Clinical Trial Report

A Comparative, Multi-Center, Double Blind, Randomized Clinical Trial to Assess the Safety and Efficacy of the "Laser Toothbrush," a Low-Level Laser Therapy Toothbrush for the Treatment of Dentin Hypersensitivity

Protocol Number: MNH-LTB-002 / Version No. 002-1

Object: Medical Instrument

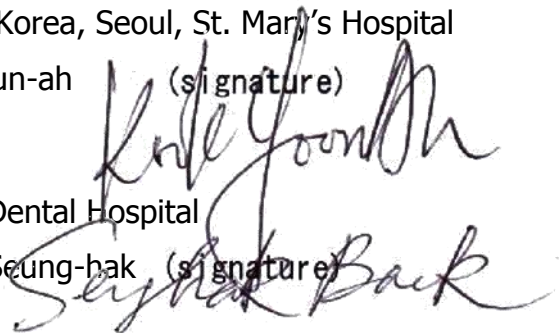Research Period: February 16, 2009 to April 8, 2009

Institutions: The Catholic University of Korea, Seoul, St. Mary's Hospital
Seoul National University Dental Hospital

Investigators: The Catholic University of Korea, Seoul, St. Mary's Hospital

Associate Professor Guk Yun-ah   (signature)

Seoul National University Dental Hospital

Associate Professor Baek Seung-hak   (signature)

[Overview]

Title of the Clinical Trial	**A Comparative, Multi-Center, Double Blind, Randomized Clinical Trial to Assess the Safety and Efficacy of the "Laser Toothbrush," a Low-Level Laser Therapy Toothbrush for the Treatment of Dentin Hypersensitivity**
Name of the Medical Instrument for the Clinical Trial	Laser Toothbrush
Indication	Dentin hypersensitivity
Institutions and Investigators	1) Institutions: The Catholic University of Korea, Seoul, St. Mary's Hospital; Seoul National University Dental Hospital 2) Investigators Guk Yun-ah: Associate Professor at Catholic University of Korea, Seoul, St. Mary's Hospital Baek Seung-hak: Associate Professor at Seoul National University Dental Hospital
Sponsor	Medical & Human Technology Co., Ltd. (hereinafter, referred to as M&H)
Research Design	Comparative, double blind, random allocation, and multi-center
Period	About 6 months after permission by the Korea Food and Drug Administration
Purpose	To assess the safety and efficacy of the "Laser Toothbrush," a low-level laser therapy toothbrush for the treatment of dentin hypersensitivity
Definitions of the Test Group and Control Group	Test Group: A group using Laser Toothbrushes Control Group: A group using placebo Laser Toothbrushes
Trial Method	The clinical trial was performed under the criteria for the management of a clinical trial for medical instruments and the Protocol approved by the commissioner of the Korea Food and Drug Administration as follows: 1. The medical instrument used for this clinical trial The selected subjects shall use the Laser Toothbrush for a tooth showing symptoms of dentin hypersensitivity in the oral cavity, and specifically on the single tooth with the most pain for one month. 2. Period of Medical Instrument Use in the Clinical Trial ① Assign subjects to the test and control groups at a ratio of 1:1, and have them use the medical instrument as follows: ② The subjects of the test group shall use Laser Toothbrushes for a tooth showing the symptoms of dentin hypersensitivity in the oral cavity, and specifically on the single tooth with the most pain for one month. ③ The subjects of the control group shall use placebo Laser Toothbrushes for a tooth showing the symptoms of dentin hypersensitivity in the oral cavity, and specifically on the single tooth with the most pain for one month. 3. Period Clinical Medical Instrument Use One month < Prohibition of Combined Medications > 1) Combined medications shall not be used, with the exception of unavoidable

	cases. 2) If any combined medications are used, this fact shall be accurately stated in the Case Report Form and related documents. ※ Toothpastes (e.g., Syrin Med F and Sensitive Teeth) specifically dedicated to sensitive teeth that contain calcium phosphate or Colloidal Anhydrous Silica, as well as their equivalent medications and medical instruments 4. Adverse Events When an unexpected adverse event occurred during the use of a Laser Toothbrush, its use was stopped. The trial investigators determined whether or not to resume using the Laser Toothbrush.
Trial Period	February 16, 2009 to April 8, 2009
Number of Trial Subjects	97 subjects were collected; 1 subject failed to pass our screening criteria. Nine subjects failed to complete the trial. A total of 87 subjects completed the clinical trial.
Criteria for the Selection of Trial Subjects	■ The trial subjects had to meet the criteria below: ① Females or males between 20 to 65 years of age ② Excellent physical health ③ Diagnosed with dentin hypersensitivity but not with periodontitis or gingivitis ④ No dental caries or tooth fractures ⑤ Ability to understand and record descriptions of quantitative measurement for dentin hypersensitivity ⑥ Written consent from themselves or their legal representatives to being trial subjects
Criteria for the Disqualification of Test Subjects	■ Disqualifying criteria for this clinical trial were: ① Lactating pregnant women or female patients ② Participation in another experimental research or use of any experimental medications or devices within 30 days of the registration of this clinical trial ③ A history of any oral tumors within the past five years ④ Active infection requiring whole-body medical treatment ⑤ Any previous disqualification as a clinical trial subject due to the presence of serious medical or psychiatric diseases ⑥ Patients with known alcohol or medication abuse, or psychological disorders ⑦ Patients with serious hemorrhagic diseases
Assessment Items	1. Efficacy Variable Pain Treatment Rate at the Primary End Point: Measure and compare Visual Analog Scale (VAS) one month after start of treatment. Secondary End Point: Measure and compare one month after start of treatment. 1) Wong-Baker Faces Scale 2) Electric Pulp Test (EPT) 3) Plaque Index Test (1) Assessment Criteria Primary Efficacy Variable: Mean variation in the VAS of dentin hypersensitivity one month after baseline: The primary efficacy variable is the mean variation in the VAS of dentin hypersensitivity measured one month after baseline against that of dentin hypersensitivity at baseline. If the mean variation in the VAS of the test group against the control group is

	greater than 2 cm, the trial is assessed to be successful.
	The treatment groups shall be compared and analyzed by performing a Student's unpaired t-test or a Wilcoxon's rank sum test depending on whether or not the pain difference value of dentin hypersensitivity meets normality. In order to check if the results of comparison between the treatment groups and analysis are different in the two trial institutions, multivariate analysis shall be performed by setting the trial institutions to be variates.
	① Pain of Dentin Hypersensitivity: A treatment rate shall be measured by comparing the pain score of dentin hypersensitivity at the screening stage with that of dentin hypersensitivity right after the one-month clinical trial is completed.
	② Measurement Method:
	Place the end of a dental air syringe perpendicular about 3 mm from the cervix surface of the target teeth. Then apply instantaneous cold air to the syringe end 2 times to assess the patient's discomfort for cold stimulation.
	(2) Assessment Method
	1) Intent-To-Treat (ITT) Set: All trial subjects registered into this clinical trial and randomly allocated
	2) Per-Protocol (PP) Set: Subjects who completed this trial in accordance with the Protocol among the subjects of the ITT Set; Any subjects deemed to have seriously broken the Protocol in the cases below shall be excluded:
	※ Subjects who give up the trial without continuing to participate in the trial for the period stated in the Protocol (Less than 70% compliance)
	※ Subjects who use prohibited combined medications or medical instruments
	※ Subjects who broke the Protocol seriously
	(3) Statistical Methods (Primary Assessment Variable)
	The main result variable for assessing the efficacy of this trial is the mean variation in the VAS in one month compared with the VAS at baseline.
Statistical Analysis	1. Method for Efficacy Analysis
	Perform either the Student's unpaired t-test or Wilcoxon's rank sum test depending on whether or not the VAS meets normality to compare and analyze the treatment groups. In order to check if the comparison and analysis results of one trial institution are different from those of the other institution, perform analysis of covariance by setting the institutions as covariates.
	2. Method for Safety Analysis
	Perform either the Chi-square test or Fisher's exact test to check if the occurrence rate of side effects reported to the subjects is different between the sets. In addition, perform a descriptive analysis of the level of difference in severity and types between the sets.
Summary of Statistical Analysis Results	1. Efficacy Analysis
	Among the 97 subjects in total, 96 subjects, with the exception of one subject disqualified from the screening, were assigned to the ITT set. 87 subjects, with the exception of 9 subjects disqualified due to decreased compliance, inability to observe, refusal to participation in the trial, and other reasons, were assigned to the PP set. At that point, two efficacy assessments were performed.
	The first efficacy assessment was performed by analyzing the statistics regarding the mean variation in the VAS in one month (Visit 3) against the VAS at baseline. The result showed a statistically significant difference between the

test group and control group in both the ITT set and the PP set (p-value = 0.0001). The result of covariance analysis did not show a statistically significant difference between the trial institutions (p-value = 0.6176).

The second efficacy assessment variables were the Wong-Baker Faces Scale, Electric Pulp Test (EPT), and plaque index test.

In the ITT set, there was a statistically significant difference on the Wong-Baker Faces Scale between the test group and control group (p-value = 0.0001). The result of the EPT did not show a statistically significant difference in one month (Visit 3) against baseline between the test group and the control group. The results of the plaque index test were the same.

In the PP set, the results of the Wong-Baker Faces Scale and EPT were the same as those of the ITT set. However, the result of the PIT showed a statistically significant difference in one month (Visit 3) against baseline between the test group and control group (p-value = 0.0162).

2. Safety Analysis

The distribution of the subjects who showed adverse events among the 96 subjects in the ITT set was analyzed. As a result, 9 subjects (18.75%) showed adverse events in the test group, while 14 subjects (29.17%) showed them in the control group. There was no statistically significant difference between the test group and control group (p-value = 0.2319). In addition, 9 (18.75%) out of 48 subjects in the test group showed 10 cases of adverse events (37.04%), and 14 (29.17%) out of 48 subjects in the control group showed 17 cases of adverse events (62.96%). The adverse events were categorized based on the WHO-ART classification table.

While this trial was being performed, adverse events related to the trial devices occurred in 2 subjects (4.17%) in the test group, and 7 subjects (14.58%) in the control group. There was no significant difference in the occurrence of adverse events related to the trial devices between the test group and the control group.

Two subjects (4.17%) in the test group and 7 subjects (14.58%) in the control group took combined medications. There was no statistically significant difference between the 2 groups (p-value = 0.1586).

As for the result of assessing medication compliance, one subject (2.08%) in the test group and one subject (2.08%) in the control group did not reach the appropriate compliance. In addition, there was no statistically significant difference between the 2 groups (p-value = 1.0000).

[Table of Clinical Trial Schedules]

Observation and Inspection Items	Sc	V1	V2	V3
	-D7	D1	D14	D28
Written Consent of Trial Subjects[2]	✗			
Screening of the Criteria for Selection/Exclusion	✗			
Basic Information on the Trial Subjects	✗			
Examining Case History/History of Drug Use	✗			
Radiation Test[1]	✗			
Randomization	✗			
Pregnancy Test	✗			✗
Use of the Clinical Medical Instruments		✗	✗	✗
VAS	✗		✗	✗
Wong-Baker Faces Scale	✗		✗	✗
Electric Pulp Test	✗		✗	✗
Plaque Index Test	✗		✗	✗
Assessment of Adverse Events and Verification of Combined Medications			✗	✗

1) [1] A panoramic test was performed to check the status of maxillofacial fracture.

2) [2] Written consent shall be received before any action related to this clinical trial.

3) Visits after start of treatment shall be performed at intervals of about two days.

