Effects on CD3, Treg, and TH17 Cell Numbers in Skin Biopsies After 16-Week Mirikizumab Treatment, Evaluated by an Epigenetic Assay

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INTRODUCTION

- Study I6T-MC-AMAF is a double-blind phase 2 trial to determine safety and efficacy of LY3074828 (mirikizumab), a humanized monoclonal antibody against the p19 subunit of interleukin (IL)-23, in patients with moderate-to-severe plaque psoriasis
- IL-23 is a proinflammatory cytokine produced primarily by myeloid cells[1]
  - It drives the secretion of IL-17 from T cells and other innate immune cells[1-3]
- Mirikizumab treatment led to a significant improvement in clinical response compared to placebo at Week 16 (66.7% of patients in 300 mg group achieved Psoriasis Area and Severity Index [PASI]90)[4]
- Past studies showed that even when psoriasis is clinically resolved, IL-17-producing cells can remain in skin after treatment[5]
  - Their presence may potentially contribute to flares after anti-IL-17 withdrawal
- To determine the cellular skin milieu of patients in the current study, we evaluated the relationships between mirikizumab exposure, efficacy, and skin biomarkers

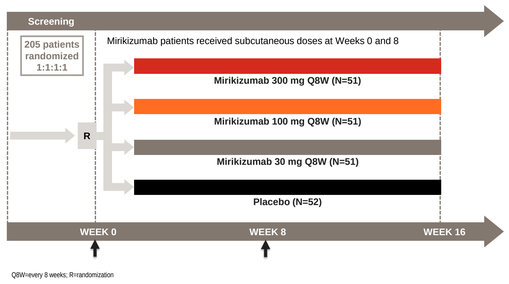
HYPOTHESIS

By blocking IL-23p19, mirikizumab decreases the IL-17-producing cells within the skin, reducing disease severity and the potential for flares

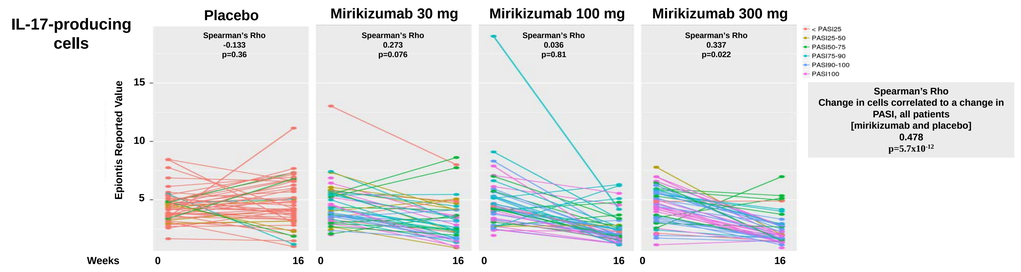
STUDY DESIGN

Mirikizumab AMAF Phase 2 Trial Design

- Study I6T-MC-AMAF is a Phase 2, multicenter, randomized, parallel-arm, placebo-controlled study of mirikizumab in subjects with moderate-to-severe plaque psoriasis (NCT02899988)
- Patients with chronic plaque psoriasis (body surface area≥10%, PASI≥12, static Physician's Global Assessment≥3) received mirikizumab 300, 100, or 30 mg subcutaneously or placebo every 8 weeks for 16 weeks
- Lesional skin biopsies from each group were assessed at baseline and Week 16 using the EpiontisID™ assay: cluster of differentiation (CD)3, regulatory T cell (Treg), IL-17-producing cells
- Post hoc analyses: (1) Fold change in cell-type frequency over baseline; (2) Correlation coefficient between cell-type frequency and Week 16 PASI changes



