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ORIGINAL ARTICLE

JEADV CLINICAL PRACTICE

Compatibility study of topical 0.25% hypericin (HyBryte™) application in subjects with mycosis fungoides: Results of the HPN-CTCL-02 study

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Abstract

Background: HyBryte™ is a photodynamic therapy of topical hypericin that has recently been shown to be safe and efficacious in early stage cutaneous T-cell lymphoma (CTCL). However, its efficacy, absorption, and effect on heart function parameters in patients who require greater HyBryte™ exposure is unknown.

Objectives: The primary objectives in this study were to assess hypericin blood levels using a validated detection method with a cut-off value of 0.05 ng/mL and to determine if topical HyBryte™ induces any electrocardiogram (EKG) changes during 8 weeks of treatment. A secondary endpoint of this study was to assess the effectiveness of HyBryte™ in this patient population as well as assessing a different additional light device than the one used in the Phase 3 HPN-CTCL-01/fluorescent light activated synthetic hypericin trial also entitled "A phase 3 multicenter randomised placebo-controlled study to determine the efficacy of topical hypericin and light irradiation for the treatment of cutaneous T-cell lymphoma".

Methods: A confirmatory, prospective, open-label, single-centre, interventional study focused on stage IB and IIA mycosis fungoides with more than 10% of their body surface areas involved was performed.

Results: Hypericin concentration in K_2EDTA whole blood samples collected before and after light activation at Weeks 4, 6 and 8 showed an average blood concentration of 0.13 ng/mL and achieved steady state by Week 4. EKGs were examined for clinical changes at each study visit, including changes in QT intervals and correction of heart rates. No significant clinical changes in EKGs were observed.

Conclusions: Hypericin does not appear to be significantly absorbed through the skin nor cause significant cardiac changes overall or prolong the QT interval when applied topically. A larger study is necessary to clearly define these results.

KEYWORDS
CTCL, cutaneous T-cell lymphoma, electrocardiogram changes, photodynamic therapy, pharmacokinetic, topical hypericin, QT prolongation

INTRODUCTION

Hypericin is a naturally occurring pigment found in *Hypericum* plants, of which St. John's Wort is most common. The antiproliferative and apoptotic effects of synthetic hypericin against malignant T-cells derived from patients with cutaneous T-cell lymphoma (CTCL) were first described by Fox et al in 1998.[1] Hypericin induces the production of reactive oxygen species that oxidise tryptophan imidazole groups in proteins and fatty acids when activated by light in the 530–600 nm wavelength.[2,3] CTCL is a slowly progressing, incurable type of non-Hodgkin's lymphoma that affects the skin, blood, lymph nodes, and viscera. Mycosis fungoides (MF) is the most common subtype and often requires long-term therapy.

Available treatments such as Psoralen and ultraviolet light A and narrow band ultraviolet B light are highly effective but induce DNA damage and increasing the risk of keratinocyte carcinomas, melanoma, phototoxicity, skin damage and photoaging.[4] Topical hypericin (HyBryte™) has recently been demonstrated to be a potentially safer and more effective alternative as it uses visible light, which is nonmutagenic.[5,6] However, data on the systemic absorption of hypericin from HyBryte™ photodynamic therapy in CTCL patients has been limited.

During the conduct of the fluorescent light activated synthetic hypericin (FLASH) clinical study,[5] systemic hypericin blood concentrations were measured in 29 patients at the time of maximum exposure to HyBryte™ therapy. Using a validated method with a detection limit of 5 ng/mL, no hypericin levels were detected in the blood. However, it is uncertain if a lower detection limit could change this outcome. Thus, the primary objectives in this study were twofold: (1) to assess hypericin blood levels with a minimal detection level of 0.05 ng/mL and (2) any electrocardiogram (EKG) changes during 8 weeks of treatment in MF patients who require an extensive application of HyBryte™. The secondary endpoint of this study was to assess the effectiveness of HyBryte™ using a different light device than the one used in the FLASH trial.

MATERIALS AND METHODS

To achieve these goals, a confirmatory, prospective, open-label, single-centre, interventional study focused on stage IB and IIA MF patients with more than 10% of their body surface areas (BSA) involved (NCT# 05380635) was performed. The first patient was recruited on 10 May 2022 after obtaining institutional review board approval. The procedures were conducted in accordance with the ethical standards of the Western Institutional Review Board committee, the Helsinki Declaration of 1975, as revised in 1983, and the Guidelines for the Monitoring of Clinical Investigations presented in the ICH Guidance on Good Clinical Practices (GCP). All members of the site team were trained on the protocol specifics, GCP, and safety reporting requirements. A total of nine evaluable subjects were enroled at the Rochester Skin Lymphoma Medical Group, PLLC located in Fairport, NY.

