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ORIGINAL RESEARCH

Results from a Pilot Study of HyBryte™ (Topical Synthetic Hypericin) Versus Valchlor® (Mechlorethamine) in the Treatment of CTCL

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ABSTRACT

Introduction: Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma (CTCL), a malignant and chronic skin disease. Early-stage MF has a generally favorable prognosis, but effective and well-tolerated skin-directed therapies are crucial for management. HyBryte™ is a photodynamic therapy of topical hypericin that was recently shown to be well tolerated and efficacious in early-stage CTCL. Valchlor® (mechlorethamine) is an approved second-line therapy for use in early-stage CTCL after other topical therapies. This study compared Valchlor® to HyBryte™ following 12 weeks of treatment. The objectives in this study were (i) to obtain preliminary comparative assessment of safety and efficacy of Valchlor® versus HyBryte™ through 12 weeks of treatment, and (ii) to better understand the impact of HyBryte™ application on the measurement of modified Composite Assessment of Index Lesion Severity (mCAILS).

Methods: This was an open-label trial enrolling 10 patients with CTCL (stage IA, IB, or IIA) randomized 1:1 to receive topical HyBryte™ or topical Valchlor® for 12 weeks.

Results: The overall response rate (ORR, i.e., complete responders + partial responders) was 60% (3/5) in the HyBryte™ treatment group and 20% (1/5; not significant) in the Valchlor® treatment group over 12 weeks. HyBryte™ demonstrated no local adverse events at application sites, while 60% (3/5) of patients treated with Valchlor® had skin reactions, including one case which led to study withdrawal.

Conclusions: This is a single-center, open-label study. It is a pilot study requiring additional research to confirm its results. This study demonstrated the favorable safety and efficacy profile of HyBryte™ compared to Valchlor® in patients with CTCL. HyBryte™ showed higher treatment success rates and was better tolerated.

Trial Registration: ClinicalTrials.gov, NCT06149247; registered November 20, 2023.

Keywords: Cutaneous T-cell lymphoma (CTCL); Mycosis fungoides (MF); Hypericin; Valchlor; Lymphoma; Photodynamic therapy

Prior Presentation: Preliminary data only from this study was presented at the 2025 American Academy of Dermatology Annual Meeting in Orland, FL (March 7–11, 2025) during the Late-Breaking Research session.

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Key Summary Points

Why carry out this study?

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL), a chronic malignancy for which effective, well-tolerated skin-directed therapies are essential for long-term management.

While Valchlor® (topical mechlorethamine) is a standard treatment, its use is often limited by significant local skin reactions and treatment compliance issues.

This pilot study asked whether topical synthetic hypericin activated with visible light (HyBryte™) could provide a faster onset of action and superior tolerability compared to daily mechlorethamine over a 12-week treatment period.

What was learned from this study?

HyBryte™ demonstrated a significantly higher lesion response rate and was statistically significantly different in plaque-type disease (75.0% vs. 16.7%; $p=0.006$), with a faster median time to response compared to Valchlor® while maintaining a superior safety profile with no application site adverse events.

The findings suggest that the rapid clinical benefit and tolerability of HyBryte™ may enhance patient compliance and provide a more favorable benefit-risk ratio than mechlorethamine for early-stage CTCL lesions.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin's lymphoma in which malignant T-cells present as patches, plaques, and tumors. While early-stage disease constitutes a chronic, malignant skin disease with good overall survival and includes the majority of patients with CTCL, it can progress to systemic disease with significantly higher mortality. There are currently no identified risk factors or markers for disease progression. However, long-term studies have suggested that plaque disease/lesions, in particular, may be correlated with progression [1]. Most approved drugs for CTCL target late-stage disease in an attempt to ameliorate mortality. Nonetheless, early-stage disease has significant physical and mental health implications which can be addressed with treatment. Moreover, treatment is believed to suppress progression to systemic disease. Accurate staging and classification of disease are important using the TNMB (skin, lymph node, visceral/metastasis, and blood) classification system to better define patient prognosis and appropriate treatment options [2].

