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ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: www.tandfonline.com/journals/ieid20

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To cite this article: James R. Poligone, Priyanka Kadam, Elaine S. Gilmore & Brian Poligone (2026) Topical hypericin: a promising photodynamic therapy for early-stage cutaneous T-cell lymphoma, Expert Opinion on Investigational Drugs, 35:4, 257-263, DOI: 10.1080/13543784.2026.2643305

To link to this article: https://doi.org/10.1080/13543784.2026.2643305

Published online: 19 Mar 2026.

EXPERT OPINION ON INVESTIGATIONAL DRUGS
2026, VOL. 35, NO. 4, 257–263
https://doi.org/10.1080/13543784.2026.2643305

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DRUG EVALUATION

Topical hypericin: a promising photodynamic therapy for early-stage cutaneous T-cell lymphoma

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ABSTRACT

Introduction: Effective skin-directed therapies (SDT) are the cornerstone for managing early-stage Cutaneous T-cell Lymphoma (CTCL). However, standard treatments like PUVA phototherapy and topical mechlorethamine carry significant drawbacks, including mutagenic risk and treatment-limiting skin reactions. This unmet need has driven demand for safer options. Topical photodynamic therapy with synthetic hypericin (research name: SGX301; trade name: HyBryte™) has emerged as a novel agent addressing this gap.

Areas covered: This review details synthetic hypericin's evolution and its unique non-mutagenic, light-activated mechanism. It generates singlet oxygen, preferentially inducing apoptosis in malignant T-cells. We analyze key clinical trials, including the pivotal Phase III FLASH study, to establish its efficacy and safety in patch- and plaque-stage mycosis fungoides, comparing it to other SDTs.

Expert opinion: Topical synthetic hypericin is a significant advancement for early-stage CTCL. Its excellent safety profile, proven efficacy, and non-mutagenic mechanism position it as a valuable first-line option. Minimal local adverse events and limited systemic absorption offer a key long-term safety advantage over conventional phototherapies. Its effectiveness in both patch and plaque lesions makes it a versatile tool, improving outcomes and quality of life for patients.

ARTICLE HISTORY
Received 10 December 2025
Accepted 6 March 2026

KEYWORDS
Topical hypericin; photodynamic therapy; lymphoma; cutaneous T-cell lymphoma; CTCL; mycosis fungoides; response rate; mCAILS; SCORD; mSWAT

1. Introduction

Primary cutaneous lymphomas are a heterogenous group of non-Hodgkin lymphomas that originate in the skin [1]. Cutaneous T-cell lymphomas (CTCLs) are the most prevalent type, accounting for 75% to 80% of all primary cutaneous lymphomas in Western countries [2]. Mycosis fungoides (MF) is the most common subtype of CTCL [2]. The classification and staging of CTCL, including MF and Sézary syndrome, are guided by the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classifications, which provide comprehensive frameworks for diagnosis and management [3].

Hypericin is a naturally occurring anthraquinone derived primarily from the *Hypericum* genus, most notably *Hypericum perforatum L.*, commonly known as St. John's wort [4] (Figure 1(a)). With a documented history of medicinal use spanning over 2000 years, St. John's wort is recognized for its broad pharmacological activities, including antidepressant, antiviral, and antibacterial [5], and hypericin itself was first isolated in 1957 from *H. perforatum* and *H. hirsutum* [4].

A defining characteristic of hypericin is its potent photosensitizing property. It exhibits maximal fluorescence spectrometry absorption at approximately 545 nm and 590 nm (yellow/red light) (Figure 1(b)). Upon exposure to visible light, hypericin efficiently generates reactive oxygen species (ROS) primarily through a Type II mechanism involving energy transfer to molecular oxygen to create a highly cytotoxic singlet oxygen. This process is distinct from the Type I mechanism that involves electron transfer reactions, leading to the formation of ionic radicals that subsequently react with oxygen to produce highly ROS [4]. The chemical structure of hypericin, with its phenolic and quinone moieties, facilitates tautomerization and hydrogen bond formation, resulting in its dissociation into hypericinate: a monobasic salt known for improved singlet oxygen generation and enhanced solubility [4]. The generation of ROS ultimately leads to apoptosis of malignant T-cells (Figure 1(c)).