Eligible subjects were adults (≥18 years old) capable of providing voluntary consent and adhering to protocol instructions. Pregnant or nursing females, individuals with hypersensitivity to HyBryte™ or its components, a history of sun hypersensitivity, photosensitive dermatosis and a spontaneous evolving disease were excluded from the study. Additionally, patients must have completed appropriate washout periods for prior CTCL therapies, have no history of systemic immunosuppression, and refrain from using photosensitising drugs within 2 weeks of starting HyBryte™ treatment.

Figure 1 displays flow-chart of the study schedule and procedures. Subjects applied HyBryte™ (manufactured by Cambrex, Mirabel) 18–24 h before biweekly light treatments with a Daavlin Series 7 Phototherapy Device with visible light lamps for 8 weeks. Light treatments could not be done on two consecutive days of the week. Light doses started at 5 J/cm^2 and individually titrated up at each visit until either subjects developed a Grade 1 erythema or reached a light intensity of 25 J/cm^2, whichever occurred first. Titration of light doses was not dependent of Fitzpatrick skin type or lesion type. Light treatments could be administered to multiple affected areas, with shielding for previously treated areas. Blood samples and 12-lead EKGs were obtained at Baseline, Week 4, Week 6, Week 8 (end of treatment), and Week 10 (2 week follow-up). Safety assessments at Baseline, Week 8, and follow-up included complete blood counts with platelet count and differential, a basic metabolic panel, and vital signs such as resting blood pressure (mmHg), heart rate, and respiratory rate. Laboratory assessments were conducted at ACM Laboratories (Rochester, NY). Concomitant medications received and any adverse events experienced during a subject's enrolment in the study and within 14 days of the last drug application were recorded.