Skin-directed therapies (SDT) are considered the gold-standard treatment for early-stage mycosis fungoides (MF) [3]. Although there is no generally agreed upon "standard" SDT, the most common, approved treatment for early-stage CTCL in the USA is Valchlor® (topical mechlorethamine), a chemotherapeutic agent. Mechlorethamine, also known as nitrogen mustard, is an alkylating agent which inhibits rapidly proliferating cells [4, 5]. Treatment with Valchlor® is associated with significant local reactions, some of which are severe and can lead to treatment cessation. Additional problems include contact contamination of caregivers and family members as cautioned against in the package insert [5]. Treatment success rates with Valchlor® in its pivotal trial were 60%, albeit after continuous daily treatment timelines up to 12 months [4]. Furthermore, real-world usage, when concomitant medications were allowed, showed a response rate of 44% at 12 months and 67% at 18 months [6]. While altered treatment regimens have been introduced post-approval to minimize local and allergic skin reactions, these side effects remain a significant hindrance for the use of Valchlor® [7]. Available unapproved treatments for skin-directed disease such as psoralen and ultraviolet A light (PUVA) and narrowband ultraviolet B light are effective but induce DNA damage and increase the risk of keratinocyte carcinomas, melanoma, phototoxicity, skin damage, and photoaging [8].

Topical hypericin (HyBryte™) was recently demonstrated to be a potentially safer and

effective alternative as it is activated with visible light, which is non-carcinogenic [9, 10], and uses hypericin, which is non-mutagenic. Hypericin is a naturally occurring pigment found in *Hypericum* plants, of which St. John's Wort is most common [11]. Hypericin possesses a potent photosensitizing property. It exhibits maximal fluorescence spectroscopy absorption at approximately 545 nm and 590 nm (yellow/red light), a unique property relative to many other photodynamic therapies that require ultraviolet light. Upon exposure to visible light, hypericin efficiently generates reactive oxygen species (ROS). The generation of ROS ultimately leads to apoptosis of malignant T-cells. The antiproliferative and apoptotic effects of light-activated synthetic hypericin against malignant T-cells derived from patients with CTCL were first described by Fox et al. in 1998 [12]. Moreover, HyBryte™ has also demonstrated significant treatment success rates within 6 to 18 weeks in a Phase 3 clinical study [9], with very few application site reactions. However, comparative assessments of safety and efficacy of HyBryte™ relative to Valchlor® have not been done.

Both phototherapy and photodynamic therapy have been used in CTCL/MF [1]. Although not commonly prescribed in the USA, direct sunlight (including ultraviolet light) has been reported to be beneficial. Similarly, ultraviolet B light is also used (more commonly as a narrowband application). Finally, another photosensitizing agent (psoralen) is activated by ultraviolet A light. While all of these therapies have efficacy, particularly in patch disease, they all also have significant limitations due to the exposure to ultraviolet light, associated with risks for melanoma and skin aging.

A pilot study was conducted to obtain preliminary comparative assessments of safety and efficacy. The primary objectives in this study were (i) to obtain preliminary comparative assessment of safety and efficacy of Valchlor® versus HyBryte™ through 12 weeks of treatment, and (ii) to better understand the impact of HyBryte™ application on the measurement of mCAILS (modified Composite Assessment of Index Lesion Severity).

MATERIALS AND METHODS

Study Design and Procedures

A randomized, prospective, single-center study focused on stage IA, IB and IIA mycosis fungoides (NCT06149247) was performed comparing topical synthetic hypericin activated with visible light (HyBryte™) with topical mechlorethamine (Valchlor®). The study was approved by the WCG institutional review board (IRB) (Puyallup, Washington, USA). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The first patient was recruited on January 9, 2024. All members of the site team were trained on the protocol specifics, GCP, and safety reporting requirements. A total of 10 subjects were enrolled at the Rochester Skin Lymphoma Medical Group, PLLC located in Fairport, New York, USA.

Inclusion required adults ≥ 18 years, with ≥ 3 treatment evaluable CTCL lesions, a diagnosis of stage IA–IIA MF, and informed consent. Exclusion criteria included prior allergic response to study drugs, recent immunosuppressive therapy, photosensitive disorders, pregnancy, and significant comorbidities. Additionally, patients must have completed appropriate washout periods for prior CTCL therapies.

Figure 1 displays a schematic of the study schedule and procedures. Patients were randomized to receive either HyBryte™ or Valchlor® for a treatment period of 12 weeks.

