# Twelve Months Follow-Up Comparison Between Autistic Children Vs. Initial Placebo (Treated) Groups

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**Abstract**

We recently examined the efficacy of low-level laser therapy (LLLT) to treat autistic children and adolescents up to 12 months after finishing LLLT therapy. In this paper, we present the follow up assessment up to 12 months after completion of LLLT procedure, demonstrating that improvement in symptoms continued in the patients initially randomized to the active (test) group, with no change at all for placebo subjects. After finishing the above-mentioned protocol, we decided to treat the initial placebo group (now, placebo cross-over group) and clinically follow up the cases up to 12-months, as we had done with the active (test) group. Hence, in this paper we compare the clinical evaluation providing progressive results for up to 12-months follow-up evaluation (relative to treatment end) for the subject groups enrolled in our protocol.

## INTRODUCTION

We recently examined the efficacy of low-level laser therapy (LLLT) to treat autistic children and adolescents up to 12 months after finishing LLLT therapy.(1-3) In this paper, we present the follow up assessment up to 12 months after completion of LLLT procedure, demonstrating that improvement in symptoms continued in the patients initially randomized to the active (test) group, with no change at all for placebo subjects.

After finishing the above-mentioned protocol,(3) we decided to treat the initial placebo group (now, placebo cross-over group) and clinically follow up the cases up to 12-months, as we had done with the active (test) group. Hence, in this paper we compare the clinical evaluation providing progressive results for up to 12-months follow-up evaluation (relative to treatment end) for the subject groups enrolled in our protocol.

## METHODS

Subjects.

1. The 21 subjects initially randomized to the active (test) treatment group
2. The 19 subjects who were initially randomized to the placebo treatment group and subsequently crossed over to receive active treatment. The results for this group of subjects are reported with respect to the active treatment received.

### *Outcome Measures*

Outcome measures included the Aberrant Behavior Checklist (ABC). The Global Score and the five subscale scores consisted of: (a) Irritability and Agitation, (b) Lethargy and Social Withdrawal, (c) Stereotypic Behavior, (d) Hyperactivity and Noncompliance and (e) Inappropriate Speech. The Global Score for the ABC was not psychometrically derived, and is not statistically valid. The ABC was designed to be completed by any adult who knows the individual well. The second outcome measure consisted of the Clinical Global Impressions (CGI) Scale that consisted of a Severity of illness scale (CGI-S) and a Global improvement/change scale (CGI-C).(4-6)

The ABC and CGI-S and CGI-C were assessed in each participant comparing baseline, end-point (4 weeks of LLLT treatment), 8 weeks, 6 and 12 months, after treatment completion.

### *Test Procedures*

The placebo cross-over group participants received 5-minute procedure administrations to the base of the brain and temporal areas with the Erchonia® EAL Laser (active or sham) across a four-week period: two procedures per week, each procedure three to four days apart at the investigator's test site.

### *Ethics*

The study received an approval: from the Helsinki Committee of the Institute for Neurology and Neurosurgery in Havana, Cuba, and was registered with the NIH (identifier: NCT03379662). Informed written consent was obtained: from the parent or guardian of each participant after a full explanation of the procedures to be undertaken. The informed consent forms, research protocol, and approvals are available for inspection in the Office of Research Integrity at the Institute of Neurology and Neurosurgery in Havana, Cuba.(1-3, 7, 8)

### *Statistical Analysis*

For the continuous primary efficacy measure of score on the ABC irritability and agitation subscale as well as the secondary measures of scores on the ABC Global scale and the remaining 4 subscales, change across baseline, 8 weeks post-procedure, 6- and 12-months post-procedure, was evaluated using analysis of variance (ANOVA). A Tukey HSD Analyses was applied to evaluate the specific statistically significant changes between and across individual evaluations.

For a complete description of the methodology, check our previous publication.(3)

## RESULTS

### ABC Global and Subscale Scores

Table 1 below shows the mean and standard deviation of the ABC Global and Subscale scores across the long-term 12-month evaluation period for subjects in the initial test (active) group.

