GENOSS
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A Randomized, Multi-Center, Patient & Evaluator-Blind, Matched Pairs, Active-Controlled Design Clinical Study to Evaluate the Efficacy and Safety of Injection with GENOSS Filler as Compared to Restylane® in Correction of Nasolabial Fold

Clinical Study Report

General Information	
Protocol No./ Final Version :	CTP-DA1102/ Version 1.2
MFDS Approval Number :	No. 398
Investigational Device :	GENOSS Filler
Phase of Trial :	Clinical trial for approval of investigational device
Indication :	Improvement of the both side nasolabial fold
CSR Kor. Version / Version Date :	Version 2.0 / 2014. 05. 14
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Date of First/Last Subject First/Last Visit :	2013. 07. 10 / 2014. 01. 22
Submission Date:	

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Sponsor :	GENOSS CO.,LTD.

Confidentiality Statement

Signature Page

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CLINICAL TRIAL SUMMARY

Title

A Randomized, Multi-Center, Patient & Evaluator-Blind, Matched Pairs, Active-Controlled Design Clinical Study to Evaluate the Efficacy and Safety of Injection with GENOSS Filler as Compared to Restylane® in Correction of Nasolabial Fold

Purpose

To verify that GENOSS Filler is not inferior to the reference device, Restylane®, in terms of efficacy and safety in the correction of nasolabial folds

Sponsor

GENOSS Co., Ltd., C.E.O.: 정성민

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Clinical Trial Design

24 weeks, multi-center, randomized, patient & evaluator-blind, matched pairs, active controlled design

Investigational Device

Investigational Device: GENOSS Filler

Reference Device: Restylane®

Target Subject

Subjects who want to improve the appearance of nasolabial folds

Clinical Trial Stage

Clinical trial for the approval of the medical device

Clinical Trial Period

6 months (Observation period per subject: 24 weeks)
• Date of the First Subject's First Visit: 10 July 2013 (Keimyung University Dongsan Medical Center)
• Date of the Last Subject's Last Visit: 22 January 2014 (Seoul National University Hospital)

The Number of Subjects (The planned number and the actual number of subjects included in the analysis results)

1. Planned Number of Subjects: 66 (66 subjects were planned, with the anticipated number of 56 assessable subjects, based on a 15% rate of withdrawal)
2. Total Number of Recruited Subjects: 66 (Screening Failure Subjects: 0, Randomized: 66)
3. Subjects Included in the Analysis Results:
   - FA Set: 65
   - PP Set: 59
   - Safety Set: 65

Inclusion Criteria

1. Male or female subjects no younger than 30 and no more than 65 years of age
2. Subjects who scored 3 or 4 on the Wrinkle Severity Rating Scale (WSRS) and want to improve the appearance of their nasolabial folds (the subject does not need to have the same score on both sides.*)

   *The scores need not to be same on both sides, but the two nasolabial folds should have symmetry in the range of 3-4.
3. Subjects who have symmetric nasolabial folds
4. Subjects who agreed to discontinue the use of any dermatological procedure or therapy, including facial wrinkle reduction procedures
5. Subjects with the ability to understand and follow the instructions and who are committed to availability for the entire study period
6. Subjects who have voluntarily decided to participate in this study and who have signed the informed consent form

Exclusion Criteria

1. Subjects who show hypersensitive skin reaction to the investigational devices, confirmed by the intradermal reaction test performed at screening
2. Subjects who received an antithrombotic agent within 2 weeks prior to screening (with the exception of low dose Aspirin 100 mg, maximum of 300 mg/day) or NSAIDs or Vitamin E within 1 week
3. Subjects with a liver problem and/or blood coagulation defect or subjects who require the administration of an antithrombotic agent during the clinical trial period (with the exception of low dose Aspirin 100 mg, maximum of 300 mg/day)
4. Subjects who have used a local ointment on their faces (medication such as steroid or retinoid are included and cosmetic products are excluded from this criterion) within 4 weeks prior to screening or subjects who are planning on using such an ointment during the clinical trial period
5. Subjects who have received treatment for wrinkles or acne within 24 weeks prior to screening
6. Subjects who have received facial (chemical) peels and/or skin rejuvenation procedures or plastic surgeries, including the injection of the Botulinum toxin, within 24 weeks prior to screening
7. Subjects who have a permanent skin expander such as soft form or silicon implanted in the regions that could affect on this clinical study
8. Subjects who have scars on the face requiring a medical treatment but who have not received any treatment for more than a year or subjects who have scars or wounds on which the test investigational devices will be applied
9. Subjects with skin disease or wound infection on the face
10. Subjects who have a low level of immunity
11. Subjects who have a history of anaphylaxis or severe complicated allergic reaction
12. Subjects who have a history of hypertrophic scars or keloid disease
13. Subjects who experience side effects from EMLA cream or other Lidocaine drugs (this criterion is not applied to subjects who have not used EMLA cream or other Lidocaine drugs)
14. Subjects who have a severe illness in their cardiovascular, digestive, pulmonary, endocrine or central nerve system, or subjects who have a current or past history of mental illness which can have a negative impact on the clinical trial
15. Subjects who have participated in any other clinical trial within 30 days prior to screening (note, however, that subjects who have participated in a clinical trial for asthetics purposes within 6 months were permitted to enroll at the investigator's discretion)
16. Any female subject with potential of pregnancy who does not consent to use medically approved methods of contraception* until the week 48 from the final application

    * Medically approved methods of contraception: condoms, oral contraceptives used for at least 3 months, contraceptive shots or suppositories, or the implantation of an intrauterine device (IUD).

17. Female subjects who are pregnant or lactating
18. Any subject otherwise judged by the principal investigator and subinvestigator to be unsuited to participate in this clinical study for any other clinically significant reason

Criteria for Evaluation

Efficacy Endpoint

1. Primary Efficacy Endpoint

The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the independent evaluator in week 24 from the final application of the investigational device

2. Secondary Efficacy Endpoint

1) The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the independent evaluator in weeks 8 and 16 from the final application of the investigational devices
2) The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational devices
3) The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational devices, in comparison with the scores obtained prior to the initial application
4) The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group evaluated by the subject in weeks 8, 16 and 24 from the final application of the investigational devices, in comparison with the scores prior to the initial application
5) The proportion of subjects whose WSRS scores (week 24 – before application) decreased at least 1 level, as evaluated by the independent evaluator in week 24 from the final application of the investigational devices, from both the GENOSS Filler group and the Restylane® group in comparison with the scores prior to the initial application
6) The proportion of subjects whose WSRS scores (week 24 – before application) decreased at least 1 level, as evaluated by the investigator in week 24 from the final application of the investigational devices, from both the GENOSS Filler group and the Restylane® group in comparison with the scores prior to the initial application

Safety Endpoint

All adverse events (AE) including the facial AE of subjects were included in the safety evaluation, and the safety of the investigational device was evaluated through the laboratory tests, vital signs and physical examinations during the clinical trial. All adverse events were recorded in the case report form and evaluated for their abnormality.

1. Adverse Events

Adverse reactions which were clinically abnormal were recorded as adverse events (AE), and the sites where the AE occurred were recorded, classified to indicate the injection site of the investigational/reference device or not an injection site. The records of all AEs also included causality and severity by the subject, according to the protocol of this clinical trial.

1) Baseline symptoms and signs, from the screening to prior to the application of the investigational device, were recorded.
2) Evaluations Performed Immediately After the Application of the Investigational Device: Adverse

events, which occurred at application sites, including hemorrhage, pain, induration, swelling, redness and pruritus, within 30 minutes after the application of the investigational device, were recorded.

3) All treatment-emergent adverse events (TEAE), which occurred from the final application of the investigational device up to the time of study termination, were recorded.

2. Laboratory Tests

The following list was tested. All the abnormal values were reported, including causality to the investigational devices, and follow-up studies were conducted.

1) Hematology Test
   : WBC, RBC, Hb, Hct, and PLT
2) Blood Biochemistry Test
   - Liver Function : ALP, AST, ALT, LDH, total bilirubin, and γ-GT
   - Metabolic Function : Total cholesterol, glucose, total protein, albumin, triglyceride, and serum creatinine
   - Electrolytes : Na, K, Cl, and Ca
3) Blood Coagulation Test: aPTT and PT
4) Urine Test: protein, glucose and blood
5) Urine Pregnancy Test: Urine HCG. Conducted on females with the possibility of pregnancy, who have not received surgery for female infertility and who are prior to menopause.

3. Vital Signs and Physical Examination

1) Vital Signs: Blood pressure taken in the sitting position, pulse and temperature

2) Physical Examination: Check for abnormal signs and symptoms

4. Concomitant Medications

The changes in all concomitant medications used after the application of the investigational devices were evaluated at each visit. The name of medication, administered dose and unit, route, frequency, purpose of use and duration of the medication use were recorded in detail in the case report form.

Method of Statistical Analysis

Data obtained from subjects in this clinical trial were divided into the Full Analysis (FA) Set, the Per-Protocol (PP) Set and the Safety Set. In this clinical study, the FA Set was used for the main analysis of the main population, the PP Set was used for additional analysis, and the Safety Set was used for safety analysis. All results were compared and all efforts were made to present the results of each method and describe in detail the reasons in the event of any differences between the groups. A one-sided confidence interval of 97.5% was used for the non-inferiority test, and all remaining differences were compared with a significance level of 5%. The confidence interval was estimated using t-distribution.

Primary Endpoint:
The trial aimed to verify that GENOSS Filler was not inferior to the Restylane® by demonstrating that the lower limit of the one-sided 97.5% confidence interval of the mean value of the differences between GENOSS Filler and Restylane® was greater than -0.29.

Secondary Endpoint:
As the secondary endpoints (1) - (4) were successive data, this study presented the mean and standard deviation in each time point and for each group. In order to compare the differences in the repeatedly measured values at each time point, the Mixed Model for Repeated Measures (MMRM) was used.
Secondary Endpoint (5) - (6) presented the proportion of subjects in each group whose mean WSRS scores decreased at least 1 level (the time point – before application, applying the 95% confidence interval. The difference in proportion between the groups was compared using McNemar's test. The study also obtained the odds ratio of the matched pair data and presented the two-sided 95% confidence interval.

Adverse Events:
In regards to adverse events, this study analysed Treatment-Emergent Adverse Events (TEAE) which occurred after the application of the investigational devices and presented the findings in a list. The incidence and the percentage of adverse events were presented classified by SOC (System Organ Class) and PT (Preferred Term). The 95% confidence interval was obtained in terms of subjects who experienced more than one incidence of adverse events. The rates of adverse events in the injection site were compared (investigational group, reference group, and investigational group + reference group) and evaluated using the Chi-square test or Fisher's exact test.

Laboratory Test / Vital Signs and Physical Examination:
The descriptive statistics for laboratory examination, vital signs and physical examination were summarized, including the average, the standard deviation, the minimum value, the maximum value and the mean value in cases where the data was continuous. Also, the changes in results before and after the application of the investigational device for clinical trial were compared to the normal and abnormal results of the physical examination, and were evaluated using the paired t-test or Wilcoxon`s signed rank test. The categorical data were presented with absolute frequency and relative frequency, and McNemar's test was conducted to compare the results before and after the application of the investigational device.

Concomitant Medication:

Concomitant medications were described by each subject and represented by level 1 and 2 of the ATC code according to the WHO Drug dictionary.

Summary and Conclusion

Efficacy Result

The Evaluation Result for the Primary Efficacy Endpoint:

In comparison of the mean WSRS scores of the FA Set (PP Set) that were assessed by the independent evaluator at Week 24 from the final application of investigational devices between the GENOSS Filler group and the Restylane® group, the mean of WSRS was 2.05±0.69 (2.03±0.64) in GENOSS Filler group and 1.98±0.72 (1.95±0.68) in the Restylane® group, and the mean of the difference between the two groups (Restylane® - GENOSS Filler) was -0.08±0.70. The lower limit of the one-sided 97.5% confidence interval in the mean difference of WSRS scores between the GENOSS Filler group and the Restylane® group was -0.24 (-0.27), which was greater than -0.29, the non-inferiority limit of this clinical trial. This proved the non-inferiority of GENOSS Filler compared to the Restylane® in both FA and PP Sets.

The Evaluation Result of the Secondary Efficacy Endpoint

1) The mean of the WSRS scores for the GENOSS Filler group and the Restylane® group rated by the independent evaluator in Weeks 8 and 16 after the application of investigational devices were compared. In the FA Set (PP Set), the means of the WSRS scores were 2.02±0.65 (2.05±0.65) in the GENOSS Filler group and 1.97±0.64 (1.97±0.64) in the Restylane® group at Week 8 after the final application of the investigational devices, and 2.25±0.71 (2.24±0.68) and 2.14±0.68 (2.14±0.68) at Week 16. The means of the difference between the two groups (Restylane® - GENOSS Filler) were -0.05±0.82 (-0.08±0.79) at Week 8 and -0.11±0.73 (-0.10±0.74) at Week 16. Although the mean of the WSRS scores for the GENOSS Filler group was higher than that of Restylane®, there was no statistically significant difference between the groups.
2) The mean of the WSRS scores for the GENOSS Filler group and the Restylane® group rated by the investigator in Weeks 8, 16 and 24 after the application of investigational devices were compared. In the FA Set (PP Set), the means of the WSRS scores were 1.80±0.54 (1.78±0.56) in the GENOSS Filler group and 1.80±0.51 (1.78±0.49) in the Restylane® group at Week 8 after the final application of the investigational devices, 2.00±0.66 (1.95±0.65) and 2.00±0.56 (1.95±0.54) at Week 16, and 2.57±0.66 (2.53±0.68) and 2.58±0.66 (2.53±0.65) at Week 24. There was no statistically significant difference between the groups, however, there were significant differences in the time points.
3) The mean of the GAIS scores for the GENOSS Filler group and the Restylane® group rated by the investigator in Weeks 8, 16 and 24 after the application of investigational devices were compared. In the FA Set (PP Set), the means of the GAIS scores were 2.11±0.64 (2.08±0.65) in the GENOSS Filler group and 2.02±0.67 (2.00±0.69) in the Restylane® group at Week 8 after the final application of the investigational devices, 1.58±0.71 (1.58±0.72) and 1.50±0.71 (1.53±0.73) at Week 16, and 1.06±0.59 (1.07±0.61) and 0.98±0.63 (1.00±0.64) at Week 24. Although the improvement degree of the GENOSS Filler group was slightly higher than that of Restylane®, there was no statistically significant difference between the groups.
4) The mean of the GAIS scores for the GENOSS Filler group and the Restylane® group rated by the subject in Weeks 8, 16 and 24 after the application of investigational devices were compared. In the FA Set (PP Set), the means of the GAIS scores were 1.45±0.73 (1.47±0.70) in the GENOSS Filler group and 1.29±0.80 (1.32±0.82) in the Restylane® group at Week 8 after the final application of the investigational devices, 1.14±0.89 (1.15±0.93) and 1.05±0.93 (1.05±0.95) at Week 16, and 1.10±1.03 (1.14±1.04) and 1.03±0.97 (1.03±0.96) at Week 24. Although the improvement degree of the GENOSS Filler group was slightly higher than that of Restylane® in all time points, there was no statistically significant difference between the groups.

5) The proportion of subjects from both the GENOSS Filler group and the Restylane® group whose WSRS scores decreased at least 1 level when assessed by the independent evaluator in Week 24 from the final application of the investigational device were compared. In the FA Set (PP Set), the proportion of subjects showing such decrease was 90.77% (93.22%) in the GENOSS Filler group and 93.85% (96.61%) in the Restylane® group. There was no statistically significant difference between the groups.
6) The proportion of subjects from both the GENOSS Filler group and the Restylane® group whose WSRS scores decreased at least 1 level when assessed by the investigator in Week 24 from the final application of the investigational device were compared. The proportion of subjects showing such decrease was 100% in both GENOSS Filler group and Restylane® group.

Safety Evaluation Result

The safety evaluation for this clinical trial was conducted with 65 subjects in the Safety Set. The number of subjects who experienced 1 or more adverse events during the clinical trial period was 18 subjects (27.69%) and the total number of adverse events was 24 cases. The mean incidence per person was 1.33. Among the adverse events, 1 case (4.17%) was adverse device event related to the investigational device or reference device, which was Injection site induration in the site of Restylane® injected. Also, 1 case was moderate, and the remaining cases were mild. As the outcome of adverse events, 15 cases were fully recovered, 8 cases were in the progress of recovery, and 1 case was recovered but left after effects. In addition, there were no clinicaliy abnormal values in vital signs, and all subjects were normal in both prior to and after the application in the physical examinations. Also, none of subject was normal or not clinically abnormal prior to the application and became clinically abnormal at Week 24 from the final application.

Conclusion

Taken together, these clinical trial results suggest that GENOSS Filler is an effective and safe medical device to use in the correction of nasolabial folds.

Date of the Clinical Study Report (Eng.)

13 June 2014

ABBREVIATION AND DEFINITIONS OF TERMS

Abbreviation	Definition of Terms
ADE	Adverse Device Effect
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT(GPT)	Alanine Transaminase(Glutamic-pyruvic Transaminase)
AST(GOP)	Aspartate Transaminase(Glutamic-oxaloacetic Transaminase)
CRF	Case Report Form
CRO	Contract Research Organization
FA	Full Analysis
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic acid
Hb	Hemoglobin
Hct	Hematocrit
IRB	Institutional Review Board
ITT	Intent-to-Treat
KGCP	Korean Good Clinical Practice
KGMP	Korean good manufacturing practice
MedDRA	The Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MMRM	Mixed Model for Repeated Measures
PP	Per Protocol
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
WSRS	Wrinkle Severity Rating Scale
WBC	White Blood Cell

1. DESCRIPTION REGARDING ETHICAL CONSIDERATIONS

1.1 Institutional Review Board (IRB)

Before initiating the clinical trial, the clinical study protocol, the information for subject consent and the informed consent form used in this clinical trial were approved by the Ministry of Food and Drug Safety (MFDS). All matters and important revisions made to this clinical trial, including any revisions to the clinical trial protocol, were approved by the MFDS or an Institutional Review Board (IRB) of institutions.

1.2 Ethical Considerations for the Clinical Trial

In order to ensure the right and safety of the subject, this clinical trial was conducted in accordance with the guidelines of the International Conference on Harmonization (ICH) and the Helsinki Declaration and in compliance with Korea Good Clinical Practice-Investigational Device (KGCP) and all related regulations.

1.3 Subject Consent

Prior to the clinical trial, the Informed Consent Form (ICF) was approved by the Institutional Review Board (IRB) in compliance with KGCP guidelines, all related regulations and ethical principles provided in the Helsinki Declaration. The copy of the original and revised informed consent forms and the written information was approved by IRB prior to being distributed to the subjects. Samples of the final manual for the subject and the approved informed consent form are attached as an Appendix (Appendix 1.3. FINAL SUBJECT MANUAL & INFORMED CONSENT FORM) to this clinical trial report. Prior to conducting any tests or enrolling any subjects into the study, the investigator provided the each subject or his or her legal guardian with the appropriate essential information about this clinical trial and documented the receipt of this information by obtaining the written informed consent form before initiating the clinical trial. The name of subject, his or her signature and the date are written on the consent form along with the signature of the person who obtained the informed consent form and the date of obtainment. The subject or his/her legal guardian was given the copy of the Informed Consent Form signed and dated by the subject and the investigators. The revised informed consent form was approved by IRB, and the investigator provided each subject or his or her legal guardian with the appropriate essential information about this revised form during the subject's visit after the approval date. The copy of this re-approved form was documented in the same manner as the previous form.

2. APPROVAL OF THE CLINICAL PROTOCOL AND REPORT

2.1 Ministry of Food and Drug Safety (MFDS)

As a result of the procedure for approval of the clinical protocol from MFDS, the initial permission was granted by MFDS on 28 June 2013. Any changes made during the clinical trial period were implemented after obtaining IRB approval regardless of direct effects on safety and efficacy evaluation. The changes did not include main clinical inspection items and methods which were directly related with changes in the clinical trial device, the subject's inclusion/exclusion criteria, the criteria of safety/efficacy evaluation, or the subject's safety. Further detailed information on protocol revision for MFDS is listed in the following table (Table 1).

Table 1. MFDS Approval for the Clinical Trial Protocol and Revision

Classification	Version	Date of Submission	Date of Approval	Major Revisions
Initial Submission	PRT V1.0 ICF V1.0	2013.03.22		-
Modification	PRT V1.1 ICF V1.1	2013.05.24	2013.06.28	Modification of regulation for victim compensation and appendices
1st Revision Report	PRT V1.2 ICF V1.2	2013.11.01	-	Correction of omissions and typos

2.2 Institutional Review Board (IRB)

This clinical trial was designed to obtain approval for the use of the medical device. The initial permission was granted by IRB in Keimyung University Dongsan Medical Center on 23 May 2013, and approval was given for the clinical trial by the institutions. The following table lists information regarding the status of initial/final approval and the status of end report approval after the completion of the clinical trial (Table 2).