HyBryte™ arm: Patients applied 0.25% synthetic hypericin twice weekly to all accessible lesions. Light treatment (starting at 6 J/cm^2) was administered 21 ± 3 h post-application with a Daavlin Series 7 Phototherapy Device equipped with visible light lamps. Light doses were adjusted or suspended depending on observed skin responses. Light doses were escalated at the physician's discretion by a maximum of 2 J/cm^2 at subsequent visits, targeting a post-light dose erythema score of 1. An erythema score of 2 or greater required the light dose to be maintained or reduced depending

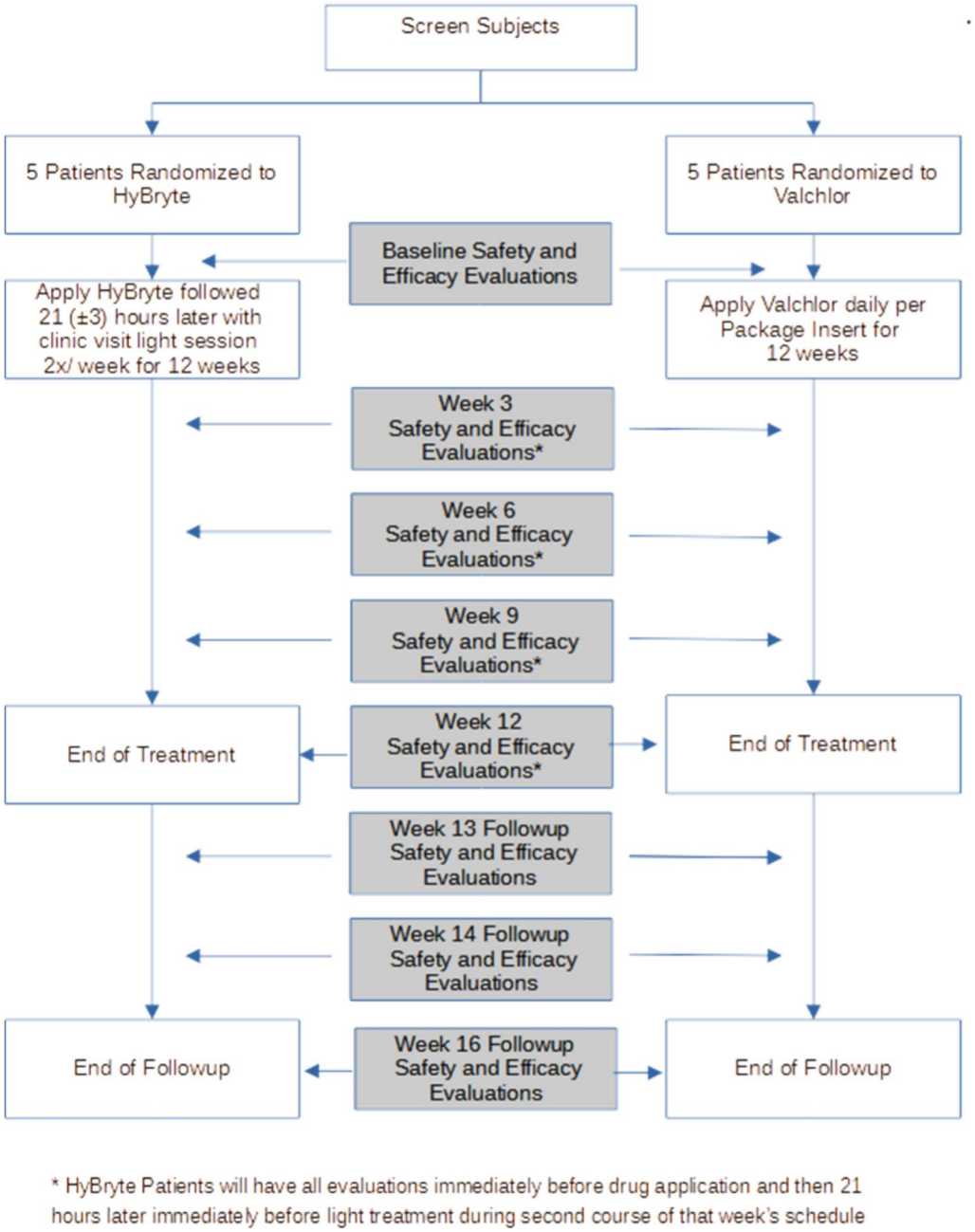

Fig. 1 Study schema

on severity of response. The maximum dose achieved per patient ranged from 30 to 50 J/cm^2, with no occurrences of grade 2 or higher erythema.