**Table 1**

Test Group: Mean ABC Global and Subscale Scores

| *Global Score* | Baseline | 8 Weeks | 6 Months | 12 Months |
|---|---|---|---|---|
| Mean | 109.38 | 54.14 | 28.95 | 34.67 |
| Standard deviation | 21.14 | 41.33 | 27.73 | 25.52 |
| *Irritability* | | | | |
| Mean | 31.14 | 13.24 | 6.71 | 9.43 |
| Standard deviation | 6.39 | 11.37 | 7.91 | 9.68 |
| *Lethargy & Social Withdrawal* | **Baseline** | **8 Weeks** | **6 Months** | **12 Months** |
| Mean | 23.24 | 11.76 | 6.81 | 5.90 |
| Standard deviation | 9.62 | 10.66 | 6.56 | 4.49 |
| *Stereotypic Behavior* | **Baseline** | **8 Weeks** | **6 Months** | **12 Months** |
| Mean | 14.14 | 7.71 | 3.95 | 4.76 |
| Standard deviation | 4.44 | 6.17 | 4.43 | 4.74 |
| *Hyperactivity & Noncompliance* | **Baseline** | **8 Weeks** | **6 Months** | **12 Months** |
| Mean | 33.25 | 17.43 | 9.14 | 11.95 |
| Standard deviation | 8.01 | 12.58 | 9.48 | 10.45 |
| *Inappropriate Speech* | **Baseline** | **8 Weeks** | **6 Months** | **12 Months** |
| Mean | 7.62 | 4.00 | 2.33 | 2.62 |
| Standard deviation | 2.88 | 2.81 | 2.39 | 2.52 |

A series of **One-Way ANOVAs for 4 correlated samples** was performed to evaluate the mean change across and between baseline, 8-weeks post-treatment, 6-months post-treatment and 12-months post-treatment for the ABC Global Score and each of the subscale sores for initial test group subjects. Each change was found to be **statistically significant**, at $p<0.0001$, as shown in Table 2 below.

**Table 2**

Test Group: ANOVA Results Across the 4 Evaluations for ABC Global and Subscale Scores

| *ABC Global Scale and Subscales* | F | df | p |
|---|---|---|---|
| Global Score | 70.42 | 3 | <0.0001 |
| Irritability | 69.20 | 3 | <0.0001 |
| Lethargy and Social Withdrawal | 34.70 | 3 | <0.0001 |
| Stereotypic Behavior | 34.26 | 3 | <0.0001 |
| Hyperactivity and Noncompliance | 44.94 | 3 | <0.0001 |
| Inappropriate Speech | 23.58 | 3 | <0.0001 |

Subsequent Tukey HSD Analyses to evaluate the specific statistically significant changes between and across individual evaluations found statistically significant changes in means ABC Global and Subscale scores to occur consistently between baseline and each of the 3 subsequent evaluations of 8 weeks, 6 months and 12 months post-treatment ($p<0.01$) for initial test group subjects. Statistically significant mean changes occasionally occurred between 8 weeks and 6 months evaluations and between 8 weeks and 12 months evaluations. Specific statistically significant changes are shown in Table 3 below.

### Table 3

Test Group: Tukey HSD Analysis Results Across the 4 Evaluations for ABC Global and Subscale Scores

| *ABC Global Scale and Subscales p-values* | Baseline to 8W Post | Baseline to 6M Post | Baseline to 12M Post | 8W to 6M Post | 8W to 12M Post | 6M to 12M Post |
|---|---|---|---|---|---|---|
| Global Score | <0.01 | <0.01 | <0.01 | NS* | <0.05 | NS |
| Irritability | <0.01 | <0.01 | <0.01 | <0.01 | NS | NS |
| Lethargy and Social Withdrawal | <0.01 | <0.01 | <0.01 | NS | <0.05 | NS |
| Stereotypic Behavior | <0.01 | <0.01 | <0.01 | NS | NS | NS |
| Hyperactivity and Noncompliance | <0.01 | <0.01 | <0.01 | NS | NS | NS |
| Inappropriate Speech | <0.01 | <0.01 | <0.01 | NS | NS | NS |

** NS = not statistically significant (p>0.05)*

Table 4 below shows the mean and standard deviation of the ABC Global and Subscale scores across the long-term 12-month evaluation period for subjects in the placebo cross-over group.