Table 2. Initial Approval of the Clinical Trial Protocol and Revision by IRB in Institutions

No.	Institution	Initial Approval	Comment(Initial/Final Approved Report)		
		End Report Approval	IB	PRT	ICF
01	Seoul National University Hospital	2013.07.04	V1.0	V1.1	V1.1

No.	Institution	Initial Approval	Comment(Initial/Final Approved Report)		
		End Report Approval	IB	PRT	ICF
		2013.12.03	V1.0	V1.2	V1.2
02	Keimyung University Dongsan Medical Center	2013.05.23	V1.0	V1.0	V1.0
		2014.02.24	V1.0	V1.2	V1.2

The protocol was revised several times during the clinical trial period, and information on revisions such as the revised approval number and the status of report approval by institutions has been attached as an Appendix to this Clinical Trial Report (Appendix 1.5. LIST OF INSTITUTIONAL REVIEW BOARDS AND RECORDS FOR REVIEW). The detailed revised contents have also been attached as an Appendix to this Clinical Trial Report (Appendix 1.2. COMPARISON TABLE FOR CHANGES IN THE CLINICAL TRIAL PROTOCOL).

3. INVESTIGATORS & INSTITUTIONS

This clinical trial was conducted by well-trained investigators at two domestic institutions. A list of the institutions, the principle investigators, the sub-investigators, the clinical trial coordinator, the device administrator, and the statistician who participated in this clinical trial and the manager involved in the safety/efficacy evaluation have been attached as an Appendix to this Clinical Trial Report (Appendix 1.9. INCLUDED INVESTIGATORS).

4. INTRODUCTION

4.1 Features of GENOSS Filler

The medical device used in this clinical trial was the GENOSS Filler manufactured by Genoss Co, Ltd. It is a disposable sterile medical device designed for one-time usage, with a transparent, gel-formulation containing stabilized hyaluronic acid. The GENOSS Filler is provided in a luer-lock glass syringe so that it can be injected into the skin for transplantation. The GENOSS Filler is able to reduce the appearance of wrinkles by extending the tissue in the transplanted area. Stabilized hyaluronic acid gradually decomposes in the body over time, and it maintains the expanded tissue for this duration. This medical device is provided in sterile condition after a moist heat sterilization process.

4.2 Hyaluronic acid

4.2.1 Characteristics of Hyaluronic acid

Hyaluronic acid (HA) is a hydrophilic biopolymer anion polysaccharide, and was first discovered in 1934 in the vitreous humour of the eyeball. HA is synthesized in the human body and is one of the main components of the extracellular matrix that is mainly distributed through connective tissue, epidermal tissue, and nervous tissue. It serves various functions, such as adjusting cell-to-cell coupling, inhibiting cell differentiation, healing wounds, regenerating cells, and building immunity. One particular advantage of HA is that it has many branches with electric charge and therefore can contain a large amount of moisture, induce a balance in the body's moisture level by means of regulating osmotic pressure, and maintain the skin's homeostasis. HA products the skin from UV and is also known to be an excellent moisturizer, and for these reasons it is widely used in cosmetic products that are applied directly on the skin.

HA is extracted from animal tissue or, in the case of non-animal HA, obtained through microbial fermentation, and its polymer structure is identical regardless of the species it originated from. When injected in the human body, it most cases it does not induce any immune response, and it is known to be safe since it is quickly decomposed by hyaluronidase, which is an HA decomposing enzyme present within the human body. When HA undergoes chemical cross-linking, it becomes an insoluble elastomer with greater resistance against the decomposing enzyme. The tissue retention of HA can also be improved through the process of separating it from the fermentation medium, removing impurities, and stabilizing the HA.

Recently, much research has been devoted to performing HA cross-linking using a chemical cross-linking agent in order to block the movement and linking of the enzyme and thereby delaying the biodegradation of HA. Researchers are developing tissue repairing biomaterials manufactured using HA with such delayed biodegradation to enable the HA to have a longer-lasting effect in the human body. In particular, products with HA cross-linked using BDDE (1,4-butanediol diglycidyl ether) have obtained approval in Korea and abroad, and are currently available on the market. Only a minimum amount of BDDE is used for cross-linking, and residues are completely removed by washing.

4.2.2 The Use of Hyaluronic Acid as a Tissue Restorative Biomaterial

Various materials have been developed over the last four decades for the use as dermal fillers. The materials have been mainly used on middle aged women to eliminate the appearance of wrinkles in the areas around the eyes and mouth, the forehead, and cheeks. Dermal fillers containing collagen have been widely used since the 1980s for cosmetic purposes. A variety of biomaterials intended for use in tissue repair are under development worldwide, and those that are currently in use include collagen implants, HA, fluid silicon, polymethylmethacrylate, polytetrafluoroethylene, and fat grafts.

HA was introduced into clinical practice around 20 years ago, and in the initial stages, it was more often used for eye surgery, arthritis treatment, or surgical treatment of injuries than for cosmetic purposes. It has been verified early on to be safe for use in the human body and the stability of the molecule has been further improved through cross-linking. HA is therefore currently highly valued as a tissue repairing biomaterial. In 2003, the United States FDA first approved the use of HA as filler for correcting the appearance of wrinkles on facial areas (such as nasolabial wrinkles) and folds, and since then various other HA products have become approved and available on the market.

5. OBJECTIVES

To verify that GENOSS Filler is not inferior to Restylane®, the reference device, in terms of efficacy and safety when used for the correction of nasolabial folds.

5.1 Primary Objective

To prove that the efficacy of GENOSS Filler in correction of nasolabial folds is not inferior to Restylane®, the reference device, based on the Wrinkle Severity Rating Scale (WSRS) assessed by the independent evaluator in weeks 24 from the final application of the investigational device.

5.2 Secondary Objective

1) To compare and evaluate the correction of folds achieved in the GENOSS Filler group and the Restylane® group, based on the WSRS assessed by the independent evaluator in weeks 8 and 16 from the final application of the investigational device.
2) To compare and evaluate the correction of folds achieved in the GENOSS Filler group and the Restylane® group, based on the WSRS assessed by the investigator in weeks 8, 16 and 24 from the final application of the investigational.
3) To compare and evaluate changes in the degree of the subjects' satisfaction in the GENOSS Filler group and the Restylane® group, based on the Global Aesthetic Improvement Scale (GAIS) scores assessed by the investigator in weeks 8, 16 and 24 from the final application of the investigational device in comparison with the scores prior to the initial application.
4) To compare and evaluate changes in the degree of the subjects' satisfaction in the GENOSS Filler group and the Restylane® group, based on the GAIS scores assessed by the subject in weeks 8, 16 and 24 from the final application of the investigational device in comparison with the scores prior to the initial application.

5) To evaluate the proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the independent evaluator in week 24 from the final application of the investigational in comparison with the scores prior to the initial application(week 24 - prior to the initial application).
6) To evaluate the proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the investigator in week 24 from the final application of the investigational device in comparison with the scores prior to the initial application(week 24 - prior to the initial application).

6. INVESTIGATIONAL DEVICE

6.1 Investigational Device

6.1.1 Name & Manufacturer

- Device Name: GENOSS Filler
- Item Name: Biomaterial used for tissue repair
- Item Number: B04230.01
- Grade: 4th grade
- Manufacturer: GENOSS Co., Ltd.
  (1F, Gyeonggi R&DB center, 105, Gwanggyo-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, Korea)

6.1.2 Raw Material

No.	Name	Raw Material or Ingredient	Dosage	Standard	Note
1	HA	Hyaluronic acid	2 %	The Korean Pharmacopoeia, Sodium Hyaluronate	Contact, Intradermal
2	PBS	PBS	98 %	Own corporate standard	Contact, Intradermal
3	BDDE	1,4- butanediol diglycidyl ether	<2 PPM	CAS# 2425-79-8	Contact, Cross-linked

				Purity: >95%	Material

6.1.3 Effect & Purpose of Use

- Used for correction of wrinkles and folds in facial tissue
- After it is injected to the facial skin layer, the wrinkles can be corrected by expanding tissue injected. The effects of wrinkle correction last for weeks to months after transplated, and the period can be changed depending on the subject's condition.

6.1.4 Product Composition and Properties

- The medical device used in this clinical trial was the GENOSS Filler manufactured by Genoss Co, Ltd. It is a disposable sterile medical device designed for one-time usage, with a transparent, gel-formulation containing stabilized hyaluronic acid. The GENOSS Filler is provided in a luer-lock glass syringe so that it can be injected into the skin for transplantation. The GENOSS Filler is able to reduce the appearance of wrinkles by extending the tissue in the transplanted area. Stabilized hyaluronic acid gradually decomposes in the body over time, and it maintains the expanded tissue for this duration. This medical device is provided in sterile condition after a moist heat sterilization process.
- The hyaluronic acid, which is the material of GENOSS Filler, was obtained directly through microbial fermentation by Genoss Co, Ltd. The microbial fermentated HA was manufactured through purification, filteration, homogenization, cross-link, and sterilization.

6.1.5 Storage & Expiration Date

- Storage: Do not freeze, and store at room temperature (1°C ~ 25°C) protected from light.
- Expiration Date: 3 years from the date of manufacture

6.2 Reference Device

6.2.1 Name & Manufacturer

- Device Name: Restylane® 1.0mL (no. 04-1163)
- Item Name: Biomaterial used for tissue repair
- Item number: B04230.01
- Manufacturer: Q-Med AB (Sweden)

6.2.2 Main Ingredient & Purpose of Use

- Main Ingredient: Hyaluronic Acid
- Purpose of use: Correction of wrinkles by injection to the facial skin layer

6.2.3 Formulation

Colourless, transparent gel form to the unaided eye

6.2.4 Storage & Expiration Date

- Storage: Store at room temperature (below 25°C) protected from light and do not freeze.
- Expiration Date: 3 years from the date of manufacture

6.3 Procedures of Investigational Device Application

6.3.1 Preparations Prior to Use

1) Before using the product, we verified the suitability of its application to the patient and reviewed the patient's medical history.
2) Prior to the procedure, the medical practitioner provided the patient with sufficient explanation regarding the product's indications, contraindications, and any potential side effects.
3) We examined the packaging to verify that it was free of any damage. If any damage was present, the product was not used.
4) This product is a medical device, and the procedure was performed by a qualified skilled doctor.

6.3.2 Method and Sequence of the Procedure

1) The treatment area was wiped clean with a disinfecting liquid. (Also, if the tester judged it to be necessary, topical anesthetic EMLA cream or an equivalent lidocaine formulation was applied to the treatment area.)
2) A syringe needle was properly connected to the syringe provided as part of the product. If the connection is improperly performed, there is a risk that the syringe and the needle will separate during injection.

3) Holding the luer-lock in one hand, the cap was removed by twisting it carefully in the opposite direction using the other hand, and the needle was connected to the syringe.
4) With one hand holding the body of the syringe, the other hand was used to remove the protective cover from the needle.
5) Before injecting this product, pressure was applied to the plunger of the syringe until the injection fluid was visible on the tip of the needle.
6) The practitioner used an injection technique suitable for the specific area targeted for treatment, and slowly injected the fluid into the treatment area.
7) The amount injected varied depending on the degree of indentation in the treatment area and the degree of corrective effect desired by the patient.
8) If the skin of the injection area turned white, we immediately stopped the injection and massaged the area until the skin returned to its original tone.
9) To ensure that the injection fluid was distributed evenly, we gently massaged the treated area. If the injection site swelled after the injection, the swelling was reduced by ice pack massages.

6.3.3 Storage and Care after Usage

1) The product is designed for one-time use only. Do not re-use the product.
2) Do not re-sterilize the product.

7. CLINICAL TRIAL DESIGN

7.1 Application of the Investigational Device

7.1.1 Intradermal Reaction Test (Week -2)

Screening numbers were sequentially assigned to all subjects who voluntarily provided the informed consent to participate in this clinical study. The subjects were then screened to determine whether they satisfied both the inclusion/exclusion criteria of this clinical trial. Next, the subjects who satisfied the inclusion/exclusion criteria received the intradermal reaction test to assess whether their skin tissue developed an allergic reaction to hyaluronic acid by receiving an injection of 0.1 mL of the investigational device into the brachial flexor surf within 2 weeks before applied the investigational device. If any subject experienced adverse reactions from the day of the intradermal reaction test, he or she was instructed to return to the institution to report their skin hypersensitivity and to receive the proper measures.

7.1.2 Initial Treatment (Week 0)

Subjects who satisfied all of the inclusion/exclusion criteria and did not show any reaction of skin hypersensitivity in the intradermal test were finally selected and received the investigational device at the time of initial treatment (Week 0). Subjects were decided which device were applied to the nasolabial folds by randomization, and they received GENOSS Filler on the nasolabial fold on one side and Restylane® on the other side (the 27×1/2 gauge needle was used for application in both cases). Also, the amount of injected volume for each side was in the range of 0.8mL ~ 1.0 mL for both devices. Only the investigator was informed of the types of the investigational device applied, following a single blind method. EMLA cream was one of the anesthetics applied to the nasolabial folds to relieve pain for subjects before the application of GENOSS Filler and Restylane®.

7.1.3 Repeat (Touch-Up) Treatment (Week 2) or Baseline (Week 2)

If subjects showed uneven intradermal structure and the WSRS scores did not decrease by at least 1 level when assessed by the investigator with the naked eye in week 2, it was planned that the repeat (touch-up) treatment was implemented on the nasolabial fold on one or both sides. At this time, the investigator was set to apply the same investigational device as the initial treatment on the repeat (touch-up) site with the same gauge of needle and the maximum amount. The repeat (touch-up) treatment was planned to perform only once, and the usage of anesthetics was planned to be the same as in the initial treatment.

7.2 Clinical Trial Protocol

This clinical trial was designed to be randomized, patient and evaluator blinded, matched pair, and active-controlled. Eligible subjects who satisfied both the inclusion/exclusion criteria and voluntarily signed the informed consent were enrolled in this clinical trial. The subjects then received the **intradermal reaction test**† for 2 weeks prior to the initial application of the investigational device and were observed for 2 weeks for the occurrence of any skin hypersensitivity. For the initial treatment (Week 0), subjects who did not show any skin hypersensitivity reaction were finally selected and were randomized to receive GENOSS Filler on one side of the nasolabial fold and Restylane® on the other. The institution limited the number of investigators performing the treatment on subjects to 2 or less in order to minimize the effects caused by different handling techniques. Subjects were monitored for possible adverse events for 30 minutes after receiving the investigational devices. When subjects

visited the institution agiain in 2 weeks, their subject diaries were submitted to the investigator. At that time, the investigator assessed the WSRS of subjects and determined whether a subject needed **repeat (touch-up) treatment**‡. The repeat treatment was planned to perform only once, and the investigator was set to apply the same investigational device as used in the initial treatment to these subjects who needed repeat treatment. Following these clinical steps, the visit in week 2 from the final application of the investigational device was planned to set as the baseline (in week 26 as the final assessment), and all subjects returned to the institutions in weeks 8, 16 and 24 from the final application. The investigator photographed each subject's treated sites and assessed the efficacy, which included the WSRS evaluated by investigator and the GAIS evaluated by investigator and subject, as well as the safety at each visit except for screening. Female subjects were required to maintain the use of contraception during the clinical trial period.

† **Intradermal Reaction Test**: The test to assess the development of allergic reactions by injecting GENOSS Filler into the skin surface.

‡ **Repeat (Touch-Up) Treatment**: Reapplication of the investigational devices when uneven intradermal structures or rough lifts on subject's nasolabial folds were noted or when the WSRS scores assessed by the investigator with the naked eye were not improved by less than 1 grade after 2 weeks from the application of the investigational device.

After the last subject completed the visit in week 24 from the final application of the investigational device in the first stage, the CRFs, efficacy evaluation records and photos of injection sites of all subjects were collected by the sponsor (or CRO) to evaluate the efficacy and safety (for the primary evaluation), in the period lasting from screening to week 24 from the final application of the investigational device. All the photos of injection sites of the subjects were randomized with a new number by an independent data manager, without regard to the group the subject belonged to and when the photo was taken. All data regarding the time the photos were taken (except for the time of the initial application of the investigational device) and information on the subjects were sent to the independent evaluator in a blind method. These pictures were sent to the independent evaluator without any information about the subject and the date of the photograph, after the independent data manager randomly assigned new numbers to these pictures of treatment sites without regard to the study group and the date of the photograph. The independent evaluator assessed the WSRS for each individual picture by equally applying the evaluation criteria, which were specifically designed for this study.

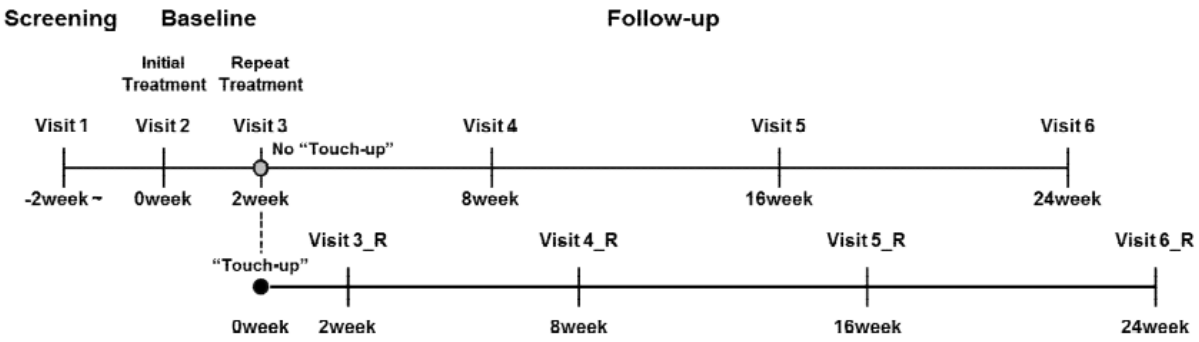


Figure 1. Protocol Design

7.3 Clinical Trial Process, Time and Protocol

The clinical trial proceeded according to the designed protocol. If the subjects could not visit at the fixed date due to unavoidable circumstances, the safety and efficacy of the subjects were evaluated within the scheduled window for the planned visit.

Period	Screening	Baseline		Follow-up		
		Initial treatment	Repeat treatment			
Visit	1	2	3	4	5	6
Day[1]	Week -2 ~	Week 0 ±4D	Week 2 ±4D after initial/final application	Week 8 ±7D after final application	Week 16 ±7D after final application	Week 24 ±7D after final application
Informed Consent Form	✓[2)]					
Inclusion/ Exclusion Criteria	✓	✓				
Randomization		✓				
Demographic Information [3)]	✓					
Medical History	✓					
Prior Treatment History	✓					
Baseline Signs and	✓	✓				

Symptoms							
Laboratory [4]	**Hematologic Test**	✓					✓
	Blood Biochemistry Test	✓					✓
	Coagulation Test	✓					✓
	Urine Test	✓					✓
	Urine Pregnancy Test	✓					✓
Vital Signs[5]		✓	✓[6]	✓[6]	✓	✓	✓
Physical Examination		✓	✓[6]	✓[6]	✓	✓	✓
Intradermal Test and Evaluation[7]		✓[6]					
Photography of the Application Site			✓[6]	✓[6]	✓	✓	✓
Application of the Investigational Device			✓	(✓)[9]			
Evaluation of WSRS[10]		✓	✓[6]	✓[6]	✓	✓	✓
Evaluation of GAIS[11]					✓	✓	✓
Assessment for Concomitant Medications			✓	✓	✓	✓	✓
Assessment for Adverse Events			✓[8]	✓	✓	✓	✓

1) The subjects were allowed a flexibility margin of ± 4 days for the initial visit and the visit in week 2 from the final application of the investigational device. They were given a flexibility margin of ±7 days for visits in weeks 8, 16, and 24. Screening and initial treatment were allowed to be conducted at the same visit day.
2) The written informed consent could be obtained before the visit for screening and was required to be obtained by the beginning of the clinical trial process, at the time of the screening.
3) Demographic information included the date of birth, gender, height and body weight.
4) The following tests were conducted for clinical laboratory assessment. When the test results obtained within 2 weeks from the screening became available, these results were allowed to serve as substitutes for the screening tests.

    - Hematology Test: WBC, RBC, Hb, Hct, PLT
    - Blood Biochemistry Test:

  - Liver Function: ALP, AST, ALT, LDH, total bilirubin, γ-GT
  - Metabolic Function: Total cholesterol, glucose, total protein, albumin, tri glyceride, serum creatinine
  - Electrolytes: Na, K, Cl, Ca
- Blood Coagulation Test: aPTT, PT
- Urine Test: Protein, glucose, blood
- Urine Pregnancy Test: Urine HCG. This test was performed only on fertile premenopausal female subjects who have not undergone sterilization.