[Acronyms or Definitions of Terminology]

AE	Adverse event
ALP	Alkaline phosphatases
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under Curve
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
ECG	Electrocardiogram
IEC	Independent Ethics Committee
ITT	Intent-to-Treat
KGF	Keratinocyte growth factor
PP	Per Protocol
RBC	Red Blood Cell
SAE	Serious Adverse Event
UNL	Upper Normal Limit
VAS	Visual Analog Scale
WBC	White Blood Cell
Clinical Medical Instruments	**Medical Instruments for the Clinical Trial (Medical Instruments for the Test Group and for the Control Group)**

Table of Contents

1. Title and Steps of the Clinical Trial

A Comparative, Multi-Center, Double Blind, Randomized Clinical Trial to Assess the Safety and Efficacy of the "Laser Toothbrush," a Low-Level Laser Therapy Toothbrush for the Treatment of Dentin Hypersensitivity

2. Clinical Trial Institutions and Investigators

2.1. Names and Addresses of the Institutions

Institution Name	Address
Catholic University of Korea, Seoul, St. Mary's Hospital	505, Banpo-dong, Seocho-gu, Seoul, Korea
Seoul National University Dental Hospital	275-1, Yeongeon-dong, Jongno-gu, Seoul, Korea

2.2. Names and Titles of the Clinical Trial Investigators and Staff

2.2.1. Clinical Trial Investigators

Name	Hospital Name and Title
Guk Yun-ah	Associate Professor at the Catholic University of Korea, Seoul, St. Mary's Hospital
Baek Seung-hak	Associate Professor at Seoul National University Dental Hospital

2.2.2. Clinical Trial Staff

Name	Hospital Name and Title
Goh Yeong-gyeong	Full-Time Instructor at the Catholic University of Korea, Seoul, St. Mary's Hospital
Park Je-eok	Associate Professor at the Catholic University of Korea, Seoul, St. Mary's Hospital
Kim Chang-hyeon	Assistant Professor at the Catholic University of Korea, Seoul, St. Mary's Hospital
Ryu Jun-ha	Dentist at the Catholic University of Korea, Seoul, St. Mary's Hospital
Seok Gyeong-eun	Dentist at the Catholic University of Korea, Seoul, St. Mary's Hospital
Park Na-seon	Dentist at the Catholic University of Korea, Seoul, St. Mary's Hospital
Gwon Sun-gil	A Student at the Graduate School of Dentistry at the Catholic University of Korea, Seoul, St. Mary's Hospital
Bayome Mohamed	A Student at the Graduate School of Dentistry at Catholic University of Korea, Seoul, St. Mary's Hospital
Jeong Ho-jeong	Research Nurse at the Department of Dentistry at the Catholic University of Korea, Seoul, St. Mary's Hospital
Kim Geun-wu	Dentist at the Department of Orthodontics, Seoul National University Dental Hospital
Kim Bo-mi	Dentist at the Department of Orthodontics, Seoul National University Dental Hospital

Ahn Hyo-won	Dentist at the Department of Orthodontics, Seoul National University Dental Hospital
Seo Yu-jin	Dentist at the Department of Orthodontics, Seoul National University Dental Hospital
Ma Su-jeong	Dentist at the Department of Orthodontics, Seoul National University Dental Hospital
Gang Mi	Dentist at the Department of Orthodontics, Seoul National University Dental Hospital

2.2.3. Clinical Statistics Staff

Name	Company Name and Title
Kim Min-won	Clinical Team at LSC Standard / Researcher

2.3. Names and Titles of the Managers for the Medical Instruments for the Clinical Trial

Name	Hospital Name and Title
Guk Yun-ah	Associate Professor at the Catholic University of Korea, Seoul, St. Mary's Hospital
Kim In-gyeong	CTC at the Clinical Research Center at Seoul National University Dental Hospital

3. Sponsor of the Clinical Trial

3.1. Sponsor of the Clinical Trial and Contact

Sponsor	Ji Man-su, CEO of M & H
Contact Name	Ji Man-su
Address	436-16, Changok-ri, Paltan-myeon, Hwaseong-si, Gyeonggi-do, Korea
Zip Code	445-949
Phone No.	Daytime: 82-31-452-1495 Night: 82-10-2065-7183
Facsimile No.	82-31-452-1497

3.2. Clinical Research Organization and Associate

Clinical Research Organization	LSC Standard
Address	Third Floor, Hansaem Building, 31-36, Nokbeon-dong, Eunpyeong-gu, Seoul, Korea
Zip Code	122-827
Phone No.	Daytime: 82-2-382-3323 Night: 82-10-2434-1121
Facsimile No.	Daytime: 82-2-357-3892

4. Background and Purpose of the Clinical Trial

Dentin hypersensitivity is a short and acute pain that occurs when thermal, evaporating, mechanical, osmotic, or chemical stimulation are applied to an exposed dentin rather than due to another decayed tooth or a disease.

Dentin hypersensitivity can occur at any age. Typically, however, the disease most frequently occurs in those in their 20's to 40's. It frequently occurs along with the recession of the gumline. At higher ages, dentin hypersensitivity can be gradually cured through treatments using the permeability of the dentin and pulpal reaction. Research has shown that this disease occurs in females more frequently than males. Its occurrence is affected by the hygiene of the oral cavity, differences in diet, and the frequency of treatments at dental clinics.
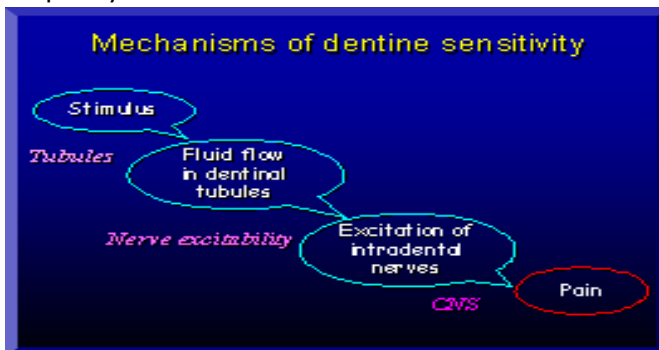
(Figure 1.) Mechanism of Dentin Hypersensitivity

The exposure of a dentine occurs mainly at the molar teeth due to periodontal diseases. Interestingly, the occurrence frequency of dentin hypersensitivity decreases at parts whose plaque index is high. Its occurrence frequency in adults ranges from 4% to 74%, and varies depending on research reports. According to the research performed at professional clinics for periodontal diseases, the occurrence frequency of dentin hypersensitivity ranges from 60.3% to 98%.

In order to understand the causes of dentin hypersensitivity, the causes of dentine exposure need to be examined. The causes include traumatic tooth preparation, bacterial contamination, desiccated dentin, hemostatic agents, removal of the smear layer, acidity of the cement, hydrostatic pressure, heavy pressure for seating the restoration, and a too-thin cement mix.

1. Loss of Periodontal Tissue (Recession of Gum): In this case, dentin hypersensitivity hardly occurs, and may occur even at a young age. The higher the age, the higher the occurrence frequency and the more severe the symptoms.

(Figure 2.) A Wide Range of Exposure of Apical Dentin due to Periodontal Diseases

(Figure 3.) Typical Hypersensitive Cervical Dentin

2. Loss of Teeth Enamel: This occurs due to attrition, abrasion, or erosion. Dental caries occur for the same causes as well. The loss of teeth enamel occurs at a buccal cervix due to interaction between abrasion and erosion as shown in Figure 3. Abrasion occurs mainly due to toothbrushing, and the

abrasive contained in toothpastes is the direct cause of abrasion. In addition, the thickness or shape of a bristle, as well as the method, frequency, or duration of toothbrushing, indirectly affect the abrasives contained in toothpastes. Erosion occurs at a low-pH value, which is acidic and caused by acid reflux, foods, or occupational characteristics. When teeth are exposed to liquids with a low pH value such as orange juice, damage to teeth is made more severe due to mechanical abrasion. It can be observed that a dentine, which is exposed and yet does not show hypersensitivity, has little dentinal tubules, but does have a smear layer, or that the dentinal tubules, if any, are clogged with mineral deposits (Figure 4).

(Figure 4.) Sclerotic Dentine Generated due to the Long-Term Exposure of the Dentin

If the exposed dentinal tubules are occluded, the penetrance of the dentin will decrease and hypersensitivity will be able to be cured. Drugs such as strontium chloride or fluoride solution can be used. Electrophoresis or a variety of laser instruments can also be used. Grossman asserted that requirements for the cure of dentin hypersensitivity were: no stimulation to pulp, no pain during intervention, no coloration, and continued effects. As a method for meeting these requirements, laser treatment is recommended.

Since treatment using the Nd:YAG laser was first performed by Mastumoto et al. to cure dentin hypersensitivity, research on diverse laser wavelengths has been performed. The He-Ne laser and the GaAlAs laser, which are low-level lasers, cause analgesic effects by the depolarizing blockade of C-type nerve fibers, while the CO_2 laser and the Er:YAG laser do so by inducing the occlusion or stricture of dentinal tubules. The Nd:YAG laser causes neuroanesthesia directly, in addition to the occlusion or stricture of dentinal tubules. Energy from the Nd:YAG laser is delivered to the pulp via the dentin, and creates thermal effects and a pulp painkilling effect through the nervous system to the microcirculation of pulp. In addition, the Nd:YAG laser blocks both C-type and Aβ nerve fibers.

In previous studies of the Nd:YAG laser, laser output ranged from 0.3W to 10W; however, 1W or 2W of output was typically applied, and the curative effect was 52% to 100%. Mastumoto et al. reported that a method of applying 10W of high output for 0.1 seconds five times created a 100% effect. Yonaga, Gelskey, and Kobayashi reported that it was more effective when black ink was applied to the dental cuticle in order to improve laser absorption. Since the Nd:YAG energy penetrates the dentin deep, thermal damage to the pulp should be always considered. White et al. reported that the pulp was not damaged when 2W and 20Hz of laser output was applied to teeth whose remaining dentin had 1 mm of thickness, and that the temperature rose by 13.4℃ in the pulp cavity when black ink was used as a sorbefacient and when 2W and 20Hz of laser output was applied for 10 seconds to teeth whose remaining dentin had 2 mm of thickness.

Recently, the Light Emitting Diode (LED) has been recognized as a light source for medical treatment, which can replace Low Level Laser Treatment (LLLT). LED was developed initially for display use; however, it is easily adapted to medical treatment as a light source at a wavelength range of a low-level, narrow bandwidth with one color.

The tissues of the human body or other substances show different absorption rates for each light wavelength. That is, the absorption of light having a specific wavelength from a specific tissue or cell causes diverse biological reactions. This phenomenon occurs the same at all light sources of the same wavelength as well. The recently developed LED, having a specific wavelength, is a light source that efficiently arouses bio-stimulation to cells or tissues in a specific body part.

The LED is the best light source for effective stimulation of tissues when constant treatment needs to be performed on a large body part; thus, it can be used clinically to ease chronic or serious pain.

There are a variety of methods for applying light at the wavelength, intensity, and frequency appropriate for human bodies relative to dentistry.

Examples of international manufacturers for these kinds of products include THOR International Ltd., Quantum Devices, Inc., and Bioscanlight, Inc. A Korean manufacturer, Biophoton Co. Ltd., is scheduled to release products using LED soon, and inventions using LED are expected to increase gradually.

In this regard, the purpose of this trial is to review the utility of the Laser Toothbrush by comparing changes in the pain and discomfort of patients who used a regular toothbrush equipped with a diode laser to teeth with dentin hypersensitivity 3 times a day for a month rather than black ink.

It is crucial to remove endogenic and exogenous acids, which are the main predisposing etiologic factors of dentin hypersensitivity, and to cure damage done to teeth by toothbrushing. Through dietary advice and training/education about proper toothbrushing methods, the secondary dentin can be created, and the entrance of the dentinal tubules can be occluded again.

The placebo product used in this clinical trial is the same as the product of the test group, with the exception of laser output, and does not affect toothbrushing; thus, the placebo product was selected to be used for the control group.

4.1 Roles of the Laser Toothbrush in Dentin Hypersensitivity

This instrument is designed to be a toothbrush utilizing a laser light source. Typically, a bristle is inserted into the main body of Laser Toothbrush before toothbrushing. The purpose of this product is to cure dentin hypersensitivity by the use of an indirectly radiating low-level laser.

4.2. Expected Side Effects of the Laser Toothbrush

During use, allergies or electric shock may occur. When one of these phenomena occurred, the trial subject was prohibited from further use of the Laser Toothbrush and received appropriate treatment from the trial investigators or a medical specialist.

5. Medical Instruments for the Clinical Trial

5.1. Code Name, Overview, and Components

● Laser Toothbrush

1) Product Name (Code Name): Laser Toothbrush

2) Overview: This instrument is designed to be a toothbrush that utilizes a laser light source. Typically, a bristle is inserted into the main body of Laser Toothbrush before toothbrushing. The purpose of this product is to cure dentin hypersensitivity by the use of an indirectly radiating low-level laser.

