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Supplementary Material

Article Title: Bright Light Therapy in the Morning or Midday for the Treatment of Nonseasonal Depression in Bipolar Disorder (LuBi): A Dose-Escalation Phase 1/2 Randomized Double-Blind Trial

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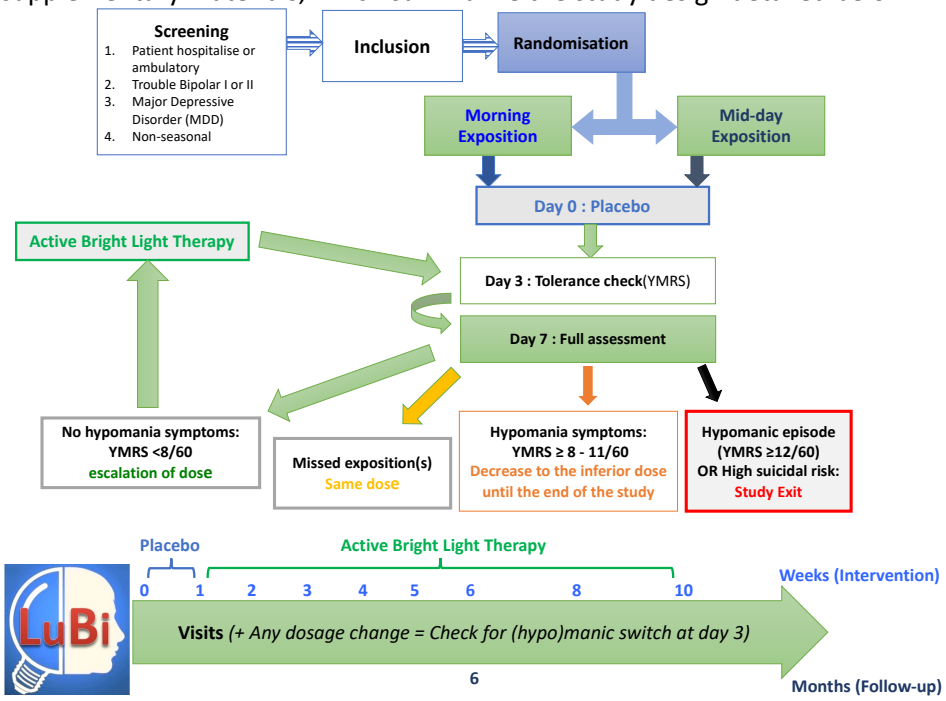
LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Appendix 1. Supplementary Methods: Study Design

This is a dose-finding study, with the dose defined as the duration of light exposure, using both inter- and intra-subject dose to determine the maximum tolerated dose (MTD) of bright light therapy (BLT) in bipolar depression. Five dose levels were evaluated (7.5, 10, 15, 30, and 45 minutes), with participants randomly assigned in a 1:1 ratio to either morning or mid-day BLT groups. The dosage depended on the therapeutic escalation. It was based on the definition of several intra-subject dose escalation schemes, with different initiation dose among 5 dose levels (7.5, 10, 15, 30 and 45 min). The intra-subject escalation scheme had to be done at most once a week.

This approach accounts for both inter- and intra-individual variability in tolerance and response, enabling cumulative toxicity modeling and maximizing each patient's likelihood of receiving an effective dose. Refer to the intra-patient dose escalation rules and figures in the supplementary materials, which summarize the study design detailed below.



Inter- and Intra-Subject Escalation

The inter-subject escalation scheme aimed to estimate the maximum tolerated dose (MTD) of the BLT, as measured on hypomanic switch, and was based on the standard '3+3' design. The first three participants (Cohort A) began with the starting dose level of 7.5 minutes. If no dose-limiting toxicity (DLT) was observed among all three, the starting dose for the next cohort (Cohort B) was increased to the next level (10 minutes). Inter-subject escalation depended on observing no DLTs in all three subjects of a cohort, or at most 1 in 6. If one participant exhibited a DLT, a second identical cohort would start at the same starting dose, and escalation to a higher dose level would only proceed if no DLT was observed in this supplemental cohort. The MTD was defined if two or three subjects in the same cohort exhibited a DLT, or if two separate cohorts at the same dose initiation level each had one participant with a DLT. If only one participant in the first cohort showed a DLT, a second cohort at the same starting dose was started to confirm the safety of that dose. This process was repeated for subsequent cohorts.