Valchlor® arm: Patients self-administered mechlorethamine (Valchlor®) per the US Food and Drug Administration (FDA)-approved package insert which involved applying a thin film of gel once daily to affected areas of the skin. Patients were advised to stop treatment with Valchlor® for any grade of skin ulceration, blistering, or moderately severe (e.g., marked skin redness with edema) or severe dermatitis (e.g., blistering). If the local side effects

improved, treatment with Valchlor® could have been restarted at a reduced frequency of once every 3 days. If reintroduction of treatment was tolerated for at least 1 week, the frequency of application could be increased to every other day for at least 1 week and then to once daily application, if tolerated.

Assessment schedule: Assessment visits were conducted every 3 weeks (baseline, weeks 3, 6, 9, 12) and at post-treatment follow-up (weeks 13, 14, and 16). Cumulative mCAILS scores of three to five index lesions [14], the modified severity-weighted assessment tool (mSWAT) [15], and physician global assessment (PGA) [16] were performed. These are known, validated tools that have been used as primary endpoints in CTCL studies [17, 18]. Safety measures included Skin Adverse Event Questionnaire (SAEQ), SCORD scoring (modified version of the Scoring Dermatitis (SCORAD) tool) [7], safety laboratory tests including hematologic and clinical chemistry results (baseline, week 12, and week 16 only), vital signs including resting blood pressure, heart rate and respiratory rate, and adverse events (AEs).

Efficacy Assessments

mCAILs, mSWAT, and PGA were performed as previously described and according to Olsen et al.'s criteria [18]. A patient was categorized as a success if they had a 50% or more reduction in the cumulative mCAILS score summed across index lesions compared to baseline. Lesions were also analyzed individually and lesion success was defined as having a 50% or more reduction in the individual lesion mCAILS score compared to baseline. Efficacy was also assessed using a ≥ 50% improvement from baseline in the mSWAT score, which estimates the percentage of body surface area (BSA) involved in disease, weighted by the severity of the lesion (patches, plaques, and tumors). The PGA was scored from 0 to 6 with treatment success defined as a score of 1 (nearly cleared from baseline) or 0 (completely cleared) [18]. The mSWAT and PGA scores were whole patient assessments that included both treated and untreated lesions.

Skin Adverse Event Questionnaire (SAEQ) Score

To assess differences in the tolerability of topical application of both therapies in this study, a SAEQ score was employed. The SAEQ was based on patient self-reported assessments of application site events over the previous 24 hr recorded using a visual analog scale (VAS) format for rash, tenderness, pain, burning, swelling, redness, blistering, and change in color. The VAS score was measured and reported as a number from 0 to 100 for each of the eight subscores.

SCORD Score

The SCORD tool is a modified version of the Scoring Atopic Dermatitis (SCORAD) tool. It was specifically designed to assess the degree and severity of dermatitis in patients with CTCL, particularly those undergoing mechlorethamine treatment [13]. As a validated tool, it allows for assessment of (1) the percentage of dermatitis in treated lesions, (2) the severity of dermatitis (redness, swelling, oozing/crusting, scratch marks, skin thickening, dryness), (3) and patient-reported itch (VAS_{itch}).

Statistical Analysis

No interim analysis was planned or conducted. All analyses were done in the intent-to-treat population, defined as all randomized patients that had at least one drug application. All patients received the drug to which they were randomized. Comparative assessment of efficacy of Valchlor® versus HyBryte™ through 12 weeks of treatment was assessed. Since the study's main focus was not efficacy, the sample size was not mathematically determined. Categorical variables were compared using the

Fisher's exact p value (all tables had at least one expected cell with $n < 5$) and continuous variables were compared with a Student's t test. Graphs and calculation of p values were completed with GraphPad Prism v. 10.5.0.