3) Materials or Ingredients / Content

Serial No.	Part Name	Part Management No. or [Material Name]	Specification	Quantity	Remarks
1	Main Body	ABS HF-380	120 ㎜ x 23.5 ㎜	1	LG Chem Co., Ltd., etc. Equivalent Products
2	Laser Emitting Diode (LLLT)	L1	Outer Diameter: 5.6 ㎜; Color: Red; Wavelength: 635 ㎚	1	Guangzhou LATOP Optics Electronics Co., LTD.
3	Bristle	Polybutylene Terephthalate (PBT)	CAS No.26062-94-2	1	DSM Engineering Plastics (Contact with oral mucosa)
4	Supporter	Polycarbonate Copolymer (PC)	CAS No.103598-77-2 Dimensions: 70 ㎜ x12 ㎜ x23 ㎜	1	Hasung Infra (Contact with oral mucosa)
5	S/W	S1	Tact switch	1	In Sung
6	IC	U2	PIC10F200	1	Microchip
		U1	ACT6305	1	Active-semi
7	Capacitor	C1	22uF/10V	1	AUK
		C2	22uF/10V	1	AUK
8	Chip Capacitor	C4	C104	1	AUK
		C5 C6 C7	C104	3	AUK
9	TR	Q1	2SC5342	1	AUK
10	Inductor	T1	4.7uH	1	AUK
11	Resistor	R1	10k	1	AUK
12	Resistor	R2	4.7K	1	AUK
13	Resistor	R3	000R/3.3V	1	AUK
14	Resistor	R5	330	1	AUK
15	Battery	BT1	AA Size	1	Market purchase
16	Software	AW071121/Laser t1	Ver Rev.0		M & H

4) Storage and Shelf Life Methods:

- Keep this instrument in a place that ensures ventilation.
- Take precautions not to expose the instrument to vibration or impact during transport or in any other cases.
- Avoid keeping this instrument in a place where chemicals are stored or that generates gas.

◆ Descriptions of the Exterior (Features of Each Part)

No.	Part Name	Details
1	Toothbrush	A bristle for replacement (Replaceable every 30 days per 1EA)
2	Laser Output	Generates 635nm/6mW of laser wavelength.
3	Mode Switch	Turn on or off laser output.
4	Battery	A 1.5V AA-size battery

● Placebo Laser Toothbrush

1) Product Name (Code Name): Placebo Laser Toothbrush

2) Overview: This instrument is designed to be a toothbrush using the low-level LED rather than a laser light source. Typically, a bristle is inserted into the main body of Laser Toothbrush before toothbrushing. This instrument was manufactured for the use of the control group in this trial. It is not available to the public.

3) Materials or Ingredients / Content

Serial No.	Part Name	Part Management No. or [Material Name]	Specification	Quantity	Remarks
1	Main Body	ABS HF-380	120 ㎜ x 23.5 ㎜	1	LG Chem Co., Ltd., etc. Equivalent Products
2	LED	L1	Outer Diameter: 5.6 ㎜; Color: Red; Wavelength: 635 ㎚	1	Guangzhou LATOP Optics Electronics Co., LTD.
3	Bristle	Polybutylene Terephthalate (PBT)	CAS No.26062-94-2	1	DSM Engineering Plastics (Contact with oral mucosa)
4	Supporter	Polycarbonate Copolymer (PC)	CAS No.103598-77-2 Dimensions: 70 ㎜ x12 ㎜ x23 ㎜	1	Hasung Infra (Contact with oral mucosa)
5	S/W	S1	Tact switch	1	In Sung
6	IC	U2	PIC10F200	1	Microchip
		U1	ACT6305	1	Active-semi
7	Capacitor	C1	22uF/10V	1	AUK
		C2	22uF/10V	1	AUK
8	Chip Capacitor	C4	C104	1	AUK
		C5 C6 C7	C104	3	AUK
9	TR	Q1	2SC5342	1	AUK
10	Inductor	T1	4.7uH	1	AUK
11	Resistor	R1	10k	1	AUK
12	Resistor	R2	4.7K	1	AUK
13	Resistor	R3	000R/3.3V	1	AUK
14	Resistor	R5	330	1	AUK
15	Battery	BT1	AA Size	1	Market purchase
16	Soft Ware	AW071121/Laser t1	Ver Rev.0		M & H

4) Storage and Shelf Life Methods:
- Keep this instrument in a place that ensures ventilation.
- Take precautions not to expose the instrument to vibration or impact during transport or in any other cases.
- Avoid keeping this instrument in a place where chemicals are stored or that generates gas.

◆ **Descriptions of the Exterior (Features of Each Part)**

No.	Part Name	Details
1	Toothbrush	A bristle for replacement (Replaceable every 30 days per 1EA)
2	Laser Output	Generates 635nm/12.9μW of laser wavelength.
3	Mode Switch	Turns on or off laser output.
4	Battery	A 1.5V AA-size battery

5.2. Labeling

The labels on the containers or packing boxes of the medical instruments for this clinical trial state the following in accordance with Article 19 of the Medical Device Act Enforcement Regulations:
- The medical instruments are used for clinical trials, and cannot be used for purposes other than clinical trials
- Name and Address of the Manufacturer or Importer
- Manufacturer (Manufacturing Country and Manufacturer Name) in Case of Imported Products
- Product Name, Type Name (Model Name), and Product Approval (Report) No.
- Manufacturing No. and Date
- Weight of Packing Unit

refill
Toothbrush

Laser beam
output

Mode switch

Battery holder
1.5V AA size×1
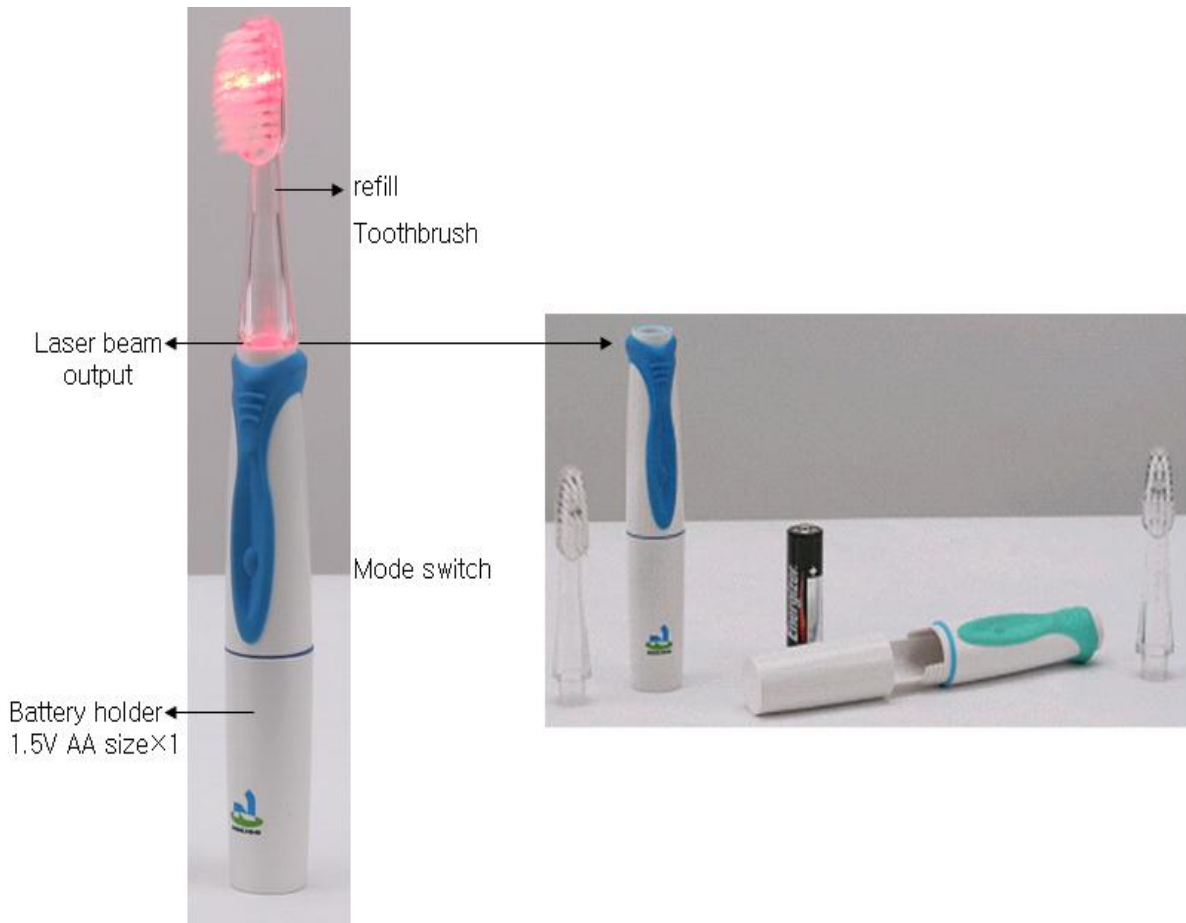
5.3. Management and Record of the Medical Instruments

The medical instruments for the clinical trial were manufactured by M&H, supplied by the trial institutions, and managed by the manager of the medical instruments appointed by the heads of the trial institutions. M&H delivered the quality warranty of the medical instruments for this clinical trial to the manager of the instruments when delivering the instruments. The manager verified if the instruments provided by the sponsor had been received and their quantity in writing, and signed the document.

The delivery of the instruments was performed in accordance with the prescription signed by the doctor who was named in the Protocol as participating in this trial. The initials of the patients in English, patient numbers, delivery dates, and quantity were recorded in the ledger for the receipt of the medical instruments.

When the quantity of the medical instruments kept by the manager was checked on a regular basis in order to check the history and details of instrument use, and when the clinical trial was completed or stopped, the collection or treatment of all the medical instruments was performed at the request of the Clinical Research Associate (CRA).

In all cases, the trial staff did not supply the medical instruments and related goods to another trial staff or institution member, and did not use them for any use other than the details stated in the Protocol before obtaining approval from the trial sponsor.

6. Target Disease

Dentin Hypersensitivity

7. Criteria for the Selection or Exclusion of Trial Subjects, Targeted Number of Subjects, and Source Data

7.1. Criteria for the Selection of Trial Subjects

▪ The trial subjects shall meet the criteria below:

① Females or males between the age of 20 to 65

② Excellent physical health

③ Diagnosed with dentin hypersensitivity but not with periodontitis or gingivitis

④ No dental caries or tooth fractures

⑤ Ability to understand and record descriptions of quantitative measurement for dentin hypersensitivity

⑥ Written consent from themselves or their legal representatives to being trial subjects

7.2. Criteria for the Exclusion of Trial Subjects

▪ Disqualifying criteria for this clinical trial were:

① Lactating pregnant women or female patients

② Participation in another experimental research or use of any experimental medications or devices within 30 days of the registration of this clinical trial

③ A history of any oral tumors within the past five years

④ Active infection requiring whole-body medical treatment

⑤ Any previous disqualification as a clinical trial subject due to the presence of serious medical or psychiatric diseases

⑥ Patients with known alcohol or medication abuse, or psychological disorders

⑦ Patients with serious hemorrhagic diseases

7.3. Targeted Number of Subjects and Source Data

7.3.1. Estimation of Trial Subjects

In this trial, the treatment efficacy of the Laser Toothbrush, a low-level laser therapy toothbrush for the treatment of dentin hypersensitivity, is assessed. The primary object of interest is the mean variation in the VAS of dentin hypersensitivity measured one month after baseline against that of dentin hypersensitivity at baseline. Dentin hypersensitivity is a unique sensory or pain reaction that occurs in the dental root exposed by thermal, mechanical, or chemical stimulation and that does not give discomfort to normal teeth. Its pain intensity is measured by the Visual Analog Scale (VAS). The unit index of the VAS is 10 cm. In a previous study where low-level laser therapy was performed for dentin hypersensitivity patients, the pain intensity of dentin hypersensitivity measured by the VAS is shown in the table below:

[Measurement Result of the VAS for Dentin Hypersensitivity]

Literature No.	Stimulation	N	Treatment Period	Test Group		Control Group	
				Before Mean S.D	After Mean S.D	Before Mean S.D	After Mean S.D
1	Air+Tactile	Test Group: 45 Control Group: 27	Pre-Treatment/Right After Treatment	4.62 1.63	1.69 1.80	4.82 1.88	3.96 2.24
2	Tactile	54 (in Total)	Pre-Treatment/Four Weeks	42.5 41.4	11.8 28.5	70 15.3	72.5 14.8
	Air		Pre-Treatment/Four Weeks	64.8 32	18.5 30.8	65.8 9.9	68.3 8.3
3	Probe	10 (in Total)	Pre-Treatment/Four Weeks	1.76 2.82	1.70 2.31	1.86 2.92	2.66 3.07
	Water		Pre-Treatment/Four Weeks	7.10 2.10	5.50 3.30	6.61 2.31	6.32 2.94
	Air		Pre-Treatment/Four Weeks	4.75 2.65	4.61 3.14	4.08 2.91	4.76 3.26
4	Air+Tactile	24 (in Total)	Pre-Treatment /Two Weeks	6.16 2.64	2.93 2.35	5.54 2.26	5.31 2.24
	Air		Pre-Treatment /Two Weeks	6.45 2.53	3.04 2.31	5.70 2.77	5.41 2.32
	Tactile		Pre-Treatment /Two Weeks	5.87 2.77	2.73 2.44	5.37 2.29	5.20 2.20
	Air+Tactile	9 (in Total)	Pre-Treatment/Four Weeks	6.50 3.38	3.06 2.58	6.44 2.33	6.11 2.05
	Air		Pre-Treatment/Four Weeks	7.44 3.17	3.56 2.74	6.78 2.44	6.22 2.17
	Tactile		Pre-Treatment/Four Weeks	5.56 3.50	2.56 2.46	6.11 2.32	6.00 2.06

Literature 2) 100mm: Unit Index of the VAS

In the table above, the mean VAS of dentin hypersensitivity ranged from 1.18 cm to 7.44 cm at baseline in the test and control groups. The VAS was measured from a variety of patients. It was reported that the treatment effect ranged from 1.18 cm to 5.50 cm in the test group, and from 2.66 cm to 7.25 cm in the control group.