Beyond its light-activated effects, hypericin demonstrates diverse biological activities in the absence of light. These include intrinsic anti-cancer properties (cytotoxicity, growth inhibition, and anti-angiogenic effects), broad-spectrum antiviral activity, and potential neuroprotective effects [4,6,7]. It also exhibits antifungal activity, with hypericin-mediated photodynamic therapy (PDT) proving effective against various fungal skin diseases [4,8]. Generally, the activity of hypericin in the dark occurs at significantly higher concentrations than its biological activity when photoactivated.

2. Topical hypericin for cutaneous T-Cell lymphoma (CTCL)

The development of a topical synthetic hypericin formulation was motivated by the significant, dose-limiting phototoxicity

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Article highlights

- Unmet Need: Standard skin-directed therapies for early-stage Cutaneous T-cell Lymphoma (CTCL), such as PUVA and topical mechlorethamine, are limited by mutagenic risks and treatment-limiting skin reactions.
- Novel Mechanism: Synthetic hypericin (HyBryte™) is a non-mutagenic, light-activated agent that preferentially induces apoptosis in malignant T-cells through the generation of singlet oxygen.
- Clinical Efficacy: Results from the pivotal Phase III FLASH study demonstrate that topical hypericin is effective for treating both patch- and plaque-stage mycosis fungoides.
- Safety Profile: The therapy offers a significant safety advantage over conventional phototherapies due to its minimal local adverse events and limited systemic absorption.
- Clinical Versatility: Its effectiveness across different lesion types makes it a versatile tool for improving patient outcomes and overall quality of life.
- Expert Verdict: Topical synthetic hypericin represents a significant advancement in the field and is positioned to be a valuable first-line treatment option for early-stage CTCL.

Box 1: Drug summary box

Drug Name: Synthetic Hypericin (HyBryte)
Phase: II/III
Indication: Pending approval for Cutaneous T-cell Lymphoma
MOA: ROS initiated apoptosis induced once exposed to visible light
Route: Topical
Chemical Structure: Figure 1(a)
Pivotal Trial(s): HPN-CTCL-01 [12]

observed with systemic hypericin in earlier clinical trials for other indications, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), and glioma [9–11]. The topical synthetic formulation (research name: SGX301; trade name: HyBryte) was designed to harness hypericin's potent photodynamic anti-cancer properties directly at the site of cutaneous disease, thereby maximizing local efficacy while eliminating systemic side effects [12].

Topical hypericin utilized for these clinical studies is synthetically produced to high purity. In contrast plant extracted materials can be both variable in potency (amount of hypericin) and in purity, including contaminants such as other potentially photo-active compounds from the plant species, which have incompletely understood function and action.

2.1. Mechanism of action for topical synthetic hypericin

Topical synthetic hypericin is a novel, first-in-class photodynamic therapy activated by safe, visible light. The drug product is a 0.25% synthetic hypericin topical formulation (either gel or ointment) applied to skin lesions, which is then activated 12 to 24 hours later by a visible light device that delivers the required light in the yellow-red spectrum (500–650 nm). This wavelength range is optimal to maximally activate hypericin as well as allowing for tissue penetrations of up to 2 mm, sufficient to treat plaque-stage lesions, while avoiding the mutagenic potential of ultraviolet (UV) light [13].

A key advantage of topical synthetic hypericin is its mechanism of action, which relies on the preferential uptake of hypericin by T-cells, and more specifically by malignant T-cells due to its lipophilic nature and interaction with cellular membranes [5]. Upon activation by light, intracellular hypericin triggers the rapid generation of ROS, which leads to oxidative stress, mitochondrial damage, and the induction of apoptotic cell death via caspase-dependent pathways [5,9]. This targeted, apoptosis-driven mechanism, coupled with its non-mutagenic nature, fundamentally differentiates it from conventional phototherapies like psoralen activated by ultraviolet A light (PUVA), which function by creating DNA cross-links and are associated with significant long-term risks, including secondary skin cancer [14].