RESULTS

Ten patients were enrolled, all of whom completed the study up until the 10th week of follow-up. The characteristics are shown in Table 1. Fifty percent (5/10) were male. Nine patients (90%) were White and 1 (10%) was Black; none considered themselves Hispanic or Latino. The mean age was 59.3 years with a standard deviation [SD] of 16.86 (range 32–86 years). All had stage IB disease, with a mean of 3.7 prior therapies (SD 2.19, median 3.5, and range 0–7). The disease-involved BSA ranged from 4% to 71%, with an average of 35% and a SD of 22.59% in the Valchlor® treatment group, and an average of 34% and a SD of 24.81% in the HyBryte™ treatment group.

Treatment Response

mCAILs

Patients receiving HyBryte™ had higher ORR compared to those receiving Valchlor® treatment (60% vs. 20%, NS) over the 12 weeks of the study. Comparison of the treatment group's time to response (as measured by mCAILS) is shown in Fig. 2. The comparison of the curves using log-rank (Mantel-Cox) p value is 0.515.

In individual index lesions, there was an increase in the number of individual lesions achieving success through week 16 in the HyBryte™-treated group (72.2%) compared to the Valchlor® group (33.3%; $p = 0.044$) as shown in Table 2. By week 12, an equal number of

Table 1 Enrolled subject characteristics

Characteristic	Distribution	
Sex ($N = 10$)	Male: 50%	Female: 50%
Race ($N = 10$)	White: 90%	Black: 10%
Ethnicity ($N = 10$)	Not Hispanic or Latino: 100%	
Age ($N = 10$)	Mean (SD): 59.3 (16.86)	Median (range): 62 (32–86)
Disease stage ($N = 10$)	1B: 100%	
Number of prior therapies		
HyBryte ($N = 5$)	Mean (SD): 4.0 (2.45)	Median (range): 4 (0–7)
Valchlor ($N = 5$)	Mean (SD): 3.4 (1.85)	Median (range): 3 (1–6)
Time from initial diagnosis (years)		
HyBryte ($N = 5$)	Mean (SD): 12.8 (10.54)	Median (range): 10.1 (0.08–31.74)
Valchlor ($N = 5$)	Mean (SD): 5.8 (4.28)	Median (range): 3.6 (2.01–14.03)
Baseline mCAILS score		
HyBryte ($N = 5$)	Mean (SD): 42 (16.6)	Median (range): 37 (26–74)
Valchlor ($N = 5$)	Mean (SD): 33 (22.3)	Median (range): 18 (11–66)

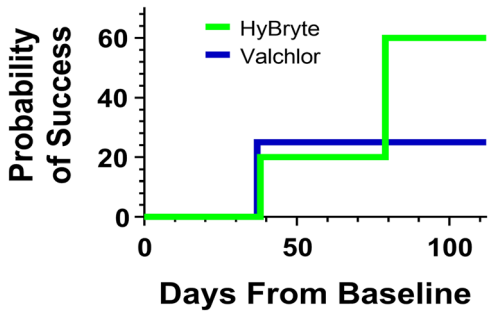

Fig. 2 Kaplan–Meier curve of treatment successes by mCAILS. mCAILS values were determined every 3 weeks. Patients were considered a treatment success if their cumulative baseline mCAILS score decreased by at least 50% at any timepoint

Table 2 Lesion mCAILS response at 16 weeks

Measurement	Responders		
All lesions	**HyBryte**	**Valchlor**	**Fisher's exact *p* value**
N[a]	18	18	
n[b]	13	6	
(% *n*/*N*)	(72.2%)	(33.3%)	0.044

[a] Number of Lesions in group

[b] Number of lesions that were classified as "Treatment Success"

Lesion responses were determined through 4 weeks of follow-up. A lesion treatment success was defined as ≥ 50% improvement of the baseline mCAILS lesion score. *N* represents the number of lesions in the group and *n* represents the number as lesions classified as having a treatment response

lesions (16.7%) had a complete response in the HyBryte™ and Valchlor® groups with an increase in the HyBryte group at week 16 (33.3%, NS).