In this study, the primary efficacy variable for assessment was pain when cold stimulation was applied by using an air syringe 4 weeks after treatment. Reference 4 shows that the mean variation in the VAS four weeks after baseline was 3.88 cm in the test group and 0.56 cm in the control group. When compared with the control group, treatment efficacy was higher by 3.32 cm in the test group.

In the reference, dentin hypersensitivity patients visited a hospital and received low-level laser therapy from a medical specialist; in this study, however, it was assumed that the estimated mean variation in the VAS in the test group against the placebo control group was less than 3.32 cm when the trial subjects directly used a low-level laser therapy toothbrush in a home-care system. Accepting the experts' opinions, the mean variation in the VAS was assumed to be 2 cm based on 60% to 70% of 3.32 cm. In addition, 40 subjects in each group were calculated at 5% of significance level and 80% of the power of test by applying 3.17 cm, the highest standard deviation in the reference. When a 15% drop-out rate was considered, there were a total of 94 subjects in both of the groups (47 subjects in each group).

The hypotheses of this research are as follows:

H_0 : The treatment effects of the test group are the same as those of the control group.

H_1 : The treatment effects of the test group are not the same as those of the control group.

$$n = \frac{2\sigma^2(z_{\alpha/2} + z_{\beta})^2}{(\mu_2 - \mu_1)^2} = 40$$

Where:

μ_1: Mean variation in the VAS until completion against baseline in the test group;

μ_2: Mean variation in the VAS until completion against baseline in the placebo group;

ϵ: Superiority margin, α:0.05, β: 0.2; two-sided test

References:

1) Jung SY, Kim GH, Goh MY, Ahn YW, Park JS. Effects of Applying the Nd:YAG Laser to Hypersensitive Teeth. Academic Journal of the Korea Society of Oral Medicine 2005;30(4):

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3) de Assis Cde A, Antoniazzi RP, Zanatta FB, Rösing CK. Efficacy of Gluma Desensitizer on dentin hypersensitivity in periodontally treated patients Braz Oral Res. 2006 Jul-Sep;20(3):252-6.

4) Choi SJ, Shin KB, Kim MH. A Clinical Study on the Therapeutic Effects of the Pulsed Nd:YAG Laser on Dentinal Hypersensitivity. Academic Journal of the Korea Society of Oral Medicine 1998;23(1):11-20.

5) Shein CC, Jun S, Wang HS. Sample size calculations in clinical research 2nd ed. Marcel Dekker, New York; 2003.

7.4. Random Allocation

7.4.1. Random Allocation Schedule

In order to ensure maximum comparability between the treatment groups and the scientific validity of this clinical trial by excluding the subjective opinions of the researchers from the allocation of treatment groups, random allocation, which is a method for allocation under probability theory, was performed. Random allocation is typically performed in accordance with a random allocation table created on a computer. Independent random allocation was performed depending on trial institutions. In addition, a randomized block design with a block size of 6 and a 1:1 ratio was used in order to perform balanced random allocation between the test groups.

[Table 1] Example of Random Allocation Schedules (Trial Institution 1 and Trial Institution 2)

Participation Sequence of Subjects	Allocated Group	Participation Sequence of Subjects	Allocated Group
1	Test Group	1	Test Group
2	Placebo Group	2	Placebo Group
3	Test Group	3	Test Group
4	Test Group	4	Test Group
5	Placebo Group	5	Placebo Group
6	Placebo Group	6	Placebo Group
7	Placebo Group	7	Placebo Group
8	Test Group	8	Test Group
9	Placebo Group	9	Placebo Group
10	Test Group	10	Test Group
11	Placebo Group	11	Placebo Group
12	Test Group	12	Test Group

7.4.2. Steps for Performing Random Allocation

Once a random allocation table was drawn up, the table became owned by LSC Standard, a third-party organization, and the Contact Research Organization (CRO).

1) The researchers received written consent from the subjects during the screening period and recorded information required to determine whether or not a subject met the criteria for selection or exclusion of trial subjects, and manifestations from physical examinations. In this case, screening numbers were given to the subjects in sequence. At Seoul National University Dental Hospital, a smaller number was given to one subject by each member of the medical team in order to prevent consultation hours from becoming overbooked. At the Catholic University of Korea, Seoul, St. Mary's Hospital, only one screening number was given to subjects.

2) Finally, whether to get each subject to participate in the clinical trial was determined, and written consent was obtained from each subject. Whether each subject was appropriate for the trial or not was verified, the subjects were registered, and a number was assigned to each subject. Based on the random allocation table kept at LSC Standard, each subject was assigned to a group depending on the assigned numbers. This clinical trial was a double blind trial.

3) The random allocation table was not known to the subjects and researchers until after the study was completed.

7.4.3. Releasing Double Blind Information

1) If blinding is released accidentally or by a serious adverse event during the clinical trial before the trial is completed, blinding shall be released under the procedure stated in the Protocol as described in 2).

2) Procedure: The clinical trial staff shall contact the Clinical Research Associate (CRA). The CRA shall send a double blind release log to the staff. The staff shall fill out the log in detail and send it to the CRA. The CRA shall exclude relevant subjects from the trial and document the log.

3) During the clinical trial, double blind data was not released.

8. Period of the Clinical Trial

About 2 months after permission was received from the Korea Food and Drug Administration

9.2 Trial Design

This trial was performed under the criteria for clinical management for medical instruments and was a comparative multi-center, double blind, random allocation clinical trial to assess the safety and efficacy of the "Laser Toothbrush", a low-level laser therapy toothbrush for the treatment of dentin hypersensitivity treatment.

The end of an dental air syringe was placed perpendicularly about 3mm from the cervix surface of the target teeth of the outpatients who suffered from discomfort to cold or warm stimulation or toothbrushing. At that time, instantaneous cold air was applied to the end of the syringe twice to assess the patient's discomfort from cold stimulation. The staff measured the discomfort level and recorded it. Or a dentistry probe was located perpendicularly, and the teeth surface scratched gently along the cervix. Reaction to the mechanical stimulation was observed. One tooth with the most pain was selected as the target tooth. The significance, purposes, and method of the test was notified to the subjects. A hypersensitivity test and EPT were performed for the subjects who submitted written consent. The subjects in the test group then used Laser Toothbrushes while those in the control group used Placebo Laser Toothbrushes for one month. In a month, trial subject VAS and Wong-Baker Faces Scale scores were measured after cold stimulation. The EPT was performed to examine variation in pain scores.

* During this trial, only the toothpastes provided shall be used.

[Table 3] Trial Steps

Dentin Hypersensitivity Patients

↓

Randomization

↙ ↘

Test Group Laser Toothbrush 1 month of use		Control Group Placebo Laser Toothbrush 1 month of use

↓

End point

Primary End Point ① Visual Analog Scale (VAS)
Secondary End Point ② Wong-Baker Faces Scale
③ Electric Pulp Test
④ Plaque Index Test

↓

Changes in Pain from Dentin Hypersensitivity
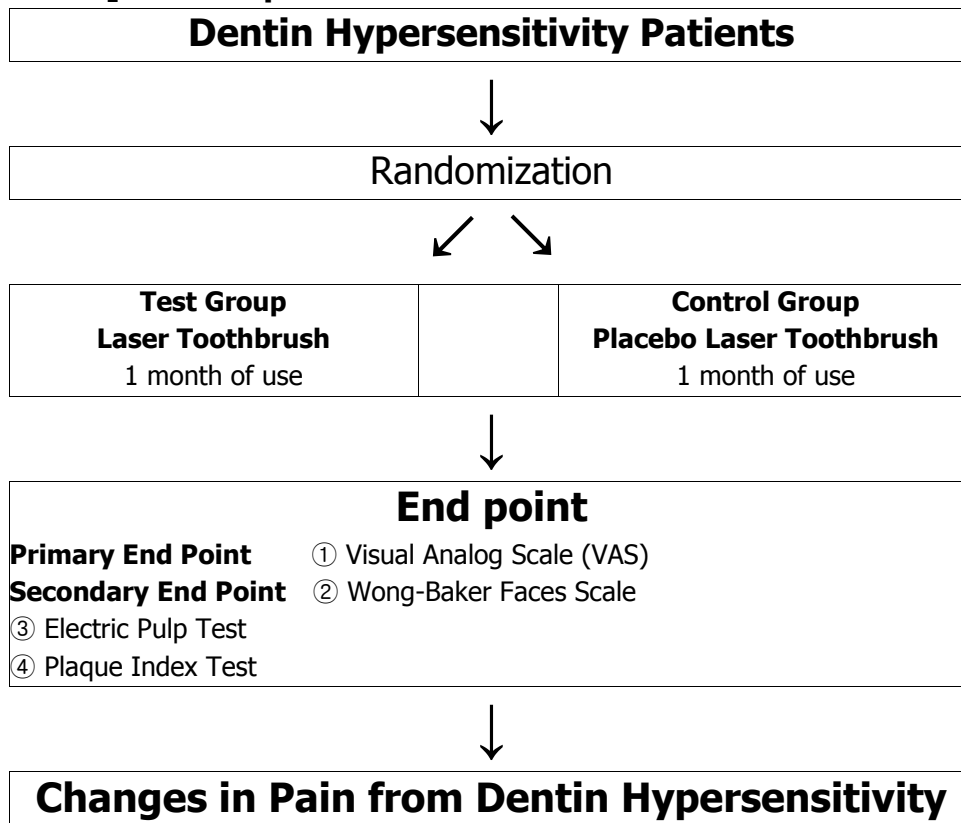
9.2.1. Process of the Clinical Trial

In this clinical trial, subjects were selected from the patients who had been diagnosed with dentin hypersensitivity by the clinical trial institutions. The subjects in the test group used Laser Toothbrushes for one month, while those in the control group used Placebo Laser Toothbrushes. Their pain was then verified and VAS, Wong-Baker Faces Scale, electric pulp tests, and plaque index

tests were performed to examine and assess changes in pain. The primary efficacy assessment intended to assess the pain reduction effect after one month.

9.3. Use of the Medical Instruments for the Clinical Trial

Laser Toothbrushes and Placebo Laser Toothbrushes were used in the test group and control group, respectively, to check pain reduction after one month.

٭ How to Use the Laser Toothbrush (Use for Four Weeks, Three Times a Day)

① Laser Toothbrush irradiates 635nm low-level semiconductor laser for medical treatment to the bristle.

② Laser Toothbrush operates under a programmed teeth management system. Once the mode switch is pressed once, the laser will turn on for 55 seconds, the recommended treatment duration. (In this case, the laser shall be irradiated to the lesion without applying toothpaste to the bristle.) The laser blinks five times at an interval of 0.5 seconds for 55 seconds to one minute. The user is informed of the completion of treatment.

