Phase 3 Efficacy with a Novel, First in Class, Well-Tolerated Photodynamic Therapy (HyBryte™) for Early Stage Cutaneous T-Cell Lymphoma

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Abstract Purpose

Cutaneous T-cell lymphoma (CTCL) is a rare subtype of non-Hodgkin's lymphoma that has substantial morbidity and potential mortality. Early stage CTCL is characterized by variable cutaneous lesions, including patches, plaques and tumors, and there is no approved front-line therapy or consensus treatment paradigm for these patients, which represent the majority of patients diagnosed with CTCL. Treatment of early stage disease is based on 3 primary factors: 1) patient discomfort and cosmetic concerns, 2) potential prevention of disease progression and 3) minimizing the long term side effects and chronic toxicity caused by the treatments, especially since patients with early stage disease may be treated for decades with CTCL as a chronic condition. In light of these considerations, a novel photodynamic therapy is being advanced, involving the use of topical synthetic hypericin ointment (HyBryte™), coupled with visible light activation. The Phase 3 study not only demonstrated the efficacy and safety of this potential treatment, but also is the largest placebo-controlled, double blind, randomized trial ever run in early stage CTCL, providing valuable information on the baseline population.

Abstract Background

In CTCL, the patient journey generally reflects a variety of approved and off-label treatments, where treatment switching is dictated by either waning efficacy or accumulating toxicity/side effects.

Topical treatments with approved therapies such as mechlorethamine gel and bexarotene gel are generally associated with high rates of skin-related and non-skin-related side effects, and are limited to use after previous therapy failure (not front-line use). Photodynamic therapy is used off-label in CTCL as a combination of psoralen (mutagenic) and ultraviolet light (carcinogenic), yielding a black box warning for potentially fatal malignant melanoma and damage to the eyes. Other phototherapies similarly use ultraviolet light.

Hypericin is a photosensitizing agent which is optimally activated by visible light (500-650 nm), resulting in the production of localized singlet oxygen causing cellular apoptosis (Figure 1). Localized application, and its selective absorption into malignant cells, yields a highly specific treatment. Visible light is also known to penetrate more deeply, allowing thick plaques and disease variants associated with deeper skin structures, potentially enabling more effective and broad-spectrum disease treatment.

In this context, topical hypericin ointment activated by visible light is potentially advantageous in terms of efficacy and safety, making its use attractive particularly in early stage patients.

Abstract Method

The Phase 3 trial enrolled 169 early stage (IA, IB, IIA) CTCL patients. Study drug was applied as a hydrophilic USP ointment (placebo or 0.25% hypericin), covered with bandaging or clothing for 18-24

hours, followed by visible light activation. Study drug was applied twice weekly to 3 representative index lesions in 6 week cycles with lesion evaluation 2 weeks later (at Study Week 8/16/24). Cycle 1 was randomized 2:1 hypericin: placebo, while Cycles 2 and 3 were open-label treatment cycles. Light activation in Cycles 1 and 2 were titrated to effect (Grade I erythema), between 5 and 12 J/cm^2 (Figure 2). Blood samples for pharmacokinetic analyses were collected 24 hours after drug application in the last 4 visits of Cycle 3 in a subset of patients. The primary endpoint for the study was the proportion of patients with a treatment response at the end of Cycle 1. Treatment response was defined as ≥50% reduction in the cumulative Composite Assessment of Index Lesion Severity (CAILS) score of the 3 index lesions at baseline. Other endpoints included subpopulation analyses, complete clinical response, and duration of response. Lesion specific responses were also evaluated (i.e., patch vs. plaque responses).

Abstract Results

HyBryte demonstrated a statistically significant improvement in treatment response with only 6 weeks of treatment relative to placebo (p=0.0416). This treatment response increased with additional treatment cycles, with a 40% treatment response rate after 12 weeks treatment (p<0.0001 vs placebo in Cycle 1) and 49% after 18 weeks of treatment (p<0.0001 vs placebo in Cycle 1; Figure 3). Both plaque (42%, p<0.0001 after 2 cycles) and patch (37%, p=0.0009) lesions were effectively treated (Figure 4). The treatment response was consistent irrespective of previous CTCL treatments used, previous duration of disease, stage of disease (IA, IIA, IB) or age/gender. Treatment responses improved with time and were more durable with additional treatment cycles.

