Background, Advances, and Design of a Phase 2 Randomized Trial of @Home Phototherapy for MS

The Silent Symptoms Trial

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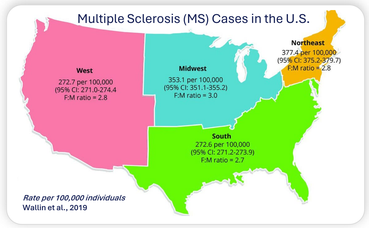
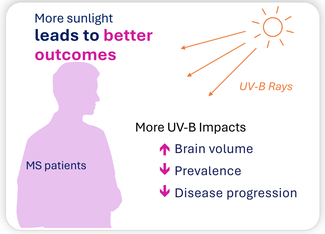
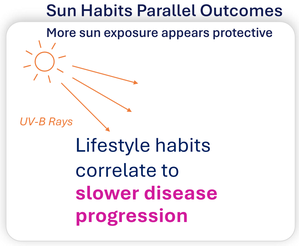
Background in MS

Multiple sclerosis (MS) prevalence is inversely proportional to exposure to environmental ultraviolet light B-band (UV-B). This phenomenon was originally coined the "latitude gradient" because UV-B is substantially reduced in winter at higher latitudes and regionally filtered by cloud cover. Reduced UV-B is associated with earlier age of onset, increased prevalence, accelerated disease severity, and decreased brain volumes.

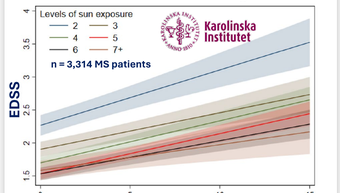




Sun Habits Parallel Outcomes



Sun Habits and Disease Progression

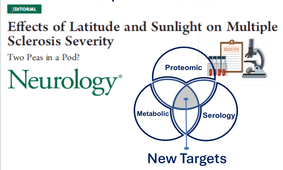


Neurologists – Call to Action for NB-UVB in MS

There has been a call to action to see if FDA-cleared phototherapy devices delivering UV-B to patients at home may mitigate these MS outcomes. Dermatologists have safely and efficaciously activated the body's photo-immune cascade with narrowband UV-B (NB-UVB) phototherapy to stabilize several autoimmune diseases with cutaneous presentations.

Call to Action

Ostkamp and Schwab 2022



Randomized Trial + Parallel OMICs

Daavlin 1 Series @home Phototherapy

Tabletop (2 feet tall)
User Interface
- Dose control mode
- Patient feedback
- Onboard record log

Starting Dose
- 1-3 min. based on skin color

FDA cleared for dermatology

FDA 510(k) K220840

Background of NB-UVB in Dermatology

Dermatologists have done the heavy lifting
NB-UVB is an Advanced Therapy.

First Line Therapy for >40 years

Side Effect of Erythema
- Recent n=700 PCORI Trial
- No lost treatments to erythema

AAD and NPF Guidelines
- Safe for pediatrics
- Safe during pregnancy

Consistently Reduces Inflammation

Psoriasis and MS Share
- CRP, Th1, Th17, IFN-γ, TNF, Tegs
- Psoriasis is a common MS co-morbidity

Efficacy
- Equivalent to biologics
- Boosts biologics when together

Patient Reported Outcomes
- 8X better than biologics

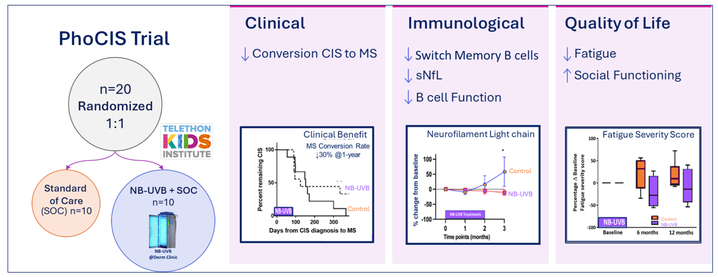
MOST COMMON MISCONCEPTION of NB-UVB is a MELANOMA RISK
Dermatologists have prescribed NB-UVB & tracked melanoma for >40 years
Their guidelines report no increased risk of melanoma from NB-UVB

Previous Phase 1 Trials of Phototherapy for MS

Three phase 1 trials of phototherapy to treat MS have been safely performed at academic institutions in Australia, Germany, and the US. The clinical signatures of benefits previously published include reductions in relapse rates, fatigue, and switch-memory B-cells, and in one study, the expansion of regulatory T-cells.