KEY RESULT



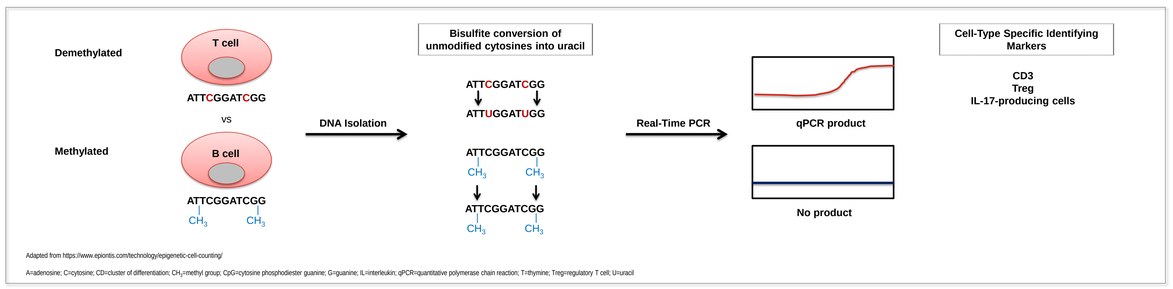
- **Reductions in IL-17-producing cells were associated with improvements in PASI**

Other Cell Types	Correlation Coefficient: Spearman's Rho, p-value Change in cells vs PASI				
	Placebo	Mirikizumab 30 mg	Mirikizumab 100 mg	Mirikizumab 300 mg	All Mirikizumab Doses
CD3	-0.123 p=0.41	0.325 p=0.029	-0.017 p=0.91	0.091 p=0.54	0.399 $p=1.7 \times 10^{-8}$
Treg	-0.149 p=0.31	0.432 p=0.0031	0.297 p=0.05	0.202 p=0.17	0.489 $p=1.8 \times 10^{-12}$

CD=cluster of differentiation; IL=interleukin; PASI=Psoriasis Area and Severity Index; Treg=regulatory T cell

EpiontisID™ Assay

- Used to identify cells within skin biopsies via cell type-specific epigenetic biomarkers in CpG-demethylated regions of DNA
  - CpG demethylation is an indicator of a cell's digital phenotype



Adapted from https://www.epiontis.com/technology/epigenetic-cell-counting/

A=adenosine; C=cytosine; CD=cluster of differentiation; CH_3=methyl group; CpG=cytosine phosphodiester guanine; G=guanine; IL=interleukin; qPCR=quantitative polymerase chain reaction; T=thymine; Treg=regulatory T cell; U=uracil

Advantages

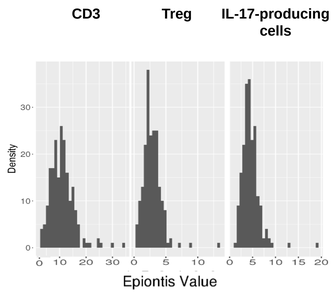
- Most clinical biopsies are limited to the detection of cell subsets either by immunohistochemistry (IHC), gene expression analysis, or flow cytometry:
  - IHC and gene expression analysis have significant problems in terms of true cell counting; both methods are limited in formal quantification of cell numbers
  - While flow cytometry allows for accurate cell enumeration, the need of fresh biopsies generates logistical challenges that would only allow a very limited subset of patients to be assessed
- The epigenetic cell counting methodology allows the assessment of the whole studied AMAF patient population → 205 patients with biopsies from 2 time points