Topical synthetic hypericin can be used on any body parts for which adequate light exposure can be achieved. Patients with <10% body surface area to >60% body surface area have been treated with no significant issue.

2.2. Clinical efficacy in early-stage CTCL/Mycosis fungoides (MF) the efficacy of topical hypericin PDT has been systematically evaluated in multiple clinical trials for early-stage CTCL (**Table 1**)

2.2.1. Phase II clinical trial (study VM-97–003)

An early placebo-controlled, Phase II study demonstrated a statistically significant reduction in early-stage MF/CTCL skin lesions. After 6 weeks of treatment with topical hypericin and a visible light emitting panel light, the overall response rate (ORR) was 58.3% (7 of 12 patients) [11], utilizing surface area as the primary endpoint. This trial provided the initial proof-of-concept for topical hypericin ointment as a well-tolerated and effective therapy. The responses observed at hypericin concentrations of 0.1% and 0.25% (41.7% and 55.6%, respectively) were significantly greater than those seen in placebo-treated lesions ($p \leq 0.04$ for both).

2.2.2. FLASH phase III randomized clinical trial (study HPN-CTCL-01; NCT02448381)

This pivotal, multicenter, placebo-controlled, double-blinded study, conducted across 39 US centers, definitively established the efficacy and safety of topical synthetic hypericin ointment (0.25%) in adults with early-stage (IA-IIA) MF [12]. Patients ($n = 166$) were randomized (2:1) to receive either hypericin or placebo topically applied to three index lesions, followed by exposure to a visible light emitting panel light (starting at 5 J/cm^2 and increasing to a maximum of 12 J/cm^2) twice weekly. The primary endpoint was the response rate of the treated index lesions after one 6-week cycle, assessed using the modified Composite Assessment of Index Lesion Severity (mCAILS) score. The index lesion response rate was 16% in the hypericin group compared to 4% in the placebo group ($p = 0.04$). Response rates demonstrated cumulative improvement with extended treatment in subsequent