The 36 individual index lesions (18 lesions in each treatment arm) were classified as either "patch" or "plaque", as defined by the lesion elevation subscore of the baseline mCAILS evaluation. By the end of the study (week 16), there was a higher percentage of lesion response rate in plaque lesions in the HyBryte™ group (75.0%) compared to the Valchlor® group (16.7%; $p = 0.006$). Similarly, by the end of study (week 16), there was a higher percentage of lesions achieving a complete response among plaque lesions in the HyBryte™ group (31.3%) compared to the Valchlor® group (0%; NS). Among patch lesions, the frequency of lesion response rate of the HyBryte™ group was 50% (1 of 2 lesions) and the Valchlor® group was 66.7% (4 of 6 lesions; NS). The frequency of lesion complete response in patch lesions was 50% in both groups. As observed in the patient response rate, the individual lesion response rate was generally faster in the hypericin-treated lesions at end of treatment (week 12), particularly in the more highly represented plaque lesions (Fig. 3).

mSWAT

One patient in each treatment group achieved a 50% reduction their baseline mSWAT score. The differences in outcome in this assessment

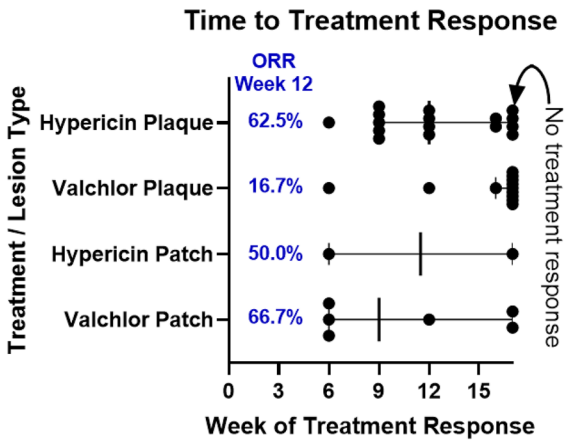

Fig. 3 Lesion treatment response time by lesion subtype and treatment group. Time to treatment response is displayed where response is defined as a ≥ 50% decrease in the baseline mCAILS score for each lesion. Lesion type was defined by the assessed baseline elevation score where elevation > 0 was defined as plaque and elevation = 0 was defined as patch. Where no lesion response was seen by the end of follow-up (week 16), the time to response was censored at 17 weeks. The overall response rate (ORR) by week 12 (end of treatment) is shown for each lesion type and treatment group. The bar and line indicate the median and 95% confidence interval of the time to response in each group.

compared to the mCAILS reflects that three of the five patients receiving HyBryte™ did not treat all their lesions, notably lesions on their face, hands, and feet; these untreated lesions were nonetheless included in all mSWAT scores. Moreover, the mSWAT essentially measures only involved surface area and lesion type whereas the mCAILS assesses other, critical characteristics of the lesion including elevation, erythema, and scaling. All patients receiving Valchlor® treated all their lesions.

PGA

By week 16, 20% of each group (1/5) achieved completely clear or almost clear (NS) as assessed by PGA.

Safety/Adverse Events

A total of eight TEAEs (treatment-emergent adverse events) were reported from five patients. These are listed by System Organ Class (SOC) and treatment group in Table 3. All of the application site TEAEs were reported from patients receiving Valchlor® and all were judged to be "related" to Valchlor®. One patient had contact dermatitis and withdrew from Valchlor® treatment. No administration site TEAEs were reported in the HyBryte™ group. The three TEAEs reported in the two patients in the HyBryte™ group were unrelated to the study drug (one patient contracted COVID-19 and reported an associated lymphadenopathy with the infection and one patient reported neck pain following trauma). Complete blood counts with a differential along with a complete metabolic panel was done in all subjects. No clinically

Table 3 Occurrence of adverse events

System Organ Class Preferred Term	HyBryte ($N=5$) *n* (%)	Valchlor ($N=5$) *n* (%)
Patients with at least 1 reported TEAE	2 (40%)	3 (60%)
Blood and lymphatic system disorders	1 (20%)	0 (0%)
Swollen lymph nodes	1 (20%)	0 (0%)
General disorders and administration-site conditions	0 (0%)	3 (60%)
Allergic contact dermatitis	0 (0%)	1 (20%)
Dermatitis	0 (0%)	1 (20%)
Rash	0 (0%)	1 (20%)
Sensitivity	0 (0%)	1 (20%)
Infections and infestations	1 (20%)	0 (0%)
COVID-19 infection	1 (20%)	0 (0%)
Musculoskeletal and connective tissue disorders	1 (20%)	0 (0%)
Neck pain/inflammation	1 (20%)	0 (0%)
Skin and subcutaneous tissue disorders	0 (0%)	1 (20%)
Id reaction	0 (0%)	1 (20%)