5) Systolic / Diastolic blood pressure in the sitting position, pulse and temperature were measured. These vitals were taken before the application of the test investigational device for the initial treatment and the repeat treatment.
6) This was conducted before the application of the test investigational device.
7) The results of Intradermal Reaction Test were completed until the investigational device was initially applied including the date of initial treatment.
8) Assessment was made of adverse events which occur within 30 minutes after the application of the investigational device.
9) If the investigator determined that a subject needs repeat (touch-up) treatment after 2 weeks from the application of the investigational device, the subject needed to participate in repeat treatment. As this time point was re-set to the baseline, taking photos after 2 weeks and clinical study were planned to continue for 24 weeks. However, there was no subject who had repeat treatment.
10) WSRS was evaluated by the investigator and independent evaluator.
11) GAIS was evaluated by the investigator and subject.

7.4 Trial Design Rationale

7.4.1 Selection of the Reference Device

Restylane®, which was selected as the reference device, is a non-animal stabilized hyaluronic acid (NASHA) that originates from bacterial fermentation. Restylane® is widely used for the treatment of skin folds and dented areas and for other aesthetic purposes. The device used in this clinical trial can be applied to any facial fold. After the injection, the NASHA which composes Restylane® is gradually absorbed into the body after combining with water molecules in the skin tissue. Restylane® is a typical filler product and its safety and volume enhancement effects have been well acknowledged. It was selected as the reference device since its components, features and high biocompatibility are similar to the investigational device, and its application site and application method are the same as those of GENOSS Filler.

7.4.2 Matched Pairs Comparison Method

In order to minimize the differences among subjects in terms of the depth and degree of folds, the application site, the conditions involved in performing the procedure (time, condition, length of procedure, etc.) and recovery status, it was decided to be proper that both test and reference devices were applied to each subject. Also, the matched-pair comparison method was selected regarding that the test and reference devices were composed of the identical main ingredient and were expected to have similar lasting duration.

7.4.3 Blind Subject

The forms of two investigational devices used in this clinical trial were not identical, and it was impossible to make placebos for the respective devices due to the features of their raw materials. For the repeat (touch-up) treatment, the investigational device used on the repeat treatment sites needed to be identical to the one used in the initial treatments. The implementation of this method was also expected to be effective because this device would be absorbed into the skin tissue without the process of applying and removing of the device.
Deliberated assignment was not predicted since the investigator was informed of the investigational device used on the nasolabial folds on each side immediately prior to the application of the investigational device. As a result, it could be concluded that investigator will have minimal bias when using each device.

7.4.4 Independent Evaluator (Blind Evaluator)

Independent evaluation was conducted by two assigned professionals who had the ability to evaluate the efficacy of this study but who were not involved in this study as the treating investigator. If the evaluation results differed from one another, one more professional would be assigned to the study that would be continued. Independent evaluation was assessed using WSRS, which was used by the investigator to evaluate the treatment site photographs sorted by the independent data manager. The independent evaluator's objectivity was ensured by means of assessing the assigned treatments and observation periods (before the initial application and weeks 8, 16 and 24 from the application of the device) in the blind setting. This removed the risk of bias that exists in the case of the single blind method. The evaluation performed by independent evaluator was described in a separate independent evaluation sheet, and this sheet was established as the source document.

7.5 Inclusion and Exclusion Criteria for Subjects

7.5.1 Inclusion Criteria

Subjects who satisfied all of the following criteria were eligible to participate in this clinical trial.

1) Male or female subjects no younger than 30 and no more than 65 years of age
2) Subjects who scored 3 or 4 on the Wrinkle Severity Rating Scale (WSRS) and want to improve the appearance of their nasolabial folds (the subject does not need to have the same score on both sides.*)
   *The scores need not to be same on both sides, but the two nasolabial folds should have symmetry in the range of 3-4.
3) Subjects who have symmetric nasolabial folds
4) Subjects who agreed to discontinue the use of any dermatological procedure or therapy, including facial wrinkle reduction procedures
5) Subjects with the ability to understand and follow the instructions and who are committed to availability for the entire study period
6) Subjects who have voluntarily decided to participate in this study and who have signed the informed consent form

7.5.2 Exclusion Criteria

Subjects to whom any of the following criteria applied were not eligible to participate in this study.

1) Subjects who show hypersensitive skin reaction to the investigational devices, confirmed by the intradermal reaction test performed at screening
2) Subjects who received an antithrombotic agent within 2 weeks prior to screening (with the exception of low dose Aspirin 100 mg, maximum of 300 mg/day) or NSAIDs or Vitamin E within 1 week
3) Subjects with a liver problem and/or blood coagulation defect or subjects who require the administration of an antithrombotic agent during the clinical trial period (with the exception of low dose Aspirin 100 mg, maximum of 300 mg/day)
4) Subjects who have used a local ointment on their faces (medication such as steroid or retinoid are included and cosmetic products are excluded from this criterion) within 4 weeks prior to screening or subjects who are planning on using such an ointment during the clinical trial period
5) Subjects who have received treatment for wrinkles or acne within 24 weeks prior to screening

6) Subjects who have received facial (chemical) peels and/or skin rejuvenation procedures or plastic surgeries, including the injection of the Botulinum toxin, within 24 weeks prior to screening
7) Subjects who have a permanent skin expander such as soft form or silicon implanted in the regions that could affect on this clinical study
8) Subjects who have scars on the face requiring a medical treatment but who have not received any treatment for more than a year or subjects who have scars or wounds on which the test investigational devices will be applied
9) Subjects with skin disease or wound infection on the face
10) Subjects who have a low level of immunity
11) Subjects who have a history of anaphylaxis or severe complicated allergic reaction
12) Subjects who have a history of hypertrophic scars or keloid disease
13) Subjects who experience side effects from EMLA cream or other Lidocaine drugs (this criterion is not applied to subjects who have not used EMLA cream or other Lidocaine drugs)
14) Subjects who have a severe illness in their cardiovascular, digestive, pulmonary, endocrine or central nerve system, or subjects who have a current or past history of mental illness which can have a negative impact on the clinical trial
15) Subjects who have participated in any other clinical trial within 30 days prior to screening (note, however, that subjects who have participated in a clinical trial for asthetics purposes within 6 months were permitted to enroll at the investigator's discretion)
16) Any female subject with potential of pregnancy who does not consent to use medically approved methods of contraception* until the week 48 from the final application
    * Medically approved methods of contraception: condoms, oral contraceptives used for at least 3 months, contraceptive shots or suppositories, or the implantation of an intrauterine device (IUD).
17) Female subjects who are pregnant or lactating
18) Any subject otherwise judged by the principal investigator and subinvestigator to be unsuited to participate in this clinical study for any other clinically significant reason

7.5.3 Early Termination & Withdrawal

If the principal investigator and the sub-investigator judge that it was inappropriate for the subject to continue the clinical trial due to the occurrence of an adverse event or the aggravation of complications or a chronic illness, they were able to terminate the subject from the clinical trial. If based on the results observed in the clinical trial it was determined that it was not reasonable to continue this clinical trial, the principal investigator had to request the termination of this trial, and the decision to terminate could be approved by the IRB. If a female subject became pregnant during the screening period or while receiving treatments, the principal investigator and sub-investigator had to

terminate the subject from the study and collect the data. All data and results regarding a subject who became pregnant were to be reported to the sponsor immediately.
In the case of subjects being terminated or withdrawn from the clinical trial according to the following criteria, all data collected until the termination and withdrawal were to be made available for the final evaluation.

1) The subject violates the inclusion and exclusion criteria of this clinical trial.
2) A serious violation of the clinical trial protocol has occurred. Violations may include the need to take medication (including medication or therapy disallowed for concomitant use), the performance of a surgery which might affect the efficacy assessment of the investigational device, or the use of any other treatment for the correction of nasolabial folds besides the investigational device.
3) An adverse event (AE), adverse device event (ADE) or serious adverse event (SAE) occurs, which can disable the subject from continuing the study.
4) The subject has a condition that is determined to make it impossible to receive the necessary test or any other reason.
5) The subject or his or her legal guardian requests to withdraw from the clinical trial.
6) The subject is lost to follow-up.
7) The investigator judges it necessary to discontinue the clinical trial for any other reason.

7.5.4 Measures for Termination & Withdrawal

The termination and withdrawal of a subject was reported to the sponsor immediately, and the progress of the subject was observed and recorded while implementing proper measures and providing treatments. The date of and the reason for the termination and withdrawal, the measures implemented, and the progress of the termination and withdrawal are all recorded in the case report form, along with all the test results obtained up to the day of termination and withdrawal.
In cases where the subject fails to visit the institution, the reason and the subsequent progress are investigated by means of mail, follow-up visit and telephone and the progression is recorded in the case report form. No replacements are made for a subject who has been terminated or withdrawn.

7.6 Subject Randomization

In this clinical test, based on the subject and blind evaluator, only the tested subjects who satisfied all of the criteria for inclusion/exclusion at the time of initial treatment (Week 0) were assigned the test subject registration number. To determine the order of assigning medical equipment based on the test

subject registration number, the statistician of the clinical test used the block randomization method to design the program, utilizing SAS. The randomized assignment numbers were assigned with sufficient size, with consideration of the pre-determined block size. The randomized assignment was implemented for each institution for this clinical test. In order to maintain the blinded condition of the subject and evaluator, until the completion of the test the subject and the independent evaluator were withheld from knowledge of which side of the nasolabial fold (left side or right side) were treated with the test device and which with the reference device. The investigators were assigned to each treatment group that used the investigational device on the nasolabial fold.

7.7 Sample Size & Rationale

7.7.1 Sample Size

This clinical trial was conducted to verify that the efficacy and safety of GENOSS Filler is not inferior to those of Restylane® in the correction of nasolabial folds. The following are the estimated sizes of the sample pools (Table 3).

Table 3. Sample Sizes

	GENOSS Filler group	Restylane® group	Total Number of Subjects
Estimated number of subjects for efficacy evaluation	56	56	56
Estimated number of subjects for efficacy evaluation (applying a 15% drop-out rate)	66	66	66

7.7.2 Rationale for Estimation

This clinical trial has a multi-center, randomized, subject and evaluator blinded, matched-pair, active-controlled design to verify that GENOSS Filler is not inferior compared to Restylane® in its efficacy in correcting the nasolabial fold. The mean of WSRS was analysed for the primary efficacy endpoint. According to the clinical revie of Restylane conducted by the FDA, the means±S.D of Wrinkle Severity Rating Score (WSRS) evaluated by investigator in week 24 after the final application of device were 2.36±0.78 in the Restylane® group and 2.94±0.76 in the past control group, and the difference between the groups (Restylane® - past control group) was -0.58. The non-inferiority limit of this clinical

trial was established as -0.29, which was the half of -0.58.

Table 4. Comparison of References for Measurement

Classification	Clinical Review of Restylane (P020023) [8]	This Clinical Trial
Investigation group/ Reference group	Restylane®/Zyplast	GENOSS Filler/Restylane®
Objective	Augmentation correction of bilateral nasolabial folds	Same as the left
Design	Multi-center (6 sites) 1:1 randomized, matched-pair, active-controlled and evaluator blinded design	Multi-center (2 sites) 1:1 randomized, matched-pair, active-controlled and evaluator blinded design
Treatment and Follow-up test	Week 0: Initial injection Week 2: Touch-up injection (repeat if needed) Weeks 8, 16, and 24 after the Baseline: Follow-up	Week 0: Initial injection Week 2: Touch-up injection (once) Weeks 8, 16 and 24 after the final application: Follow-up
Time Point of Primary Efficacy Evaluation	6 months after post-baseline	Same as the left
Time Point of Secondary Efficacy Evaluation	At month 6	Same as the left
Safety Evaluation	Subject diary (2 weeks) follow-up	Observation of Adverse Events
Subject Population	Pre-treatment: 138 Baseline: 137 6 Months: 134 (4: lost f/u)	56 subjects (66 subjects including a 15% drop-out rate)
Analysis Set for Primary Efficacy Evaluation	1) ITT set (n=137) 2) PP Set (n=134)	ITT set

Measurement of Missing Data	Replace with pre-treatment value	Same as the left

The standard deviation (σ_D) of the mean difference between the investigational group and the reference group was needed to measure sample size, which was estimated by the standard deviation in the Restylane® group with reference to the result from the FDA. The standard deviation, however, needed to be measured for the difference of each group, and the correlation coefficient was necessary for this measurement. This correlation coefficient was generally over '0', and the closer correlation coefficient was to '1', the higher the correlation. Since there were no references suggesting this correlation coefficient, it was determined to be '0.5,' which was the lowest value within the range of 0.5-0.7 (Nevid, 2008; A-11), and the standard deviation of the mean difference between the investigation group and the reference group was calculated as below.

$$\sigma^2_D = Var(X_{ref} - X_{inv})$$
$$= Var(X_{ref}) + Var(X_{inv}) - 2Cov(X_{ref}, X_{inv})$$
$$= Var(X_{ref}) + Var(X_{inv}) - 2(\rho)SD(X_{ref})SD(X_{inv})$$
$$= 0.76^2 + 0.78^2 - 2(0.5)(0.76)(0.78) = 0.5932$$
$$\sigma_D = \sqrt{0.5932} = 0.770$$

In this formula, X_{ref} is the WSRS for the reference group and X_{inv} is the WSRS for the investigational group. ρ is the correlation coefficient between the two groups.

With the above non-inferiority limit and the standard deviation of the mean difference, the sample size was measured based on the following assumptions:

1) The true mean difference between the reference group and the investigation group was assumed to be '0.'
2) S.D (σ_D) was estimated to be '0.77,' based on the correlation coefficient of '0.5,' which was the lowest value within the range of 0.5-0.7 (FDA clinical review). The effective size* of this value was 0.29/0.77=0.3766.
   *Effective size: The standardized size of 'difference of effects / standard deviation of difference.'
3) The level of significance was assumed to be α=0.025 ($Z_\alpha = Z_{0.025} = 1.96$).
4) Assuming that the type 2 error (β) was '0.2', the power of the test was to be 80% ($Z_\beta = Z_{0.2} = 0.842$).
5) The non-inferiority limit of this clinical trial was assumed to be -0.29, in accordance with the reference.

7.7.2.1 Hypothesis

The null hypothesis and alternative hypothesis for testing the inferiority were below.

$$H_0 : \mu_D \leq -\delta \text{ vs } H_1 : \mu_D > -\delta$$

The S.D (μ_D) in the difference of the WSRS was evaluated by an independent evaluator in Week 24 after the final application of the device. This measurement verified that the lower limit of the one-sided 97.5% confidence interval is greater than -0.29, which was the non-inferiority limit of this clinical trial.

7.7.2.2 Formula for the Estimated Sample Size

$$n = \frac{\sigma_D^2 (z_\alpha + z_\beta)^2}{(\mu_D - \delta)^2} = \frac{0.770^2 \times (1.96 + 0.842)^2}{0.29^2} \approx 56$$

The number of estimated subjects needed for efficacy evaluation is 56. Anticipating a drop-out rate of 15%, a total of 66 subjects were enrolled.

7.8 Concomitant Medication and Therapy

7.8.1 Disallowed Concomitant Medications

1) The use of the following medications were disallowed because they can cause ecchymosis or bleeding.
   - The use of any antithrombotic agent with the exception of low dose Aspirin (100 mg, maximum of 300 mg/day) is disallowed in the period from 2 weeks prior to the application of the investigational device and up to the time of study termination.
   - The use of Vitamin E or NSAID is disallowed 1 week before and 1 week after the application of the investigational device.
2) The following facial procedures were disallowed during the clinical trial period.
   - Fillers
     - Collagen implants
     - Hyaluronic acid
     - Fluid silicon
     - Poly-methyl methacrylate
     - Polytetra-fluoro-ethylene
     - Fat graft

- Botulism treatment for the enhancement of folds
- Chemical peeling and laser procedures
- Non-invasive skin rejuvenating laser procedures (cool touch)
- Retinoid (This only refers to medication containing Retinoid. Skin products are excluded.)
- Steroid ointment (This only refers to medication containing Steroid. Skin products are excluded. Note, however, that the use of steroid ointment for a short time (sequentially within 14 days) is permitted for the treatment of adverse events.)

3) The use of the following medications was disallowed during the clinical trial period.
   - Antithrombotic agents (Low dose aspirin (100 mg, maximum of 300 mg/day) was excluded.)
   - Systemic adrenal cortical hormones (Note, however, that it is permitted to apply a standardized dose of an adrenal cortical hormone, such as beclomethasone, triamcinolone, fluticasone, flunisolide or budesonide.)
4) The use of any other medications considered to affect the efficacy evaluation of this clinical trial was disallowed.

7.8.2 Allowed Concomitant Medications

The use of the following medications was allowed during the clinical trial period.

1) Any other medications that were not considered to affect the interpretation of the results were permitted at the investigator's discretion, even in the case of medications that the subject had taken within 4 weeks prior to the participation in this clinical trial.
2) Any medication used for the treatment of other illnesses or the temporary treatment of other conditions was permitted to be administered concurrently after consulting with the investigator.

When the subject was administered concomitant medications (including medication used for other illnesses or adverse reactions), the medication information (including name, purpose of use, administered dose and route, duration of the medication use) was documented in detail in the case report form.

8. EFFICACY & SAFETY ENDPOINT

8.1 Efficacy Endpoint

The primary and secondary endpoints to evaluate the results of clinical trial were as follows. All subjects were evaluated for all endpoints.

8.1.1 Primary Endpoint

The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the independent evaluator in week 24 from the final application of the investigational device

The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the independent evaluator in week 24 from the final application of the investigational device were compared.

*** Scoring and Evaluation**

The WSRS scores were evaluated for all subjects by the independent evaluator in week 24 from the final application of the investigational device, considering the depth of both nasolabial folds . All photos of subjects were sent to the independent evaluator in a blinded condition. The WSRS scores were evaluated in the range of 1~5. The following table presents the detailed contents.

Table 5. The Wrinkle Severity Rating Scale (WSRS)

Score	Content
□ 5	Extreme: Extremely deep and long folds; 2-4 mm visible v-shaped fold when stretched; detrimental to appearance; unlikely to have satisfactory correction with injectable implant alone.
□ 4	Severe: Very long and deep fold; prominent facial feature; less than 2 mm of the fold is visible when stretched.
□ 3	Moderate: Moderately deep fold; clear facial feature visible at normal appearance but not when stretched. Excellent correction expected.
□ 2	Mild: Shallow but visible fold with slight indentation; minor facial feature.
□ 1	Absent: No visible fold; continuous line.

*** Rationale for the Selection of WSRS**

WSRS is the optical method for evaluating wrinkle severity and it had been widely used for clinical trials, especially for the study of facial folds [3-6]. WSRS was also used for primary efficacy evaluation in the clinical trial of Restylane® for the purpose of obtaining FDA approval [1]. In addition, WSRS includes detail descriptions for evaluating the severity of wrinkles. For these reasons, WSRS was selected to evaluate the primary efficacy in this clinical trial.

8.1.2 Secondary Endpoint

1) **The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the independent evaluator in weeks 8 and 16 from the final application of the investigational devices**

   The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the independent evaluator in weeks 8 and 16 from the final application of the investigational devices were compared.

   *** Scoring and Evaluation**

   The independent evaluator assessed the WSRS scores by reflecting the depth of both nasolabial folds with the photos for all subjects at weeks 8 and 16 from the final application of the investigational devices.

2) **The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational devices**

   The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational devices were compared.

   *** Scoring and Evaluation**

   The investigator assessed the WSRS scores by observing directly the depth of both nasolabial folds for all subjects at weeks 8, 16 and 24 from the final application of the investigational devices.

3) **The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational devices, in comparison with the scores obtained prior to the initial application**

   The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational devices were compared with the scores obtained prior to the initial application.

   *** Scoring and Evaluation**

The GAIS scores of all subjects from both groups were assessed by the investigator in weeks 8, 16 and 24 from the final application, considering the severity of both nasolabial folds in comparison to the condition prior to the initial application (Week 0) with the photos taken at Week 0. The GAIS scores were in the range of -1-3. The detail contents are described in the following.

Table 6. Global Aesthetic Improvement Scale (GAIS)

Score	Content
□ **3**	Very much improved
□ **2**	Much improved
□ **1**	Improved
□ **0**	No change
□ **-1**	Worse

*** Rationale for the Selection of GAIS**

GAIS has a range of 5 scores (-1 – 3). As GAIS is simple to evaluate and allows easy comparison of results, it has been widely used for clinical trials to evaluate satisfaction in wrinkle correction. For these reasons, GAIS was selected to evaluate the secondary efficacy in this clinical trial.