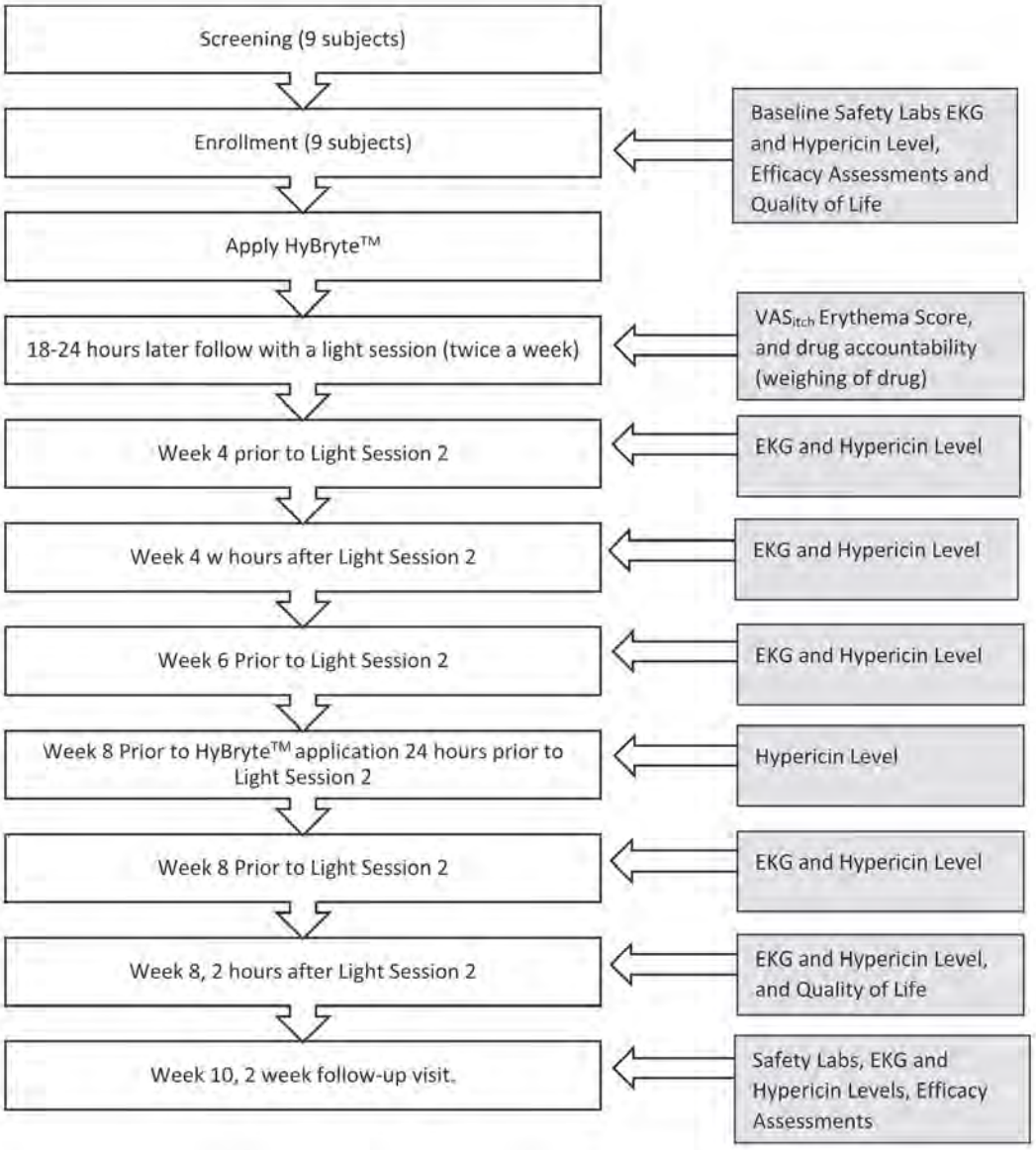

FIGURE 1 Study schema.

Efficacy assessments

Cumulative modified Composite Assessment of Index Lesion Severity (mCAILS) scores of three index lesions,[7] the modified Severity-Weighted Assessment Tool (mSWAT),[8] and Physicians Global Assessment (PGA)[9] were done to determine response after an 8 week course of therapy. These are well-studied tools used as primary endpoints in CTCL studies.[10]

For mCAILS, a lesion response was defined as having a 50% or more reduction in its individual CAILS score. A patient response, which is reported herein, was defined as having a 50% or more reduction in the cumulative mCAILS score sum for all three index lesions chosen. The treatment response was also quantified with the mSWAT, which estimates the percentage of BSA involved and assignes weights to patches, plaques, and tumours to calculate a score. Response criteria have been described elsewhere.[11] The PGA was scored from 0 to 6 with zero meaning complete clearance of disease, was assessed at Week 10/End of Study.[7]

Itch

To assess changes in pruritus over 24 h, a visual analogue scale for itch (VAS_{itch})[12] was administered, and a shift analysis compared it to Baseline. Itch severity was categorised as no itch (score 0), mild itch (score >0 and <3), moderate itch (score ≥3 and <7), and severe itch (score ≥7).

Electrocardiograms

To measure HyBryte's™ effect on the heart, site personnel were trained to evaluate EKGs for interval changes. EKGs were performed at Baseline, Week 4, Week 6, and Week 8 immediately before light treatments. EKGs were also obtained at Week 4 and Week 8 2 h postlight session, with another EKG at the Week 10 follow-up. Heart rate-corrected QT intervals were calculated using Bazett's formula[13] and Fridericia's Formula.[14]

Pharmacokinetics

Hypericin serum levels were measured at several timepoints: Baseline (before drug administration), before and at 2 h after the Week 4 Session 2 light treatment, immediately before the Week 6 Session 2 light treatment, before drug application, 2 h after the Week 8 session, and at the Week 10/End of Study follow-up visit. Blood was collected in K_2EDTA, chilled, transferred to 2 mL amber vials and frozen at −20°C. These were sent to Syneos (a central laboratory) for measuring blood hypericin levels using a validated LC/MS-MS method with a minimum quantification range of 0.05 ng/mL.

Statistical analysis

No interim analysis was conducted. All patients completed the study. Based on prior preclinical results and the HPN-CTCL-01 study,[5] hypericin levels were expected to remain very low. The results of this study are descriptive in nature. Since the study's main focus was not efficacy, the sample size was not mathematically determined. Averages with standard deviations, and median ranges were tabulated for each assessment score. The absolute and percent change from Baseline (% reduction) in mSWAT scores was also calculated. A shift analysis was done for VAS scores relative to Baseline. All patient data available for each patient was included in each analysis. No inferred or derived data was used for missing data.

