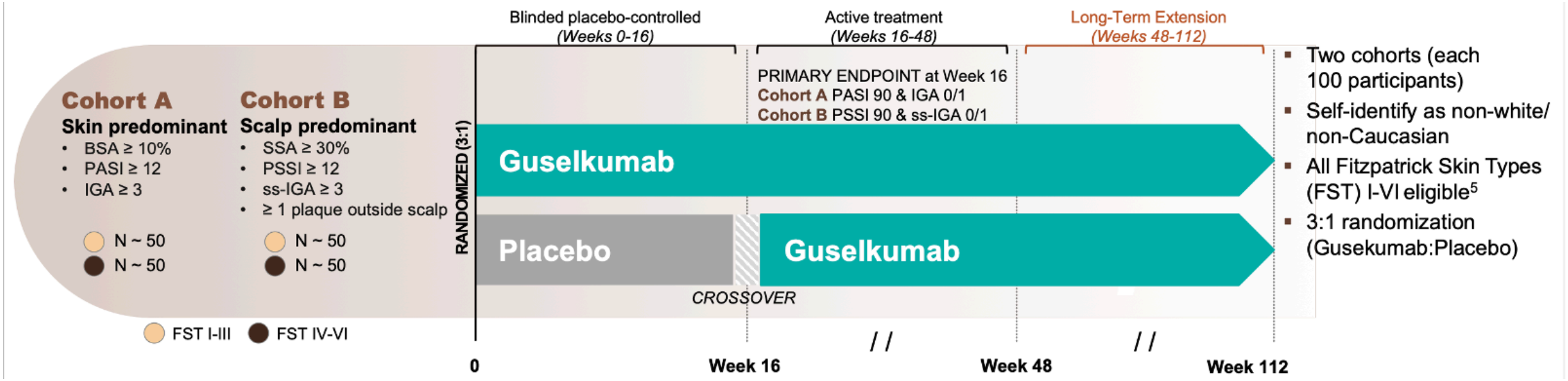
Nwankwo C et al. Int J Womens Dermatol. 2024 Aug 19;10(3):e173

What Progress Have We Made?

VISIBLE and ADmirable Studies

VISIBLE Study: Evaluating Safety and Efficacy of GUS for Psoriasis Across Skin Tones

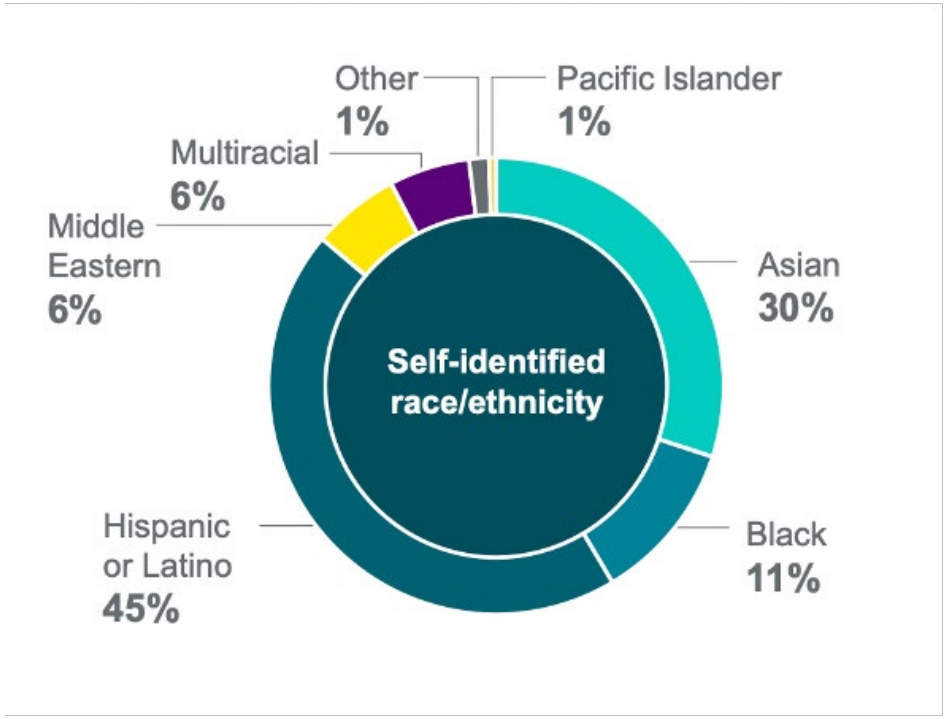
- First large-scale, prospective study dedicated to the evaluation of psoriasis and treatment outcomes in SOC patients across all skin tones