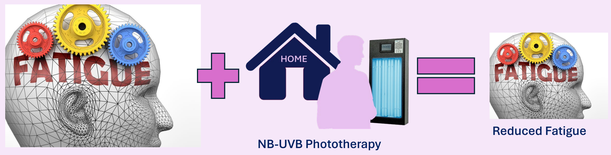
The results of the randomized controlled PhoCIS trial of in-clinic NB-UVB for patients with clinically isolated syndrome had the greatest breadth, longest follow-up, and most extensive peer-reviewed manuscripts.

The Phase 2 – Silent Symptoms Trial is powered by the PhoCIS results.



Hypothesis

90 days of phototherapy will significantly reduce inflammation and MS fatigue.



Treatment

FDA-cleared at-home narrowband ultraviolet B light (NB-UVB) from dermatology.

Primary Outcome

Fatigue by Modified Fatigue Impact Scale

Secondary and Exploratory Outcomes

Correlating fatigue & cognition with objective biomarkers

Methods – Silent Symptoms Trial Design

Addressing the biggest unmet needs in MS

A randomized, placebo-controlled, crossover, multicenter trial is proposed. Patients will be provided adjunctive NB-UVB phototherapy units at home and treated daily for 90 days. Patients will be randomized 1:1 to a treatment light or a placebo light. At 90 days, the placebo cohort will crossover, which ensures all patients will be provided treatment within the first 6 months. The primary outcome is the change in MFIS at 90 days.

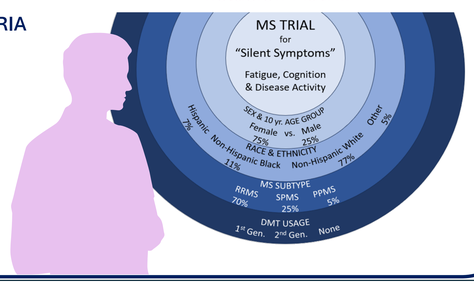
Secondary and exploratory outcomes will include proteomics as measured by the Octave MS Disease Activity test, cognition as measured by BICAMS, and neurological assessments. Fatigue and cognition as measured by BICAMS have previously been correlated in MS (Bellew et al, 2022). This trial follows the axis of – NB-UVB reduced inflammation to provide cellular, organ, and cerebral rest, resulting in reduced fatigue and improved cognition.

A pragmatic patient population

The latitude gradient is ubiquitous in MS, and independent of disease subset or DMT class. The patient subgroups more significantly impacted by latitude and disease severity are people of color, women, and the elderly. The enrollment goals represent the real-world of MS patients and are consistent with FDA guidance for inclusion. Given American Academy of Dermatology guidance, this trial will also provide a therapeutic option for pregnant women.

A Real-World Inclusion Matrix

INCLUSION CRITERIA
- MFIS > 41
- Ages 18-88
- RRMS, SPMS & PPMS
- Pregnant women
- All DMTs



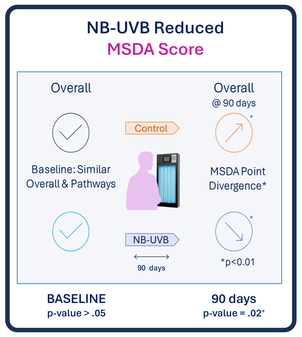
Advances - NB-UVB and Targeted MS Proteomics

Correlating NB-UVB with inflammatory biomarkers

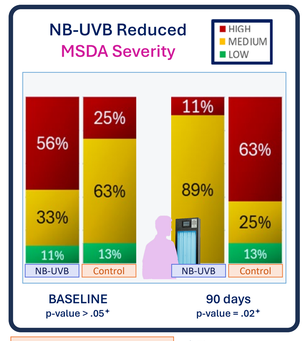
PhoCIS investigators provided biobanked samples from their Phase 1 trial so that Cytokind could perform previously unavailable OMICs assessments. The OMICs assessments included proteomic and metabolic assays. The proteomics included independent broad and MS targeted assays by Olink Target 96 Inflammation Panel, Uppsala, Sweden, and targeted MS Disease Activity (MSDA), Octave, Menlo Park, CA, respectively.