③ Once treatment to the lesion is completed, apply toothpaste to the bristle and brush the teeth for two minutes.

④ Then the laser blinks 3 times at an interval of 0.5 seconds.

⑤ Wash the toothbrush clean with flowing water, and brush teeth with clean water for one minute and 57 seconds. Then treat the lesion before storing the instrument.

⑥ Laser Toothbrush operates for five minutes total after the mode switch is turned on. Then the laser will turn off and all programs will be closed. The Laser Toothbrush switches to sleep mode.

* Irradiate the laser on the surface of exposed dental roots to treat the lesion. Irradiate the laser into the entire oral cavity to wash the oral cavity.

9.4. Period of Using the Medical Instruments

A period was given at a ratio of 1:1 to the test group (Laser Toothbrush Group) and the control group (Placebo Laser Toothbrush Group).

The subjects assigned to the test group used Laser Toothbrushes for their teeth for one month.

The subjects assigned to the control group used Placebo Laser Toothbrushes for their teeth for one month.

9.5. Prohibited Combined Medications

< Prohibited Combined Medications >

1. Combined medications shall not be used with the exception of unavoidable cases.

2. If any combined medications are used, this fact shall be accurately stated in the Case Report Form and related documents.

※ Toothpastes (e.g., Syrin Med F and Sensitive Teeth) dedicated to use for sensitive teeth, which contain calcium phosphate or Colloidal Anhydrous Silica, as well as their equivalent medications and medical instruments

9.6. Pain Severity

9.6.1. Visual Analog Scale (VAS)

Pain from dentin hypersensitivity was objectively assessed by using the VAS. The VAS was categorized into No Pain (0), Light Pain (1 to 4), Intermediate (5 and 6), and Severe (7 to 10) categories to assess pain in accordance with the flow chart.

The clinical trial staff told the subject, "Please mark or say the number indicating your pain severity." The subject marked a number on the table shown below:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Extremely Severe Pain

9.6.2. Wong-Baker Faces Pain Rating Scale

The Wong-Baker Faces Pain Rating Scale was categorized into 10 levels. The end of a dental air syringe was located perpendicularly about 3 mm from the cervix surface of the target teeth. Then instantaneous cold air was applied to the end of the syringe twice to assess the patient's discomfort due to cold stimulation. The staff measured the discomfort level and recorded it.

9.6.3. Electric Pulp Test

After reactions to cold and mechanical stimulation were checked, the pain threshold of the tooth having the most severe pain from electric stimulation was verified by using the Digitest PULPTESTER manufactured by PARKELL Inc. located in New York, USA. The voltage values of the device were set to 0 to 64. The pain threshold was the voltage right when the first pain occurred as electric stimulation to the tooth was getting stronger.

9.7. Observation of Adverse Events

When an unexpected adverse event occurred during the use of the medical instruments, instrument use was halted. The trial staff determined whether or not to resume instrument use.

9.8. Education of the Trial Subjects

Since keeping medical instrument usage compliance high during the period of use was a crucial factor in assessing the efficacy of the target instruments, the trial staff provided the subjects with education and made every effort to enhance medical instrument usage compliance by contacting the subjects during this trial.

9.9. Journal of Medical Instrument Use to Assess Compliance

The trial subjects had to use the medical instruments provided by M&H for about 5 minutes and for 3 times on a daily basis in accordance with the Protocol, and wrote whether or not they used the instruments in a journal of medical instrument use. The journal was submitted to trial investigators on the next day's visit. The investigators reckoned the number of days the instruments were used. The subjects with compliance of less than 70% were disqualified from the trial.

10. Observation and Test Items and Methods
10.1. Visit Schedules and Test Items

1) Screening 1

The trial staff selected patients during their visit for screening under the criteria for selection and exclusion stated in the Protocol. Any and all observations related to the trial were performed after written consent was received.

① Hearing Case History and Clinical Observation
※ Written consent of the subjects
※ Checking the background of the subjects (e.g., sex, age, drinking history, and smoking history)
※ Checking case history and history of drug use
※ Determining whether the subject meets the criteria for selection or exclusion
② Pregnancy Test (Urine hCG Test)
③ Measuring the VAS
④ Radiation Test (Regular Panorama)
⑤ Random Allocation: Random allocation was performed after the results of all tests were verified.
⑥ Measuring the Wong-Baker Faces Pain Rating Scale
⑦ Electric Pulp Test
⑧ Plaque Index Test

2) Visit 1 (D1)

All the trial subjects completed receiving test results and diagnosis on the day of screening. On that day, the medical instruments were assigned to them, and they started to use the instruments. Thus, the screening date was the same as the date of Visit 1.

Medical instruments for the clinical trial, including toothpaste and journals, were distributed.

3) Visit 2 (D14)

① The medical instruments were used
② The VAS was measured
③ The Wong-Baker Faces Pain Rating Scale was measured
④ Electric Pulp Test
⑤ Plaque Index Test
⑥ Adverse events were evaluated, and combined medications were verified

4) Visit 3(D28)

① The use of the medical instruments was completed
② The VAS was measured
③ The Wong-Baker Faces Pain Rating Scale was measured
④ Electric Pulp Test
⑤ Plaque Index Test

⑥ Pregnancy Test (Urine hCG test)

⑦ Adverse events were evaluated, and combined medications were verified

⑧ The medical instruments were collected

10.2. Leading Test

A leading test was performed during the screening visit.

① Radiation Test (Panorama)

The trial staff classified dentin hypersensitivity patients depending on the case history of the subjects and by performing a leading test. The source data were recorded in the Case Report Form in detail, and as a result of the test, all the subjects turned out to be normal.

10.3. Pregnancy Test

When the subjects visited the institutions, urine hCG tests were performed for fertile women in order to check if they were pregnant. During the trial period, there were no pregnant subjects.

10.4. Electric Pulp Test

After reactions to cold and mechanical stimulation were checked, the pain threshold of the tooth having the most severe pain from electric stimulation was verified by using the Digitest PULPTESTER manufactured by PARKELL Inc. located in New York, USA. The voltage values of the device were set to 0 to 64. The pain threshold was the voltage right when the first pain occurred while electric stimulation to the tooth was getting stronger.

① Explain the methodology of the Electric Pulp Test to patients.

② Perform simple moisture-proofing with cotton rolls.

③ Dry the teeth surface and apply electric conduction substances to the teeth. Increase the current.

④ Observe the index when the subject reacts and record it.

⑤ Measure the index of the target teeth.

⑥ Consider any teeth showing a reaction at similar indexes to be normal.

10.5. Plaque index measurement (plaque index: Silness & Loe 1964)

Explorer, not dye, was used to identify the existence of plaque on subjects' teeth, and the plaque index was measured accordingly.

0 : No presence of plaque

1 : Thin layer of plaque around the rim of gums that is visible only by scraping it off the tooth surface

2 : Excess of clearly visible plaque around the rim of gums, but no plaque in between teeth

3 : Serious amount of plaque build-up around the rim of gums and in between teeth.

10.6. Verification of any simultaneous medication use

During the clinical study of the medical instrument, at each visit made by subjects for the recording of measurements, the subjects were checked for any medication use. If medication use was found, it was recorded. If the patient was under any medication, the amount of medication, the reason for taking it, the beginning date of medication use, and other data were recorded in detail in the case records.

10.7. Unscheduled Visits

If the subject made an unscheduled visit due to changes made by the clinical trial instrument,

adverse events, changes in simultaneous medication use, dropping out of the study, medical care needed as result of clinical examination, and other causes, it was recorded.

10.8. Definition of adverse event

Adverse event refers to any medical incident that is harmful for the subject, and does not necessarily have to relate to teeth treatment. Therefore, adverse events can include any undesirable, unexpected symptoms (including notable abnormalities of clinical procedure), or disease related to the use of the medical device or timing of use.

However, if the progression or symptoms of the disease in question is clearly related to the disease being studied, it was not regarded as adverse event.

10.8.1. Definition of SAE (Serious Adverse Event)

SAE refers to the following serious medical cases in which occurred during the use of the medical instrument.

• Causes death

• Threatens the life of the subject: The examiner thinks the subject's life is in danger at the onset of the incident.   This does not include actual death.

• Causes physical impairment or malfunction.

• Causes birth defects to subject's unborn child.

• Causes hospitalization or prolonged hospitalization: This does not include planned hospitalization related to clinical study or hospitalization needed solely for clinical study purposes.

This also refers to official hospitalization and does not include admission to the Emergency Room (unless in the ER for over 6 hours). This also does not include hospitalization that was scheduled prior to participating in the clinical study. If the subject had symptoms prior to participating in the clinical study, and if those symptoms have not worsened, SAE classification did not apply. If the hospitalization was for aesthetic reasons (such as plastic surgery) or any other reasons considered non-medical, SAE classification did not apply.

• Cases that do not fall into the categories above but still require serious medical attention.

10.8.2. Evaluation of adverse events listed as possible clinical symptoms

If adverse events occurred due to the use of the medical device, the symptoms, date of onset, date of disappearance of symptoms, degree of severity, relation to control group's or test group's use of medical device, handling of adverse events, treatment, result, and other factors was recorded on the case report form.

1) Criteria regarding the degree of adverse event

① Mild: Subject feels discomfort but the symptoms do not hinder the subject's daily activity.

② Moderate: Subject feels discomfort and the symptoms hinder the subject's daily activity.

③ Severe: Subject's symptoms hinder the subject to the point that the subject is unable to carry out his or her daily routine.

2) Relation to the medical instrument being tested

The researcher must make his or her decisions soundly based on a variety of factors, including patient history, health, the time medicine was consumed, the condition in which medicine was taken, and other factors.

① Definitely not related

Cases in which the adverse events clearly had no relation with the medical device.

②　　　Probably not related

Cases in which it is reasonable to suspect a reason other than the medical device which caused the reactions

③　　　Possibly related

Cases in which the timing of the onset of adverse events correlate with the timing of the use of the medical device; for this reason the medical device cannot be ruled out as the cause.

④　　　Probably related

The onset of the adverse event occurs with the use of the device and disappears with the cessation of use, and the use of the medical device serves as a better explanation of cause than other suspected reasons.

⑤　　　Definitely related

The onset of the adverse event occurs with the use of the device, disappears with the cessation of use, and reappears when device is used again.

⑥　　　Unknown

3) Measures taken if adverse events occur

① Do nothing

② Temporarily stop use of the device

③ Exclude the subject from study

4) Treatment

① Do nothing

② Prescribe medication

③ Hospitalize the patient

④ Other

5) Result

① Problem settled

② Problem continued

③ Death

10.8.3. Checking and reporting of subjects' adverse events

During each visit, subjects were checked for any signs of adverse event. If found, detailed information on the reaction (date of onset, date of disappearance, level of severity, relation to medical device, treatment, result) was recorded on the patient records and case report form.

The responsibilities of the clinical trial investigator in relation to severe adverse event occurrence during clinical study included the following:

1) Responsibilities of the clinical trial investigator

If any severe adverse events occur during the clinical study, the clinical trial investigator must report to the sponsor immediately and submit a detailed report later on.

If any unexpected severe adverse event occurs, the person in charge must immediately report to the sponsor and the Institutional Review Board.

When this is the case, in the immediate report and the detailed following report, the Subject Identification Code should be used in place of the subject's name, social security number, and address to protect the identity of the subject. Also, the clinical trial investigator must follow the guidelines set forth from prior reports that correlate with the adverse events, if such guidelines exist.

The clinical trial investigator plays a critical role in safety evaluation, so he or she must report to the sponsor according to reporting procedure and within the time frame specified on the clinical study protocol regarding adverse events, abnormality found from laboratory figures, and other areas specified.

In case of death, the clinical trial investigator must turn in an autopsy report (if an autopsy was done) and the death certificate to the sponsor and the Institutional Review Board.

2) Responsibilities of the clinical trial staff

The clinical trial staff must report to the clinical trial investigator and sponsor, and report any follow-up information. If any unexpected adverse events occur, he or she must immediately report to the sponsor and the Institutional Review Board.

3) Responsibilities of the Institutional Review Board

In case of occurrence of an unexpected, severe adverse event, or if new information is found regarding factors that may adversely affect the study or the safety of the subjects, the members of the Institutional Review Board must promptly alert the clinical trial investigator on what actions must be taken.