### Table 4

Placebo Cross-Over Group: Mean ABC Global and Subscale Scores

| *Global Score* | Baseline | 8 Weeks | 6 Months | 12 Months |
|---|---|---|---|---|
| Mean | 112.22 | 53.26 | 31.16 | 32.11 |
| Standard deviation | 20.93 | 31.25 | 28.12 | 25.88 |
| *Irritability* | | | | |
| Mean | 30.37 | 12.84 | 8.05 | 7.47 |
| Standard deviation | 12.84 | 9.42 | 7.81 | 7.16 |
| *Lethargy & Social Withdrawal* | Baseline | 8 Weeks | 6 Months | 12 Months |
| Mean | 25.58 | 12.63 | 6.37 | 7.58 |
| Standard deviation | 5.75 | 9.94 | 8.86 | 9.16 |
| *Stereotypic Behavior* | Baseline | 8 Weeks | 6 Months | 12 Months |
| Mean | 12.53 | 7.00 | 4.16 | 4.05 |
| Standard deviation | 5.86 | 5.02 | 5.73 | 5.15 |
| *Hyperactivity & Noncompliance* | Baseline | 8 Weeks | 6 Months | 12 Months |
| Mean | 37.42 | 17.00 | 10.16 | 10.63 |
| Standard deviation | 8.14 | 9.75 | 8.28 | 7.37 |
| *Inappropriate Speech* | Baseline | 8 Weeks | 6 Months | 12 Months |
| Mean | 6.42 | 3.79 | 2.42 | 2.37 |
| Standard deviation | 3.96 | 2.97 | 1.80 | 2.43 |

A series of **One-Way ANOVAs for 4 correlated samples** was performed to evaluate the mean change across and between baseline, 8-weeks post-treatment, 6-months post-treatment and 12-months post-treatment for the ABC Global Score and each of the subscale sores placebo cross-over group subjects. Each change was found to be **statistically significant**, at p<0.0001, as shown in Table 5 below.

### Table 5

Placebo Cross-Over Group: ANOVA Results Across the 4 Evaluations for ABC Global and Subscale Scores

| *ABC Global Scale and Subscales* | F | df | p |
|---|---|---|---|
| Global Score | 117.54 | 3 | <0.0001 |
| Irritability | 104.83 | 3 | <0.0001 |
| Lethargy and Social Withdrawal | 69.06 | 3 | <0.0001 |
| Stereotypic Behavior | 31.35 | 3 | <0.0001 |
| Hyperactivity and Noncompliance | 94.00 | 3 | <0.0001 |
| Inappropriate Speech | 18.23 | 3 | <0.0001 |

Subsequent Tukey HSD Analyses to evaluate the specific statistically significant changes between and across individual evaluations found statistically significant changes in means ABC Global and Subscale scores to occur consistently between baseline and each of the 3 subsequent evaluations of 8 weeks, 6 months and 12 months post-treatment (p<0.01) for placebo cross-over group subjects. Statistically significant mean changes occurred for all but the subscale score of Inappropriate Speech between 8 weeks and 6 months post-treatment and between 8 weeks and 12 months post-treatment evaluations. Specific statistically significant changes are shown in Table 6 below.

### Table 6

Placebo Cross-Over Group: Tukey HSD Analysis Results Across the 4 Evaluations for ABC Global and Subscale Scores

| *ABC Global Scale and Subscales p-values* | Baseline to 8W Post | Baseline to 6M Post | Baseline to 12M Post | 8W to 6M Post | 8W to 12M Post | 6M to 12M Post |
|---|---|---|---|---|---|---|
| Global Score | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | NS |
| Irritability | <0.01 | <0.01 | <0.01 | <0.05 | <0.01 | NS |
| Lethargy and Social Withdrawal | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | NS |
| Stereotypic Behavior | <0.01 | <0.01 | <0.01 | <0.05 | <0.05 | NS |
| Hyperactivity and Noncompliance | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | NS |
| Inappropriate Speech | <0.01 | <0.01 | <0.01 | NS* | NS | NS |

** NS = not statistically significant (p>0.05)*

Chart 1 below illustrates the progressive change in the mean ABC Global score from baseline through 8 weeks, 6 months and 12 months post-treatment evaluation for subjects in the initial test group and subjects in the placebo cross-over group. It is noted that the progressive improvement (decrease) in ABC Global scores across study duration is substantial and almost identical between treatment groups.