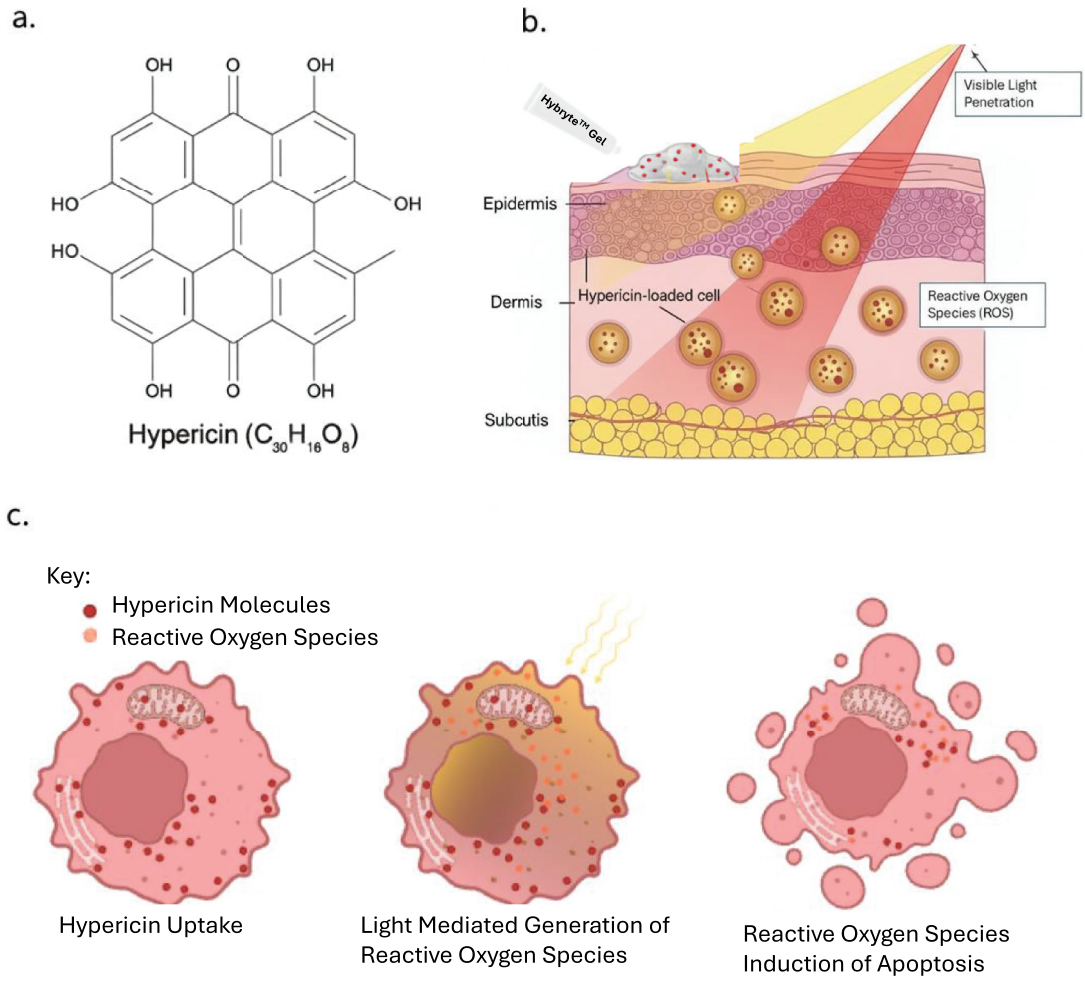

Figure 1. Structure and Function of Hypericin. a) Hypericin is a large polycyclic aromatic hydrocarbon with 8 fused rings. The structure gives it a dark red color and the potent ability to absorb visible light and generate reactive oxygen species. b) topical synthetic hypericin applied to the skin is absorbed into the epidermis and dermis and taken up by malignant T cells. Visible light in the yellow-red spectrum excites the drug. c) Hypericin is absorbed preferentially into malignant T-cells, where it is subsequently photoactivated by visible light (500–650 nm). Excited hypericin initially achieves a singlet state which then converts to a triplet state, which can interact with locally available oxygen, creating an excited singlet oxygen state that then creates reactive oxygen species. These reactive oxygen species subsequently cause localized cellular apoptosis, resulting in the targeted termination of the malignant T-cell.

Table 1. Clinical efficacy in early-stage CTCL/Mycosis Fungoides (MF).

Study (Identifier)	Phase	Design	Patient population	Key efficacy endpoint(s) & results	Key safety findings
VM-97–003	II	Placebo-controlled	12 patients with early-stage MF/CTCL	Overall Response Rate (ORR) at 6 weeks: 58.3% for hypericin vs. placebo. Statistically significant reduction in lesions ($p < 0.04$).	Well-tolerated with no significant adverse events reported.
FLASH (NCT02448381)	III	Multicenter, placebo-controlled, double-blind	166 adults with early-stage (IA-IIA) MF	Index Lesion Response Rate (mCAILS): Cycle 1 (6 wks): 16% vs 4% (placebo, $p = 0.04$) Cycle 2 (12 wks): 40% Cycle 3 (18 wks): 49%	Mild, transient local skin reactions were most common. No systemic absorption detected. Discontinuation rate of 1.2%.
HPN-CTCL-02 (NCT05380635)	IIa	Open-label, compatibility study	9 patients with early-stage MF (more extensive disease)	Improvement at 8 weeks: 36.4% mean improvement in cumulative mCAILS. 14.8% of lesions completely resolved.	Favorable safety profile confirmed. No clinically significant systemic absorption or impact on EKGs.
HPN-CTCL-04 (NCT06149247)	IIa (Pilot)	Open-label, comparative study	10 patients with stage IA-IIA MF	ORR at 12 weeks: 60% (3/5) for SGX301 vs. 20% (1/5) for mechlorethamine. Higher response in plaque lesions (62.5% vs 16.7%, $p = 0.024$).	No discontinuations in the SGX301 arm vs. one for severe dermatitis in the mechlorethamine arm.

open-labeled extension phases, increasing to 40% after two cycles (12 weeks) and 49% after three cycles (18 weeks) (Figure 2). Notably, responses were observed in both patch and thicker plaque lesions. The study also documented responses in a patient with folliculotropic mycosis fungoides, a more difficult to treat variant [15].