Results

Nine patients were enroled, all who completed the study up until the 10th week of follow-up. Subject characteristics are summarised in Table 1. Fifty six percent (5 out of 9) were male. The majority were Caucasian (8 patients, 89%) and 1 (11%) of the nine patients was Black; none considered themselves Hispanic or Latino. The mean age was 62+/−8 years (range 52–73 years). Most had Stage IB disease (seven patients, 78%), with a mean of five prior therapies (standard deviation (SD) 2, median 6, and range 2–6).

TABLE 1 Characteristics of subjects enrolled.

	Number of subjects (n = 9)
Sex	
Male	5
Female	4
Race	
Caucasian	8
Black	1
Ethnicity	
Not Hispanic or Latino	9
Age (years)	
Mean (SD)	62 (8)
Median (range)	62 (52-73)
Disease stage	
IB	7
IIA	2
Prior therapies received (#)	
Mean (SD)	5 (2)
Median (range)	6 (2-6)
Time from initial diagnosis (years)	
Mean (SD)	9 (4)
Median (range)	8 (3-15)
Baseline CAILS Score	
Mean (SD)	42 (16)
Median (range)	43 (23-70)
Estimated baseline body surface area with lesions (based on mSWAT)	
Mean (SD)	27% (20%)
Median (range)	18% (11%-65%)

Abbreviation: SD, Standard deviation.

Treatment response

When assessing response in target lesions after 8 weeks of treatment, two (22%) of the nine patients had a 50% or more improvement in their cumulative mCAILS score (Table 2). Seven lesions (26%) of the 27 treated had ≥50% improvement in their mCAILS score after 8 weeks of treatment. Complete treatment response (cumulative mCAILS score of 0 at 10 weeks) was reported in 1 (11%) of the nine patients and in 4 (15%) of the 27 index

TABLE 2 Composite assessment of index lesion severity (CAILS) scores at baseline and week 10.

	Baseline				Week 10					
Patient	Index lesion #1	Index lesion #2	Index lesion #3	*Cumulative total*	Index lesion #1	Index lesion #2	Index lesion #3	*Cumulative total*	Change from baseline (%)	Pt. Responder?[a]
01-001	16	17	24	*57*	13	17	17	*47*	−18%	N
01-002	18	15	10	*43*	13	14	9	*36*	−16%	N
01-003	16	18	17	*51*	5	5	17	*27*	−47%	N
01-004	6	9	9	*24*	5	7	8	*20*	−17%	N
01-005	8	6	9	*23*	5	0	3	*8*	−65%	Y
01-006	15	14	6	*35*	0	0	0	*0*	−100%	Y
01-007	8	7	11	*26*	7	4	9	*20*	−23%	N
01-008	16	14	20	*50*	16	14	16	*46*	−8%	N
01-009	27	32	11	*70*	17	18	11	*46*	−34%	N
Average (SD)				*42 (16)*				*28 (17)*	−36 (30)	
Med. (Min, Max)				*43 (23, 70)*				*27 (0, 47)*	−23 (−100, −8)	

Abbreviations: Med, median; Min, minimum; Max, maximum; SD, standard deviation.

[a]Responder, ≥50% decrease in the cumulative CAILS score.

lesions. Similar responses were observed for patches and plaques (25% vs. 28%, respectively). The average cumulative mCAILS score at Baseline was 42+/−16 (range 23-70) versus 28+/−17 (range 0–47) at 10 weeks, indicating an average percent reduction of 36+/−30 points (range −100, −8).

The average mSWAT score at Baseline was 33+/−30 (range 11–98) and reduced to 26+/−27 (range 1–79) at Week 10 (Table 3). The average point reduction from Baseline was −8+/−5 (range −19 to −2) with a percent reduction of −32%+/−26% (range −92% to −5%). The median improvement was 29%. One (11%) of the nine patients met partial response criteria on the skin with a 92% change from Baseline. One patient had a complete resolution of their plaques, and another one experienced over a 50% reduction in their Baseline plaque mSWAT scores (data not shown).

The average PGA at Week 8 was a moderate improvement. Four (44%) of the nine patients had at least a moderate improvement of ≥25% but <50%, two (22%) of the nine patients had marked improvement, with a ≥50% improvement but <90%, one (11%) of the nine patients F was almost clear with a ≥90% improvement but <100%, and none was clear with no evidence of disease.