4) Responsibilities of the sponsor

If the sponsor receives a report on an unexpected, severe adverse event from the clinical trial staff, the sponsor must notify the Institutional Review Board and the Korea Food and Drug Administration within 15 days. If death has occurred or if a subject's life is believed to be in danger, the sponsor must report within 7 days upon the notification, and must submit a detailed report within the following 8 days. When the sponsor submits a Serious Adverse Event Report Form, he must attach with it any other material received from the clinical trial investigator and staff.

The sponsor must report periodically on additional safety information regarding the case until the adverse event ceases to occur (until the symptoms disappear or follow-ups cannot be done). The subject must fully cooperate in sharing information and providing materials about the case.

Medical & Human Technology Co., Ltd. (M&H)	**Contact Information : 436-16 Changgok-ri, Paltan-myeon, Hwaseong-si, Gyeonggi-do, Korea** **Contact : Ji Man-soo, President / TEL : 031-452-1495**
LSC-Standard Co., Ltd.	**Contact Information : #3F, Hansaem Building, 31-36, Nokbeon-dong, Eunpyeong-gu, Seoul, Korea** **Contact : Park Song-eun CRA / TEL : 02)382-3892**

10.8.4. Immediate report of serious adverse events (SAEs)

During the clinical study, if any serious adverse event (SAE) occurs, whether or not it is related to the use of the medical device, the sponsor has to be notified immediately. The report can be made through fax, mail, or e-mail to M&H and its Contract Research Organization (CRO).

Table 2 is a summary of the deadlines and documents needed for reporting adverse events

If the adverse event requires hospitalization, the clinical research institution must try to obtain the discharge summary.

Table 2 Guideline for reporting adverse events

Time limit	Within 24 hrs of receiving notification of adverse event by the clinical research institution	Within 24 hrs of receiving additional information by the clinical research institution

Documents	• For initial report or adverse event
	  - All diagnosis
	  - Case Report Form on adverse events
	  - Case Report Form on any medication taken during study
		• Follow-up report on serious adverse event
		• Renewal of submitted Case Report Form if needed
		• Discharge summary if needed
		  • Related medical diagnosis and examination/report

11. Precautions for use of the medical device and for expected adverse events

In case of allergic reactions or tissue damage during use of the Laser Toothbrush, subjects were advised to stop use of the toothbrush and receive appropriate care from an attending physician.

Direct exposure from the laser to the eye will damage the retina and may even cause serious damage such as loss of eyesight.

Subjects were instructed not to apply the laser to the eye and on the gums for prolonged periods, and they were also instructed to place the laser toothbrush in a place out of reach of children.

11.1 Normal cases

With normal cases, all violations of the plan were discussed prior to the start of the clinical study with M&H, the sponsor, and were all recorded on the case report form or protocol deviation (violation) form.

12. Standards of violation, suspension, and withdrawal

12.1. Violation

No serious deviation/violation occurred except for a case with delayed recording of a subject's EMR due to unfamiliarity with clinical trial protocol. Information regarding this was recorded in detail in the Investigator File.

12.2. Standards on suspension and withdrawal

Suspension or withdrawal due to incompatibility with trial standards was recorded in detail on the case report form.

Even if the subject was randomly assigned and used the medical device, if, for any reason, the subject was not able to participate for the duration of the study; he or she was categorized as a 'withdrawal' subject. If in any case, the subject voiced his desire to withdrawal or the researcher deemed the subject unfit for the study, the subject was dropped from the study, but included in the safety evaluation.

The reasons for withdrawal were as follows.

1) Patient or the patient's caretaker requested termination of medical device usage
2) Patient withdrew his or her agreement
3) Continuation of trial became difficult due to a serious abnormal event
4) Continuation of trial became difficult due to complications risen from serious illness

5) Continuation of trial became difficult due to worsening of patient's health

6) Violation of enrollment requirements and protocol found at any time during clinical trial

7) Subject took prohibited medication or used prohibited medical devices (According to the list of prohibited medications and medical devices, or according to the judgment of the researcher)

8) Patient fails to keep his appointment for follow-up

9) Assigned physician deems the subject unqualified for further study

10) Compliance of 70% or less to protocol

11) Subject becomes pregnant during study period

For subjects declining visits, the researcher tried all ways possible to contact and made house visits to not lose sight of any sign of adverse events.

12.3 Pregnancy

During the screening of subjects for determining eligibility, those with positive pregnancy test results were dropped and a pregnancy test was done again during Visit 3. Subjects were instructed to promptly notify the researcher in case of pregnancy. If subject was found to be pregnant, she was withdrawn from the study.

The effects that the medical device will have on pregnancy are insignificant, so follow-up was not done in these cases. The researcher was also instructed to notify M&H if any subject became pregnant.

12.3.1 Pregnancies in partners of trial subjects

In case of adverse events due to exposure of the subject's unborn child, newborn or infant to the medical device (if the subject deemed the exposure possible or probable), it must be considered as a case of the subject's own adverse event and reported in the same manner.

13. Guidelines and methods for evaluation of safety and efficacy; Method of statistical analysis

13.1. Study Population

13.1.1. ITT(Intent-to-treat) set

All subjects listed and selected by random allocation were included in this set.

13.1.2. PP(Per-Protocol) set

Subjects in the ITT set regarded as serious violators of the clinical trial protocol were excluded from this set.

‣ Subjects who dropped out without completing the set duration of the trial (Compliance 70% or less)

‣ Subjects who took prohibited medication or used prohibited medical devices

‣ Any other cases in which the protocol was violated

13.1.3. Safety set

Subjects listed in the clinical trial that satisfy all inclusion/exclusion criteria had safety related data verified.

13.1.4 Management of clinical trial data with missing values

If a patient drops out before the conclusion of the clinical trial, if missing value occurs in any valid variable, or if measurement is obtained after the given screening period, the last measurement obtained will be used in place of missing values for analysis (Last Observation Carried Forward).

13.2. Baseline Comparability

This is a procedure to verify that subjects in treatment and placebo groups do not have differences before they are listed in the clinical trial.

All patients in the ITT set will be analyzed according to factors such as age, gender, socio-demographic variables, results of various medical exams, illnesses prior to the start of clinical study, medication use, and other factors.

13.3. Efficacy Analysis

The main group for efficacy analysis will be the ITT (Intent-to-treat) set, and the supporting group for the analysis will be the PP (Per-Protocol) set.

13.3.1. Assessment Variable of the Primary Efficacy Endpoint
1. Primary Efficacy End Point
(1) Assessment Standard
Assessment variable of Primary Efficacy Endpoint:
The mean change in pain (VAS) due to dentin hypersensitivity at one-month time point:

The primary efficacy endpoint refers to the mean change in pain (VAS) from baseline a month into the start of the trial.

If the mean change of the treatment group was over 2 cm compared with the control group, the trial was deemed successful.

Student's unpaired t-test or Wilcoxon's rank sum test was used to compare and analyze the differences among treatment groups regarding pain due to dentin hypersensitivity, with the assumption that the standards for normality was kept.

In order to find out whether results would differ from one institution's treatment group to another, multivariate analysis was performed using treatment groups from different research institutions.

> Dentin hypersensitivity pain score: Differences in pain scores at screening and at primary end point was calculated to find the healing rates of patients.

② Measurement method:

A dental air-water syringe was used twice on the cervical surface of the tooth to evaluate the patient's response to cold stimulation. The nozzle of the syringe was placed at a right angle about 3mm away from the affected tooth.

13.3.2. Assessment Variable of the Secondary Efficacy Endpoint
1) Wong-Baker Faces Scale
Student's unpaired t-test or Wilcoxon's rank sum test was used to compare and analyze the differences among treatment groups regarding the Wong-Baker Faces Scale, with the assumption that the standards for normality was kept.
2) Electric Pulp Test (EPT)
At the one-month time point (Visit 3), normal/abnormal changes were noted in contrast to the subject's baseline measurement. The Chi-square test or Fisher's exact test was used to compare the differences between the two groups.
3) Plaque index measurement
At the one-month time point (Visit 3), the plaque index was recorded in contrast to the subject's baseline measurement. The Chi-square test or Fisher's exact test was used to compare the differences between the two groups.

13.4. Safety Assessment Standards and Methods

Subjects in the safety set were evaluated on safety. Data included in the assessment were newly acquired adverse events after the use of the medical device.

1) Adverse events

Subject adverse events were analyzed in the two groups tested by the Chi-square test or Fisher's exact test. In addition, the occurrence rate on correlation of the reaction to the use of the medical device and the severity of the reaction were calculated and analyzed.

14. Trial Subjects

14.1 Participation of Clinical Trial Subjects

A total of 97 subjects participated in the clinical trial. Of he 97, one participant did not pass screening. For the ITT Set, 48 (49.48%) subjects from the treatment group and 48 (49.48%) from the control group were included. For the PP Set, 43 subjects from the treatment group (45.36%) and 44 subjects from the control group (45.36%) were included. Five subjects from the treatment group (4.12%) and four from the control group (4.12%) were dropped during the clinical trial. [See Table 1]

[Table 1] Distribution of participants and drop-outs in the clinical study

	Treatment Group		Control Group		Total	
	Nt	%	Nc	%	N	%
Subjects selected for screening					97	100.00%
Subjects rejected after screening					1[1]	1.03%
Subjects who received patient numbers (ITT Group)	48	49.48%	48	49.48%	96	98.97%
Subjects who completed the trial (PP Group)	43	44.33%	44	45.36%	87	89.69%
Drop-outs	5	5.15%	4	4.12%	9	9.28%
Side effects	0	0.0%	0	0.0%	0	0.0%
Lack of healing effect	0	0.0%	0	0.0%	0	0.0%
Lack of compliance	1	1.03%	1	1.03%	2[2]	2.06%
Protocol violation	0	0.0%	0	0.0%	0	0.0%
Impossible to do follow-up observation	2	2.06%	2	2.06%	4[3]	4.12%
Refusal to participate	1	1.03%	0	0.0%	1[4]	1.03%
Death of the subject	0	0.0%	0	0.0%	0	0.0%
Other	1	1.03%	1	1.03%	2[5]	2.06%

1) Violation of inclusion/exclusion criteria
2) Low compliance : R107, R130
3) Impossible to do follow-up observation : R114, R116, R129, R132
4) Subject refusal to participate : R120
5) Other: R140 (Does not meet inclusion/exclusion criteria), R242 (Unable to come in during study for a check-up due to business trips)

15. Clinical Trial Results

15.1 Basic information on subjects

15.1.1 Statistical analysis of population studied

Statistical analysis was performed on subjects who took part in this clinical trial. No notable difference was observed in terms of gender and age between the control group and treatment group. [See Table 2]

[Table 2] Demographic characteristics

Category		Treatment Group (Nt=48)	Control Group (Nc=48)	Total (N=96)	P-value
Gender	Male	17 (35.42%)	16 (33.33%)	33 (34.38%)	0.8299[1]
	Female	31 (64.58%)	32 (66.67%)	63 (65.63%)	
Age	Mean ± Standard deviation Min. − Max.	40.75 ± 8.89 25 − 55	39.44 ± 10.93 21 − 63	40.09 ± 9.93 21 − 63	0.5203[2]

1) Chi-square test
2) Student's unpaired t-test

15.1.2 Pregnancy Test

During screening and at Visit 3, female patients took pregnancy tests. 59 out of 63 female participants were tested during screening, and all tested negative. The four females excluded from the pregnancy test were excluded because they were women in menopause. At Visit 3, a total of 56 females took the pregnancy test and again tested negative. The drop in the number of females taking the pregnancy test was due to 3 females who dropped out (R114, R129, and R242) in addition to the 4 women in menopause. Subject distribution was the same for both the control and treatment groups.

15.1.3 Radiological examination

All subjects had a radiological examination during screening. Subject distribution was the same for both the control and treatment groups.