4) The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group evaluated by the subject in weeks 8, 16 and 24 from the final application of the investigational devices, in comparison with the scores prior to the initial application

The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group evaluated by the subject in weeks 8, 16 and 24 from the final application of the investigational devices were compared with the scores prior to the initial application.

*** Scoring and Evaluation**

The GAIS scores of all subjects from both groups were assessed by the subject in weeks 8, 16 and 24 from the final application, considering the severity of both nasolabial folds in comparison to the condition prior to the initial application (Week 0) with the photos.

5) The proportion of subjects whose WSRS scores (week 24 – before application)

decreased at least 1 level, as evaluated by the independent evaluator in week 24 from the final application of the investigational devices, from both the GENOSS Filler group and the Restylane® group in comparison with the scores prior to the initial application

The proportion of subjects whose WSRS scores (week 24 – before application) decreased at least 1 level, as evaluated by the independent evaluator in week 24 from the final application of the investigational devices, from both the GENOSS Filler group and the Restylane® group was compared with the scores prior to the initial application.

*** Scoring and Evaluation**

The GENOSS Filler group and the Restylane® group were compared in terms of the proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the independent evaluator at Week 24 from the final application, in comparison to the condition prior to the initial application (Week 0).

6) **The proportion of subjects whose WSRS scores (week 24 – before application) decreased at least 1 level, as evaluated by the investigator in week 24 from the final application of the investigational devices, from both the GENOSS Filler group and the Restylane® group in comparison with the scores prior to the initial application**

The proportion of subjects whose WSRS scores (week 24 – before application) decreased at least 1 level, as evaluated by the investigator in week 24 from the final application of the investigational devices, from both the GENOSS Filler group and the Restylane® group was compared with the scores prior to the initial application.

*** Scoring and Evaluation**

The GENOSS Filler group and the Restylane® group were compared in terms of the proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the investigator at Week 24 from the final application, in comparison to the condition prior to the initial application (Week 0).

8.1.3 Safety Endpoint

All adverse events (AE) including the facial AE of subjects were evaluated for inclusion in the safety endpoint. Also, the safety of the investigational device was evaluated through the laboratory tests, vital signs and physical examinations perform during the clinical trial. All adverse events were recorded in the case report form and evaluated for inclusion in the safety endpoint.

- **Adverse Events**

  Adverse reactions which were clinically abnormal were recorded as adverse events (AE), and the sites where the AE occurred were recorded, classified to indicate the injection site of the investigational/reference device or the absence of an injection site. The records of all AEs also included causality and severity, according to the protocol of this clinical trial.

  1) Baseline signs and symptoms, from the screening to prior to the application of the investigational device, were recorded.
  2) Evaluations Performed Immediately After the Application of the Investigational Device: Adverse events, which occurred at application sites, including hemorrhage, pain, induration, swelling, redness and pruritus, within 30 minutes after the application of the investigational device, were recorded.
  3) All treatment-emergent adverse events (TEAE), which occurred from the final application of the investigational device up to the time of study termination, were recorded.

- **Laboratory Test**

  The following is the list of the tests performed. All the abnormal values were reported, including causality, and follow-up studies were conducted.

  1) Hematology Test: WBC, RBC, Hb, Hct, PLT
  2) Blood Biochemistry Test
  - Liver Function : ALP, AST, ALT, LDH, total bilirubin, and γ-GT
  - Metabolic Function : total cholesterol, glucose, total protein, albumin, triglyceride, and serum creatinine
  - Electrolytes : Na, K, Cl, Ca
  3) Blood Coagulation Test: APTT and PT
  4) Urine Test: protein, glucose and blood
  5) Urine Pregnancy Test: urine HCG. Conducted on females with the possibility of pregnancy, who have not received surgery for female infertility and who are prior to menopause.

- **Vital Signs and Physical Examination**

  1) Vital sign: Blood pressure taken in the sitting position, pulse, and temperature
  2) Physical examination: Check for abnormal signs and symptoms

8.2 Data Assurance

Monitoring and data management were conducted by Seoul CRO Co., Ltd. to secure the quality of the data during the clinical trial. The case report form was recorded by the principal investigator, the sub-investigator or other designees authorized by the investigator. When correction was necessary, a single line was drawn over an error and the correction was documented along with the signature of the corrector and the date the correction was made, without using whiteout. Data documented in the case report form corresponded to the source document, and for data that did not correspond, detailed explanation was added by providing an explanatory statement or report. The monitors (CRAs or designees) authorized by the investigator paid regular visits to the institution and reviewed whether documentations were accurate and in compliance with the clinical trial protocol and the KGCP regulations. Especial caution was taken to ensure that all errors, omissions, or unreadable contents in the case report form were notified to the investigator and properly confirmed (with a provided reason, the date of revision and signature) by the investigator with authority regarding revision. The case report forms of the subjects were sent to the sponsor after completing the process of the case report form and source documentation verification (SDV).
Clinical trial data were documented in the case report forms, which were stored at the base. The data was also stored in an electronic database and the DMSys 5.1 version was used for data processing. The data entry personnel entered the contents of the case report form into the database in a double data entry format. All adverse events and concomitant medications were coded using MedDRA 16.0 and the ATC-code (2013). The CMC (Certified MedDRA Coder) conducted the coding and reviewing. The quality of the data entered into the database was assured by applying the systemic logical query and the medical query written based on the standard of the Data Validation Specification by the DBA (Data Base Associate) and CDA (Clinical Data Associate) who had medical background. Any query requiring resultant corrections were documented in the Data Correction Form, and all the corrections made were reviewed and approved by the investigator. After the answers were applied to the Database, Database Locking was implemented. No audit was conducted for reliability assurance in this clinical trial.

8.3 Statistical Analysis for Assessment

8.3.1 Analysis Sets

Data obtained from subjects in this clinical trial were divided into the Full Analysis (FA) Set, the Per-Protocol (PP) Set and the Safety Set. In this clinical study, the FA Set was used for the main analysis of the main population, the PP Set was used for additional analysis, and the Safety Set was used for safety analysis. All results were compared and all efforts were made to present the results of each

method and describe in detail the reasons in the event of any differences between the groups. A one-sided confidence interval of 97.5% was used for the non-inferiority test, and all remaining differences were compared with a significance level of 5%. The confidence interval was estimated using t-distribution.

The Target of the FA Set:

After randomization, subjects who were applied with the investigational device at least once and measured at least one variable of the efficacy evaluation were included in the analysis.

The Target of the PP Set:

The PP Set refers to those subjects from the FA Set who completed the trial according to the clinical trial protocol, and the following subjects were excluded from this PP Set.

1) Subjects who withdrew from the clinical trial without fulfilling the period specified in the protocol
2) Subject who received a disallowed concomitant medication and concomitant therapy
3) Subjects who violated the inclusion / exclusion criteria
4) Other subjects who committed what can be considered a serious violation of protocol

The Target of the Safety Set:

Subjects who received the application of the investigational device at least once were included in the analysis.

Handling Missing Values:

If missing data occurred at some point for an outcome variable, or if a subject withdrew before the end of clinical trial, all missing values were analysed by replacing them with pre-treatment values. This was the application of the "Worst Observation Carried Forward (WOCF)" method, which assumes that the pre-treatment value is the worst. This method was applied only to handling missing values in the FA Set. Analysis was conducted using the same available data set and missing values were not replaced for other Sets.

8.3.2 Analysis Methods for Demographic and Medical History Data

The data of all subjects included in this clinical trial were assessed by each treatment group and each institution, and presented by calculating the mean, the standard deviation, the minimum and the maximum value of continuous data and by obtaining the absolute and relative frequency of categorical data. Because this clinical trial had a matched-pair design, no comparison was made between the

treatment groups in terms of demographic variables and baseline variables. Demographic variables prior to the treatment (in screening) between the institutions (2 sites), however, were compared and evaluated. For continuous variables, the difference between the institutions was compared by using the independent t-test or Wilcoxon`s rank sum test, and categorical variables were compared using the Mantel-Haenszel test, in regards to the stratification factor of the institutions. Analysis of covariance was conducted for the adjustment of the variables in the efficacy evaluation. The variables of the institutions were compared to determine whether there were significant differences in age, gender, body weight among the institutions. A significance level of 5% was applied to this analysis.

8.3.3 Analysis of the Primary Efficacy Endpoint

In this clinical trial, the primary efficacy endpoint was the mean of the WSRS scores from the GENOSS Filler group and the Restylane® group, which was assessed by independent evaluators at Week 24 after the final application of the investigational device for clinical trial. The trial aimed to verify that GENOSS Filler was not inferior to the Restylane® by demonstrating that the lower limit of the one-sided 97.5% confidence interval of the mean value of the differences between GENOSS Filler and Restylane® was greater than -0.29. If well-randomized, no differences would occur between the groups in terms of the WSRS values on the baseline before the application of the investigational device for clinical trial. If differences occurred, attempt was made to adjust the baseline as follows. First, comparisons of the baseline between the groups were performed using the paired t-test, and efficacy endpoint was evaluated at Week 24 using covariance analysis, which would adjust the baseline to the covariates if there were any differences between the groups.

The analysis of the sub-groups for the primary efficacy endpoint was planned to conduct depending on the conditions of each institution and the repeat (touch-up) treatment, as follows. However, the analysis was not conducted as there was no subject who had repeat treatment.
Using the t-test or Wilcoxon`s Rank-sum test, it was examined whether there was a validity difference between the laboratories in regards to the WSRS differences between the control and test values assessed by independent evaluators in week 24 after the final application of the investigational device. If there was a difference, all reasons were supposed to be described in detail and incorporated in the results, however, there was no difference.

- **The statistical model to determine whether there are differences between the groups at the baseline**

  Since this study applied a matched-pair design using both the GENOSS Filler and the Restylane® on a subject, the MMRM was considered as follows in order to adjust the baseline value. This

model can be implemented by using SAS PROC MIXED. In this expression, the time point to be considered is the value in week 24 corresponding to the main effect variable, and the baseline values were adjusted to the covariates. It should be noted that this expression does not apply a repetition time: subjects in the GENOSS Filler group and the Restylane® group were measured simultaneously.

$$y_{it_i} = \beta_0 + \beta_1 t_i + \beta_2 x_{it_i} + \gamma_i + \varepsilon_{it_i}$$

In this expression,

y_{it_i} : WSRS at 24 weeks of the i-th subject (t_i) in the corresponding group

t_i = { 1 the i-th subject in the test group; 0 the i-th subject in the control group

x_{it_i} : Baseline value of the i-th subject in the corresponding group

β_0 : Intercept

β_1 : The fixed regression coefficients in groups (the estimates of the value is the difference between the adjusted groups in the baseline value)

β_2 : The fixed regression coefficients prior to applying the medical devices

$\gamma_i \sim N\left(0, \sigma_\gamma^2\right)$: Random effects

$\varepsilon_{it_i} \sim N(0, \sigma^2)$: Error

In this model, the fixed effect was the same population specific effect in any object and the difference between the parameter and the group to be estimated in this study. Meanwhile, the random effect was the person specific effect and the effect to be considered to adjust the effect of repeated measurements in the object. This, however, was not a concern in this clinical trial. If this object effect in the model was included as the fixed effect, the nuisance parameter should be considered to be as many as the number of objects in the model. Therefore, it was assumed that this effect was extracted randomly from the typical normal distribution (average of "0"and variance of σ_γ^2).
By considering this effect, the matter in the object can be considered to be as follows.

$$Cov\left(\begin{pmatrix} y_{i0} \\ y_{i1} \end{pmatrix}\right) = \begin{bmatrix} \sigma_\gamma^2 + \sigma_\varepsilon^2 & \sigma_\gamma^2 \\ \sigma_\gamma^2 & \sigma_\gamma^2 + \sigma_\varepsilon^2 \end{bmatrix}$$

$$Corr\left(y_{i0}, y_{i1}\right) = \frac{\sigma_\gamma^2}{\sigma_\gamma^2 + \sigma_\varepsilon^2}$$

8.3.4 Analysis of the Secondary Efficacy Endpoint

1) The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the independent evaluator in weeks 8 and 16 from the final application of the investigational device

The Mixed Model Repeated Measures (MMRM) were used to compare the WSRS value-differences between the groups measured repeatedly by the independent evaluator over time. The groups and the time points in this model were considered to be categorical variables and were included as covariates. The interactions of group and time were considered as covariates. When applying MMRM, the correlation among objects caused by the repeated measures was considered and all available data were included in the analysis. After comparing the models, the model determined to have the most appropriate covariance structure was adopted for use.

2) The mean of the WSRS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the investigator at weeks 8, 16 and 24 from the final application of the investigational device

MMRM was used to compare the WSRS scores-differences between the groups measured repeatedly by the investigator over time. The groups and the time points in this model were established as the categorical variables and included as covariates. The interactions of group and time were considered as covariates. When applying MMRM, the correlation among objects caused by the repeated measures was considered and all available data in the analysis were included. After comparing the models, the model determined to have the most appropriate covariance structure was adopted for use.

3) The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the investigator in weeks 8, 16 and 24 from the final application of the investigational device in the first stage in comparison with the scores obtained prior to the initial application

MMRM was used to compare GAIS score-differences between the groups measured repeatedly by the investigator over time. The group and the time point were established to be categorical variables in this model and were included as covariates. The interactions of group and time were considered as covariates. When applying MMRM, the correlation among objects caused by the repeated measures was considered and all available data was included in the analysis. After comparing the models, the model determined to have the most appropriate covariance structure was adopted for use.

4) **The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the subject in weeks 8, 16 and 24 from the final application of the investigational device in the first stage, in comparison with the scores prior to the initial application**

MMRM was used to compare the GAIS score-differences between the groups measured repeatedly, by subject and by the time point. The group and the time in this model were set as the categorical variables and were included as covariates. The interactions of group and time were considered as covariates. When applying MMRM, the correlation between objects caused by the repeated measures was considered and all available data was included in the analysis. After comparing the models, the model determined to have the most appropriate covariance structure was adopted for use.

5) **The proportion of subjects whose WSRS scores decreased at least 1 level, as evaluated by the independent evaluator in week 24 from the final application of the investigational device in the first stage, from both the GENOSS Filler group and the Restylane® group in comparison with the scores prior to the initial application**

The proportion of subjects in each group whose WSRS scores decreased by 1 (at each time point – prior to the initial application) and the double sided 95% confidence interval were determined. The differences in proportion between the groups were compared using McNemar's test.

6) **The proportion of subjects whose WSRS scores decreased at least 1 level, as evaluated by the investigator at week 24 from the final application of the investigational devices in the first stage, from both the GENOSS Filler group and the Restylane® group in comparison with the scores prior to the initial application**

The proportion of subjects in each group whose WSRS scores decreased by 1 (at each time point – prior to the initial application) and the double sided 95% confidence interval were determined. The differences in proportion between the groups were compared using McNemar's test.

8.3.5 Safety Evaluation Method

1) Adverse Events

In this clinical trial, adverse events were classified as adverse events that occurred before the application of investigational device for clinical trial (i.e., baseline signs and symptoms) and adverse events that occurred after the application of the investigational device for clinical trial (TEAE). Adverse events that occurred after the application of the investigational device for clinical trials were further classified as adverse events that occurred for the first time after the application of the investigational device for clinical trial and adverse events in which the baseline signs and symptoms that occurred

before the application of the investigational device for clinical trial became worse after application. All adverse events that occurred after the application of the investigational device were analysed and they were organized by listing. By using the MedDRA (Medical Dictionary for Regulatory Activities), all adverse events were standardized in terms of SOC (System Organ Class) and PT (Preferred Term). If adverse events (TEAE) that were the same as defined by SOC and PT occurred more than once in one person, these were considered as one case. If the same adverse events differed in their severities, the worst severity was taken as the data. If the same adverse events (TEAE) in one person involved different causality, the one with more relevance for the investigational device was taken as the data. The number and percentage of adverse events as defined by SOC and PT and the 95% confidence intervals for a subject who experienced more than one adverse event were determined. The Chi-square test or Fisher′s exact test was used to compare the frequencies of adverse events, comparing the investigational group and the reference group and the investigational group + reference group.

2) Laboratory Tests / Vital Signs and Physical Examination

The descriptive statistics for laboratory examinations, vital signs and physical examinations were summarized, including information on the average, standard deviation, minimum value, maximum value and the mean value if the data was continuous. Also, the paired t-test or Wilcoxon`s signed rank test was used to evaluate the change before and after the application of the investigational device for clinical trial, compared to the normal and abnormal results of physical examination. The categorical data was presented with absolute frequency and relative frequency, and McNemar's test was conducted to compare the results before and after the application of the investigational device.

3) Concomitant Medication

Concomitant medications were described by each subject and represented by level 1 and 2 of the ATC code, as defined in the WHO Drug Dictionary.

9. STUDY SUBJECTS

9.1 Status of Subjects' Participation

This clinical trial was conducted at a total of two institutions from July 10th, 2013 (the initial subject visit to Keimyung University Dongsan Medical Center) to January 22th, 2013 (the last subject visit to Seoul National University Hospital). Table 7 shows the distribution of the participating and withdrawn subjects in this clinical trial, organized by institution. A total of 66 subjects were enrolled in this clinical trial after signing the written informed consent form. All of 66 subjects were judged to be eligible for the study and randomized. Among these, however, as 1 subject violated the inclusion/ exclusion criteria, the remaining 65 subjects (98.48%) were received the application of investigational devices. Then, 2 subjects were withdrawn from the study for follow-up failure, and the remaining total of 63 subjects (95.45%) completed this clinical trial.

Table 7. Subject Participation

Subject Participation	Institution		Total
	Seoul National University Hospital	Keimyung University Dongsan Medical Center	
Screened	33(100)	33(100)	66(100)
Screening Failure	0(0)	0(0)	0(0)
Randomized	33(100)	33(100)	66(100)
Treated	32(96.97)	33(100)	65(98.48)
Not Treated	1(3.03)	0(0)	1(1.52)
Withdrawn	3(9.09)	0(0)	3(4.55)
Follow-up Failure	2(66.66)	0(0)	2(66.66)
Violation of the Inclusion/ Exclusion criteria	1(33.33)	0(0)	1(33.33)
Completed	30(90.91)	33(100)	63(95.45)
Subject Disposition by Analysis Sets			
Safety Set	32(100)	33(100)	65(100)
FA (Full-Analysis) Set	32(100)	33(100)	65(100)
Excluded from FA Set	0(0)	0(0)	0(0)
PP (Per-protocol) Set	30(93.75)	29(87.88)	59(90.77)
Excluded from PP Set	2(6.25)	4(12.12)	6(9.23)

Subject Participation	Institution		Total
	Seoul National University Hospital	Keimyung University Dongsan Medical Center	
Follow-up Failure	2(100)	0(0)	2(33.33)
Taking Disallowed Concomitant Medications	0(0)	4(100)	4(66.66)

Table 8 below provides information on the 3 subjects withdrawn from this clinical trial. The total of 3 subjects included 2 subjects of follow-up failure and 1 subject of violation of the inclusion/ exclusion criteria.

Table 8. Withdrawn Subjects (n=6)

Institution*	Subject No.	Gender	Age	Date of signing the informed consent form	Date of the application of the medical device	Date of discontinuance	Reason
1	R1-01	Female	43	2013/07/31	2013/07/31	2013/11/27	Follow-up Failure
1	R1-16	Female	45	2013/08/03	2013/08/03	2013/11/22	Follow-up Failure
1	R1-26	Female	56	2013/08/07	-	2013/08/07	Violation of the Inclusion/ Exclusion criteria

* Institution: 1. Seoul National University Hospital, 2. Keimyung University Dongsan Medical Center

9.2 Violation of the Clinical Study Protocol

There were 4 subjects who deviated from the clinical trial protocol by taking the disallowed concomitant medications (Table 9). These 4 subjects were included not in the PP Set, but FA Set (Appendix 2.2. LIST OF SUBJECTS EXCLUDED FROM THE EFFICACY ANALYSIS).