The intra-subject escalation scheme aimed to account for individual variability in the definition of the MTD [34], allowing each subject to receive the maximum dose that he(she) tolerates. The intra-subject dose escalation occurred only once a week for each patient. The intra-patient dose escalation took into account any DLTs (ie, hypomanic switches) observed during the escalation on the previous cohorts, through the observation of so-called "Target Ceiling Dose" (TCD)[35].

Rules for this escalation were summarized in the supplementary materials. If a patient presented a DLT during this escalation, the escalation was abandoned for this patient and the dose defined the DLT for this patient. If 2 DLTs occurred at a same dose, the "Target Ceiling Dose" (TCD) was defined -which is the highest theoretical dose that can be administered to a patient [35]- and lead to a maximum dose for all participants at a dose below the TCD such as the dose level immediately lower if it exists.

The TCD concept guided both intra- and inter-subject escalations (i.e., between cohorts of three patients starting at the same dose), where no cohort could begin at a dose equal to the TCD. Intra-subject escalation could be interrupted at the dose where a patient reached his(her) DLT or when a TCD was defined for two patients in the study, after which the TCD was applied to subsequent cohorts. TCDs determined during intra-subject escalation were promptly communicated to investigators upon inclusion, with real-time updates sent to the site and clinicians alerted by email as needed (*see supplemental Figures 1 to 4*).

Intrapatient dose escalation rules

- All patients start with a first week with a placebo for 10 minutes. This week with placebo aims to have a zero-dose measurement of light therapy; it also allowed the patient to get used to the device.
- In the absence of DLT (YMRS score < 8), active treatment at the initial dose was started.
- If the subject has DLT (YMRS score ≥ 8) within one week after treatment onset, the patient had to discontinue the treatment with planned management of the mood episode; this DLT was recorded and used for the following cohorts.
- Otherwise, an intra-subject escalation of the dose administered on the next week to the upper level (immediately above) occurred.
  - If YMRS score < 8 has been observed in the patient, escalation was proposed to the higher dose (if available) after 1 week at the same dose.
  - If YMRS score between 8 and 12, defining sub-syndromic hypomanic symptoms, the intensity of light therapy was reduced to the previous level (de-escalation to the lower dose, if it existed, and if not, this resulted in the study termination).
  - If YMRS score between 12 and 20, the light therapy was interrupted, and the study ended for the subject with planned management of the thymic episode (see below).
  - If YMRS score ≥ 21, it defined a manic episode, this led to the same result as a previously described hypomanic episode, namely the treatment discontinuation and usual psychiatric hospital care.

Intervention

The BLT was administered using Luminette® glasses, a medical device produced by Lucimed (EAN: 0702382929671). The device weighed 0.6 kg and measured 22 x 11 x 11 cm. It provided daily exposure to fluorescent light with a perceived intensity of 10,000 Lux, included a UV filter, and met CE standards. For this study, the Luminette® glasses were set at intensity 2/3, emitting blue-enriched light at 1000 Lux, equivalent to 10,000 Lux in traditional BLT [32].

A Placebo exposure was established using the same Luminette® device, adhering to CE standards, but emitting a fluorescence of 50 Lux, similar to ambient light and considered ineffective.

The modes of administration were the same for the subjects exposed in the morning and those exposed at mid-day, and was done at a fixed time and common to all centers: i) BLT in the morning: 8 am ± 30 min; ii) BLT at midday: 12 hours (noon) ± 30 min; during which patients could continue normal activities.

Patients received instructions on using the Luminette®, with adherence tracked through daily logs. This method, proven effective in recent studies, required no prior training [33]. The device's simple operation involved a push-button for on/off and a rechargeable battery.