15.1.4 Medical history / Current medical condition

The medical history and current medical conditions of the subjects were studied during screening. No notable differences were observed in all categories. [Table 3]

[Table 3] Results of medical history/current medical condition

Category		Treatment Group (Nt=48)	Control Group (Nc= 48)	Total (N=96)	P-value
Allergy or hypersensitive response	Yes	4 (8.33%)	2 (4.17%)	6 (6.25%)	0.6773[2]
	No	44 (91.67%)	46 (95.83%)	90 (93.75%)	
History of dental illness	Yes	6 (12.50%)	3 (6.25%)	9 (9.38%)	0.4860[2]
	No	42 (87.50%)	45 (93.75%)	87 (90.63%)	
History of internal/external illness	Yes	11 (22.92%)	6(12.50%)	17 (17.71%)	0.1813[1]
	No	37 (77.08%)	42 (87.50%)	79 (82.29%)	
Medication history	Yes	9 (18.75%)	7 (14.58%)	16 (13.67%)	0.5839[1]
	No	39 (81.25%)	41 (85.42%)	80 (83.33%)	

1) Chi-square test
2) Fisher`s exact test

15.2 Primary efficacy analysis

15.2.1 The mean change in pain (on VAS) due to dentin hypersensitivity at the one-month time point

Statistical analysis was done on mean change of pain caused by dentin hypersensitivity at the one-month time point (Visit 3) in comparison with baseline in both the ITT Set and the PP Set. At the one-month time-point (Visit 3) for the ITT Set, the mean differed with the baseline by -3.31±1.79 for the treatment group, and by -0.88±1.86 for the control group. Also, when normality was tested, it did not sufficiently meet the qualifications for normality, so the Wilcoxon's rank sum test was used to see if any difference existed in the two groups. The results showed that significant differences did exist between the control group and the treatment group (p-value = 0.0001). After analysis of the PP Set [Table 5], significant differences were found to also exist between the control and treatment groups (p-value = 0.0001). In addition, after multivariate analysis of the statistics, no significant difference among research institutions was shown (p-value = 0.6176).

[Table 4] The mean change in pain (on VAS) due to dentin hypersensitivity at the one-month time point (ITT)

VAS	Treatment Group (Nt=48)			Control Group (Nc=48)			p-value[2]
	Baseline	After one month	Diff[1]	Baseline	After one month	Diff[1]	
Mean± Standard deviation	5.83± 1.19	2.52± 1.79	-3.31± 1.79	6.44± 1.24	5.56± 1.95	-0.88± 1.86	0.0001**

1) Difference value from baseline after one month
2) Wilcoxon's rank sum test
**) Statistically significant

[Table 5] The mean change in pain (on VAS) due to dentin hypersensitivity at the one-month time point (PP)

VAS	Treatment Group (Nt=43)			Control Group (Nc=44)			p-value[2]
	Baseline	After one month	Diff[1]	Baseline	After one month	Diff[1]	
Mean± Standard deviation	5.79± 1.15	2.26± 1.59	-3.53± 1.68	6.43± 1.28	5.50± 2.02	-0.93± 1.93	0.0001**

1) Difference value from baseline after one month
2) Wilcoxon's rank sum test
**) Statistically significant

15.3 Secondary efficacy analysis

15.3.1 Wong-Baker Faces Scale

Analysis of the ITT Set [Table 6] revealed that a month into the clinical study, changes in Wong-Baker Faces Scale in comparison with baseline showed significant statistical differences (p-value = 0.0001). Analysis of the PP Set [Table 7] also showed significant statistical differences.

[Table 6] Changes in the Wong-Baker Faces Scale from baseline at the one-month time point (ITT)

Category		Baseline	After one month	Diff[1]	p-value[2]
Treatment Group (Nt=48)	Mean ± Standard deviation	6.29 ± 1.70	1.88 ± 2.00	-4.42 ± 2.37	0.0001**
Control Group (Nc=48)	Mean ± Standard deviation	6.33 ± 1.67	5.08 ± 2.30	-1.25 ± 1.96	

1) Difference value from baseline after one month
2) Student's Unpaired t-test
**) Statistically significant

[Table 7] Changes in the Wong-Baker Faces Scale from baseline at the one-month time point (PP)

Category		Baseline	Visit 3	Difference	p-value[1]
Treatment Group (Nt=43)	Mean ± Standard deviation	6.28 ± 1.67	1.53 ± 1.56	-4.74 ± 2.23	0.0001**
Control Group (Nc=44)	Mean ± Standard deviation	6.27 ± 1.70	4.91 ± 2.30	-1.36 ± 2.01	

1) Difference value from baseline after one month
2) Student's Unpaired t-test
**) Statistically significant

15.3.2 Electric Pulp Test (EPT)

Analysis of the ITT Set revealed no statistically significant difference from baseline was observed in each group regarding frequency rate at the one-month time point. Also, at each time point, no statistically significant difference was seen between the treatment group and the control group.
Analysis of the PP Set [Table 9] revealed same results as above with the ITT Set.

[Table 8] Electric pulp test(ITT)

Category		Treatment Group (Nt=47)		Control Group (Nc=48)		p-value[1]
		Negative	Positive	Negative	Positive	
Baseline	Frequency rate (%)	2 4.26%	45 93.75%	0 0.00%	48 100.00%	0.2421
After one month	Frequency rate (%)	2 4.26%	45 93.75%	0 0.00%	48 100.00%	0.2421
p-value[1]		1.0000		1.0000		

1) Fisher`s exact test
* Subject from treatment group unfit for EPT: R140(Subject dropped due to gold crown placement which is incongruent with inclusion/exclusion criteria)
* Negative Subject: R001(Subject in the middle of corrective dental treatment)/ R132(Subject dropped due to impossible follow-up)

[Table 9] Electric pulp test (PP)

Category		Treatment Group (Nt=43)		Control Group (Nc=44)		p-value[1]
		Negative	Positive	Negative	Positive	
Baseline	Frequency rate (%)	1 2.33%	42 95.45%	0 0.00%	44 100.00%	0.4943
After one month	Frequency rate (%)	1 2.33%	42 95.45%	0 0.00%	44 100.00%	0.4943
p-value[1]		1.0000		1.0000		

1) Fisher`s exact test
* Negative Subject: R001(Subject in the middle of corrective dental treatment)

15.3.3 Plaque index measurement

Analysis of the results from the ITT Set [Table 10] showed no statistically significant difference in frequency between measurements at the one-month time point (Visit 3) and baseline. There was also no statistically significant difference between the control group and treatment group.

In the PP Set [Table 11], no statistically significant difference between the two groups was shown, but a significant difference was observed for the treatment group between measurements of the one-month time point (Visit 3) and baseline (p-value = 0.0162). However, no statistically significant difference in frequency for the control group was shown between the one-month time point (Visit 3) and baseline.

[Table 10] Plaque index measurement (ITT)

Category		Treatment Group (Nt=48)				Control Group (Nc=48)				p-value[1]
		0	1	2	3	0	1	2	3	
Baseline	Frequency rate (%)	17 35.42%	25 52.08%	4 8.33%	2 4.17%	23 47.92%	23 47.92%	1 2.08%	1 2.08%	0.4028
After one month	Frequency rate (%)	26 54.17%	22 45.83%	0 0.00%	0 0.00%	28 58.33%	20 41.67%	0 0.00%	0 0.00%	0.8371
p-value[1]		0.2519				0.4706				

1) Fisher`s exact test
0: No layer of plaque
   1: Thin layer of plaque around the rim of gums that is visible only by scraping it off of the tooth surface
   2: Excess of clearly visible plaque around the rim of gums but no plaque in between teeth
3: Serious amount of plaque build-up around subject's gums and in between teeth

[Table 11] Plaque index measurement (PP)

Category		Treatment Group (Nt=43)				Control Group (Nc=44)				p-value[1]
		0	1	2	3	0	1	2	3	
Baseline	Frequency rate (%)	15 34.09%	22 52.27%	4 9.09%	2 4.55%	20 45.45%	22 50.00%	1 2.27%	1 2.27%	0.4700
After one month	Frequency rate (%)	25 56.82%	18 43.18%	0 0.00%	0 0.00%	25 56.82%	19 43.18%	0 0.00%	0 0.00%	1.0000
p-value[1]		0.0165**				0.4519				

1) Fisher`s exact test
**) Statistically significant
0: No layer of plaque
   1: Thin layer of plaque around the rim of gums that is visible only by scraping it off of the tooth surface
   2: Excess of clearly visible plaque around the rim of gums but no plaque in between teeth
3: Serious amount of plaque build-up around subject's gums and in between teeth

15.4 Safety Evaluation

15.4.1 Adverse events

1) Occurrence rate of adverse events

Out of the 96 subjects, the distribution of subjects with adverse events was analyzed. It was found that 9 subjects (18.75%) from the treatment group and 14 subjects (29.17%) from the control group had adverse events. No statistically significant differences were seen in both groups (p-value = 0.2319). [Table 12]

[Table 12] Occurrence rate of adverse events

Adverse Event	Treatment Group (Nt=48)		Control Group (Nc=48)		Total (N=96)		P-value[1]
Did not occur	39	81.25%	34	70.83%	73	76.04%	0.2319
Did occur	9	18.75%	14	29.17%	23	23.96%	

1) Chi-square test

2) Adverse events according to system

Out of the 48 subjects from the treatment group, 9 subjects (18.75%) and up to 10 cases (37.04%) showed adverse events. Out of the 46 subjects from the control group, 14 subjects (29.17%) and up to 17 cases (62.96%) showed adverse events. The categorization of adverse events was done according to coding with WHO-ART [Table 13].

[Table 13] List of adverse events categorized by system

Category	Treatment Group		Control Group		Total sum	
	# of cases	%	# of cases	%	# of cases	%
Application site disorder	**6**	**60.00%**	**10**	**58.82%**	**16**	**59.26%**
Application site reaction	6	60.00%	10	58.82%	16	59.26%
Central & peripheral nervous system disorders	**1**	**10.00%**	**3**	**17.65%**	**4**	**14.81%**
Headache	1	10.00%	3	17.65%	4	14.81%
Gastro-intestinal system disorders	**1**	**10.00%**	**0**	**0.00%**	**1**	**3.70%**
Vomiting	1	10.00%	0	0.00%	1	3.70%
Reproductive disorders	**0**	**0.00%**	**1**	**5.88%**	**1**	**3.70%**
Cervical uterine polyp	0	0.00%	1	5.88%	1	3.70%
Respiratory system disorders	**1**	**10.00%**	**0**	**0.00%**	**1**	**3.70%**
Coryza	1	10.00%	0	0.00%	1	3.70%
Skin and appendages disorders	**1**	**10.00%**	**0**	**0.00%**	**1**	**3.70%**
Ulticaria	1	10.00%	0	0.00%	1	3.70%
Special sense other, disorders	**0**	**0.00%**	**1**	**5.88%**	**1**	**3.70%**
Parosmia	0	0.00%	1	5.88%	1	3.70%
Vision disorders	**0**	**0.00%**	**2**	**11.76%**	**2**	**7.41%**
Conjunctivitis	0	0.00%	2	11.76%	2	7.41%
Sum	**10**	**100%**	**17**	**100%**	**27**	**100%**

3) Drop-outs due to adverse event
No drop-outs due to adverse event occurred.

4) Adverse events related to use of the medical device
During the duration of the clinical trial, 2 subjects from the treatment group (4.17%) and 7 subjects from the control group (14.58%) showed adverse events related to the use of the medical device. No significant difference was observed between the treatment group and the control group regarding the occurrence of adverse events related to the used of the medical device. [Table 14] The following is a list [Table 15] of adverse events that occurred with relation to the medical device.

[Table 14] Occurrence rate of adverse events related to the medical device

Serious adverse event	Treatment Group (Nt=48)		Control Group (Nc=48)		Total (N=96)		p-value[1]
Did occur	2[†]	4.17%	7[‡]	14.58%	9	9.38%	0.1586
Did not occur	46	95.83%	41	85.42%	87	90.63%	

1) Fisher's exact test
† : R203/R213
‡ : R121/R209/R212/R215/R228/R241/R248

[Table 15] List of adverse events categorized by system

Category	Treatment Group		Control Group		Total Sum	
	# of cases	%	# of cases	%	# of cases	%
Application site disorder	**2**	**20.00%**	**8**	**80.00%**	**10**	**100.00%**
Application site reaction	2	20.00%	8	80.00%	10	100.00%

5) Serious adverse events
No serious adverse events occurred in the treatment group or the control group.

15.4.2 Use of medication
Two subjects from the treatment group (4.17%) and 7 subjects from control group (14.58%) took medication during the course of the study, but did not show any significant differences in statistics (p-value = 0.1586).