Table 9. List of Subjects Who Violated the Protocol (n=4)

Institution*	Subject No.	Gender	Age	Date of the application of the medical device	Date of Discontinuation	Reason	Details
2	R2-24	Female	44	2013/07/11	2013/12/27	Taking Disallowed Concomitant Medications	-
2	R2-28	Female	43	2013/07/11	2013/12/26	Taking Disallowed Concomitant Medications	-

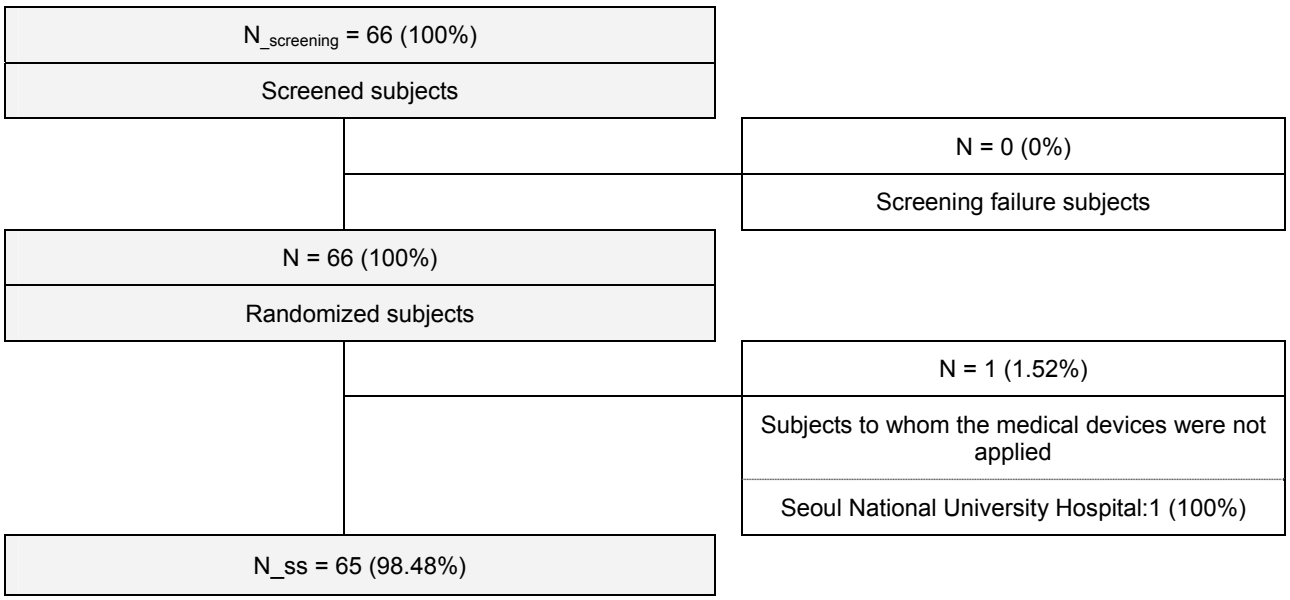
Institution*	Subject No.	Gender	Age	Date of the application of the medical device	Date of Discontinuation	Reason	Details
2	R2-29	Female	49	2013/07/11	2013/12/26	Taking Disallowed Concomitant Medications	-
2	R2-33	Female	43	2013/07/12	2013/12/26	Taking Disallowed Concomitant Medications	-

*Institution: 1- Seoul National University Hospital, 2- Keimyung University Dongsan Medical Center

10. EFFICACY EVALUATION

10.1 Selection of the Subject Group for Analysis

Figure 2 shows details regarding the the status of subjects for analysis. A total of 66 subjects were signed the informed consent form, and they were screened after receiving their screening numbers. Although all of 66 subjects were judged to be eligible for the study, the remaining 65 subjects (98.48%) were received the application of investigational devices as 1 subject (1.52%) violated the inclusion/ exclusion criteria. These subjects were selected for the FA Set, but 59 subjects (89.39%) remained the PP Set after the exclusion of 2 subjects of follow-up failure and 4 subjects of taking the disallowed concomitant medications. The Safety Set included the 65 subjects (98.48%) to whom the investigational devices were applied at least once in a randomly allocated manner.



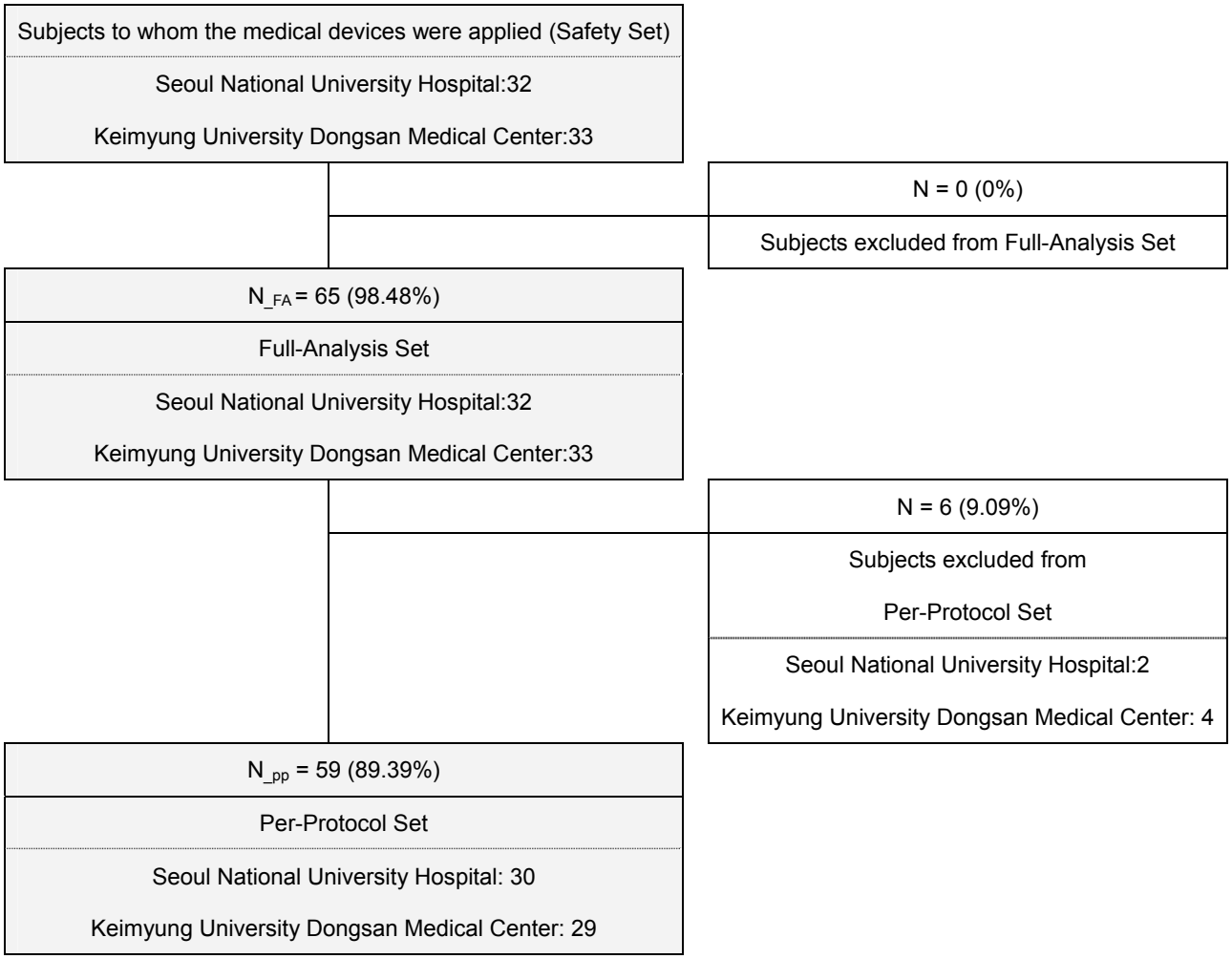


Figure 2. Disposition of Enrolled Subjects

10.2 Demographic Data of Subjects & Comparisons of Other Pre-treated Characteristics

Demographic data (including age, gender, weight, height and status of menstruation and pregnancy for female subjects), past/current medical history, symtoms and signs at the baseline were investigated to collect the demographic data and pre-treated features of the subjects. All results were analyzed in the Safety Set.

10.2.1 Demographic Data

Among the subjects participating in this clinical trial, the proportion of female subjects was significantly higher than that of male subjects: the clinical trial consisted of 2 (3.08%) male subjects and 63 (96.92%) female subjects. The mean age of subjects participating in the study was 49.89±6.91 years, the mean height was 157.43±5.69 cm, and the mean weight was 56.55±7.81 kg. There were no significant differences between the two institutions in regards to these data (Table 10).

Table 10. Demographic Data (Safety)

Demographic data		Institution: Seoul National University Hospital n_1=32	Institution: Keimyung University Dongsan Medical Center n_2=33	Total N=65	p-value
Gender					
Male	n (%)	1(3.13)	1(3.03)	2(3.08)	0.982*
Female	n (%)	31(96.88)	32(96.97)	63(96.92)	
Age (years)	n	32	33	65	0.928**
	Mean±SD	49.81±6.30	49.97±7.55	49.89±6.91	
	Median	50.50	49.00	50.00	
	Min, Max	35.00~61.00	30.00~62.00	30.00~62.00	
Height (cm)	n	32	33	65	0.901**
	Mean±SD	157.34±5.72	157.52±5.75	157.43±5.69	
	Median	158.00	157.00	157.30	
	Min, Max	149.00~171.00	147.00~176.80	147.00~176.80	
Body Weight (kg)	n	32	33	65	0.212**
	Mean±SD	57.78±8.17	55.35±7.37	56.55±7.81	
	Median	56.50	56.60	56.60	
	Min, Max	44.00~87.00	39.00~77.40	39.00~87.00	

*Chi-square test
**Two sample t-test

As regards the status of menstruation and pregnancy for 63 female subjects among 65 subjects, there was no post-menopaused female and all of 63 (100%) females were fertile. All fertile female subjects received negative pregnancy results in the urine-HCG test (Table 11).

Table 11. Pregnancy Test

Pregnancy Test	Institution		Total N=65	p-value
	Seoul National University Hospital n_{1_Female}=31	Keimyung University Dongsan Medical Center n_{2_Female}=32		
Menstrual Status				
Fertility	31(100.0)	32(100.0)	63(100.0)	NA*
Infertility (post-menopaused)	0(0)	0(0)	0(0)	
Pregnancy Test				
Negative	31(100.0)	32(100.0)	63(100.0)	NA*
Positive	0(0)	0(0)	0(0)	

*NA : Not available

10.2.2 Past and Current Medical History

The medical histories of the subjects were investigated to confirm whether the subjects had received any dermatological facial treatments or plastic surgery within one year before the subject's participation in the clinical trial. Among the 65 subjects in the Safety Set, there were 27 subjects (41.54%) who had a relevant past medical history. The total number of events was 64, and there were 2.37 cases per subject. Among these cases of past medical histories, Gastrointestinal disorders was the most frequent disorder, constituting 10 cases in 7 subjects (10.77%). Among them, 7 cases were Gastritis in 6 subjects (9.23%). In addition, 5 subjects (7.69%) had 8 cases, 6 cases, 5 case each in Eye disorders, Musculoskeletal and connective tissue disorders, and Hepatobiliary disorders. Other cases included 5 cases of Nervous system disorders, 5 cases of Skin and subcutaneous tissue disorders, 4 cases of Vascular disorders, each involving 4 subjects (6.15%). Detailed information regarding past medical history is presented in Table 12.

Table 12. Past Medical History (Safety)

Past Medical History	Institution		Total N=65
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	
Subjects with Past Medical History	13(40.63)	14(42.42)	27(41.54)

95%CI	23.61-57.64	25.56-59.29	29.56-53.52
Total Cases	19	45	64
Cases per Subject	1.46	3.21	2.37
System Organ Class*			
Preferred Term*			
Gastrointestinal disorders	1(3.13), [1]	6(18.18), [9]	7(10.77), [10]
· Gastritis	0(0.0), [0]	6(18.18), [7]	6(9.23), [7]
· Dental caries	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Haemorrhoids	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Malocclusion	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Eye disorders	1(3.13), [1]	4(12.12), [7]	5(7.69), [8]
· Blepharitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Chorioretinopathy	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Conjunctivitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Dacryostenosis acquired	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Dry eye	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Glaucoma	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Keratitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Trichiasis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Musculoskeletal and connective tissue disorders	2(6.25), [2]	3(9.09), [4]	5(7.69), [6]
· Arthralgia	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Intervertebral disc protrusion	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Myofascial pain syndrome	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Osteopenia	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Rotator cuff syndrome	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Spinal ligament ossification	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Hepatobiliary disorders	1(3.13), [1]	4(12.12), [4]	5(7.69), [5]

· Gallbladder polyp	1(3.13), [1]	2(6.06), [2]	3(4.62), [3]
· Hepatic steatosis	0(0.0), [0]	2(6.06), [2]	2(3.08), [2]
Nervous system disorders	1(3.13), [1]	3(9.09), [4]	4(6.15), [5]
· Headache	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Hypoaesthesia	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Migraine	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Neuralgia	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Neuritis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Skin and subcutaneous tissue disorders	1(3.13), [2]	3(9.09), [3]	4(6.15), [5]
· Chloasma	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Dermatitis contact	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Eczema nummular	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Post inflammatory pigmentation change	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Pruritus	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Vascular disorders	1(3.13), [1]	3(9.09), [3]	4(6.15), [4]
· Hypertension	0(0.0), [0]	2(6.06), [2]	2(3.08), [2]
· Essential hypertension	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Varicose vein	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Metabolism and nutrition disorders	0(0.0), [0]	3(9.09), [4]	3(4.62), [4]
· Hyperlipidaemia	0(0.0), [0]	2(6.06), [2]	2(3.08), [2]
· Hypercholesterolaemia	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Obesity	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Endocrine disorders	3(9.38), [3]	0(0.0), [0]	3(4.62), [3]
· Hyperthyroidism	2(6.25), [2]	0(0.0), [0]	2(3.08), [2]
· Hypothyroidism	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Reproductive system and breast disorders	2(6.25), [2]	1(3.03), [1]	3(4.62), [3]
· Breast mass	2(6.25), [2]	0(0.0), [0]	2(3.08), [2]
· Breast calcifications	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]

Infections and infestations	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
· Cervicitis	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Herpes zoster	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
· Adrenal neoplasm	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Ovarian cancer	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Social circumstances	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
· Menopause	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
Cardiac disorders	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Coronary artery disease	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Investigations	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Chest x-ray abnormal	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Psychiatric disorders	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Somatoform disorder	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Respiratory, thoracic and mediastinal disorders	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Rhinitis allergic	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Uterine, pelvic and broad ligament disorders	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Endometrial hypertrophy	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

There were 13 subjects (20.00%) who had a current medical history at the time of the screening. The total number of events was 33, and there were 2.54 cases per subject. Among these cases of with current medical history, the greatest number was Infections and infestations, of which there were 6 cases in the 6 subjects (9.23%) each. There was also 5 cases of Nervous system disorders in 5 subjects (7.69%), 7 cases of Gastrointestinal disorders and 4 cases of Injury, poisoning and procedural complications each in 4 subjects (6.15%). Detailed information on the subjects' current medical history is presented in Table 13.

Table 13. Current Medical History (Safety)

Current Medical History	Institution	Total

	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	N=65
Subjects with Current Medical History	4(12.50)	9(27.27)	13(20.00)
95%CI	1.04-23.96	12.08-42.47	10.28-29.72
Total Cases	5	28	33
Cases per Subject	1.25	3.11	2.54
System Organ Class*			
Preferred Term*			
Infections and infestations	1(3.13), [1]	5(15.15), [5]	6(9.23), [6]
· Acute tonsillitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Gingivitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Herpes zoster	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Periodontitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Pharyngitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Upper respiratory tract infection	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Nervous system disorders	1(3.13), [1]	4(12.12), [4]	5(7.69), [5]
· Headache	0(0.0), [0]	2(6.06), [2]	2(3.08), [2]
· Brain mass	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Cerebrovascular accident	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Dizziness	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Gastrointestinal disorders	0(0.0), [0]	4(12.12), [7]	4(6.15), [7]
· Abdominal discomfort	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Dental caries	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Diarrhoea	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Gastritis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Haemorrhoids	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Nausea	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Periodontal disease	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]

Injury, poisoning and procedural complications	1(3.13), [1]	3(9.09), [3]	4(6.15), [4]
· Ligament sprain	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
· Tooth fracture	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Wound	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Musculoskeletal and connective tissue disorders	0(0.0), [0]	3(9.09), [3]	3(4.62), [3]
· Costochondritis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Flank pain	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Neck pain	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Reproductive system and breast disorders	1(3.13), [1]	1(3.03), [2]	2(3.08), [3]
· Bartholin's cyst	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Uterine haemorrhage	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Vaginal haemorrhage	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Eye disorders	0(0.0), [0]	1(3.03), [2]	1(1.54), [2]
· Blepharitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Conjunctivitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Ear and labyrinth disorders	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Vertigo positional	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
General disorders and administration site conditions	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Pyrexia	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Skin and subcutaneous tissue disorders	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Papule	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

10.2.3 Prior Concomitant Medications and Therapies

The prior concomitant medications and therapies were investigated at the screening and initial treatment. It covered the case of subjects who had received facial (chemical) peels and/or skin rejuvenation procedures or plastic surgeries (including the injection of the Botulinum toxin) and

treatment for wrinkles or acne within 24 weeks prior to screening, and also covered the case of subjects who had used a local ointment on their faces (medication such as steroid or retinoid were included and cosmetic products were excluded from this criterion) within 4 weeks prior to screening or subjects who were using such an ointment during the clinical trial period. Among the 65 subjects in the Safety Set, there were 10 subjects (15.38%) who had a past history of concomitant medication use prior to the application of the investigational device. The total number of events was 33, and there were 3.30 cases per subject. The investigated concomitant medications were classified into Level 1 and 2 according to the ATC code in the WHO Drug Dictionary. According to this classification, the highest number, consisting of 7 cases in 4 subjects (6.15%), belonged to the category of Sensory organs. In addition, 4 subjects (6.15%) had 4 cases of each Alimentary tract and metabolism and Systemic hormonal preparations, excl. sex hormones and insulins. Also, 3 subjects (4.62%) had 4 cases in Genito urinary system and sex hormones, 2 subjects (3.08%) had 4 cases in Cardiovascular system, 2 subjects (3.08%) had 3, 2 and 2 cases each in Respiratory system, Blood and blood forming organs and Nervous system. As the aspirin, one of the analgesics in Nervous system, was the disallowed concomitant medications (Exclusion Criteria “2”: Subjects who received an antithrombotic agent within 2 weeks prior to screening (with the exception of low dose Aspirin 100 mg, maximum of 300 mg/day) or NSAIDs or Vitamin E within 1 week), the subject R1-26 was withdrawn without application of the investigational devices due to taking aspirin. Detailed information regarding concomitant medication is presented in Table 14.

Table 14. Concomitant Medication (Prior) (Safety)

Concomitant Medication (Prior)	Institution		Total N=65
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	
Subjects with Concomitant Medication	5(15.63)	5(15.15)	10(15.38)
95%CI	3.04-28.21	2.92-27.38	6.61-24.16
Total Cases	14	19	33
Cases per Subject	2.80	3.80	3.30
Level 1*			
Level 2*			
Sensory organs	2(6.25),[4]	2(6.06),[3]	4(6.15),[7]
· Ophthalmologicals	2(6.25),[4]	2(6.06),[3]	4(6.15),[7]
Alimentary tract and metabolism	2(6.25),[2]	2(6.06),[2]	4(6.15),[4]
· Drugs for acid related disorders	1(3.13),[1]	1(3.03),[1]	2(3.08),[2]

Concomitant Medication (Prior)	Institution		Total
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	N=65
· Mineral supplements	1(3.13),[1]	0(0.0),[0]	1(1.54),[1]
· Vitamins	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Systemic hormonal preparations, excl. sex hormones and insulins	1(3.13),[1]	3(9.09),[3]	4(6.15),[4]
· Thyroid therapy	1(3.13),[1]	2(6.06),[2]	3(4.62),[3]
· Corticosteroids for systemic use	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Genito urinary system and sex hormones	2(6.25),[3]	1(3.03),[1]	3(4.62),[4]
· Sex hormones and modulators of the genital system	2(6.25),[3]	1(3.03),[1]	3(4.62),[4]
Cardiovascular system	0(0.0),[0]	2(6.06),[4]	2(3.08),[4]
· Agents acting on the renin-angiotensin system	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Lipid modifying agents	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
Respiratory system	1(3.13),[2]	1(3.03),[1]	2(3.08),[3]
· Drugs for obstructive airway diseases	1(3.13),[1]	1(3.03),[1]	2(3.08),[2]
· Antihistamines for systemic use	1(3.13),[1]	0(0.0),[0]	1(1.54),[1]
Blood and blood forming organs	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Antithrombotic agents	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
Nervous system	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Analgesics	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
· Psychoanaleptics	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Antineoplastic and immunomodulating agents	1(3.13),[2]	0(0.0),[0]	1(1.54),[2]
· Antineoplastic agents	1(3.13),[2]	0(0.0),[0]	1(1.54),[2]
Dermatologicals	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
· Antibiotics and chemotherapeutics for dermatological use	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]

*ATC Code 2013
n(%), [case]

Among 65 subjects in the Safety Set, 2 subjects (3.08%) received 2 cases of concomitant therapies, which was 1 case per subject. These were the Surgical and medical procedures of Laser therapy and Skin cosmetic procedure (Table 15).