Alexis A, et al. AAD Annual Meeting; March 2023; New Orleans, LA

The Approach to Increasing Diversity-Enrollment

- Diverse demographic-driven site selection
- Inclusion of new investigators who they themselves came from diverse backgrounds
- Cultural Sensitivity Training for all sites
- Assisting subjects with barriers to trial participation like language barriers, transportation barriers, etc.

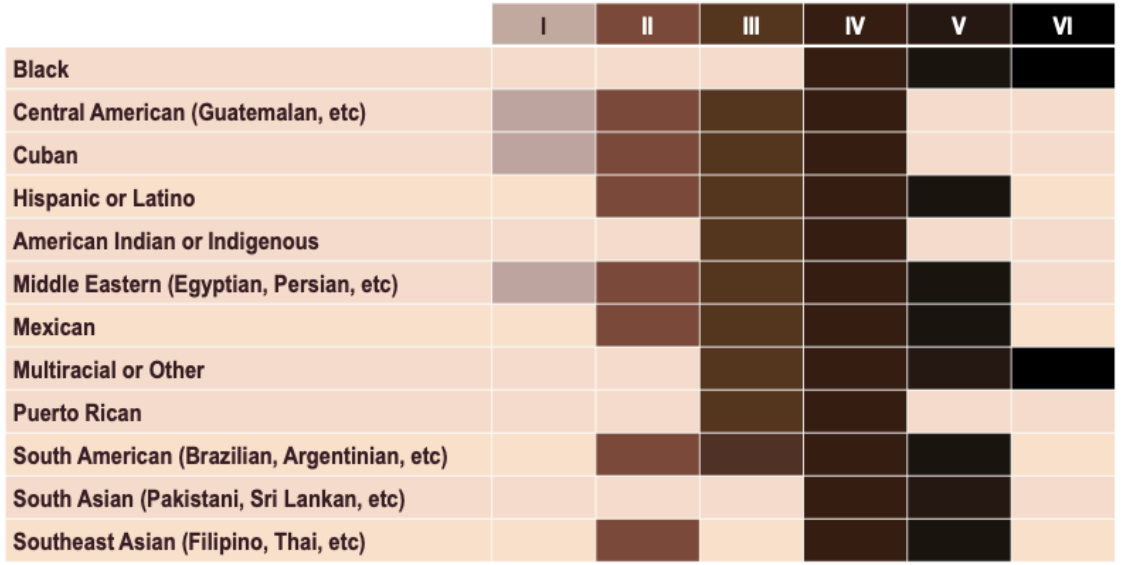


Alexis A, et al. AAD Annual Meeting; March 2023; New Orleans, LA

The Approach to Increasing Diversity-Inclusivity

- Inclusion of FST I-VI and all who self-identify as non-white

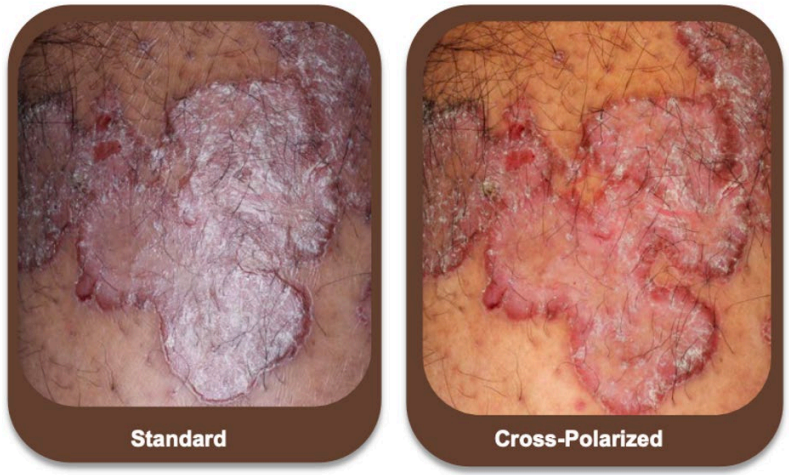
Fitzpatrick Skin Type: Race/Ethnicity Distribution in VISIBLE*