The most common AEs were Grade 1-2 local application site skin reactions (15% of subjects) and only 1% of subjects discontinued due to AEs. There were 8 severe AEs reported from 7 patients in the trial. There was no apparent consistent increase in severe AEs other than drug site application pain and erythema. AEs were consistent with the age of the patient population. No drug-related serious AEs occurred. Drug was not found systemically.

HyBryte is effective in early stage CTCL with a favorable safety profile.

Abstract Conclusion

This trial was designed to evaluate whether a short, 6-week course of HyBryte therapy could result in a statistically significant improvement of lesion response and to evaluate the improvement afforded by an additional 6-week cycle of open-label drug use. ***Both goals of the trial were achieved.*** Moreover, drug efficacy was found to be independent of disease characteristics at baseline, including disease stage, number of prior CTCL treatments and prior disease duration, and was found to be similarly beneficial in both patch and plaque lesions. As expected, longer treatment resulted in higher response rates and more durable response. HyBryte had a benign safety profile.

This trial is the largest placebo-controlled, randomized trial conducted to date in early stage CTCL and is a marked improvement over the previous observational trial designs. Placebo treatment provided an important benchmark to understanding the CTCL patient population, particularly as it incorporated a heterogeneous population representative of the clinical population.

As anticipated in orphan indications, enrollment was a prolonged process over 3.9 years. This study benefited from close collaboration with patient advocacy groups, and demonstrated the importance of patient representation in clinical research.

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Figure 1: Mechanism of action of hypericin after selective absorption into malignant T-cells and activation by visible light

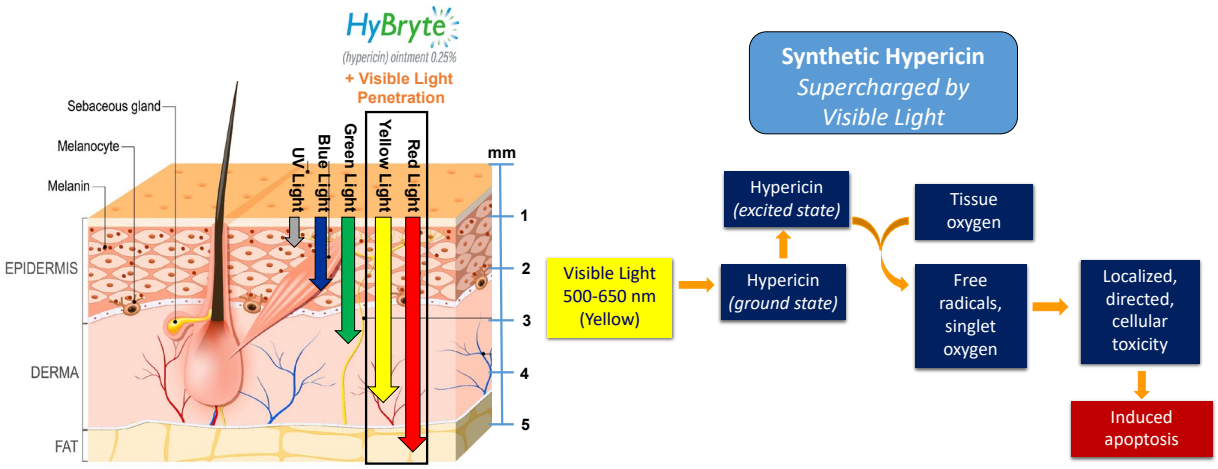

Figure 2: Design of the largest placebo-controlled, randomized study in early stage CTCL