AMAF Study Outcomes at Week 16

NRI and n (%) unless otherwise specified[a]	Placebo (N=52)	Mirikizumab 30 mg (N=51)	Mirikizumab 100 mg (N=51)	Mirikizumab 300 mg (N=51)
PASI score (observed), mean (SD)	19.5 (8.4)	6.0 (5.6)***	2.7 (4.2)***	2.5 (4.2)***
PASI 100	0	8 (15.7)*	16 (31.4)**	16 (31.4)**
PASI 90	0	15 (29.4)**	30 (58.8)***	34 (66.7)***
PASI 75	2 (3.8)	27 (52.9)***	40 (78.4)***	38 (74.5)***
PASI ≤1	0	8 (15.7)*	23 (45.1)**	27 (52.9)***
PASI ≤3	2 (3.8)	21 (41.2)***	37 (72.5)***	36 (70.6)***
PASI ≤5	2 (3.8)	28 (54.9)***	41 (80.4)***	41 (80.4)***
sPGA 0/1	1 (1.9)	19 (37.3)***	36 (70.6)***	35 (68.6)***
sPGA 0	0	8 (15.7)*	16 (31.4)**	16 (31.4)**
BSA ≤1%	1 (1.9)	10 (19.6)*	28 (54.9)***	30 (58.8)***
DLQI 0/1	2 (3.8)	18 (35.3)***	25 (49.0)***	24 (47.1)***

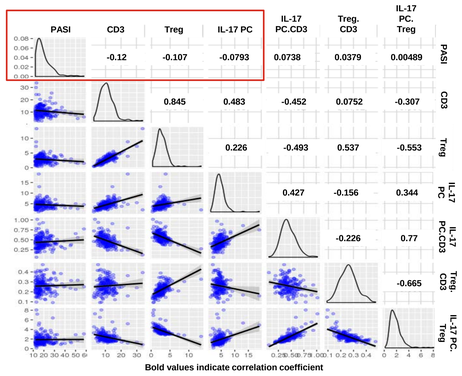
*p<0.05; **p<0.01; ***p<0.001 vs. placebo.
BSA=body surface area; DLQI=Dermatology Life Quality Index; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PASI 75=75% reduction in the Psoriasis Area and Severity Index; PASI 90=90% improvement in Psoriasis Area and Severity Index; PASI 100=100% improvement in Psoriasis Area and Severity Index; SD=standard deviation; sPGA=static Physician's Global Assessment

Distribution of Cell Populations Within Skin Biopsies



- Frequencies of Treg and IL-17-producing cells at baseline were similar to those described in the literature[6]

Baseline Cell Frequencies Do Not Correlate With Baseline PASI Scores



CD=cluster of differentiation; IL=interleukin; PASI=Psoriasis Area and Severity Index; PC=producing cells; Treg=regulatory T cell

Mirikizumab Decreases Frequency of Resident Skin Immune Cells

Analyte	Mirikizumab 30 mg	Mirikizumab 100 mg	Mirikizumab 300 mg	Mirikizumab 30 mg	Mirikizumab 100 mg	Mirikizumab 300 mg	Residual Coefficient of Variation
	Change from baseline to Week 16, mirikizumab vs placebo						
	Adjusted p-value			Fold change			
CD3	1.405×10^{-4}	8×10^{-7}	3.4×10^{-6}	-1.59	-1.78	-1.73	40.9
Treg	1.68×10^{-5}	<0.000001	3×10^{-7}	-1.85	-2.26	-2.05	50.0
IL-17-producing cells	2.811×10^{-4}	<0.000001	<0.000001	-1.50	-1.92	-1.86	36.9

CD=cluster of differentiation; IL=interleukin; Treg=regulatory T cell

- Regardless of dose, mirikizumab significantly reduced the number of immune cell subsets compared to placebo

DISCUSSION

- Mirikizumab decreased T cell frequency within psoriasis skin
- IL-17-producing cells, specifically, showed a reduction that inversely correlated with clinical response
- Mirikizumab may, through its unique mechanism of action, create a different skin milieu after treatment in psoriatic skin than anti-IL-17 and anti-TNF treatments

LIMITATIONS

- Exploratory
- Single, small (n~50/arm) phase 2 study
- Correlation with clinical data (flare frequencies after last dose at Week 16) not done

CONCLUSIONS

- **In an exploratory assessment, mirikizumab's inhibition of IL-23 reduced the total number of IL-17-producing cells**
- **This may lead to a more stable response with longer periods of skin clearance without flares**
- **To further understand the mechanism of action of mirikizumab, future translational trials are needed**

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