Table 15. Concomitant Therapies (Prior) (Safety)

Concomitant Therapies (Prior)	Institution		Total
	Seoul National University Hospital	Keimyung University Dongsan Medical Center	N=65
	n1=32	n2=33	
Subjects with Concomitant Therapies	-	2(6.06)	2(3.08)
95%CI	-	0.00-14.20	0.00-7.28
Total Cases	-	2	2
Cases per Subject	-	1.00	1.00
System Organ Class*			
Preferred Term*			
Surgical and medical procedures	0(0), [0]	2(6.06), [2]	2(3.08), [2]
· Laser therapy	0(0), [0]	1(3.03), [1]	1(1.54), [1]
· Skin cosmetic procedure	0(0), [0]	1(3.03), [1]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

10.3 Efficacy Endpoint Results

10.3.1 General Principle of Analysis

The main population of this clinical trial was the FA Set and additional analysis was conducted on the PP Set. The results of each analysis were described, and also the reasons were provided in detail when the results between the groups were significantly different. The non-inferiority test was conducted with a one-sided 97.5% confidence interval, and the rest of differences were compared by a two-tailed test with a significance level of 5%.

The primary efficacy endpoint of this clinical trial was the mean value of WSRS differences between the GENOSS Filler group and the Restylane® group, as assessed by the independent evaluator at Week 24 from the final application of investigational devices. The verification that GENOSS Filler was not inferior to Restylane® was made by showing that the lower limit of the one-sided 97.5%

confidence in mean differences of both the GENOSS Filler group and the Restylane® group was greater than -0.29. The secondary efficacy endpoint indicates all of the following: 1) the mean of WSRS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the independent evaluator at Weeks 8 and 16 from the final application of the investigational devices, 2) the mean of WSRS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the investigator at Weeks 8, 16 and 24 from the final application of the investigational devices, 3) the mean of the Global Aesthetic Improvement Scale (GAIS) scores from both the GENOSS Filler group and the Restylane® group, evaluated by the investigator at Weeks 8, 16 and 24 from the final application of the investigational devices in comparison with the condition prior to the initial application, 4) the mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group, evaluated by the subject at Weeks 8, 16 and 24 from the final application of the investigational devices, in comparison with the condition prior to the initial application, 5) the proportion of subjects from both the GENOSS Filler group and the Restylane® group whose WSRS score decreased at least 1 level when evaluated by the independent evaluator at Week 24 from the final application of the investigational devices, in comparison to the condition prior to the initial application, and 6) the proportion of subjects from both the GENOSS Filler group and the Restylane® group whose WSRS score decreased at least 1 level when evaluated by the investigator at Week 24 from the final application of the investigational devices, in comparison to the condition prior to the initial application.

10.3.2 Efficacy Evaluation by the Independent Evaluator

Independent evaluation was conducted by two assigned professionals who had the ability to evaluate the efficacy of this study but who were not involved in this study as the treating investigator. If the evaluation results differed from one another, one more professional would be assigned to the study that would be continued. Independent evaluation was assessed using WSRS, which was used by the investigator to evaluate the treatment site photographs sorted by the independent data manager. The independent evaluator's objectivity was ensured by means of assessing the assigned treatments and observation periods (before the initial application and weeks 8, 16 and 24 from the application of the device) in the blind setting. This removed the risk of bias that exists in the case of the single blind method. The evaluation performed by independent evaluator was described in a separate independent evaluation sheet, and this sheet was established as the source document.

10.3.3 Statistical Correction

10.3.3.1 Measures for Missing Data or Withdrawn Subject

If there were missing data for the efficacy endpoint or withdrawn subject before termination of the clinical trial, all missing values were replaced with the data at pre-treatment and analysed. This measurement was applied only to the FA Set, and other items for observation were analysed with the available data set without replacing the missing data.

10.3.4 Results of the Primary Efficacy Evaluation

The primary efficacy evaluation results were analysed using the FA Set and PP Set. The results are summarized in Table 16. In the FA Set, the mean of WSRS was 2.05±0.69 in GENOSS Filler group and 1.98±0.72 in the Restylane® group, and the mean of the difference between the two groups (Restylane® - GENOSS Filler) was -0.06±0.70. The lower limit of the one-sided 97.5% confidence interval in the mean difference of WSRS scores between the GENOSS Filler group and the Restylane® group was -0.24, which was greater than -0.29, the non-inferiority limit of this clinical trial. This proved the non-inferiority of GENOSS Filler (Table 16). In the PP Set, the mean of WSRS was 2.03±0.64 in GENOSS Filler group and 1.95±0.68 in the Restylane® group, and the mean of the difference between the two groups (Restylane® - GENOSS Filler) was -0.08±0.70. The lower limit of the one-sided 97.5% confidence interval in mean difference of the WSRS scores between the GENOSS Filler group and the Restylane® group was -0.27, which was greater than -0.29 as in the case of the FA Set. This proved the non-inferiority of GENOSS Filler (Table 16).

Table 16. Comparison of the Means of WSRS Assessed by Independent Evaluators at Week 24

Analysis Set	WSRS				Difference (Reference Device- Investigational Device)	One-Sided 97.5% Confidence Interval	Non-Inferiority Limit
	Investigational Device (GENOSS Filler)		Reference Device (Restylane®)				
	n	Mean±SD	n	Mean±SD			
FAS(N_{FA}=65)	65	2.05±0.69	65	1.98±0.72	-0.06±0.70	-0.24	-0.29
PP (N_{PP}=59)	59	2.03±0.64	59	1.95±0.68	-0.08±0.70	-0.27	-0.29

In order to assess the presence of difference in the WSRS scores between the GENOSS Filler group and the Restylane® group, the baseline values from both groups were compared. According to the results of the FA Set, the mean of WSRS, prior to the application of investigational devices, was 3.58±0.50 in GENOSS Filler group and 3.54±0.50 in the Restylane® group, and the mean of the

difference between the two groups was -0.05±0.48. There was no statistical significant difference between the two groups (p=0.443). The difference between the two groups in the PP Set was -0.05±0.47, which was also statistically insignificant (p=0.410) as the results of FA Set. Analysis of covariance was to be conducted if there was any difference in the WSRS scores between the GENOSS Filler group and the Restylane® group, however, it was not applicable (Table 17).

Table 17. Comparison of the Means of WSRS Assessed By Independent Evaluators at the Baseline

Analysis Set	WSRS				Difference (Reference Device- Investigational Device)	P-value
	Investigational Device (GENOSS Filler)		Reference Device (Restylane®)			
	Mean±SD	Median (Min,Max)	Mean±SD	Median (Min,Max)	Mean±SD	
FAS(N_{FA}=65)	3.58±0.50	4.00 (3.00, 4.00)	3.54±0.50	4.00(3.00, 4.00)	-0.05±0.48	0.443*
PP (N_{PP}=59)	3.61±0.49	4.00(3.00, 4.00)	3.56±0.50	4.00(3.00, 4.00)	-0.05±0.47	0.410*

*Paired t-test

10.3.5 Results of the Secondary Efficacy Evaluation

10.3.5.1 Comparison in WSRS by the independent evaluator

The means of the WSRS scores for the GENOSS Filler group and the Restylane® group rated by the independent evaluator in Weeks 8 and 16 after the application of investigational devices were compared. In the FA Set, the means of the WSRS scores were 2.02±0.65 in the GENOSS Filler group and 1.97±0.64 in the Restylane® group at Week 8 after the final application of the investigational devices, and 2.25±0.71 and 2.14±0.68 at Week 16. The means of the difference between the two groups (Restylane® - GENOSS Filler) were -0.05±0.82 at Week 8 and -0.11±0.73 at Week 16. It was considered that Restylane® was more effective for correction of nasolabial folds than GENOSS Filler. MMRM was applied to compare the differences of WSRS between the groups in each time points, additionally assessed by repetition. There was no statistically significant difference between the groups interacted with the time points of Weeks 8 and 16 (p=0.687), and also it was not statistically significant between the groups (p=0.231), however, there were significant differences in the time points (p=0.020) (Table 18).

Table 18. Comparison of the Means of WSRS Scores Assessed by Independent Evaluators at Weeks 8 and 16 (FAS)

Time Point	WSRS						Difference
	Investigational Device (GENOSS Filler)			Reference Device (Restylane®)			(Reference Device-Investigational Device)
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	65	2.02±0.65	2.00 (1.00, 4.00)	65	1.97±0.64	2.00 (1.00, 3.00)	-0.05±0.82
Week 16	65	2.25±0.71	2.00 (1.00, 4.00)	65	2.14±0.68	2.00 (1.00, 4.00)	-0.11±0.73
MMRM RESULTS[1]							P-value
Interactions between injection sites (groups) and time points (group and time)							0.687[2]
Difference between the injection sites of groups (group)							0.231[2]
Difference between the time points (time)							0.020[2]

1) Mixed model for repeated measures (MMRM)
2) F-test

The results from the PP Set are provided in Table 19. The means of the WSRS scores were 2.05±0.65 in the GENOSS Filler group and 1.97±0.64 in the Restylane® group at Week 8 after the final application of the investigational devices, and 2.24±0.68 and 2.14±0.68 at Week 16. MMRM was applied to compare the differences of WSRS between the groups in each time points, additionally assessed by repetition. There was no statistically significant difference between the groups interacted with the time points of Weeks 8 and 16 (p=0.970), and also it was not statistically significant between the groups (p=0.135), however, there were significant differences in the time points (p=0.030) as the results of the FA Set (Table 19).

Table 19. Comparison of the Means of WSRS Scores Assessed by Independent Evaluators at Weeks 8 and 16 (PP)

Time Point	WSRS						Difference
	Investigational Device (GENOSS Filler)			Reference Device (Restylane®)			(Reference Device-Investigational Device)
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week	59	2.05±0.65	2.00	59	1.97±0.64	2.00	-0.08±0.79

8			(1.00, 4.00)			(1.00, 3.00)	
Week 16	59	2.24±0.68	2.00 (1.00, 4.00)	59	2.14±0.68	2.00 (1.00, 4.00)	-0.10±0.74

MMRM RESULTS[1]	P-value
Interactions between injection sites (groups) and time points (group and time)	0.970[2]
Difference between the injection sites of groups (group)	0.135[2]
Difference between the time points (time)	0.030[2]

1) Mixed model for repeated measures (MMRM)
2) F-test

10.3.5.2 Comparison of WSRS Scores Assessed by the Investigator

The means of the WSRS scores for the GENOSS Filler group and the Restylane® group rated by the investigator in Weeks 8, 16 and 24 after the application of investigational devices were compared. In the results of that, the means of the WSRS scores were 1.80±0.54 in the GENOSS Filler group and 1.80±0.51 in the Restylane® group at Week 8 after the final application of the investigational devices, and the mean of the difference between the two groups (Restylane® - GENOSS Filler) were 0.0001±0.47 at Week 8. Also, the means of the WSRS scores were 2.00±0.66 in the GENOSS Filler group and 2.00±0.56 in the Restylane® group at Week 16, and the mean of the difference between the two groups was 0.0001±0.47 at Week 16. In addition, the results were 2.57±0.66, 2.58±0.66 and 0.02±0.52 at Week 24. MMRM was applied to compare the differences of WSRS between the groups in each time points, additionally assessed by repetition at Weeks 8, 16 and 24. There was no statistically significant difference between the groups interacted with the time points and between the groups (p=0.989, p=840), however, there were significant differences in the time points (p<0.0001) (Table 20).

Table 20. Comparison of the Means of WSRS Scores Assessed by Investigator at Weeks 8, 16 and 24 (FAS)

Time Point	WSRS						Difference(Reference Device-Investigational Device)
	Investigational Device(GENOSS Filler)			Reference Device(Restylane®)			
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	65	1.80±0.54	2.00 (1.00, 3.00)	65	1.80±0.51	2.00 (1.00, 3.00)	0.0001±0.47[3]

Week 16	65	2.00±0.66	2.00 (1.00, 3.00)	65	2.00±0.56	2.00 (1.00, 3.00)	0.0001±0.47[3]
Week 24	65	2.57±0.66	3.00 (1.00, 4.00)	65	2.58±0.66	3.00 (1.00, 4.00)	0.02±0.52
MMRM RESULTS[1]							P-value
Interactions between injection sites (groups) and time points (group and time)							0.989[2]
Difference between the injection sites of groups (group)							0.840[2]
Difference between the time points (time)							P<0.0001[2]

1) Mixed model for repeated measures (MMRM)
2) F-test
3) The mean score became '0' by rounding off the numbers to three decimal places

The results from the PP Set are provided in Table 21. The means of the WSRS scores were 1.78±0.56 in the GENOSS Filler group and 1.78±0.49 in the Restylane® group, and the mean of the difference between the two groups (Restylane® - GENOSS Filler) were 0.0001±0.45 at Week 8. Also, the results were 1.95±0.65, 1.95±0.54 and 0.0001±0.49 at Week 16, and 2.53±0.68, 2.53±0.65 and 0.0001±0.53 at Week 24. As the results of FA Set, when MMRM was applied to compare the differences of WSRS between the groups in each time points, additionally assessed by repetition, there was no statistically significant difference between the groups interacted with the time points and between the groups, however, there were significant differences in the time points (p<0.0001) (Table 21).

Table 21. Comparison of the Means of WSRS Scores Assessed by Investigator at Weeks 8, 16 and 24 (PP)

Time Point	WSRS						Difference(Reference Device-Investigational Device)
	Investigational Device(GENOSS Filler)			Reference Device(Restylane®)			
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	59	1.78±0.56	2.00 (1.00, 3.00)	59	1.78±0.49	2.00 (1.00, 3.00)	0.0001±0.45[3]
Week 16	59	1.95±0.65	2 (1.00, 3.00)	59	1.95±0.54	2.00 (1.00, 3.00)	0.0001±0.49[3]
Week 24	59	2.53±0.68	3.00 (1.00, 4.00)	59	2.53±0.65	3.00 (1.00, 4.00)	0.0001±0.53[3]
MMRM RESULTS[1]							P-value

Interactions between injection sites (groups) and time points (group and time)	1.000[2)]
Difference between the injection sites of groups (group)	1.000[2)]
Difference between the time points (time)	P<0.0001[2)]

1) Mixed model for repeated measures (MMRM)
2) F-test
3) The mean score became '0' by rounding off the numbers to three decimal places

Before the application of the investigational devices, the WSRS scores evaluated by the investigator at the baseline were compared to assess the difference between the GENOSS Filler group and the Restylane® group. As the results in the FA Set, the means of WSRS prior to the application of the investigational devices were 3.51±0.50 in the GENOSS Filler group and 3.54±0.5 in the Restylane® group, and the mean of difference was not statistically significant as 0.03±0.25 (p=0.321). Also, the mean of difference between the groups was not statistically significant as 0.02±0.23 (p=0.568) (Table 22).

Table 22. Comparison of the Means of WSRS Scores Assessed by Investigator at the Baseline

Analysis Set	WSRS				Difference(Reference Device-Investigational Device)	P-value
	Investigational Device(GENOSS Filler)		Reference Device(Restylane®)			
	Mean±SD	Median (Min,Max)	Mean±SD	Median (Min,Max)	Mean±SD	
FAS(N_{FA}=65)	3.51±0.50	4.00 (3.00, 4.00)	3.54±0.50	4.00 (3.00, 4.00)	0.03±0.25	0.321*
PP (N_{PP}=59)	3.49±0.50	3.00 (3.00, 4.00)	3.51±0.50	4.00 (3.00, 4.00)	0.02±0.23	0.568*

*Paired t-test

10.3.5.3 Comparison of GAIS Scores Assessed by the Investigator

Analysis was performed on the means of the GAIS scores from both the GENOSS Filler group and the Restylane® group assessed by the investigator in Weeks 8, 16 and 24 after the final application of the investigational device, in comparison to the condition prior to the initial application. Among the 65 subjects in the FA Set, GAIS was analysed for 64 subjects at Week 16 and 63 subjects at Week 24, since there was no pre-treatment value for the GAIS eventhough the missing data of the 2 withdrawn subjects, due to the follow-up failure, were supposed to be replaced with pre-treatment value. As the results, the means of GAIS were 2.11±0.64 in the GENOSS Filler group and 2.02±0.67 in the Restylane® group at Week 8, 1.58±0.71 and 1.50±0.71 at Week 16, and 1.06±0.59 and 0.98±0.63 at

Week 24. It suggested that the means of GAIS in the GENOSS Filler group were higher than that of the Restylane® group at Weeks 8, 16 and 24. In the results of MMRM application, there was no statistically significant difference between the groups interacted with the time points and between the groups (p=0.991, p=0.261), however, there were significant differences in the time points (p<0.0001) (Table 23).

Table 23. Comparison of the Means of GAIS Assessed by Investigators at Weeks 8, 16 and 24 (FAS)

Time Point	GAIS						Difference(Reference Device-Investigational Device)
	Investigational Device(GENOSS Filler)			Reference Device(Restylane®)			
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	65	2.11±0.64	2.00 (1.00, 3.00)	65	2.02±0.67	2.00 (0.00, 3.00)	-0.09±0.49
Week 16	64	1.58±0.71	2.00 (0.00, 3.00)	64	1.50±0.71	1.50 (0.00, 3.00)	-0.08±0.48
Week 24	63	1.06±0.59	1.00 (0.00, 3.00)	63	0.98±0.63	1.00 (0.00, 3.00)	-0.08±0.58
MMRM RESULTS[1]							P-value
	Interactions between injection sites (groups) and time points (group and time)						0.991[2]
	Difference between the injection sites of groups (group)						0.261[2]
	Difference between the time points (time)						P<0.0001[2]

1) Mixed model for repeated measures (MMRM)
2) F-test

In the results from the PP Set, the means of GAIS were 2.08±0.65 in the GENOSS Filler group and 2.00±0.69 in the Restylane® group at Week 8, 1.58±0.72 and 1.53±0.73 at Week 16, and 1.07±0.61 and 1.00±0.64 at Week 24. It suggested that the means of GAIS in the GENOSS Filler group were higher than that of the Restylane® group at Weeks 8, 16 and 24, but there was no statistically significant difference between the groups interacted with the time points and between the groups, however, there were significant differences in the time points (p<0.0001) (Table 24).

Table 24. Comparison of the Means of GAIS Assessed by Investigators at Weeks 8, 16 and 24 (PP)

Time	GAIS	Difference(Reference

Point	Investigational Device(GENOSS Filler)			Reference Device(Restylane®)			Device-Investigational Device)
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	59	2.08±0.65	2.00 (1.00, 3.00)	59	2.00±0.69	2.00 (0.00, 3.00)	-0.08±0.50
Week 16	59	1.58±0.72	2.00 (0.00, 3.00)	59	1.53±0.73	2.00 (0.00, 3.00)	-0.05±0.47
Week 24	59	1.07±0.61	1.00 (0.00, 3.00)	59	1.00±0.64	1.00 (0.00, 3.00)	-0.07±0.58
MMRM RESULTS[1]							P-value
Interactions between injection sites (groups) and time points (group and time)							0.957[2]
Difference between the injection sites of groups (group)							0.411[2]
Difference between the time points (time)							P<0.0001[2]

1) Mixed model for repeated measures (MMRM)
2) F-test

10.3.5.4 Comparison of GAIS Scores Assessed by the Subject

Analysis was performed on the mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group assessed by the subject in Weeks 8, 16 and 24 after the final application of the investigational device, in comparison to the condition prior to the initial application. Among the 65 subjects in the FA Set, GAIS was analysed for 64 subjects at Week 16 and 63 subjects at Week 24, since there was no pre-treatment value for the GAIS eventhough the missing data of the 2 withdrawn subjects, due to the follow-up failure, were supposed to be replaced with pre-treatment value. As the results, the means of GAIS were 1.45±0.73 in the GENOSS Filler group and 1.29±0.80 in the Restylane® group at Week 8, 1.14±0.89 and 1.05±0.93 at Week 16, and 1.10±1.03 and 1.03±0.97 at Week 24. It suggested that the means of GAIS in the GENOSS Filler group were higher than that of the Restylane® group at Weeks 8, 16 and 24. In the results of MMRM application, there was no statistically significant difference between the groups interacted with the time points and between the groups (p=0.929, p=0.331), however, there were significant differences in the time points (p=0.002) (Table 25).