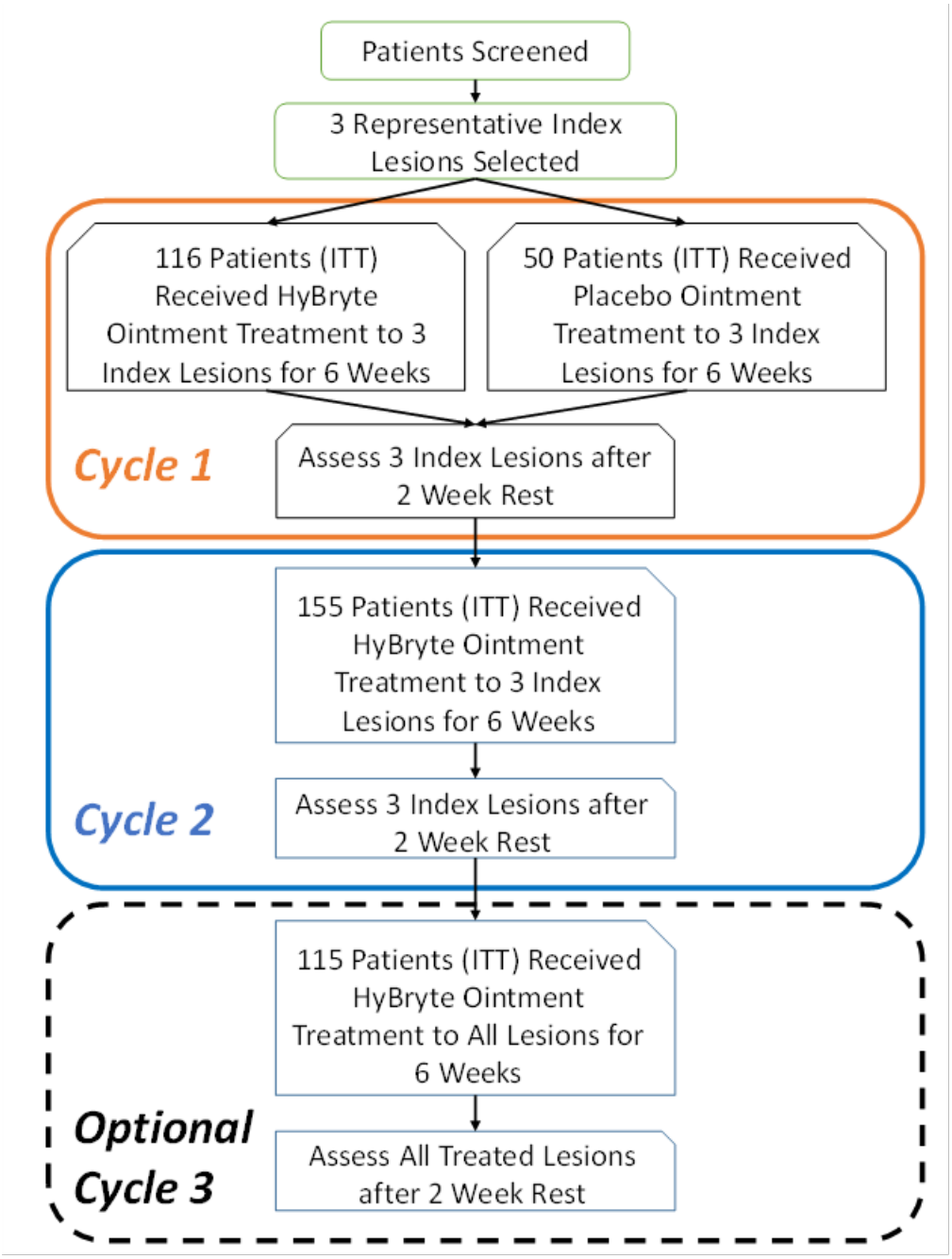

Figure 3: Treatment response rate as a function of treatment duration

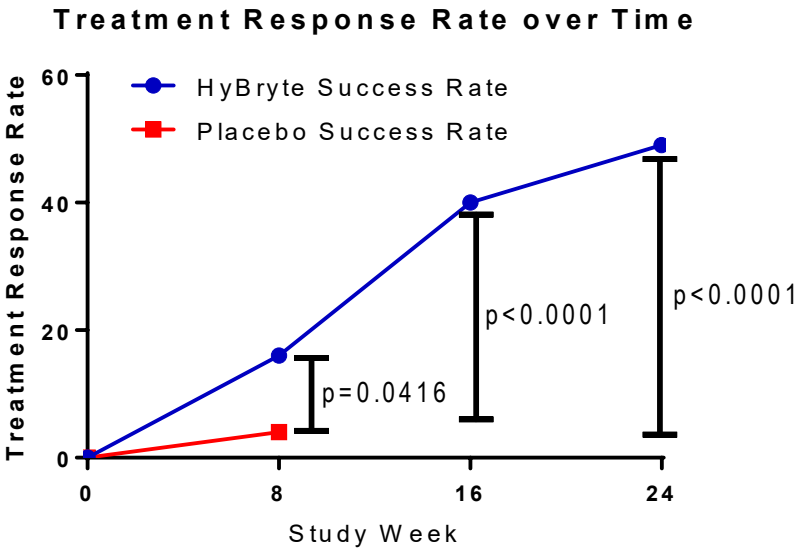

Figure 4: Lesion treatment response rate as a function of treatment duration and lesion type