**Chart 1**

Mean ABC Global Score Across Long-Term 12-Month Evaluation

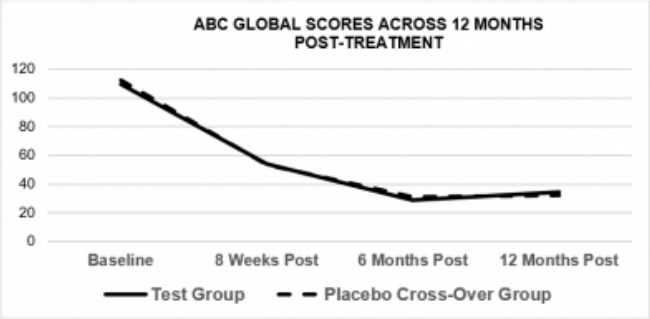



Chart 2 below illustrates the progressive change in the mean ABC Irritability and Agitation subscale scores from baseline through 8 weeks, 6 months and 12 months post-treatment evaluation for subjects in the initial test group and subjects in the placebo cross-over group. As with the mean Global score, the progressive improvement (decrease) in the ABC Irritability and Agitation subscale score across study duration is substantial and almost identical between treatment groups.

**Chart 2**

Mean ABC Irritability and Agitation Subscale Score Across Long-Term 12-Month Evaluation

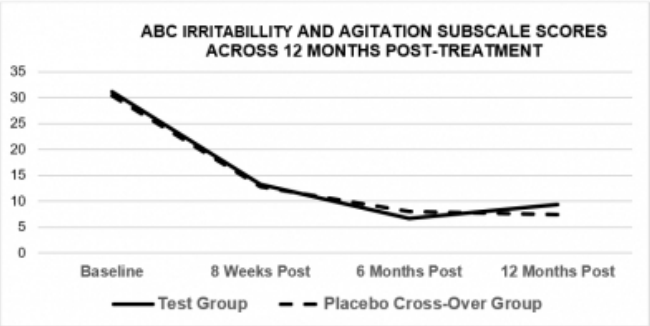



Chart 3 below illustrates the progressive change in the mean ABC Lethargy and Social Withdrawal subscale scores from baseline through 8 weeks, 6 months and 12 months post-treatment evaluation for subjects in the initial test group and subjects in the placebo cross-over group. Again, the progressive improvement (decrease) in the ABC Lethargy and Social Withdrawal subscale score across study duration is substantial and almost identical between treatment groups.

**Chart 3**

Mean ABC Lethargy and Social Withdrawal Subscale Score Across Long-Term 12-Month Evaluation


Chart 4 below illustrates the progressive change in the mean ABC Stereotypic Behavior subscale scores from baseline through 8 weeks, 6 months and 12 months post-treatment evaluation for subjects in the initial test group and subjects in the placebo cross-over group. Again, the progressive improvement (decrease) in the ABC Stereotypic Behavior subscale score across study duration is substantial and almost identical between treatment groups.

**Chart 4**

Mean ABC Stereotypic Behavior Subscale Score Across Long-Term 12-Month Evaluation

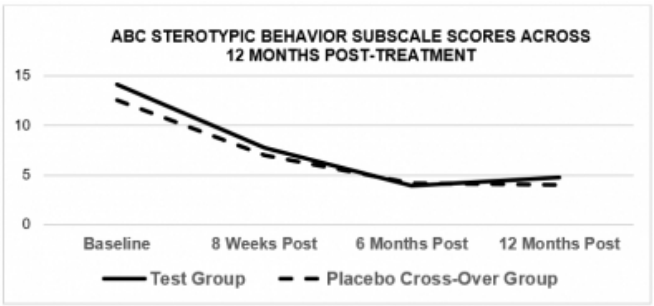



Chart 5 below illustrates the progressive change in the mean Hyperactivity and Noncompliance subscale scores from baseline through 8 weeks, 6 months and 12 months post-treatment evaluation for subjects in the initial test group and subjects in the placebo cross-over group. Again, the progressive improvement (decrease) in the ABC Hyperactivity and Noncompliance subscale score across study duration is substantial and almost identical between treatment groups.