TABLE 3 Modified severity weighted assessment tool (mSWAT) scores.

Patient	mSWAT Score		
Lesion area	Baseline	Week 10	Change from baseline (% reduction)
01-001	*68.5*	*62.5*	*−6 (9%)*
01-002	*30.5*	*29*	*−1.5 (5%)*
01-003	*98*	*79*	*−19 (19%)*
01-004	*14.5*	*9.5*	*−5 (35%)*
01-005	*17*	*9.5*	*−7.5 (44%)*
01-006	*12*	*1*	*−11 (92%)*
01-007	*24*	*17*	*−7 (29%)*
01-008	*11*	*9*	*−2 (18%)*
01-009	*25.5*	*15.5*	*−10 (39%)*
Total Score (n = 9)			
Average (SD)	*33 (30)*	*26 (27)*	*−8 (5) (−32% ± 26%)*
Med (Min, Max)	*24 (11, 98)*	*16 (1, 79)*	*−7 (−19, −2)(−29% (−92%, −5%))*

Abbreviations: Med, median; Max, maximum; Min, minimum; SD, standard deviation.

Pruritus

VAS itch scores were collected at each visit (Table 4). One patient reported no itch (01-008), six of the nine had mild itch (a score greater than zero but less than three), one patient (001-007) had moderate itch (a score greater than three but less than seven) and one patient (001-009) had severe itch (a score >7). However, many patients had

TABLE 4 Vas itch scores per patient per visit.

Time	Patient									Average (SD)	Med. (Min, Max)
	01-001	01-002	01-003	01-004	01-005	01-006	01-007	01-008	01-009		
Baseline	0.4	0.7	6.9	1.5	0.7	0.7	5.8	0	6.5	2.6 (2.91)	0.7 (0, 6.9)
Week 1/Session 1	0.4	0.8	2.6	0.2	0.7	1.1	6.4	0	6.3	2.1 (2.55)	0.8 (0, 6.4)
Week 1/Session 2	0.8	0.9	2.9	ND	1	1.7	7.3	0	5	2.5 (2.51)	1.4 (0, 7.3)
Week 2/Session 1	0.6	0.7	1.8	0.3	0.9	5.1	7.3	0	3.5	2.2 (2.53)	0.9 (0, 7.3)
Week 2/Session 2	0.9	0.7	1.7	2.3	2.3	1.9	7.3	0	3.7	2.3 (2.16)	1.9 (0, 7.3)
Week 3/Session 1	0.8	0.7	2.2	1.2	1.1	1.6	7.2	0	7.5	2.5 (2.83)	1.2 (0, 7.5)
Week 3/Session 2	1.9	0.7	2.8	1.3	2.7	3	7.9	0	7.9	3.1 (2.88)	2.7 (0, 7.9)
Week 4/Session 1	1	1.1	1	ND	1.5	1.8	7.1	0	7.4	2.6 (2.91)	1.3 (0, 7.4)
Week 4/Session 2	0.9	1	0.7	0.3	0.4	2.2	7.1	0	7.6	2.2 (2.96)	0.9 (0, 7.6)
Week 5/Session 1	1.1	0.6	0.6	0.7	2	1.9	7.5	0	8	2.5 (3.05)	1.1 (0, 8)
Week 5/Session 2	0.9	0.7	2.8	0.6	ND	1	6.5	0	7.5	2.5 (2.90)	1.0 (0, 7.5)
Week 6/Session 1	0.9	0.5	4.5	0.5	0.7	1.5	5.5	0	7.8	2.4 (2.79)	0.9 (0, 7.8)
Week 6/Session 2	1	0.4	2.3	0.6	0.2	0.7	5.6	0	7.3	2.0 (2.64)	0.7 (0, 7.3)
Week 7/Session 1	1.4	0.4	1.9	0.4	0.2	0.6	5.6	0	8	2.1 (2.82)	0.6 (0, 8)
Week 7/Session 2	0.9	0.5	1.9	0.4	0.3	0.5	5.1	0	8	2.0 (2.76)	0.5 (0, 8)
Week 8/Session 1	1.3	0.5	2.5	0.5	0.5	0.7	5.8	0	7.7	2.2 (2.74)	0.7 (0, 7.7)
Week 8/Session 2	1.3	0.3	0.8	0.4	0.3	0.6	5.3	0	7.9	1.9 (2.78)	0.6 (0, 7.9)
Week 10 Follow-up	1.5	0.2	3.8	0.6	0.3	0.3	5.6	0	7.8	2.2 (2.84)	0.6 (0, 7.8)
Average (SD)	1 (0.38)	0.6(0.24)	2.4 (1.52)	0.7 (0.56)	0.90(0.77)	1.5(1.15)	6.4 (0.90)	0.0 (0.0)	7.0 (1.44)		
Med (Min, Max)	0.9 (0.4,1.9)	0.7 (0.2,1.1)	2.25 (0.6,6.9)	0.55 (0.2,2.3)	0.70 (0.2,2.7)	1.30 (0.3,5.1)	6.45 (5.1,7.9)	0 (0,0)	7.55 (3.5,8)		
Total body surface area involved	57%	27%	65%	13%	15%	12%	24%	11%	18%		
Average HyBryte™ applied (g)[a]	6.78	7.11	10.31	1.69	2.74	2.16	4.19	2.37	8.43		
Ratio drug used: BSA	0.11	0.26	0.16	0.13	0.18	0.14	0.17	0.22	0.47		

