Topical hypericin ointment (SGX301) photodynamic therapy is effective and safe in CTCL: results from the multicenter Phase 3 FLASH study

Kim EJ[1], Poligone B[2], Mangold A[3], DeSimone J[4], Seminario-Vidal L[5], Wong H[6], Guitart J[7], Appel J[8], Geskin L[9], Pullion C[10], Straube R[10], on behalf of all FLASH study investigators.

[1]University of Pennsylvania, [2]Rochester Skin Lymphoma, [3]Mayo Clinic, [4]Inova Cancer Center, [5]University of South Florida Health, [6]University of Arkansas, [7]Northwestern University, [8]PMG Research Wilmington, [9]Columbia University, [10]Soligenix.

Background: Given early-stage MF/CTCL chronicity, additional skin directed therapies (SDTs) with minimal short- and long-term side effects are urgently needed. Topical synthetic hypericin ointment 0.25% (SGX301) activated with external cool-white visible light (500-650 nm) is a novel, non-mutagenic photodynamic therapy (PDT).

Methods (Figure 1): We conducted a randomized, placebo-controlled, observer-blinded multicenter Phase 3 trial (FLASH study, HPN-CTCL-01, NCT02448381) evaluating its efficacy and safety in early stages IA-IIA CTCL at 37 U.S. sites. SGX301 or placebo was applied to 3 index lesions twice weekly, 18-24 hours prior to light therapy (starting dose 5J/cm2, increased as tolerated to max 12J/cm2) for a 6-wk cycle followed by a 2-wk break, for a total of 3 treatment cycles. Cycle 1 (randomized to SGX301 vs placebo) and Cycle 2 (all received SGX301) were required; Cycle 3 (index and additional lesions treated with SGX301) was optional. Index lesion response rate (ILRR) and adverse events (AEs) were assessed at end of each cycle, then monthly for 6 months. The trial primary endpoint was ILRR based on ≥ 50% improvement in the cumulative modified Composite Assessment Index for Lesion Severity, mCAILS, score.

Results: 169 patients were enrolled (**Figure 2)** with 166 randomized, median age 57-59 y.o., M:F ratio1.2-1.5:1, 72% white/24% black/4% other, majority Stage IA (62%) at study entry, median time since diagnosis 2-3 years, and median # prior therapies was 2-3 (range 0-19). After Cycle 1, ILRR for SGX301 (n=116 patients) vs placebo (n=50) was 16% vs 4% (p=0.04) (**Figure 3**). Cycle 2 ILRR for subjects who received 2 cycles of SGX301 (n=110) was 40% (p<0.0001 vs Cycle 1 SGX301). In subjects who received 3 cycles of SGX301 (n=78), ILRR increased to 49% (p<0.0001 vs Cycle 1 SGX301). Clinical responses were observed in both patch and plaque lesions, reflecting the deeper dermal penetration predicted with SGX301/visible light PDT. The most common observed AEs were Grade 1-2 local application site skin reactions (16% of subjects, **Figure 4**) such as pruritus, erythema, and hyperpigmentation. Severe AEs were seen in 4% of study drug subjects and the treatment-phase study dropout rate was only 5% in the SGX301 treated patients. No drug-related serious AEs occurred and SGX301 was not detected systemically.

Conclusion: The FLASH Study is the largest multicenter, randomized, double-blind, placebo-controlled SDT study in MF/CTCL to date and demonstrated topical synthetic hypericin SGX301 PDT is effective in early stage CTCL with similar response rate kinetics as other currently approved SDTs, with a highly favorable short term safety profile. It's non-mutagenic mechanism of action is less likely to induce actinic damage or increase risk of skin cancers and may be safer long term than traditional phototherapy.

References:

1. Thomas, C., et al., *Photoactivation of hypericin generates singlet oxygen in mitochondria and inhibits succinoxidase.* Photochem Photobiol, 1992. 55(1): p. 47-53.

2. SRS, I.C., *An Open Label Phase I/II Study to Determine the Safety and Efficacy of Hypericin After Topical Application and Light Irradiation for Inflammatory Skin Diseases and Warts: Evaluation of Photodynamic Therapy.* Clinical Study Report, 2001.

3. Blank, M., et al., *Wavelength-dependent properties of photodynamic therapy using hypericin in vitro and in an animal model.* Photochem Photobiol, 2002. 76(3): p. 335-40.

4. Rook, A.H., et al., *A phase II placebo-controlled study of photodynamic therapy with topical hypericin and visible light irradiation in the treatment of cutaneous T-cell lymphoma and psoriasis.* J Am Acad Dermatol, 2010. 63(6): p. 984-90.

Figure 1: FLASH Study Design

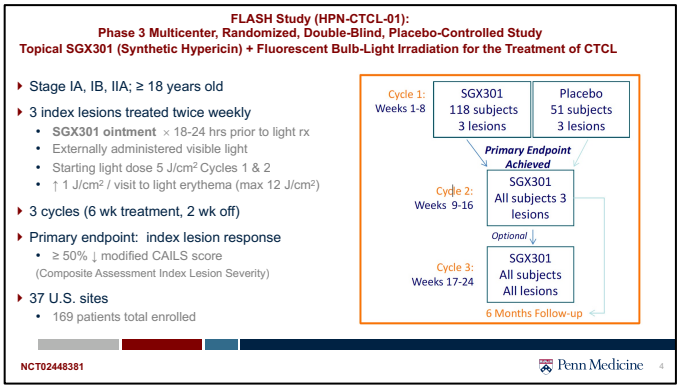
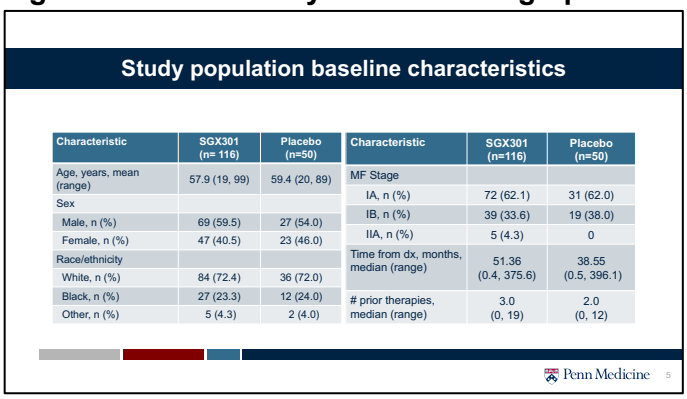