**Chart 5**

Mean ABC Hyperactivity and Noncompliance Subscale Score Across Long-Term 12-Month Evaluation

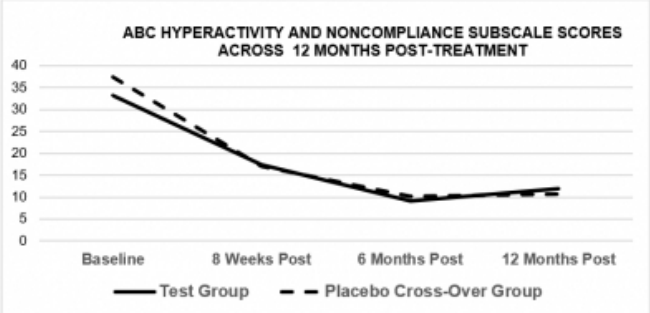
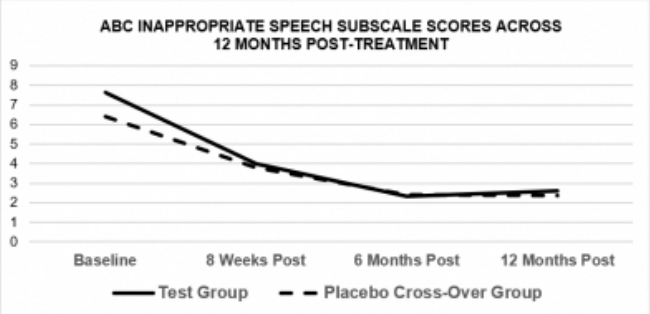



Chart 6 below illustrates the progressive change in the mean Inappropriate Speech subscale scores from baseline through 8 weeks, 6 months and 12 months post-treatment evaluation for subjects in the initial test group and subjects in the placebo cross-over group. Again, the progressive improvement (decrease) in the ABC Inappropriate Speech subscale score across study duration is substantial and almost identical between treatment groups.

**Chart 6**

Mean ABC Inappropriate Speech Subscale Score Across Long-Term 12-Month Evaluation




Charts 1 through 6 above illustrate the continuing progressive reduction of key characteristic behavioral symptoms of autism, with all symptom expression continuing to improve across the 8-week, 6-month and 12-month post-treatment evaluations in subjects treated with the active Spectrum by Erchonia Laser.

**CGI-S Ratings**

Tables 7 and 8 below show the number of subjects within each CGI-S category across the long-term 12-month evaluation period for subjects in the test group and for placebo cross-over group subjects, respectively.

**Table 7**

Test Group Subjects: CGI-S Ratings Across Study Long-Term Evaluation

| *CGI-S (n=21)* | Baseline | Week 8 | 6 Months | 12 Months |
|---|---|---|---|---|
| 7: Amongst most extreme | 3 | 1 | - | - |
| 6: Severe | 14 | 2 | 3 | 2 |
| 5: Marked | 4 | - | 1 | 3 |
| 4: Moderate | - | 9 | 1 | 3 |
| 3: Mild | - | 6 | 10 | 6 |
| 2: Borderline | - | 3 | 3 | 4 |
| 1: Normal | - | - | 3 | 3 |

**Table 8**

Placebo Cross-Over Group Subjects: CGI-S Ratings Across Study Long-Term Evaluation

| *CGI-S (n=19)* | Baseline | Week 8 | 6 Months | 12 Months |
|---|---|---|---|---|
| 7: Amongst most extreme | 2 | 2 | 1 | - |
| 6: Severe | 14 | - | 1 | 2 |
| 5: Marked | 3 | 5 | - | - |
| 4: Moderate | - | 7 | 8 | 9 |
| 3: Mild | - | 4 | 8 | 7 |
| 2: Borderline | - | - | - | - |
| 1: Normal | - | 1 | 1 | 1 |

The substantial progressive improvements in CGI-S ratings across study evaluation were maintained through to the 12-month follow-up evaluation for both subjects in the initial test and placebo cross-over groups. Only 2 subjects remained in the '6: severe' category at 12 months post-treatment compared with 14 in each group at baseline evaluation. Sixteen of 21 test group subjects (76%) were in the '1: normal' to '4: moderate' category at 12 months post-treatment compared with none at baseline evaluation. Seventeen of 19 placebo cross-over group subjects (89.5%) were in the '1: normal' to '4: moderate' category at 12 months post-treatment compared with none at baseline evaluation.