Abbreviations: Med, median; Min, minimum; Max, maximum; SD, standard deviation.

[a]Calculated as total divided by 16 doses.

lower scores at the end of the study compared to baseline. Notably, itch severity was not related to the total amount of drug used.

A shift analysis relative to Baseline was conducted for each treatment visit (data not shown). After the last light treatment, itch was stable relative to Baseline in seven patients, but improved and worsened in one patient, respectively. After the 2 weeks follow-up, once erythema resolved, the Baseline itch was the same for eight patients but worsened for one. Throughout the study, there was variation in changes in pruritus (as expected in this disease), but more worsening of itch was observed during the first 5 weeks of treatment. Overall, itch remained stable between baseline and end of treatment for most patients. Despite this, the patients who responded to treatment noted to be 45%–57% less itchy than at Baseline.

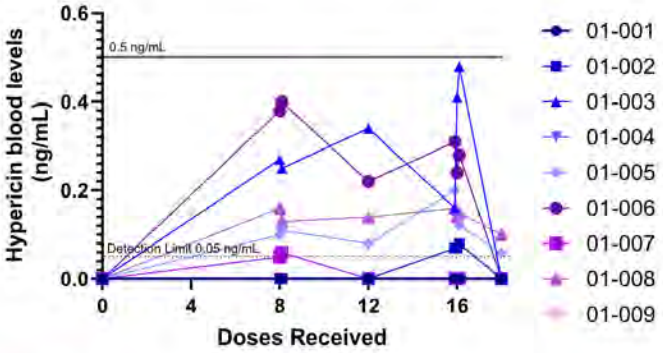

FIGURE 2 Hypericin blood concentration by patient.

Hypericin blood levels

Hypericin concentration in K_2EDTA whole blood samples collected before and after light activation at Weeks 4, 6 and 8 showed an average blood concentration of 0.13 ng/mL and achieved steady state by Week 4, as determined with a validated assay with a detection limit of 0.05 ng/mL (Figure 2).

Patients within the study had a large range of disease involvement (11%–65% BSA) and average dose application (maximum 1.7–10.3 g HyBryte per application, Table 4). Cumulative doses received ranged from 27.0 g to 164.9 g (data not shown). Maximum obtained circulating blood concentration was not well correlated with either parameter (data not shown). There was also no discernible role of gender or race on the measured systemic concentration (data not shown). No patient had a blood level >0.5 ng/mL at any timepoint (Figure 2).

Blood levels were below detection limits for six out of eight patients by the end of study visit (2 weeks after cessation of dosing), with the remaining two patients recording blood concentrations of 0.06 ng/mL and 0.10 ng/mL (Supplemental Table 1). Assuming a blood detection level of 0.05 ng/mL, the average levels of hypericin in blood ranged from 0.11 ng/mL to 0.15 ng/mL during the drug application period and dropped to a mean of 0.06 ng/mL after the 2-week follow-up period. The steady state mean was 0.13+/−0.11 ng/mL (Table 5).

TABLE 5 Average blood HyBryte™ results (ng/mL).