Table 25. Comparison of the Means of GAIS Assessed by Subjects at Weeks 8, 16 and 24 (FAS)

Time	GAIS	Difference(Reference

Point	Investigational Device(GENOSS Filler)			Reference Device(Restylane®)			Device-Investigational Device)
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	65	1.45±0.73	1.00 (0.00, 3.00)	65	1.29±0.80	1.00 (-1.00, 3.00)	-0.15±0.69
Week 16	64	1.14±0.89	1.00 (0.00, 3.00)	64	1.05±0.93	1.00 (-1.00, 3.00)	-0.09±0.75
Week 24	63	1.10±1.03	1.00 (-1.00, 3.00)	63	1.03±0.97	1.00 (-1.00, 3.00)	-0.06±0.76
MMRM RESULTS[1]							P-value
Interactions between injection sites (groups) and time points (group and time)							0.929[2]
Difference between the injection sites of groups (group)							0.331[2]
Difference between the time points (time)							0.002[2]

1) Mixed model for repeated measures (MMRM)
2) F-test

In the results from the PP Set, the means of GAIS were 1.47±0.70 in the GENOSS Filler group and 1.32±0.82 in the Restylane® group at Week 8, 1.15±0.93 and 1.05±0.95 at Week 16, and 1.14±1.04 and 1.03±0.96 at Week 24. It suggested that the means of GAIS in the GENOSS Filler group were higher than that of the Restylane® group at Weeks 8, 16 and 24, but there was no statistically significant difference between the groups interacted with the time points and between the groups (p=0.963, p=0.288), however, there were significant differences in the time points (p=0.002) (Table 26).

Table 26. Comparison of the Means of GAIS Assessed by Subjects at Weeks 8, 16 and 24 (PP)

Time Point	GAIS						Difference(Reference Device-Investigational Device)
	Investigational Device(GENOSS Filler)			Reference Device(Restylane®)			
	n	Mean±SD	Median (Min,Max)	n	Mean±SD	Median (Min,Max)	Mean±SD
Week 8	59	1.47±0.70	1.00 (0.00, 3.00)	59	1.32±0.82	1.00 (-1.00, 3.00)	-0.15±0.66
Week 16	59	1.15±0.93	1.00 (0.00, 3.00)	59	1.05±0.95	1.00 (-1.00, 3.00)	-0.10±0.76

Week 24	59	1.14±1.04	1.00 (-1.00, 3.00)	59	1.03±0.96	1.00 (-1.00, 3.00)	-0.10±0.76

MMRM RESULTS[1)]	P-value
Interactions between injection sites (groups) and time points (group and time)	0.963[2)]
Difference between the injection sites of groups (group)	0.288[2)]
Difference between the time points (time)	0.002[2)]

1) Mixed model for repeated measures (MMRM)
2) F-test

10.3.5.5 Comparison of the Improvement Ratio of the WSRS Scores Assessed by the Independent Evaluator

Analysis was performed on the proportion of subjects from both the GENOSS Filler group and the Restylane® group whose WSRS scores decreased at least 1 level when assessed by the independent evaluator at Week 24 from the final application of the investigational device, compared to the condition prior to the application of the investigational device. The analysis results for the FA Set showed that the number of subjects showing such decrease was 59 (90.77%) in the GENOSS Filler group and 61 (93.85%) in the Restylane® group. It suggested that the proportion of the subjects whose WSRS scores were improved in the Restylane® group was higher than that of the GENOSS Filler group, however, they were not statistically significant in the difference (p=0.317). In addition, the results of the PP Set were 55 (93.22%) subjects in the GENOSS Filler group and 57 (96.61%) subjects in the Restylane® group, however, they were not statistically significant in the difference (p=0.317) (Table 27).

Table 27. Comparison of the Improvement Ratio (at Least -1) of WSRS Assessed by Independent Evaluators

Analysis Set	Investigational Device (GENOSS Filler)		Reference Device (Restylane®)		Total			p-value
	N(%)	95% C.I	N(%)	95% C.I	N(%)	95% C.I	Odds ratio, (95% C.I) (ref= Restylane®)	
FAS(N_{FA}=65)	59(90.77)	87.10-99.04	61(93.85)	84.99-98.30	120(92.31)	87.73-96.89	0.645 (0.173-2.401)	0.317*
PP (N_{PP}=59)	55(93.22)	83.54-	57(96.61)	90.91-	112(94.92)	90.95-	0.482	0.317*

	98.12	99.96	98.88	(0.085-2.741)

*McNemar's test

10.3.5.6 Comparison of the Improvement Ratio of the WSRS Scores Assessed by the Investigator

Analysis was performed on the proportion of subjects from both the GENOSS Filler group and the Restylane® group whose WSRS scores decreased at least 1 level when assessed by the investigator at Week 24 from the final application of the investigational device, compared to the condition prior to the application of the investigational device. In the analysis for the FA Set, there was no difference between the GENOSS Filler group and the Restylane® group as the results were 100%(65 subjects) in both the GENOSS Filler group and the Restylane® group. Also, there was no difference between the groups as the results were 100%(59 subjects) in the both groups of the PP Set (Table 28).

Table 28. Comparison of the Improvement Ratio (at Least -1) of WSRS Assessed by the Investigator

Analysis Set	Investigational Device (GENOSS Filler)		Reference Device(Restylane®)		Total			p-value*
	N(%)	95% C.I	N(%)	95% C.I	N(%)	95% C.I	Odds ratio, (95% C.I) (ref= Restylane®)	
FAS(N_{FA}=65)	65(100)	-	65(100)	-	130(100)	-	-	-
PP (N_{PP}=59)	59(100)	-	59(100)	-	118(100)	-	-	-

*McNemar's test

10.4 Final Conclusion Regarding Efficacy

The efficacy evaluation in this clinical trial was conducted using 65 subjects in the FA Set used for main analysis and 59 subjects in the PP Set used for additional analysis. If there was a difference in PP Set compared with that of FA Set, all reasons were supposed to be described in detail. However, there was no difference between the analysis sets.

Comparisons were made for the for the primary efficacy endpoint, between the GENOSS Filler group and the Restylane® group, in terms of the mean difference of WSRS scores that were assessed by

the independent evaluator at Week 24 from the final application of investigational devices. In the results of FA Set, the means of WSRS scores were 2.05±0.69 in the GENOSS Filler group and 1.98±0.72 in the Restylane® group. The mean of difference between the two groups was -0.06±0.70, and the lower limit of the one-sided 97.5% confidence was -0.24, in the mean difference between the GENOSS Filler group and the Restylane® group. This value was greater than -0.29, the originally targeted non-inferiority limit. This proved that the GENOSS Filler group was not inferior to the Restylane® group. The lower limit of the one-sided 97.5% confidence was -0.27, in the mean difference between the GENOSS Filler group and the Restylane® group of PP Set. This value was also greater than -0.29. In order to assess whether additional analysis was needed, comparison was made of the mean of the WSRS scores in the GENOSS Filler group and the Restylane® group as assessed by the independent evaluator prior to the application of investigational devices, but no significant difference was found.

In regards to the secondary efficacy results, comparison was made of the mean of the WSRS scores assessed by the independent evaluator in Weeks 8 and 16 from the final application of the investigational device. The results indicated that the means of the WSRS scores were 2.02±0.65 in the GENOSS Filler group and 1.97±0.64 in the Restylane® group at Week 8 after the final application of the investigational devices, and 2.25±0.71 and 2.14±0.68 at Week 16. The WSRS scores from the GENOSS Filler group were higher than those from the Restylane® group although they were not statistically significant. In addition, compared to the mean of the WSRS scores at screening, which were 3.58±0.50 in the GENOSS Filler group and 3.54±0.50 in the reference group, constituted a “3” rating indicating a “moderate” condition, the WSRS scores were found to have improved to the latter of “1” rating indicating an “absent” or the early “2” rating indicating an “mild” conditions for the GENOSS Filler group in regards to the degree of nasolabial folds.

Comparison was made of the mean of the WSRS scores assessed by the investigator at Weeks 8, 16 and 24 from the final application of the investigational device. The results indicated that the means of the WSRS scores were 1.80±0.54 in the GENOSS Filler group and 1.80±0.51 in the Restylane® group at Week 8 after the final application of the investigational devices, 2.00±0.66 and 2.00±0.56 at Week 16, and 2.57±0.66 and 2.58±0.66. There were no statistically significant differences between the groups interacted with the time points and between the groups.

Analysis was performed on the mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group assessed by the investigator at Weeks 8, 16, and 24 after the final application of investigational devices, compared to the condition prior to the initial application. The results indicated that the means of the GAIS scores were 2.11±0.64 in the GENOSS Filler group and 2.02±0.67 in the Restylane® group at Week 8 after the final application of the investigational devices, 1.58±0.71 and 1.50±0.71 at Week 16, and 1.06±0.59 and 0.98±0.63. As the results, the means of the GAIS score in the GENOSS Filler group were higher than that of the Restylane® group in all the time points, and

after the analysis with MMRM application the GENOSS Filler group were higher than that of the Restylane® group although there were no statistically significant differences between the groups.
Analysis was performed on the mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group assessed by the subject at Weeks 8, 16, and 24 after the final application of investigational devices, compared to the condition prior to the initial application. The results indicated that the means of the GAIS scores were 1.45±0.73 in the GENOSS Filler group and 1.29±0.80 in the Restylane® group at Week 8 after the final application of the investigational devices, 1.14±0.89 and 1.05±0.93 at Week 16, and 1.10±1.03 and 1.03±0.97. As the results, the means of the GAIS score in the GENOSS Filler group were higher than that of the Restylane® group in all the time points as the results by the investigator. However, there were no statistically significant differences between the groups interacted with the time points and between the groups.
The proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the independent evaluator at Week 24 from the final application of the investigational device was 90.77 % in the GENOSS Filler group and was 93.85 % in the Restylane® group. These results, however, did not constitute a statistically significant difference between the two groups.
The proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the investigator at Week 24 from the final application of investigational devices was 100% both in the GENOSS Filler group and in the Restylane® group, and the results thus showed that there was no difference between the groups.

In conclusion, the primary objective was achieved, since the non-inferiority of GENOSS Filler compared to Restylane® was proved in both the FA Set and the PP Set, according to the primary efficacy results. Also, the secondary efficacy results proved the improvement in the degree of nasolabial folds, based on the WSRS scores assessed by the independent evaluator and the investigator. In regards to the satisfactoriness of the procedure, the GAIS scores asessed by the investigator and subjects showed that the scores in the GENOSS Filler group was higher than that of the Restylane® group at Week 24, although the results were not statistically significant. In addition, the proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the independent evaluator and investigator at Week 24 from the final application of investigational devices was not statistically significant in the GENOSS Filler group and the Restylane® group. All the results obtained from PP Set as the additional analysis group were also similar the results described above.

All of the above analyses verified that GENOSS Filler, which is used on bilateral nasolabial folds, was effective in the correction of facial nasolabial folds when judged in comparison with Restylane® as the reference device.

11. SAFETY EVALUATION

11.1 Analysed Data Sets

Safety evaluation was conducted on the 65 subjects in Safety Set who received at least 1 application of the investigational device after signing the informed consent form.

11.2 Repeat treatment of Investigational Devices

The 65 subjects received application of GENOSS Filler on the nasolabial fold on one side and application of Restylane® on the other side at least once after randomization. No subject received a repeat (touch-up) treatment after 2 weeks from the baseline during this clinical trial.

11.3 Adverse Events

11.3.1 Summary of Adverse Events

Among the 65 subjects in the Safety Set, the number of subjects who experienced 1 or more adverse events after the application of the investigational device was 18 subjects (27.69%). In addition, 1 subject (1.54%) experienced adverse device events; however, none of the subjects experienced serious adverse events and were withdrawn from this study due to an adverse event (Table 29).

Table 29. Current State of Adverse Events (Safety)

Current State of Adverse Events	Institution		Total N=65
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	
Adverse Event (AE)	10(31.25)	8(24.24)	18(27.69)
Adverse Device Event (ADE)	1(3.13)	0(0)	1(1.54)
Serious Adverse Event (SAE)	0(0)	0(0)	0(0)
Serious Adverse Device Event (SADE)	0(0)	0(0)	0(0)
Withdrawal due to an Adverse Event	0(0)	0(0)	0(0)

11.3.2 Detailed Classification of Occurred Adverse Events

Adverse events were classified according to the location where they occurred and were further sub-classified in terms of the number of subjects with adverse events, seriousness, whether the adverse event occurred within 30 minutes after the application of the device, the degree of severity, the site of the occurrence, measures taken according to the applied device, other actions, the causality to the applied devices, outcome, TEAE, ADE and SAE. The results are summarized in Table 30.

Among the 65 subjects in the Safety Set, 18 subjects (27.69%) experienced a total of 24 cases of adverse events. The number of adverse event occurrences per subject was 1.33. None of the cases were Serious Adverse Event and 1 case (4.17%) occurred within 30 minutes after the application of the device. As for severity, 23 cases (95.83%) were mild, 1 case (4.17%) was moderate and none of severe case. Adverse events occurred in injection site included none of case in the GENOSS Filler group but 1 case in the Restylane® group. Other 23 cases (95.83%) occurred in other sites without relation with the investigational devices. There were no actions taken in regards to the investigational device. The other actions taken were the administration of drugs in 6 cases (25.00%), hospitalization or length of hospital stay in 16 cases (66.67%), both hospitalization or length of hospital stay and other measures in 2 cases (8.33%), and none of therapeutic or diagnostic procedure. Regarding the causality to the investigational devices, 23 cases (95.83%) were judged to have no relation by the investigator, however, 1 case (4.17%) had probably related. There were 15 cases (62.50%) recovered, 8 cases (33.33%) with recovery in progress and 1 case (4.17%) recovered but left after effects. Among the 24 cases, there were 23 cases (95.83%) of TEAE, 1 case (4.17%) of ADE and none of SAE. Detailed classifications of adverse events by each institution are presented in Table 30 as below.

Table 30. Detailed Classification of Adverse Events (Safety)

Adverse Events	Institution		Total
	Seoul National University Hospital	Keimyung University Dongsan Medical Center	N=65
	n_1=32	n_2=33	
Subjects with Adverse Events	10(31.25)	8(24.24)	18(27.69)
95%CI	15.19-47.31	9.62-38.86	16.81-38.57
Total Cases	13	11	24
Cases per Subject	1.30	1.38	1.33
Serious events			
Yes	0(0.00)	0(0.00)	0(0.00)
No	13(100.0)	11(100.0)	24(100.0)

Adverse Events	Institution		Total
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	N=65
Adverse events within 30 minutes after the application of the clinical device			
Yes	1(7.69)	0(0.00)	1(4.17)
No	12(92.31)	11(100.0)	23(95.83)
Severity			
Mild	13(100.0)	10(90.91)	23(95.83)
Moderate	0(0.00)	1(9.09)	1(4.17)
Severe	0(0.00)	0(0.00)	0(0.00)
Site of occurrence			
Injection site	1(7.69)	0(0.00)	1(4.17)
Investigational device	0(0)	0(0)	0(0)
Reference device	1(100.0)	0(0)	1(100.0)
Other site except for injection site	12(92.31)	11(100.0)	23(95.83)
Actions taken with respect to medical devices, case (%)			
Not applicable	13(100.0)	11(100.0)	24(100.0)
Temporarily discontinued	0(0)	0(0)	0(0)
Not changed in dosage	0(0)	0(0)	0(0)
Permanent discontinued	0(0)	0(0)	0(0)
Other measures			
No	0(0)	0(0)	0(0)
Administration of drugs	4(30.77)	2(18.18)	6(25.00)
Hospitalization / Length of hospital stay	9(69.23)	7(63.64)	16(66.67)
Therapeutic or diagnostic procedures	0(0)	0(0)	0(0)
Others	0(0)	0(0)	0(0)
Hospitalization / Length of hospital stay + Others	0(0.00)	2(18.18)	2(8.33)
Causality to the applied medical devices			

Adverse Events		Institution		Total
		Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	N=65
Related	Definitely related	0(0)	0(0)	0(0)
	Much related	0(0)	0(0)	0(0)
	Probably related	1(7.69)	0(0.00)	1(4.17)
	Probably not related	0(0)	0(0)	0(0)
	Not tested	0(0)	0(0)	0(0)
Not related	Definitely not related	12(92.31)	11(100.0)	23(95.83)
Outcome				
Recovery		9(69.23)	6(54.55)	15(62.50)
Recovery, but left after effects		0(0.00)	1(9.09)	1(4.17)
Recovery in progress		4(30.77)	4(36.36)	8(33.33)
Not recovered		0(0)	0(0)	0(0)
Death		0(0)	0(0)	0(0)
Not tested		0(0)	0(0)	0(0)
TEAE[1)]				
Yes		13(100.0)	10(90.91)	23(95.83)
No		0(0.00)	1(9.09)	1(4.17)
ADE				
Yes		1(7.69)	0(0.00)	1(4.17)
No		12(92.31)	11(100.0)	23(95.83)
SAE				
Yes		0(0)	0(0)	0(0)
No		13(100.0)	11(100.0)	24(100.0)

1) Yes=AE after application of investigational device, No= AE before application of investigational device

11.3.2.1 Adverse Events by System Organ Class

In regards to the rate of adverse events occurred by system organ class, there were 1 case (1.54%) occurred in the injecton sites, which was Injection site induration (Table 31), and remaining cases

occurred not in the injection sites (Table 32). Among the adverse events occurred out of the injection sites, the most number of cases was 7 with Infections and infestations in 7 subjects (10.77%), and there were 4 cases with Musculoskeletal and connective tissue disorders in 4 subjects (6.15%) as followed. Also, there were 3 cases with Gastrointestinal disorders in 3 subjects (4.62%) and 2 cases each with 'Injury, poisoning and procedural complications' and 'Respiratory, thoracic and mediastinal disorders' in 2 subjects (3.08%). Other detailed results of the advere events by system organs are presented in Table 32.

Table 31. Expression Rate of Adverse Events in the Injection Site Classified by System Organ Class (Safety)

System Organ Class*	Investigational Device	Reference Device	Total
Preferred Term*	n=65	n=65	N=65
General disorders and administration site conditions	0(0.0), [0]	1(1.54), [1]	1(1.54), [1]
· Injection site induration	0(0.0), [0]	1(1.54), [1]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

Table 32. Expression Rate of Adverse Events Not in the Injection Site Classified by System Organ Class (Safety)

System Organ Class*	Institution		Total
Preferred Term*	Seoul National University Hospital n1=32	Keimyung University Dongsan Medical Center n2=33	N=65
Eye disorders	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Glare	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Gastrointestinal disorders	1(3.13), [1]	2(6.06), [2]	3(4.62), [3]
· Abdominal discomfort	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Colitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Gastritis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
General disorders and administration site conditions	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Injury associated with device	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Infections and infestations	4(12.50), [4]	3(9.09), [3]	7(10.77), [7]
· Cystitis	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Herpes zoster	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]

System Organ Class* / Preferred Term*	Institution: Seoul National University Hospital n1=32	Institution: Keimyung University Dongsan Medical Center n2=33	Total N=65
· Nasopharyngitis	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Vaginal infection	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Gingivitis	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Otitis media acute	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Upper respiratory tract infection	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Injury, poisoning and procedural complications	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
· Laceration	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Thermal burn	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Musculoskeletal and connective tissue disorders	1(3.13), [1]	3(9.09), [3]	4(6.15), [4]
· Musculoskeletal chest pain	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Intervertebral disc disorder	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Osteopenia	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Trigger finger	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Nervous system disorders	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Dizziness	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Reproductive system and breast disorders	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Breast mass	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
Respiratory, thoracic and mediastinal disorders	1(3.13), [1]	1(3.03), [1]	2(3.08), [2]
· Rhinitis allergic	1(3.13), [1]	0(0.0), [0]	1(1.54), [1]
· Dysphonia	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Skin and subcutaneous tissue disorders	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Dermatitis contact	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

11.3.2.2 Adverse events occurred within 30 minutes after the application of the investigational devices

Among the adverse events occurred, there was 1 case occurred within 30 minutes after the application of the investigational devices. It was Injection site induration as mild, and it occurred in the left injection sites for the Restylane®. It was recovered at the day and had no actions taken for the device. The subject was not withdrawn due to the adverse event.

Subject No.	Gender	Age	Adverse events (PT)	Date of occurrence	Date of discontinuance	Severity	Site of occurrence	Outcome	Causality to the applied devices	Actions taken with respect to devices	Withdrawal
R1-24	Female	54	Injection site induration	2013/08/07	2013/08/07	Mild	Left	Recovery	Probably related	NA	No

11.3.2.3 Expression Rate of Adverse Events Classified by Severity

There was 1 case (1.54%) as mild, which occurred in the injection site.

Table 33. Expression Rate of Adverse Events in the Injection Site Classified by Severity (Safety)

System Organ Class*	Investigational Device n=65			Reference Device n=65			Total N=65
Preferred Term*	Mild	Moderate	Severe	Mild	Moderate	Severe	
General disorders and administration site conditions	0(0.0), [0]	0(0.0), [0]	0(0.0), [0]	1(1.54), [1]	0(0.0), [0]	0(0.0), [0]	1(1.54), [1]
· Injection site induration	0(0.0), [0]	0(0.0), [0]	0(0.0), [0]	1(1.54), [1]	0(0.0), [0]	0(0.0), [0]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

Among the adverse events not in the injection site, 1 case (3.03%) was moderate with Musculoskeletal and connective tissue disorders and none of severe case. The other adverse events were mild (Table 34).