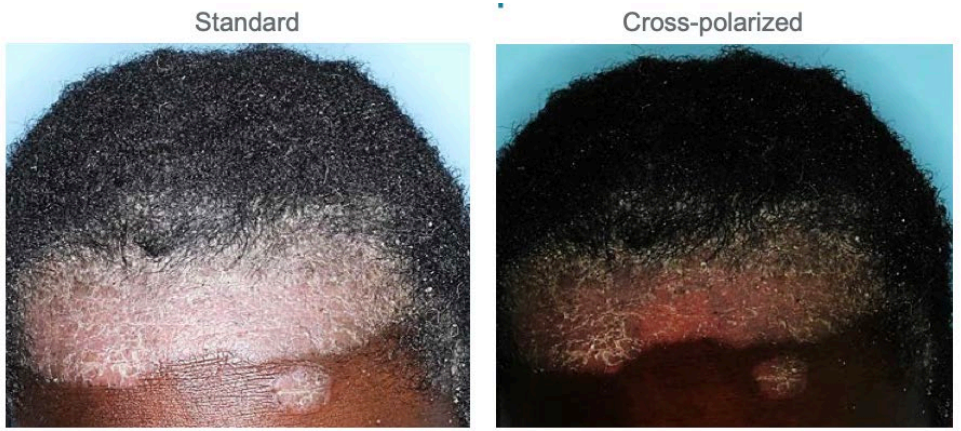


Alexis A, et al. AAD Annual Meeting; March 2023; New Orleans, LA

The Approach to Increasing Diversity- Diagnosis and Disease Progression

- Screening photos could be submitted to an expert panel to confirm the PsO diagnosis and confirm study eligibility
- Measurement of erythema in PsO and melanin in post-inflammatory pigment alteration (PIPA) via colorimetry
- Use of cross-polarized light and photography to objectively evaluate the progression/improvement of psoriasis plaques and PIPA over time
- Creation of a database of about 20,000 clinical images showcasing the presentation of PsO across skin tones





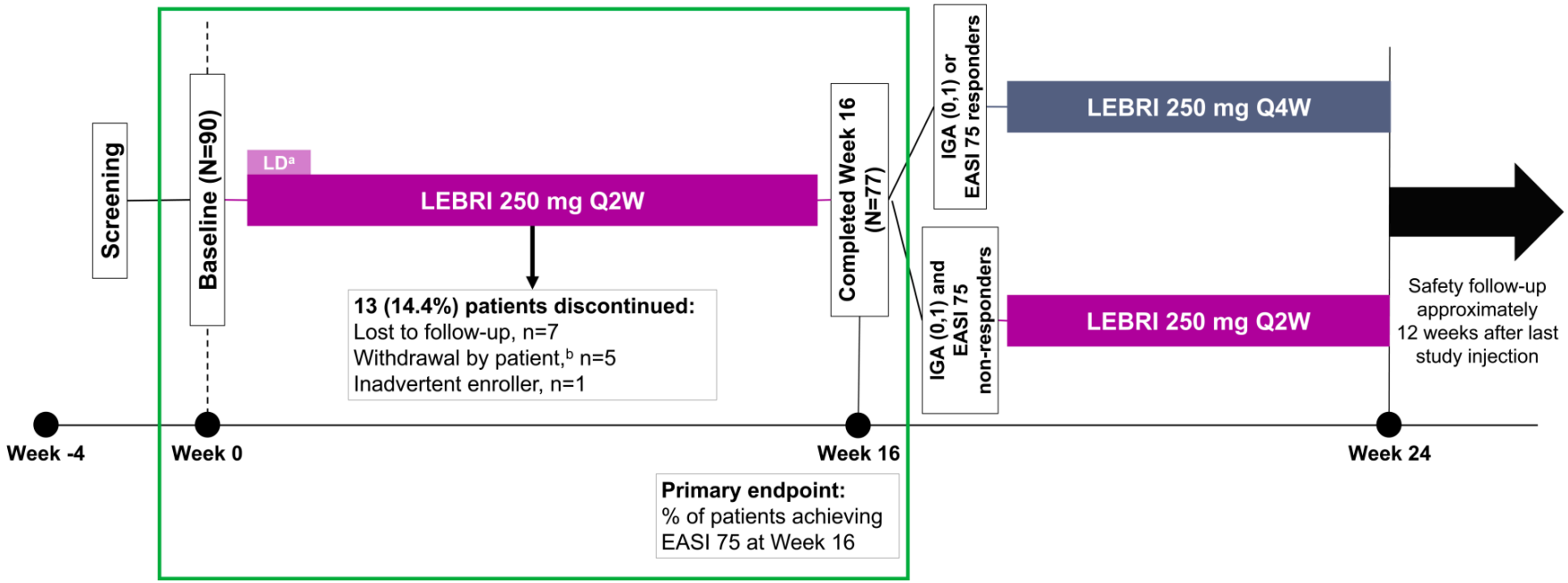
Alexis A, et al. AAD Annual Meeting; March 2023; New Orleans, LA