Treatment emergent adverse events (TEAEs) were captured for all patients from baseline through end of study. All events were classified by System Organ Class (SOC) and Preferred Term (PT). Only categories with at least one occurrence are listed in the table

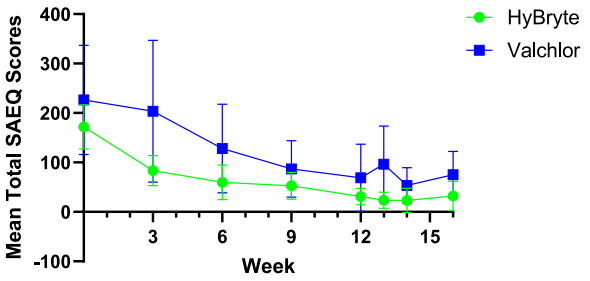

Fig. 4 Mean SAEQ scores over time. Mean and standard deviation for the sum of all SAEQ (Skin Adverse Event Questionnaire) questions in the HyBryte ($N=5$) and Valchlor ($N=5$) treatment groups

significant abnormalities were found throughout the study. No significant abnormalities were noted in the vital signs (heart rate, respiratory rate, and blood pressure) collected at each study visit (data not shown).

As shown in Fig. 4, the total SAEQ scores dropped more rapidly in the HyBryte™-treated group compared to the Valchlor®-treated group although none of the timepoints were statistically significant. The SAEQ subscores, in general, showed similar trends. Patient 01-004 developed severe contact dermatitis associated with Valchlor® therapy. The patient's SCORD score at week 3 was 44.6, which would indicate moderate to severe contact dermatitis. None of the HyBryte™-treated patients had an elevated SCORD score during the study.

Comparing HyBryte™ to Valchlor®

The comparison between HyBryte™ and Valchlor® treatments had to be unblinded because of their fundamentally different application methods. HyBryte™ requires light exposure twice weekly in the clinic, while Valchlor® is a daily topical treatment that can be applied at home. During this trial, HyBryte™ demonstrated improved efficacy compared to Valchlor® over the 12-week treatment period. Additionally, application site AEs were minimal for HyBryte™ and more prominent for Valchlor®, leading to treatment modifications and one discontinuation in the patients receiving Valchlor®.

Compliance was also notably higher with HyBryte™ (97%) compared to Valchlor® (67%), with no Valchlor®-treated patients completing the treatment regimen as planned (i.e., a total of 24 HyBryte treatments and 84 Valchlor treatments per plan). The alignment of treatment schedules also presented an inherent difficulty in maintaining balance. HyBryte™-treated patients came into the clinic twice per week for light therapies, whereas the Valchlor® application was done at home and required fewer visits to the clinic. Even with these notable differences, however, compliance with HyBryte™ application schedules was superior to Valchlor®.

By the end of treatment, there was a higher percentage of lesion successes in plaque lesions in the HyBryte™ group (62.5%) compared to the Valchlor® group (16.7%; $p=0.024$).

Impact of Timing on the Ease of Measuring mCAILS During Treatment

The active ingredient of HyBryte™, hypericin, is naturally dark purple in color. Because of this, it was possible that erythema assessment of lesions for the mCAILS could be confounded by any staining due to the application of HyBryte™, as well as by any flushing/erythema engendered by the light treatment itself. Therefore, a comparison of the mCAILS score on a per lesion and cumulative basis, as assessed before drug application and before light treatment for the first three patients at the week 3 drug application and light treatment visits was performed. As shown in Table 4, these evaluations revealed no substantive difference in the erythema assessments between before and after application. Dermatological assessment of each patient before and after light treatment also did not change.