2.2.3. Compatibility study (HPN-CTCL-02; NCT05380635)

An open-label compatibility study evaluated the safety and efficacy of topical 0.25% hypericin ointment in nine patients with early-stage MF who were selected to have more skin extensive disease to better represent a real-world patient population [16]. After 8 weeks of twice-weekly treatment using light doses administered with a visible light emitting light starting at 5 J/cm^2 and increasing to a maximum of 20 J/cm^2, the overall response rate was 22%, with an average improvement of 36.4% in the cumulative mCAILS score (Figure 2). Furthermore, 25.9% of index lesions showed at least a 50% improvement, and 14.8% of lesions completely resolved. The study confirmed the therapy's favorable safety profile, with only low and limited levels of systemic hypericin detected and no observable impact on electrocardiograms (EKGs) [16].

2.2.4. Pilot study comparing to mechlorethamine (HPN-CTCL-04; NCT06149247)

An open-label pilot study directly compared topical synthetic hypericin with topical mechlorethamine gel (Valchlor®), a standard therapy, in stage IA, IB, and IIA MF patients [13]. Five participants utilized topical 0.25% hypericin ointment applied twice weekly, with light doses given with a visible light unit starting at 6 J/cm^2 and increasing to a maximum of 50 J/cm^2. Similarly, 5 participants applied mechlorethamine gel daily as per the package insert. Over 12 weeks, the ORR was 60% (3/5) in the topical synthetic hypericin group compared to 20% (1/5) in the mechlorethamine group, using a ≥50% improvement in the Baseline mCAILS score as the response metric. This study also highlighted a significantly higher percentage of lesion treatment response in plaque lesions for the participants receiving topical hypericin vs. those receiving mechlorethamine (62.5% vs 16.7%; $p = 0.024$), supporting its efficacy in more infiltrated lesions (Figure 2). Additionally, application site adverse events (AEs) were minimal for topical synthetic hypericin and more prominent for mechlorethamine, leading to treatment modifications and one study discontinuation in the mechlorethamine treated participants. Compliance was also notably higher with topical synthetic hypericin (97%) compared to mechlorethamine (67%), with no participants receiving mechlorethamine completing the treatment regimen as planned. Although the sample size was small, the potential advantages in topical hypericin treatment relative to mechlorethamine appeared to include more rapid onset of efficacy, improved compliance and reduced application site adverse events. These findings were consistent with the other studies described herein.

2.2.5. Ongoing study (HPN-CTCL-03-EUR; NCT06470451)

Currently, 18 weeks of treatment with topical synthetic hypericin gel (i.e., HyBryte™) is being evaluated in a second confirmatory Phase III study (FLASH2) with an interim analysis expected in the first half of 2026. Again, the determinant of response is a ≥50% improvement in Baseline mCAILS score. Confirmatory results will hopefully allow FDA and EMA to support future regulatory approval worldwide. This would lead to availability to patients outside of clinical trials.

2.3. Safety and tolerability

Across all clinical trials, topical synthetic hypericin has demonstrated a consistently favorable safety and tolerability profile. Including all completed clinical studies evaluating topical synthetic hypericin as a treatment for CTCL, 187 participants have been treated with topical hypericin. Current contraindications include severe allergic reaction to hypericin, photoactive conditions such as lupus or porphyria, and pregnant or breast-feeding women.