Results

- GUS met all primary endpoints and was safe and effective in treating PsO across all skin tones
- Benefits went beyond the endpoints
  - Shed light on the SOC patient journey with PsO
  - Helped us understand and troubleshoot reasons for under-enrollment of SOC patients in PsO studies
  - What we have learned will help guide inclusive clinical trial design for years to come

ADmirable Study: Evaluating Safety and Efficacy of LEB for Atopic Dermatitis in SOC

- First prospective study dedicated to the evaluation of atopic dermatitis and treatment outcomes in SOC patients with types IV, V and VI skin

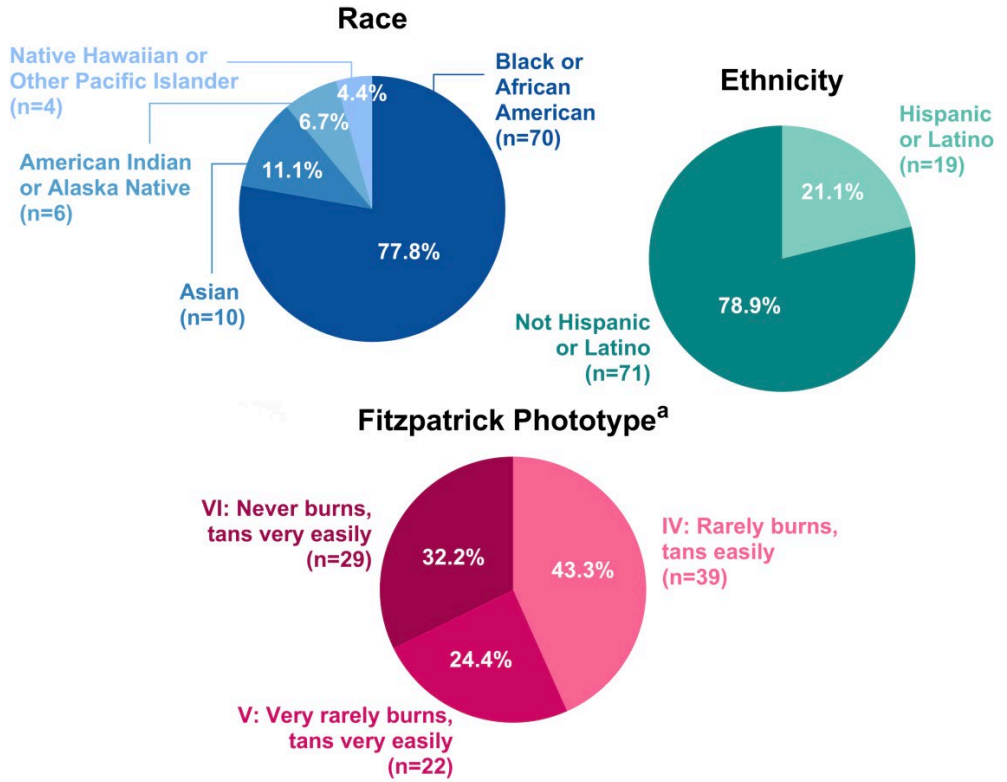


Alexis et al, Fall Clinical 2024, Las Vegas, NV

The Approach to Increasing Diversity-Inclusivity

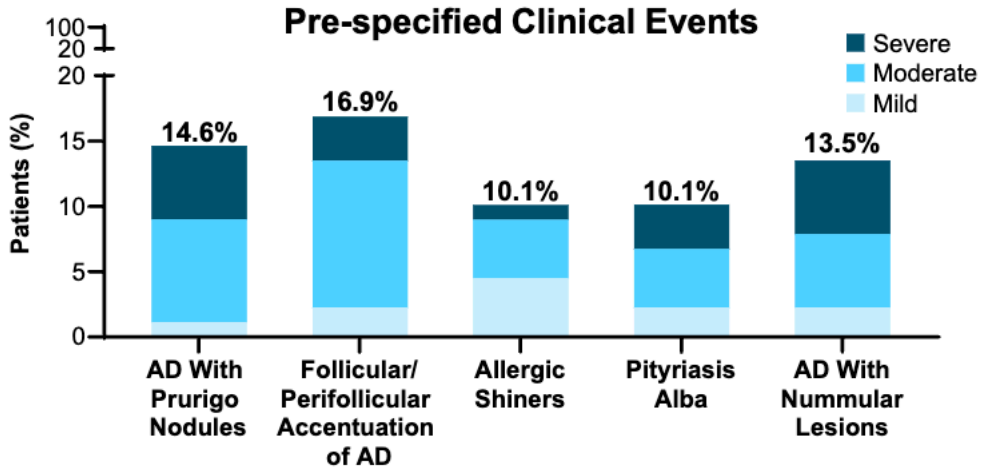
- Included patients with a self-reported race other than white
- FST IV-VI

	LEBRI 250 mg Q2W (N=90)
Age, years	40.7 (19.6)
Adult (≥18 years), n (%)	76 (84.4)
Adolescent (≥12 to <18 years), n (%)	14 (15.6)



Alexis et al, Fall Clinical 2024, Las Vegas, NV

The Approach to Increasing Diversity- Diagnosis and Disease Progression



Post-inflammatory hypopigmentation				Post-inflammatory hyperpigmentation		
-3	-2	-1	0	+1	+2	+3
Severe hypopigmentation	Moderate hypopigmentation	Mild hypopigmentation	Normal skin tone	Mild hyperpigmentation	Moderate hyperpigmentation	Severe hyperpigmentation
Prominent hypopigmentation	Clearly perceptible hypopigmentation	Barely perceptible hypopigmentation		Barely perceptible hyperpigmentation	Clearly perceptible hyperpigmentation	Prominent hyperpigmentation

Alexis et al, Fall Clinical 2024, Las Vegas, NV

Results

- LEB met all primary endpoints and was safe and effective in treating AD in both adults and adolescents
- Benefits went beyond the endpoints
  - Helped us understand and troubleshoot reasons for under-enrollment of SOC patients in clinical trials for AD
  - Studied varying morphologies of AD that is more prevalent in melanin rich skin
  - Data is still undergoing analysis so we have so much more to learn from this trial!

Take Home Points

- The diversity of the patients we study in clinical trials should resemble the diversity of real-world clinical practice
- Though, historically, trials have had limited age, gender and racial/ethnic diversity, measures are being taken to prioritize clinical trial diversity
- The VISBLE study in psoriasis and ADmirable study in AD represent a turning point in the clinical study of patients with SOC
- As the US population continues to diversify, maintaining diversity in clinical trials is key to ensure novel therapies are safe and effective across ALL patients