**CGI-C Ratings**

Tables 9 and 10 below show the number of subjects within each CGI-C category across the long-term 12-month evaluation period for subjects in the initial test group and placebo cross-over group, respectively.

**Table 9**

Test Group: CGI-C Ratings Across 12 Months Evaluation

| *CGI-C Rating (n=21)* | Week 8 | 6 Months | 12 Months |
|---|---|---|---|
| 1: Very Much Improved | 10 | 12 | 12 |
| 2: Much Improved | 8 | 6 | 5 |
| 3: Minimally Improved | 3 | 2 | 3 |
| 4: No Change | - | - | - |
| 5: Minimally Worse | - | 1 | 1 |
| 6: Much Worse | - | - | - |
| 7: Very Much Worse | - | - | - |

**Table 10**

Placebo Cross-Over Group: CGI-C Ratings Across 12 Months Evaluation

| *CGI-C Rating (n=19)* | Week 8 | 6 Months | 12 Months |
|---|---|---|---|
| 1: Very Much Improved | 5 | 8 | 9 |
| 2: Much Improved | 11 | 7 | 7 |
| 3: Minimally Improved | 2 | 3 | 3 |
| 4: No Change | 1 | - | - |
| 5: Minimally Worse | - | - | - |
| 6: Much Worse | - | - | - |
| 7: Very Much Worse | - | 1 | - |

CGI-C ratings progressively improved from 8 weeks through 12 months post-treatment evaluation for both subject groups. At 12 months post-treatment, 17 of 21 (81%) initial test group subjects and 16 of 19 (84%) placebo cross-over group subjects were rated as being '1: very much improved' or '2: much improved'

## DISCUSSION

It called the attention the very similar statistical findings for both groups of autistics when the initial placebo was also treated with the same methodology use for the initial active group. Therefore, these findings strongly illustrate that not only does application of the spectrum by Erchonia Laser device effect a sizable, statistically significant and clinically meaningful improvement in all of the key evaluable behaviors characteristic of autism disorder in children and adolescents, but it continues to affect a progressive and meaningful improvement in symptoms for up to 12 months following completion of the treatment administration protocol, during which time no additional treatment administrations were applied and no changes were made in subjects' non-study medication and/or therapy use to treat autistic symptoms.

We had demonstrated that LLLT can be an effective tool for reducing irritability and other symptoms and behaviors associated with ASD in children and adolescents. It is necessary to discuss now the pathophysiology to explain that improvement continued increasing over time until 12 months, after finishing LLLT treatment.(1-3, 7)

Several authors have suggested that applying near-infrared light to the head of animals that have suffered TBI produces improvement in neurological functioning, lessens the size of the brain lesion, reduces neuroinflammation, and stimulates the formation of new neurons.(9-11) Other authors have emphasized that photobiomodulation using LLLT has been demonstrated to be as safe and effective technique in significantly improving the memory, attention, and mood performance in for patients with chronic traumatic brain injury.(1, 9, 12-16)

It has been argued that LLLT promotes cell and neuronal repair and brain network rearrangement in many neurologic disorders. LLLT fast tracks wound-healing as mitochondria respond to light in the red and near infrared (NIR) spectrum. (1, 9, 12-16) It has been demonstrated that weak light directs the leading edge of growth cones of a nerve. Some authors have demonstrated that is capable of enhancing peripheral nerve regeneration following a crush injury. (17-20) Reports are now emerging that LLL T and photobíomodulation significantly upregulate brain-derived neurotrophic factor (BDNF), a factor highly associated with dendritic sprouting, neuroplasticity, and brain connectivity.(3, 14, 15, 21) In summary, nerve cells appear to thrive and grown in the presence of low energy light, and we think that the effect seen here is associated with rearrangements of connectivity.(1, 3, 22, 23)

Therefore, we argue once more, that clinical improvement of the key evaluable behaviors characteristic of autism disorder in children and adolescents, for up to 12 months after following treatment completion, might be patho-physiologically supported with the fact that LLLT progressively rearrange anatomical, functional and effective connectivity, modifying those neuronal networks related to the complex symptoms in autistics.(1, 3, 8, 22)

We conclude that LLLT is a promising and non-invasive tool to treat ASD patients, offering the possibility of clinical improvements in a syndrome where current treatment methods are scarce and not effective.

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