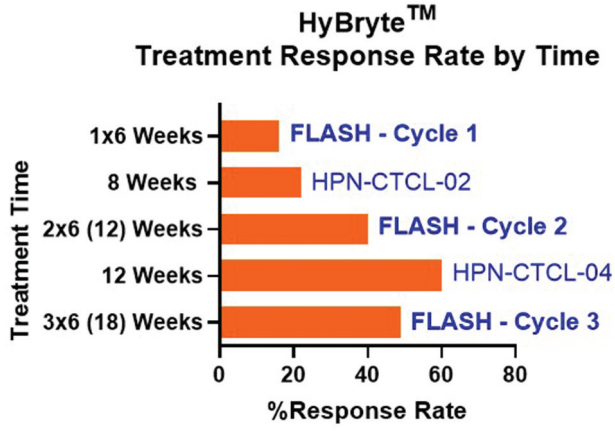

Figure 2. Summary of efficacy results obtained with the application of 0.25% topical synthetic hypericin twice weekly for various overall treatment times. Note that the results from the FLASH study include treatment interruptions, whereas the ongoing confirmatory double-blind, placebo-controlled Phase III study (FLASH2) utilizes continuous treatment.

2.3.1. Local skin reaction

The most common treatment-related adverse events (AEs) were mild, transient, local skin reactions at the application site, including pruritus, hyperpigmentation, burning, pain, and irritation. In the large FLASH study, these reactions were predominantly mild (23% of patients), with moderate AEs occurring in 9% (38 patients) and severe AEs in only 2% (3 patients) of all patients [12]. Crucially, these reactions were manageable and rarely led to treatment interruption [12,13,16].

2.3.2. Systemic safety

No drug-related serious AEs or deaths have been reported. No clinically meaningful changes in hematologic or clinical chemistry parameters, or vital signs, were observed [12]. A key safety feature is the lack of systemic absorption. Pharmacokinetic analyses showed no detectable hypericin in blood samples (detection limit 5 ng/mL), even after extensive treatment periods (up to 18 weeks, 36 applications) across multiple body regions [12]. This was confirmed in a dedicated safety study (NCT05380635) in patients with ≥10% body surface area involvement, where using a much more sensitive assay (detection limit 0.05 ng/mL), the average detected hypericin in the bloodstream was 0.13 ng/mL [16].

2.3.3. Comparison with other therapies

The safety profile of topical synthetic hypericin compares favorably to other standard SDTs. In the head-to-head pilot study with mechlorethamine, no subjects discontinued topical synthetic hypericin due to AEs, whereas one subject in the mechlorethamine arm discontinued due to severe contact dermatitis [13]. The SCORD (Scoring of Contact Dermatitis) system, developed to assess dermatitis from topical therapies like mechlorethamine [13,16], showed no moderate to severe dermatitis in the hypericin arm, while moderate-to-severe dermatitis was present in the mechlorethamine arm [13]. This superior tolerability also translated to better long-term patient adherence.

A more general comparison of tolerability of topical hypericin versus commonly used topical therapeutics in CTCL is presented in Table 2. The use of topical hypericin is more favorable in terms of both application site tolerability, reported adverse events and potential long-term toxicity.

3. Expert opinion

Topical synthetic hypericin represents a paradigm shift in the skin-directed management of early-stage CTCL. Its unique mechanism,

Table 2. Reported side effects of HyBryte and other approved skin-directed therapies.

Drug	Disease	Size	Dropouts 'Early'	Overall dropouts	Related side effects	Reference[a]
HyBryte drug (Topical Synthetic Hypericin)	IA, IB, IIA	116	5%	–	Severe AEs: 4% (1 related to drug): Abdominal pain; Gallbladder obstruction; Site pain during light therapy; Severe erythema; Invasive ductal breast carcinoma; pneumonia	Kim et al. [12]
HyBryte placebo	IA, IB, IIA	50	10%	–	Severe AEs: 2% (angioedema)	
Topical Bexarotene Gel	IA, IB, IIA refractory to ≥2 previous treatments	67	6%	NR	Treatment limiting toxic events: 24% Rash: 10% Pain: 7% Vesiculobullous rash: 3% Facial edema: 1% Neuralgia: 1% Skin necrosis: 1% Skin ulcer: 1%	Breneman et al. [17]
Topical Bexarotene Gel	IA, IB, IIA refractory to ≥2 other Rx	50	16%	94%	26% (moderate to severe) Irritant dermatitis: Rash 74% Pruritus 40% Pain 32% Skin disorder 26% Contact dermatitis 14% AEs requiring dose adjustment: 64% AEs leading to discontinuation: Directly: 6% Indirectly: 10% Hematologic AEs: Lymphocytopenia 11% Granulocytopenia: 4% Low CD4+ counts: 16% Hyper-triglyceridemia: 4% High glucose levels 11%	Heald et al. [18]
MCH ointment		130	NR	17%	Allergic contact dermatitis: 13% Local 'related' skin AEs: 50%	Lessin et al. [19]
MCH gel	IA, IB, IIA	130	NR	20%	Allergic contact dermatitis: 16% Local related skin AEs: 62%	Lessin et al. [19]