[Table 16] Comparison of medical use distribution

Use of medication	Treatment Group (Nt=48)		Control Group (Nc=48)		Total (N=96)		p-value[1]
Yes	2[†]	4.17%	7[‡]	14.58%	9	9.38%	0.1586
No	46	95.83%	41	85.42%	87	90.63%	

1) Fisher's exact test
† : R203/R213
‡ : R121/R209/R212/R215/R228/R241/R248

[Table 27] List of medications

Medication category	Treatment group (Ng=48)		Control group (Np=48)		Total (N=96)	
	# of cases	%	# of cases	%	# of cases	%
Musculo-Skeletal System	**0**	**0.00%**	**1**	**5.56%**	**1**	**2.44%**
Anti-Inflammatory Enzymes	0	0.00%	1	5.56%	1	2.44%
Endocrine & Metabolic System	**1**	**4.35%**	**1**	**5.56%**	**2**	**4.88%**
Antithyroids Agents	1	4.35%	1	5.56%	2	4.88%
Genito-urinary System	**0**	**0.00%**	**1**	**5.56%**	**1**	**2.44%**
Drugs Acting on Uterus	0	0.00%	1	5.56%	1	2.44%
Gastrointestinal System	**6**	**26.09%**	**1**	**5.56%**	**7**	**17.07%**
Antacids & Antiulcerants	3	13.04%	0	0.00%	3	7.32%
GIT Regulators, Antiflatulents & Anti-inflammatories	1	4.35%	0	0.00%	1	2.44%
Antispasmodics	1	4.35%	0	0.00%	1	2.44%
Digestives	0	0.00%	1	5.56%	1	2.44%
Other Gastrointestinal Drugs	1	4.35%	0	0.00%	1	2.44%
Cardiovascular & Hematopoietic System	**7**	**30.43%**	**2**	**11.11%**	**9**	**21.95%**
ACE Inhibitors	1	4.35%	1	5.56%	2	4.88%
Calcium Antagonists	2	8.70%	0	0.00%	2	4.88%
Other Antihypertensives	1	4.35%	0	0.00%	1	2.44%
Diuretics	1	4.35%	0	0.00%	1	2.44%
Anticoagulants, Antiplatelets & Fibrinolytics (Thromboltrics)	1	4.35%	1	5.56%	2	4.88%
Other Antihypertensives	1	4.35%	0	0.00%	1	2.44%
Allergy & Immune System	**1**	**4.35%**	**0**	**0.00%**	**1**	**2.44%**
Antihistamines & Antiallergics	1	**4.35%**	0	0.00%	1	2.44%
Nutrition	**1**	**4.35%**	**0**	**0.00%**	**1**	**2.44%**
Supplements & Adjuvant Therapy	1	4.35%	0	0.00%	1	2.44%
Anti-Infectives (Systemic)	**2**	**8.70%**	**1**	**5.56%**	**3**	**7.32%**
Cephalosporins	0	0.00%	1	5.56%	1	2.44%
Antifungals	2	8.70%	0	0.00%	2	4.88%
Central Nervous System	**3**	**13.04%**	**10**	**55.56%**	**13**	**31.71%**
Antidepressants	2	8.70%	0	0.00%	2	4.88%

Medication category	Treatment group (Ng=48)		Control group (Np=48)		Total (N=96)	
	# of cases	%	# of cases	%	# of cases	%
Analgesics: Non-Opioid & Antipyretics	1	4.35%	5	27.78%	6	14.63%
Non-Steroidal Anti-Inflammatory Agents (NSAIDs)	0	0.00%	5	27.78%	5	12.20%
Hormones	**1**	**4.35%**	**0**	**0.00%**	**1**	**2.44%**
Oestrogens & Progesterones & Related Synthetic Drugs	1	4.35%	0	0.00%	1	2.44%
Respiratory System	**1**	**4.35%**	**1**	**5.56%**	**2**	**4.88%**
Cough & Cold Preparations	1	4.35%	1	5.56%	2	4.88%
Total Sum	**23**	**100.0%**	**18**	**100.0%**	**41**	**100.0%**

15.4.3 Evaluation of compliance

After evaluation of medication compliance, one subject (2.08%) from the treatment group and one subject (2.08%) from the control group were disqualified. There was no statistically significant difference between the treatment group and the control group (p-value = 1.0000).

[Table 18] Evaluation of compliance

Serious adverse event	Treatment group (Nt=48)		Control group (Nc=48)		Total (N=96)		p-value[1]
70% and over	47	97.92%	47	97.92%	94	97.92%	1.0000
Under 70%	1[†]	2.08%	1[‡]	2.08%	2	2.08%	

1) Fisher's exact test
† : R107
‡ : R130

15.5 Evaluation of efficacy results

Out of the 97 subjects recruited, except for the one subject who did not pass screening, 96 subjects were included in the ITT Set. 87 subjects were included in the PP Set after 9 were dropped due to reasons such as low compliance, impossible follow-up, and refusal to participate. The 87 subjects in the PP Set were evaluated on primary and secondary efficacy.

Primary efficacy was evaluated based on mean change of pain (VAS) due to dentin hypersensitivity between measurements at the one-month time point (Visit 3) and baseline. The efficacy evaluation results for both the ITT Set and PP Set revealed that in both sets, statistically significant differences between the treatment group and the control group existed (p-value = 0.0001). Multivariate analysis showed that no statistically significant difference existed among different institutions (p-value = 0.6176).

Variables for the secondary efficacy evaluation include the results of the Wong-Baker Faces Scale, electric pulp test, and plaque index measurement.

For the ITT Set, the results of the Wong-Baker Faces Scale showed statistically significant differences between the treatment group and control group (p-value = 0.0001). The electric pulp test showed no significant differences between the measurements at the one-month time point (Visit 3) and baseline in both groups. The plaque index measurement also did not show any significant differences between

the measurements at the one-month time point (Visit 3) and baseline in both the treatment and control groups.

For the PP Set, the Wong-Baker Faces Scale and electric pulp test showed identical results as those of the ITT Set. However, the plaque index measurement showed statistically significant differences between measurements at the one-month time point and baseline for the treatment group (p-value = 0.0162).

15.6 Safety Evaluation Results

Out of the 96 subjects in the ITT Set, analysis of the distribution of those that showed adverse events was done. Adverse events occurred in 9 subjects (18.75%) from the treatment group and 14 subjects (29.17%) from the control group. No statistically significant difference was seen between the two groups (p-value = 0.2319). 10 cases (37.04%) from 9 out of 48 subjects (18.75%) in the treatment group and 17 cases (62.96%) from 14 out of 48 subjects (29.17%) displayed adverse events. The adverse events were categorized according to the WHO-ART classification table.

During the clinical trial, 2 subjects (4.17%) from the treatment group and 7 subjects (14.58%) from the control group showed adverse events due to the use of the medical device. No significant difference related to the medical device was observed between the treatment group and the control group.

Intake of simultaneous medication was found in 2 subjects (4.17%) from the treatment group and in 7 subjects (14.58%) from the control group. No statistically significant difference existed between these two groups (p-value = 0.1586).

Results of the compliance test revealed a lack of compliance from one subject (2.08%) in the treatment group, and from one subject (2.08%) in the control group. No statistically significant difference existed between these two groups (p-value = 1.0000).

16. Conclusion and Review

Patients suffering from dentin hypersensitivity are usually discovered in clinical practice. Most of the time, the condition is related to the abrasion of the cervical area or exposure of root surface area caused by reduced periodontium. A tooth with dentin hypersensitivity has dentinal tubules twice the size of a normal tooth's dentinal tubules. The purpose of treatment of hypersensitivity is to reduce the enlarged diameter of the affected dentinal tubules. Treatment of dentine hypersensitivity includes closure of exposed dentinal tubules and lessening gum stimulation. For these purposes, treatment methods such as the application of tooth desensitizer, development of better tooth brushing habits, diet change, endodontic treatment, and laser therapy have been created.

Low level laser therapy causes closure or narrowing of the dentinal tubules of the hypersensitive tooth. This is effective in that it hinders the delivery of stimulant through the dentinal tubules or blocks the delivery of painful stimuli by closing the matrix region of the tubules. Therefore, it provides direct alleviation of pain on the nerve endings located on the borders between the pulp and the tooth. In this clinical study, a low-level "Laser-Toothbrush" was used for a month to test its effects on treatment and lessening of pain due to dentin hypersensitivity. In two institutions, a total of 96 subjects with dentin hypersensitivity were studied.

According to the statistical analysis of the population studied, the ratio difference of male versus female participants was 35.42%: 64.58% (17:31) for the treatment group and 33.33%: 66.67% (16:32) for the control group. From this it can be seen that dentin sensitivity is more prevalent in females than males. For evaluation of the research or treatment of dentin sensitivity, an accurate measure of subject pain was needed, and the study had to be reproducible. For this reason, the VAS (Visual Analogue Scale) was used to objectively evaluate pain, which is subjective.

The mean change in pain (VAS) due to dentin hypersensitivity at the one-month time point (Visit 3) compared with baseline came out to be -3.31±1.79 for the treatment group, and -0.88±1.86 for the control group. Wilcoxon's rank sum test was performed and its results were analyzed to look for any differences in the two groups because the standards for normality were not met. Statistically significant differences did exist between the treatment group and the control group (p-value = 0.0001). The results of the PP Set analysis also showed statistically significant differences between the two groups (p-value = 0.0001).

To judge the efficacy difference, evaluation criteria were set for the second efficacy analysis. The Wong-Baker Faces Pain Rating Scale was used. It is divided into 10 scales. A dental air syringe was placed at a right angle, with the nozzle 3 mm away and directly facing the cervical area of the tooth interface, and cold air was sprayed twice to assess the pain felt by the patient. A statistically significant difference between the Wong-Baker Faces Scale measurements at the one-month time point and baseline was observed in the two groups of the ITT Set (p-value = 0.0001).

In the electric pulp test, reactions to cold and mechanical stimulation were checked. On the most problematic tooth, an electric pulp tester was used to determine the pain threshold on electric stimulation. The voltage of the electric pulp tester was kept at values between zero and 64. The first sign of pain as the electric stimulation gradually increased was determined as the pain threshold. According to the analysis of the ITT Set, the frequency stayed the same for both groups between the one-month time point (Visit 3) and baseline. Therefore no statistically significant difference was observed (p-value = 1.0000). Also, there was no statistically significant difference at each time point between the treatment group and the control group.

In the plaque index measurement, there was no statistically significant difference in frequency between the one-month time point and baseline. This was also the case between the treatment group and the control group at each time point.

In the PP Set [Table 11], no statistically significant difference between the treatment group and the control group was shown, but a significant difference was observed for the treatment group between

measurements at the one-month time point (Visit 3) and baseline (p-value = 0.0162).   However, no such frequency difference was observed in the control group.

For safety evaluation purposes, subjects that had cases of adverse events were analyzed.   Nine subjects from the treatment group (18.75%) and 14 subjects from the control group (29.17%) had cases of adverse events. But there was no statistically significant difference between the treatment group and the control group (p-value = 0.2319).

Adverse events in systems of the body occurred in 10 cases (37.04%) from 9 out of 48 subjects (18.75%) from the treatment group, and in 17 cases (62.96%) from 14 subjects (29.17%) from the control group.

Adverse events caused by the medical device occurred in 2 subjects (4.17%) from the treatment group, and 7 subjects (14.58%) from the control group. No notable difference was observed between the adverse events related with the device used by the treatment group or the control group.

Before the study of the low level "Laser-Toothbrush" in comparison to the placebo laser toothbrush, differences in VAS between the treatment group and the control group did not exist.   However, after the study, a significant effect was observed in the treatment group. Although the effective outcome can be attributed somewhat to the placebo laser toothbrush, the treatment group was able to lower the sensation of pain by a remarkable difference: 2.44±1.83 in VAS. Therefore it can be said that the effectiveness of laser toothbrush use compared with placebo is clear.   Alleviation of pain was also seen in the control group, even though its subjects were using a placebo toothbrush. This was due to physiological and psychological factors. While the patient unknowingly received placebo laser treatment on his hypersensitive tooth, the patient received a sense of hope from the trust that the physician would help to alleviate the pain.

For the above reasons, we find that the low-level "Laser-Toothbrush" is considered to be an effective clinical tool for reducing pain that arises from dentin hypersensitivity.

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Appendix 1. Final Copy of Clinical Study Protocol

Appendix 2. Final Copy of Case Report Form

Appendix 3. List of Trial Subjects