DISCUSSION

Patients receiving HyBryte™ demonstrated higher ORR compared to those receiving Valchlor® treatment (60% vs. 20%, NS) over the 12 weeks of the study. The safety profile also appeared to favor HyBryte™. None of the HyBryte™ recipients reported application

Table 4 mCAILS assessment prior to drug application and prior to subsequent light treatment at the week 3 treatment visit

Patient ID	Timepoint	L1	L2	L3	L4	L5	Total	Change (%)
01-001	DA	12	13	14	15	15	69	− 2 (− 3%)
	LT	12	12	14	15	14	67	
01-002	DA	4	13	15	6	NA	38	0
	LT	4	13	15	6	NA	38	
01-005	DA	15	6	4	NA	NA	25	+ 1 (4%)
	LT	14	7	5	NA	NA	26	

Index lesions were assessed with mCAILS prior to drug application (DA) and after drug application but prior to light treatment (LT) to assess the potential impact of drug staining on the assessment. The change is calculated as the score at DA minus the score at LT, and the %change is calculated relative to the score at DA

NA not applicable

site AEs whereas those in the Valchlor® group reported administration site AEs (including a dropout due to severe administration contact dermatitis), which is consistent with published Valchlor® data [4]. As CTCL is a chronic long-term condition that may require decades of treatment over a patient's life, the importance of the safety profile for therapy options cannot be overstated.

In comparative terms, the quicker onset of action and lower AE rate of HyBryte™ could lead to higher dropout rates in the Valchlor® group in a larger study, particularly since study blinding is not feasible. This imbalance further complicates comparative studies. Moreover, the recommended use duration of HyBryte™ is 18 weeks per course, rendering any comparison beyond that timeframe less meaningful. These findings suggest that a short-term, active-controlled trial comparing Valchlor® to HyBryte™ may not be justified, given the unfavorable benefit–risk ratio associated with Valchlor® in this timeframe.

These results align with previously published data on each drug. HyBryte™ had a 60% ORR similar to the published 40% rate after 12 weeks of therapy from HPN-CTCL-01 [13] that used a less aggressive treatment (lower light levels and treatment interruptions for assessments) than this trial while the 20% rate in the Valchlor® group is similar to the 22% rate estimated from the phase 3 Valchlor® study Kaplan–Meier plot [4].

The limitations of this study included being a single-center, open-label study. The analyzed cohort of patients is limited to 10 patients and the sample size was not based on a statistical power calculation. A Phase 3 placebo-controlled, randomized clinical trial is ongoing (NCT06470451) to further assess the treatment benefits with 18 weeks of continuous HyBryte™ treatment.

While not addressed in the current study, future studies could evaluate HyBryte™ treatment with in-office PDT compared to daylight (sunlight) PDT. Activation of HyBryte™ with sunlight could allow patients to better access PDT and could improve therapy acceptance; however, this would be offset by the increased exposure to the UV component of sunlight and the reduced ability to control light intensity to ensure optimal activation of hypericin.

CONCLUSION

This early indication of treatment benefit is especially important in the CTCL landscape as patients using currently approved drugs often discontinue therapy because of lack of

improvement in the initial months of treatment—before most of the drugs' beneficial effects are observed. The rapid benefit of HyBryte™, compared to Valchlor®, may be clinically important if it provides motivation for patients to continue therapy due to observable benefit. The earlier resolution of lesions has also been shown to correlate with symptomatic resolution, which highlights the importance of quicker response times for patients. Moreover, given the link between disease progression and plaque lesions [1, 3], the effectiveness of HyBryte™ against plaque lesions is clinically meaningful. The findings of this trial reinforce the potential of HyBryte™ as a well-tolerated and effective treatment for CTCL. A phase 3 placebo-controlled, randomized clinical trial is ongoing (NCT06470451) to assess the treatment benefits with 18 weeks of continuous HyBryte™ treatment.

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Data Availability. The data that support the findings of this study are openly available in ClinicalTrials.gov, NCT06149247.

Declarations

Conflict of Interest. Mr. Adam Rumage and Drs. Christoper Pullion, Richard Straube, Oreola Donini and Christopher Schaber are employed by Soligenix. Dr. Elaine S. Gilmore reports research grants and consulting fees from Soligenix. Dr. Brian Poligone reports research grants and consulting fees from Soligenix, and serves on the Medical Advisory Board for Soligenix, Inc.

Ethical Approval. The study was approved by the WCG institutional review board (IRB) (Puyallup, Washington, USA). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All patients in this manuscript have given written informed consent for participation in the study and the use of their de-identified, anonymized, aggregated data and their case details for publication.

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