MCH = mechlorethamine.
[a]Source.

excellent safety profile, and robust clinical efficacy position it as a formidable new agent in the therapeutic armamentarium.

The most significant advantage of topical synthetic hypericin is its non-mutagenic mechanism of action. This provides a critical long-term safety advantage over PUVA phototherapy, which, despite its efficacy, induces DNA damage and carries a well-documented, persistent increased risk of developing non-melanoma skin cancers, including aggressive squamous cell carcinomas [20–22]. For a chronic disease like MF that often requires decades of management, minimizing iatrogenic cancer risk is of paramount importance.

Furthermore, topical synthetic hypericin addresses the primary limitation of topical mechlorethamine: tolerability. Mechlorethamine is associated with a high rate of contact dermatitis, which can be severe enough to force treatment discontinuation in a substantial portion of patients [13,19]. The mild and transient nature of local reactions to topical synthetic hypericin suggests it will be a much more patient-friendly option, likely leading to improved adherence and better overall outcomes.

Based on current evidence, topical synthetic hypericin is a robust option for patients with early-stage (IA-IB) patch and plaque MF, a position supported by the 2023 EORTC consensus recommendations [3]. Its ability to effectively treat plaque lesions, as suggested in clinical studies, is particularly noteworthy, as thicker lesions are often less responsive to other topical agents. Moreover, with a potential link between plaque lesions and disease progression being noted, plaque lesions are also considered a higher priority therapeutic target. The ability to target thicker lesions may also have implications for challenging variants like folliculotropic MF (FMF), where perifollicular infiltrates are deeper in the dermis. While systemic agents are often required for FMF, the deeper penetration of hypericin's activating light wavelength compared to UV light warrants further investigation of its potential role in this subtype.

While topical synthetic hypericin is an exciting novel therapy, some questions will only be answered with longer-term data, particularly regarding the durability of patient responses. Furthermore, the logistical requirement of twice-weekly, in-office light activation may pose an adherence or access challenge for some patients. Future innovations, such as the development of a safe and effective home-based light source, could significantly mitigate this barrier. Ultimately, real-world clinical experience following regulatory approval will be crucial for optimizing treatment protocols and fully defining this therapy's role.

Topical synthetic hypericin represents a major step forward in the skin-directed therapy of early-stage CTCL, directly addressing the critical unmet needs for safer and better-tolerated long-term treatments. Its novel, non-mutagenic mechanism of action provides a clear safety advantage over traditional phototherapies like PUVA, while its excellent tolerability overcomes the primary limitation of topical mechlorethamine. With substantial clinical data demonstrating efficacy in both patch and plaque-stage disease, topical synthetic hypericin is poised to become a first-line standard of care, offering patients an effective, patient-friendly option that significantly improves the therapeutic landscape and quality of life for this chronic malignancy.

Funding

This paper was not funded.

Disclosure statement

B Poligone and E Gilmore report having received research grants and consulting fees from Soligenix. B Poligone serves on the Medical Advisory Board for Soligenix, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

We wish to express our deepest gratitude to the participants of these studies and their families. Their commitment to the clinical trial process, including the frequent travel required for treatments, was essential to the completion of this research. The authors used Gemini 3 for proofreading and linguistic editing only. All scientific data interpretation and manuscript drafting were performed by the authors.

Declaration of generative AI in scientific writing

During the preparation of this work the authors used Gemini 3 exclusively for proofreading and minor grammatical corrections. All sentences revised by Gemini 3 were reviewed and verified by the authors. No content was generated by Gemini 3 or any other AI service. All scientific data interpretation and manuscript drafting were performed by the authors.

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