At 90 days, the difference in overall MSDA scores between the standard of care cohort and the NB-UVB cohort was significantly different. Additionally, the categorization of MSDA severity of the MSDA scores was significantly reduced in the NB-UVB cohort.

These findings inform the timepoint for the Silent Symptoms trial of 90 days.



* On average, the difference in MSDA scores was 1.79 (out of 10) lower in NB-UVB vs. control (p-value = .004).



Control = Standard of Care Arm

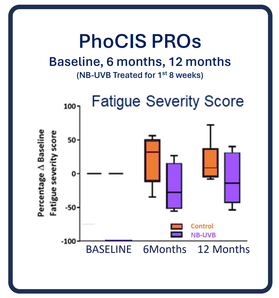
\+ Fisher's exact test

Powering Fatigue as the Primary Endpoint

Correlating Fatigue and MS Disease Activity

The PhoCIS trial reported improvements in patient-reported outcomes (PROs), including fatigue, as measured by Fatigue Severity Score, and Social Functioning, as measured by SF-36. These PROs were measured at baseline, 6 months, and 12 months. The improvement in FSS of 24.2% from the PhoCIS trial was conservatively modeled for this Phase 2 trial at **18%** with a placebo effect of **5%**, approximately 25% of the NB-UVB treatment effect. The previously published immunological improvements from the PhoCIS trial suggested a parallel between subjective PROs and objective immunological stabilization.

With that in mind, the ensemble fatigue scores were assessed for correlation with MSDA scores at all time points. The MSDA general score was statistically correlated to FSS scores across all time points. These findings inform the inclusion of objective MSDA tests at baseline, 90, and 180 days in the Silent Symptoms trial.



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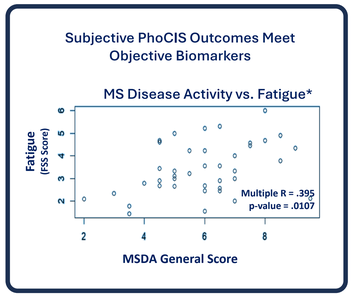

*Test for correlation between paired samples using Pearson's product-moment correlation coefficient.

Summary

The Silent Symptom trial design represents an opportunity to test the hypothesis that the largest unmet needs in MS may be addressed with translational phototherapy from dermatology. Performed with parallel OMICs the trial may also uncover new links between systemic inflammation, fatigue, and cognition in a real-world MS cohort.

DESIGN
Crossover, randomization 1:1
BLINDING
Double-blind and placebo-controlled

1st Endpoint: Fatigue (MFIS) at 90 days
2nd Endpoint: Cognition (BICAMS) & MSDA

POPULATION
Pragmatic – Real-world Profile
KEY INCLUSION
Fatigue >41 on MFIS scale @ baseline
TREATMENT
Daily escalating NB-UVB for 90 days
Starting dose of 1-3 minutes/day

Fatigue Power Calculations

Phase 1 Treatment Effect = (-24.2%)

FOLLOW-UP
Baseline, 90, 180, & 365 days

ASSUMPTIONS
- MFIS = 54.5 ± 16
- Treatment Effect = (-18%)
- Placebo Effect = (-5%)*
- α = .05
- β = .80
- Drop-out/erosion rate = 20%

TARGET ENROLLMENT
n = 142
Randomized 1:1
Crossover allows all enrollees to get Tx within 6 months

PI (proposed)
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Medical College of Wisconsin

OMICs COLLABORATORS
Octave
General Metabolics
augmenta