Time[a]	Mean (SD)[e]	Geometric mean[e]	Steady state mean (SD)
Baseline	NA	NA	
W4/S2 prior to light[b]	0.13 (0.12)	0.09	
W4/S2 post-light[c]	0.14 (0.13)	0.10	
W6/S2 prior to light[b]	0.11 (0.10)	0.09	0.13(0.11)
W8/S2 prior to drug[d]	0.12 (0.09)	0.10	
W8/S2 prior to light[b]	0.15 (0.13)	0.11	
W8/S2 post-light[c]	0.14 (0.15)	0.10	
End of study	0.06 (0.02)	0.06	

Abbreviations: NA, not applicable; SD, standard deviation.

[a]W/S = week of study/light session that week.

[b]Prior to light = 18 to 24 hours post drug application and immediately prior to starting light treatment.

[c]Post-light = 18 to 24 hours post drug application and 2 hours after completing the light treatment.

[d]Prior to drug = immediately prior to drug application.

[e]Calculated assuming BDL = 0.05 ng/mL.

HyBryte™ effects on the heart

One of primary objectives of this study was to carefully examine EKG readings in patients with extensive HyBryte™ exposure, this subjects with a BSA affected by MF of more than 10% were enroled and treated. EKGs were examined for clinical changes, including variation in the QT intervals both measured and corrected hear rate. No significant clinical changes in EKGs were observed (Supplemental Tables 2 and 3).

At Baseline, the overall average measured QT (QT_m) was 399+/−24 msec (range 356–424 msec). The average corrected QT using Bazett's formula (QT_{cB}) was 432+/−22 msec (range 397–459 msec) and the average QT using Fridericia's formula was 421+/− 20 msec (range 387–444 msec). During the study visits, no patient had an absolute QT interval >500 ms at any time and no patient had a change in QTc (using either the Bazett's or Fridericia's formulae) of more than 60 ms (Supplemental Table 3). There was moderate variability of QT intervals of up to 30 ms prolongation and up to 33 ms shortening of the interval, although the average changed within 1 standard deviation of 0 at all timepoints.

Subject 4 experienced a mild QT interval prolongation with a change of 30 or 21 msec using Bazett's or Fridericia's formula, respectively at Week 4 (Over 450 msec). This subject had below detectable levels of hypericin in blood throughout the study, did not take any medications that are known to prolong the QT interval, and had no medical conditions or electrolyte imbalances that would cause QT prolongation. Similarly, Subject 9 experienced an increase of 15 msec from Baseline meeting criteria for a prolonged QT using Bazett's formula at Week 6 and another increase of 16 msec from Baseline with a QT_{CB} of 475 msec during Week 10. She had a left axis deviation of the heart on EKG present at Baseline and no electrolyte imbalances were noted during the study. This subject also had below detectable levels of hypericin in the blood for all samples analysed. However, the subject was on a stable dose of citalopram while on study, which is known to prolong the QT interval. Due to both instances happening when the levels of hypericin were below detectable limits, the principal investigator deemed these prolongations as not related to the Investigational product. These increases in QTc did not put subjects at an increased risk of Torsades de Pointes since none of these intervals were >500 msec or increased by more than 30 msec. However, the relationship between the slight increase in intervals remains unclear as no hypericin levels were detectable.

Adverse events

There was a total of seven AEs during the study, which were observed in three (33%) of the (nine) patients. None of them were severe, all were mild in severity. Six were deemed not related to HyBryte™, and one (photo-toxicity) was deemed related. A summary of the AEs experienced during the study, severity, and relatedness to the drug can be found in Table 6.

Other safety assessments

Complete blood counts with a differential along with a complete metabolic panel was done in all subjects. No clinically significant abnormalities were found throughout the study. A summary of these results can be found in the

TABLE 6 Summary of adverse events experienced during the study.

Organ system AE term	*n* (%)	Severity	Relatedness to HyBryte™
Skin and subcutaneous tissue disorders total	3 (33%)	-	
Pruritus[a]	1 (11%)	Mild	Not related
Pruritus[a]	1 (11%)	Mild	Not related
Urticaria	1 (11%)	Mild	Not related
Photosensitivity	1 (11%)	Mild	Not related
Infections and infestations total	2 (22%)	-	
Coronavirus infection	1 (11%)	Mild	Not related
Skin infection	1 (11%)	Mild	Not related
General disorders and administration site conditions	1 (11%)	-	
Chills	1 (11%)	Mild	Not related

Abbreviation: IP, investigational product.

[a]Pruritus happened on two separate instances with the same patient.