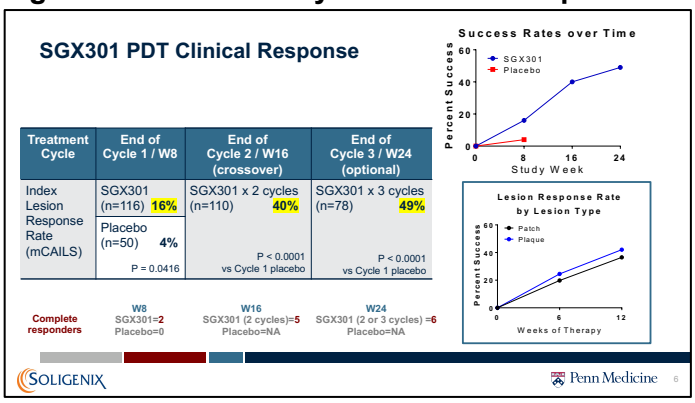
Figure 2: FLASH Study Patient Demographics



Characteristic	SGX301 (n= 116)	Placebo (n=50)
Age, years, mean (range)	57.9 (19, 99)	59.4 (20, 89)
Sex		
Male, n (%)	69 (59.5)	27 (54.0)
Female, n (%)	47 (40.5)	23 (46.0)
Race/ethnicity		
White, n (%)	84 (72.4)	36 (72.0)
Black, n (%)	27 (23.3)	12 (24.0)
Other, n (%)	5 (4.3)	2 (4.0)

Characteristic	SGX301 (n=116)	Placebo (n=50)
MF Stage		
IA, n (%)	72 (62.1)	31 (62.0)
IB, n (%)	39 (33.6)	19 (38.0)
IIA, n (%)	5 (4.3)	0
Time from dx, months, median (range)	51.36 (0.4, 375.6)	38.55 (0.5, 396.1)
# prior therapies, median (range)	3.0 (0, 19)	2.0 (0, 12)

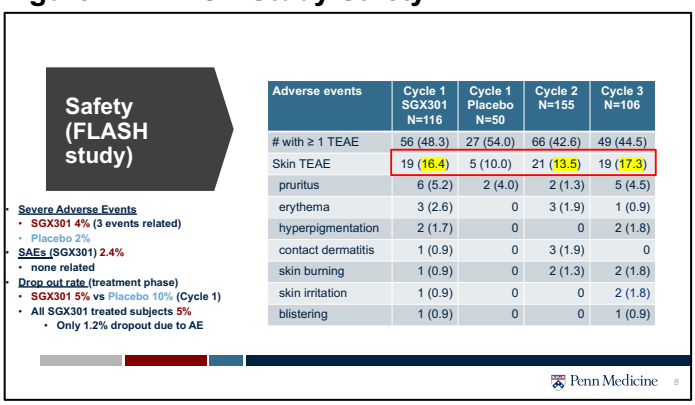
Figure 3: FLASH Study Index lesion response rate



Treatment Cycle	End of Cycle 1 / W8	End of Cycle 2 / W16 (crossover)	End of Cycle 3 / W24 (optional)
Index Lesion Response Rate (mCAILS)	SGX301 (n=116) 16%	SGX301 x 2 cycles (n=110) 40%	SGX301 x 3 cycles (n=78) 49%
	Placebo (n=50) 4%		
	P = 0.0416	P < 0.0001 vs Cycle 1 placebo	P < 0.0001 vs Cycle 1 placebo

Complete responders	W8	W16	W24
	SGX301=2 Placebo=0	SGX301 (2 cycles)=5 Placebo=NA	SGX301 (2 or 3 cycles) =6 Placebo=NA

Figure 4: FLASH Study Safety



- Severe Adverse Events
  - SGX301 4% (3 events related)
  - Placebo 2%
- SAEs (SGX301) 2.4%
  - none related
- Drop out rate (treatment phase)
  - SGX301 5% vs Placebo 10% (Cycle 1)
  - All SGX301 treated subjects 5%
    - Only 1.2% dropout due to AE

Adverse events	Cycle 1 SGX301 N=116	Cycle 1 Placebo N=50	Cycle 2 N=155	Cycle 3 N=106
# with ≥ 1 TEAE	56 (48.3)	27 (54.0)	66 (42.6)	49 (44.5)
Skin TEAE	19 (16.4)	5 (10.0)	21 (13.5)	19 (17.3)
pruritus	6 (5.2)	2 (4.0)	2 (1.3)	5 (4.5)
erythema	3 (2.6)	0	3 (1.9)	1 (0.9)
hyperpigmentation	2 (1.7)	0	0	2 (1.8)
contact dermatitis	1 (0.9)	0	3 (1.9)	0
skin burning	1 (0.9)	0	2 (1.3)	2 (1.8)
skin irritation	1 (0.9)	0	0	2 (1.8)
blistering	1 (0.9)	0	0	1 (0.9)