An independent nurse, blinded to the treatment assignment and not involved in patient evaluations, administered either the active or placebo device. Patients remained blinded to their assigned condition throughout the study. Furthermore, the investigator responsible for patient evaluations was also blinded to the type of device used, as it was distributed solely by the independent nurse.

Supplementary Table 1: Centers

Center	**Total (n=34)**	**Morning (n=18)**	**Mid-day (n=16)**
Paris - Bichat - Psychiatry	20 (59 %)	10 (56 %)	10 (62 %)
Paris - Fernand Widal - Psychiatry	7 (21 %)	4 (22 %)	3 (19 %)
Lille - Fontan - Psychiatry	3 (9 %)	2 (11 %)	1 (6 %)
Montpellier - Lapeyronie - Psychiatry	2 (6 %)	1 (6 %)	1 (6 %)
Colombes - Louis Mourier - Psychiatry	1 (3 %)	1 (6 %)	0
Paris - Sainte Anne - Psychiatry	1 (3 %)	0	1 (6 %)

Supplementary Table 2: Psychotropic medications

Treatment	**Total (n=34)**	**Morning (n=18)**	**Mid-day (n=16)**
Mood stabilizer	**27 (79%)**	**14 (78%)**	**13 (81%)**
Lithium	22	11	11
Lamotrgine	7	3	4
Valpromide	3	2	1
Valproate	1	0	1
Atypical antipsychotic	**18 (53%)**	**10 (56%)**	**8 (50%)**
Aripiprazole	7	3	4
Quetiapine	7	5	2
Olanzapine	2	1	1
Risperidone	1	1	0
Amisulpride	1	0	1
Clozapine	1	1	0
Benzodiazepine/ Anxiolytic	**13 (38%)**	**6 (33%)**	**7 (44%)**
Antidepressant	**11 (32%)**	**6 (33%)**	**5 (31%)**
SSRIs (Selective Serotonin Reuptake	7	3	4
ŠNŘIs (Serotonin-Norepinephrine Reuptake Inhibitors)	4	3	1
Typical (Conventional) antipsychotic	**2 (6%)**	**1 (6%)**	**1 (6%)**
Melatonin	**1 (3%)**	**0**	**1 (6%)**

Supplementary Table 3. Estimated effects of time (week), initial allocated dose (duration), randomization (Morning vs Mid-Day) and current dose with potential heterogeneity in effect over time of both initial dose and randomization, on secondary outcomes - Statistically significant results depicted in colored-cells

Estimated β (SE) ; p-value	Week	Initial duration	Morning vs Mid-Day	Current dose	Interaction week: Initial dose	Interaction week: Morning vs Mid-Day
PSQI score	0.089 (0.114) p=0.43	0.069 (0.037) p=0.068	-1.550 (1.007) p=0.13	-0.021 (0.015) p=0.17	-0.006 (0.003) p=0.080	-0.020 (0.081) p=0.81
CSM score	-0.276 (0.205) p=0.18	-0.010 (0.110) p=0.93	0.061 (3.152) p=0.98	-0.008 (0.027) p=0.77	0.012 (0.006) p=0.056	-0.021 (0.145) p=0.88
CTI (FR)	-0.121 (0.129) p=0.35	0.020 (0.052) p=0.71	3.329 (1.475) **p=0.031**	-0.027 (0.017) p=0.11	0.008 (0.004) **p=0.042**	0.069 (0.090) p=0.44
CTI (LV)	0.218 (0.173) p=0.209	0.018 (0.075) p=0.81	-1.029 (2.133) p=0.63	-0.010 (0.023) p=0.65	-0.007 (0.005) p=0.22	0.085 (0.120) p=0.48
ESS score	-0.073 (0.177) p=0.68	0.022 (0.063) p=0.73	-1.097 (1.751) p=0.53	0.033 (0.023) p=0.14	-0.001 (0.005) p=0.84	0.043 (0.119) p=0.72

Supplementary Figure 1: Study flowchart of the LuBi study