Supplementary Tables 4 and 5. Moreover, no significant abnormalities were noted in the vital signs (heart rate, respiratory rate, and blood pressure) collected at each study visit (data not shown).

Discussion

Recently, the results from a Phase 3 clinical trial evaluating the safety and efficacy of HyBryte™ in patients with CTCL stages IA-IIA with limited BSA treated showed no systemic effects of HyBryte™ therapy.[5] Here, the systemic exposure of HyBryte™ in patients with a larger BSA affected (mean 27%) was assessed. This study further suggests that topical treatment with HyBryte™ leads to minimal serum hypericin concentrations and does not correlate with significant cardiac abnormalities.

The average dose of HyBryte™ applications ranged from 1.7 to 10.3 g per patient (BSA affected ranged from 11% to 65%). Cumulative doses received ranged from 27.0 g to 164.9 g. Blood hypericin at steady state averaged 0.13 ng/mL with a range of 0.05–0.48 ng/mL achieved by Week 4. Despite the high doses of HyBryte™ used, there was no evidence of cardiac effects either overall or causing significant prolongation of the QT interval. There were two patients with a mild increase in QTc intervals who did not have detectable levels of hypericin in their blood. Even though these did not increase the risk of Torsades de Pointes, the reason behind these mild increases in the QTc intervals are unknown and should warrant further investigation. No significant changes in safety assessments were observed. Throughout the study, pruritus varied as expected in this disease. Some worsened within the first 5 weeks of treatment, but this may have been due to tumour cell death. However, itch levels decreased by about half that of Baseline among those that reached at least a partial response to treatment.

The only treatment related AE was for phototoxicity in one patient (11%) which limited increases in light dose. This patient averaged 8.43 g per application of HyBryte™ at the time. His phototoxicity could have been related to the amount of HyBryte he was applying as he had the highest ratio of HyBryte™ applied over BSA, (Table 4). Phototoxicity is an expected side effect of HyBryte™ and may be contributing to its therapeutic effect against MF.[15–17] Regardless of the dose used, the subject experienced nearly a 40% reduction and a 34% reduction in their mSWAT and mCAILS scores, respectively. The subject had below detection limits of hypericin in the blood.

Despite being a small single-centre study, this trial robustly confirms the results of the pivotal Phase 3 study, with a response rate of 22% after 8 weeks of therapy, as opposed to the previously reported 16% response rate after 6 weeks of therapy. It is important to note that the patients in this study were deliberately chosen to have more extensive disease. Here, all patients had about a 37% improvement in their cumulative mCAILS score. Individual lesion results showed that 7/27 index lesions (26%) had at least a 50% improvement in their mCAILS score and 4/27 index lesions (15%) completely resolved. Moreover, plaque disease also responded to treatment, supporting HyBryte's penetration into deeper levels of the skin. Complete treatment response was reported in 1 patient (11%) and in 4/27 index lesions (15%). This is especially important given the short duration of treatment in this study compared to the duration of treatment for other CTCL therapies.[18,19] In CTCL, response typically accumulates with treatment duration. It is worth mentioning that these results were also achieved using a different, more flexible light device and treatment protocol than that used previously, potentially benefiting patients who can tolerate lower doses without experiencing photosensitivity, which is the case for most patients. Overall, this study provides insight into the systemic effects of HyBryte™ treatment and supports the findings of the FLASH study.

AUTHOR CONTRIBUTIONS

Carolina V. Alexander-Savino wrote the manuscript and created the tables and figures. Adam Rumage, Christopher Pullion, Richard Straube, Christopher J Schaber were involved in interpretation of the data and revising the manuscript. Elaine S. Gilmore was involved in study design, data acquisition, revising the manuscript, and statistical analysis of the data. Brian Poligone was involved in all aspects of the study including design, acquisition of data, analysis and interpretation of data, drafting and revising the manuscript, revising figures and tables, and supervision of the research team.

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CONFLICT OF INTEREST STATEMENT

Ms. Alexander-Savino reports no conflicts. Mr. Rumage and Drs. Pullion, Straube, and Schaber are employed by Soligenix. Dr. Gilmore reports grants and consulting fees from Soligenix. Dr. Poligone reports grants and consulting fees from Soligenix.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at ClinicalTrials.gov, NCT# 05380635.

ETHICS STATEMENT

All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details for publication. The study was approved by the WCG institutional review board (IRB) (Puyallup, Washington, USA).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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