Table 34. Expression Rate of Adverse Events Not in the Injection Site Classified by Severity (Safety)

System Organ Class* Preferred Term*	Institution*						Total N=65
	Seoul National University Hospital n1=32			Keimyung University Dongsan Medical Center n2=33			
	Mild	Moderate	Severe	Mild	Moderate	Severe	
Eye disorders	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Glare	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
Gastrointestinal disorders	1(3.13), [1]	0(0), [0]	0(0), [0]	2(6.06), [2]	0(0.0),[0]	0(0), [0]	3(4.62), [3]
· Abdominal discomfort	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Colitis	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Gastritis	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
General disorders and administration site conditions	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Injury associated with device	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
Infections and infestations	4(12.50), [4]	0(0), [0]	0(0), [0]	3(9.09), [3]	0(0.0),[0]	0(0), [0]	7(10.77), [7]
· Cystitis	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Gingivitis	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Herpes zoster	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Nasopharyngitis	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Otitis media acute	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Upper respiratory tract infection	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Vaginal infection	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
Injury, poisoning and procedural complications	1(3.13), [1]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	2(3.08), [2]
· Laceration	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Thermal burn	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]

System Organ Class* Preferred Term*	Institution*						Total N=65
	Seoul National University Hospital n1=32			Keimyung University Dongsan Medical Center n2=33			
	Mild	Moderate	Severe	Mild	Moderate	Severe	
Musculoskeletal and connective tissue disorders	1(3.13), [1]	0(0), [0]	0(0), [0]	2(6.06), [2]	1(3.03), [1]	0(0), [0]	4(6.15), [4]
· Intervertebral disc disorder	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Musculoskeletal chest pain	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Osteopenia	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Trigger finger	0(0.0),[0]	0(0), [0]	0(0), [0]	0(0.0),[0]	1(3.03), [1]	0(0), [0]	1(1.54), [1]
Nervous system disorders	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Dizziness	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
Reproductive system and breast disorders	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Breast mass	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
Respiratory, thoracic and mediastinal disorders	1(3.13), [1]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	2(3.08), [2]
· Dysphonia	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Rhinitis allergic	1(3.13), [1]	0(0), [0]	0(0), [0]	0(0.0),[0]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
Skin and subcutaneous tissue disorders	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]
· Dermatitis contact	0(0.0),[0]	0(0), [0]	0(0), [0]	1(3.03), [1]	0(0.0),[0]	0(0), [0]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

11.3.3 Analysis of Adverse Device Events (ADE)

In regards to the causality to the applied device, ‘not related’ means there is no relation, less relation and no testing, and ‘related’, which were classified to ADE, can range from definitely related to much

related or probably related. Among the 24 adverse events, 1 case was adverse device event. Detailed information is presented as below (Table 35).

Table 35. List of the Subject with ADE (Safety)

Institution	Subject No.	Gender	Age	Adverse events (PT)	Date of occurrence	Date of discontinuance	Severity	Site of occurrence	Outcome	Causality to the applied devices	Actions taken with respect to devices	Withdrawal
Seoul National University Hospital	R1-24	Female	54	Injection site induration	2013/08/07	2013/08/07	Mild	Left	Recovery	Probably related	NA	No

11.4 Serious Adverse Events (SAE)

In this clinical trial, there was no serious adverse event (SAE).

11.5 Evaluation of Adverse Events in Laboratory Tests

The laboratory tests were conducted before the application of the investigational device (Visit 1) and after Weeks 24 (Visit 6) from the final application of the investigational device. Appendix 2.3 (INFORMATION ON LABORATORY TEST RESULTS BY SUBJECT) presents the test results organized by the means, the differences in the means before and after application, and min/max. In addition, Table 36-42 shows the clinical significance (CS/NCS) of the abnormal values as judged by the investigator. In these laboratory tests, the subjects who had clinically significant abnormal cases continued the clinical trial if the investigator decided that the abnormal cases had no effects on this clinical trial.

11.5.1 Hematology Test

The hematology test was conducted to check WBC, RBC, Hemoglobin, Hematocrit and Platelet. The detailed results are presented in Table 36. The results of Visit 6 were analysed for 63 subjects except for the 2 withdrawn subjects (R01-01, R01-16). There were subjects who had abnormal values; however, they were not clinically significant (Table 37).

Table 36. Basic Statistics on the Hematology Test (Safety)

		N	Mean± SD	Median	Min, Max	P-value[1)]
WBC	Visit1	65	5.93±1.23	5.95	3.48~9.06	
	Visit6	63	5.85±1.23	5.93	3.69~9.25	
	Change[2)]	63	-0.13±1.12	-0.18	-2.40~3.92	0.369*
RBC	Visit1	65	4.13±0.30	4.15	3.50~5.01	
	Visit6	63	4.18±0.33	4.17	3.58~4.91	
	Change	63	0.05±0.22	0.10	-0.57~0.45	0.091*
Hemoglobin	Visit1	65	12.47±1.32	12.70	7.20~15.30	
	Visit6	63	12.67±1.15	12.80	7.10~15.10	
	Change	63	0.13±0.60	0.20	-1.50~1.30	0.080*
Hematocrit	Visit1	65	37.03±3.08	37.30	25.70~43.30	
	Visit6	63	42.03±39.27	37.10	25.30~348.00	
	Change	63	4.84±39.54	0.20	-5.60~313.30	0.335*
Platelet	Visit1	65	255.29±54.86	251.00	160.00~453.00	
	Visit6	63	260.02±67.72	250.00	131.00~625.00	
	Change	63	6.27±37.66	4.00	-87.00~172.00	0.191*

1) paired t-test
2) Change:Visit1-Visit6

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6

Table 37. HematologyTest (Safety)

	Visit6 / Visit1	Clinical Significance		
		Normal	Abnormal NCS†	Abnormal CS‡
WBC (n=63)	Normal	45(71.43)	7(11.11)	0(0)
	Abnormal NCS†	4(6.35)	7(11.11)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
RBC (n=63)	Normal	30(47.62)	4(6.35)	0(0)
	Abnormal NCS†	6(9.52)	23(36.51)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Hemoglobin (n=63)	Normal	45(71.43)	2(3.17)	0(0)
	Abnormal NCS†	6(9.52)	10(15.87)	0(0)

	Visit6 / Visit1	Clinical Significance		
		Normal	Abnormal NCS†	Abnormal CS‡
	Abnormal CS‡	0(0)	0(0)	0(0)
Hematocrit (n=63)	Normal	29(46.03)	7(11.11)	0(0)
	Abnormal NCS†	4(6.35)	23(36.51)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Platelet (n=63)	Normal	62(98.41)	0(0)	0(0)
	Abnormal NCS†	0(0)	1(1.59)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)

Abnormal NCS†: Not Clinically Significant
Abnormal CS‡: Clinically Significant

11.5.2 Blood Chemistry Test

The blood biochemistry test was conducted to check ALP, AST, ALT, LDH, Total Bilirubin, γ-GT, Total Cholesterol, Glucose, Total Protein, Albumin, Triglyceride, Serum Creatinine, Na, K, Cl, Ca. The test results are presented in Table 38. The results of Visit 6 were analysed for 63 subjects except for the 2 withdrawn subjects (R01-01, R01-16). In the blood biochemistry test, the results for LDH, γ-GT, Triglyceride were analysed for 33 subjects at Visit 1, since all of 33 subjects in the Seoul National University Hospital were missed to test at Visit 1. Also, Total Cholesterol was analysed for 32 subjects at Visit 1 except for the 33 subjects missed in the Keimyung University Dongsan Medical Center at Visit 1. However, there were 33 subjects for each LDH, γ-GT, Triglyceride and 30 subjects for Total Cholesterol in the results of difference between Visit 1 and Visit 6, since all of 63 subjects except for the 2 subjects withdrawn were tested at Visit 6. There were significant differences between Visit 1 and Visit 6 in Total Bilirubin($p=0.008$), Albumin($p=0.001$), Serum Creatinine($p<0.0001$), Cl($p<0.0001$) and Ca($p=0.025$), all changes were in the clinically normal range. The changes of clinical abnormality in the blood biochemistry test did not include the data that was not conducted at Visit 1. There was no subject who was normal or NSC at Visit 1 and CS at Visit 6. As the results of the abnormal values at Visit 6, 1 subject (1.59%) was normal at Visit 1 and NCS at Visit 6 in each ALP, AST and ALT. 33 subjects were analysed for LDH and γ -GT, and there were 2 subjects (6.06%) with normal at Visit 1 to NCS at Visit 6 and 3 subjects (9.09%) with NCS at Visit 1 to normal at Visit 6. There was 1 subject (1.59%) with normal at Visit 1 to NCS at Visit 6 in Total bilirubin. Also, there were 2 subjects (6.06%) with normal at Visit 1 to NCS at Visit 6 in Total cholesterol and 12 subjects (19.05%) with normal at Visit 1 to NCS at Visit 6 in Glucose. There were 3 subjects (4.76%) with normal at Visit 1 to NCS at Visit 6 in Total Protein, and all the subjects were normal at both Visit 1 and 6 in Albumin. 33 subjects

were analysed for Triglyceride, and there was 1 subject (3.03%) with normal at Visit 1 to NCS at Viit 6. In Serum Creatinine, 17 subjects (26.98%) were normal at Visit 1 and NCS at Visit 6. In addition, there was no subject who was normal at Visit 1 and NCS at Visit 6 in Na, K and Cl. Also, there were 10 subjects (15.87%) with normal at Visit 1 to NCS at Visit 6 (Table 39).

Table 38. Basic Statistics on the Blood Chemistry Test (Safety)

		N	Mean± SD	Median	Min, Max	P-value[1)]
ALP	Visit1	65	124.03±82.75	121.00	37.00~373.00	
	Visit6	63	135.97±99.72	136.00	34.00~567.00	
	Change[2)]	63	9.38±42.77	2.00	-38.00~304.00	0.087*
AST	Visit1	65	20.09±6.73	19.00	12.00~53.00	
	Visit6	63	21.11±7.97	19.00	13.00~61.00	
	Change	63	0.79±6.16	0.00	-13.00~37.00	0.310*
ALT	Visit1	65	16.95±10.95	14.00	6.00~81.00	
	Visit6	63	17.13±10.95	14.00	7.00~63.00	
	Change	63	0.10±6.57	-1.00	-22.00~29.00	0.909*
LDH	Visit1	33	381.04±55.44	375.20	253.20~489.30	
	Visit6	63	285.76±120.59	301.20	69.00~569.20	
	Change	33	8.54±47.44	10.70	-95.90~121.80	0.309*
Total bilirubin	Visit1	65	0.71±0.28	0.64	0.38~1.90	
	Visit6	63	0.62±0.26	0.60	0.28~1.74	
	Change	63	-0.08±0.24	-0.06	-1.05~0.40	0.008*
γ-GT	Visit1	33	17.58±12.13	14.00	6.00~68.00	
	Visit6	63	20.41±19.28	14.00	6.00~114.00	
	Change	33	1.39±7.54	0.00	-6.00~33.00	0.296*
Total cholesterol	Visit1	32	198.91±30.78	195.00	134.00~279.00	
	Visit6	63	200.46±34.68	198.00	132.00~294.00	
	Change	30	3.80±22.84	3.50	-58.00~43.00	0.370*
Glucose	Visit1	65	103.11±16.53	99.00	79.00~154.00	
	Visit6	63	103.06±22.97	99.00	69.00~177.00	
	Change	63	-0.46±27.53	-1.00	-53.00~83.00	0.895*
Total protein	Visit1	65	7.29±0.33	7.30	6.60~8.20	

		N	Mean± SD	Median	Min, Max	P-value[1)]
	Visit6	63	8.45±9.42	7.30	6.40~82.00	
	Change	63	1.17±9.37	0.00	-0.80~74.30	0.325*
Albumin	Visit1	65	4.37±0.24	4.40	3.80~4.80	
	Visit6	63	4.28±0.27	4.20	3.70~4.80	
	Change	63	-0.09±0.20	-0.10	-0.60~0.30	0.001*
Triglyceride	Visit1	33	109.21±54.03	99.80	39.00~264.30	
	Visit6	63	110.97±63.00	100.00	30.00~383.00	
	Change	33	0.49±50.19	-3.70	-82.90~126.40	0.956*
Serum Creatinine	Visit1	65	0.69±0.11	0.69	0.50~0.94	
	Visit6	63	0.64±0.10	0.63	0.44~0.94	
	Change	63	-0.06±0.09	-0.04	-0.37~0.11	p<0.0001*
NA	Visit1	65	139.91±2.41	140.00	133.00~146.00	
	Visit6	63	139.44±2.08	140.00	135.00~144.00	
	Change	63	-0.54±2.86	-1.00	-6.00~7.00	0.139*
K	Visit1	65	4.05±0.30	4.00	3.50~5.30	
	Visit6	63	4.04±0.29	4.00	3.50~4.80	
	Change	63	-0.01±0.36	0.00	-1.00~1.20	0.890*
Cl	Visit1	65	104.74±2.58	104.00	99.00~111.00	
	Visit6	63	103.03±1.99	103.00	98.00~108.00	
	Change	63	-1.75±3.04	-1.00	-10.00~4.00	p<0.0001*
Ca	Visit1	65	9.15±0.39	9.10	8.20~10.00	
	Visit6	63	9.02±0.42	9.10	8.00~10.00	
	Change	63	-0.13±0.45	-0.20	-1.00~0.90	0.025*

1) paired t-test
2) Change:Visit1-Visit6
※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6
※ Not tested for 33 subjects in LDH-Seoul National University Hospital
※ Not tested for 33 subjects in γ -GT-Seoul National University Hospital
※ Not tested for 33 subjects in Triglyceride-Seoul National University Hospital
※ Not tested for 33 subjects in Total cholesterol-Keimyung University Dongsan Medical Center

Table 39. Blood Chemistry Test (Safety)

	Visit6	Clinical Significance

	Visit1	Normal	Abnormal NCS†	Abnormal CS‡
ALP (n=63)	Normal	60(95.24)	1(1.59)	0(0)
	Abnormal NCS†	0(0)	2(3.17)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
AST (n=63)	Normal	60(95.24)	1(1.59)	0(0)
	Abnormal NCS†	1(1.59)	1(1.59)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
ALT (n=63)	Normal	59(93.65)	1(1.59)	0(0)
	Abnormal NCS†	0(0)	3(4.76)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
LDH (n=33)	Normal	27(81.82)	2(6.06)	0(0)
	Abnormal NCS†	3(9.09)	1(3.03)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Total bilirubin (n=63)	Normal	60(95.24)	1(1.59)	0(0)
	Abnormal NCS†	1(1.59)	1(1.59)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
γ-GT (n=33)	Normal	27(81.82)	2(6.06)	0(0)
	Abnormal NCS†	3(9.09)	1(3.03)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Total cholesterol (n=33)	Normal	27(81.82)	2(6.06)	0(0)
	Abnormal NCS†	3(9.09)	1(3.03)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Glucose (n=63)	Normal	35(55.56)	12(19.05)	0(0)
	Abnormal NCS†	9(14.29)	7(11.11)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Total protein (n=63)	Normal	58(92.06)	3(4.76)	0(0)
	Abnormal NCS†	1(1.59)	1(1.59)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Albumin (n=63)	Normal	63(100.0)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)

	Visit6 / Visit1	Clinical Significance		
		Normal	Abnormal NCS†	Abnormal CS‡
Triglyceride (n=33)	Normal	30(90.91)	1(3.03)	0(0)
	Abnormal NCS†	0(0)	2(6.06)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Serum Creatinine (n=63)	Normal	14(22.22)	17(26.98)	0(0)
	Abnormal NCS†	2(3.17)	30(47.62)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Na (n=63)	Normal	62(98.41)	0(0)	0(0)
	Abnormal NCS†	1(1.59)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
K (n=63)	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Cl (n=63)	Normal	60(95.24)	0(0)	0(0)
	Abnormal NCS†	3(4.76)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Ca (n=63)	Normal	49(77.78)	10(15.87)	0(0)
	Abnormal NCS†	1(1.59)	3(4.76)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)

Abnormal NCS†: Not Clinically Significant

Abnormal CS‡: Clinically Significant

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6
※ Not tested for 33 subjects in LDH-Seoul National University Hospital
※ Not tested for 33 subjects in γ -GT-Seoul National University Hospital
※ Not tested for 33 subjects in Triglyceride-Seoul National University Hospital
※ Not tested for 33 subjects in Total cholesterol-Keimyung University Dongsan Medical Center

11.5.3 Blood Coagulation Test

The blood coagulation test was conducted to check aPTT and PT, and the test results are presented in Table 40. The analysis was conducted for 63 subjects except for 2 subjects withdrawn at Visit 6. As the results of the blood coagulation test, there was no subject with CS at Visit 6 (Table 41).

Table 40. Basic Statistics for the Blood Coagulation Test (Safety)

Blood Coagulation Test		N	Mean± SD	Median	Min, Max	p-value[1)]
aPTT	Visit1	65	28.40±4.30	28.70	18.50~37.40	
	Visit6	63	28.04±4.72	28.00	20.10~37.20	
	Change[2)]	63	-0.28±1.97	-0.10	-5.30~4.70	0.260*
PT	Visit1	65	10.86±0.58	11.00	9.80~12.50	
	Visit6	63	10.44±0.67	10.30	9.40~12.50	
	Change	63	-0.41±0.61	-0.40	-1.80~0.90	p<0.0001*

1) paired t-test
2) Change:Visit1-Visit6

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6

Table 41. Blood Coagulation Test (Safety)

	Visit6 / Visit1	Clinical Significance		
		Normal	Abnormal NCS†	Abnormal CS‡
aPTT (n=63)	Normal	57(90.48)	1(1.59)	0(0)
	Abnormal NCS†	2(3.17)	3(4.76)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
PT (n=63)	Normal	49(77.78)	11(17.46)	0(0)
	Abnormal NCS†	0(0)	3(4.76)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)

Abnormal NCS†: Not Clinically Significant
Abnormal CS‡: Clinically Significant

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6

11.5.4 Urine Test

Urine tests were conducted to check Protein, Glucose, RBC(blood). The urine test results showed that there were no subjects who had been normal or NCS at Visit 1 and became CS at Visit 6. As the results of the abnormal values at Visit 6, none of subjects was normal at Visit 1 and NCS at Visit 6 in Protein. Also, all subjects were normal at both Visit 1 and 6 in Glucose, and there was no subject with normal at Visit 1 to NCS at Visit 6 (Table 42).

Table 42. Urine Test (Safety)

	Visit6 / Visit1	Clinical Significance		
		Normal	Abnormal NCS†	Abnormal CS‡
Protein (n=63)	Normal	60(95.24)	0(0)	0(0)
	Abnormal NCS†	0(0)	3(4.76)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Glucose (n=63)	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
RBC(Blood) (n=63)	Normal	52(82.53)	0(0)	0(0)
	Abnormal NCS†	0(0)	11(17.46)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)

Abnormal NCS†: Not Clinically Significant

Abnormal CS‡: Clinically Significant

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6

11.6 Vital Signs, Physical Examination and Other Safety Assessment Data

Body temperature, systolic and diastolic blood pressure and pulse rate were measured before the application of the investigational devices (Visit 2) and after Weeks 24 (Visit 6) from the final application of the investigational devices. The results were analysed in terms of the mean and the difference (Visit 2 - Visit 6) in mean values, and these are presented in Table 43. None of the parameters of systolic and diastolic blood pressure and pulse rate showed statistical significant differences between Visit 2 and Visit 6 except for body temperature ($p<0.0001$), however, all these values were stayed within the normal range.

Table 43. Vital Signs

Vital Signs		N	Mean±SD	Median	Min, Max	P-value[1)]
SBP [mmHg]	Visit2	65	121.54±13.79	121.00	94.00~154.00	
	Visit3	65	117.62±12.11	117.00	97.00~154.00	
	Visit4	65	119.20±10.44	120.00	93.00~148.00	
	Visit5	64	120.45±11.80	119.00	95.00~146.00	
	Visit6	63	121.89±11.27	122.00	101.00~147.00	

Vital Signs		N	Mean±SD	Median	Min, Max	P-value[1)]
	DIFF(Visit2-Visit6)	63	0.27±11.43	0.00	-24.00~30.00	0.852*
DBP [mmHg]	Visit2	65	74.20±9.65	74.00	51.00~95.00	
	Visit3	65	72.51±9.87	72.00	49.00~98.00	
	Visit4	65	72.80±8.38	72.00	48.00~92.00	
	Visit5	64	74.28±9.41	75.50	48.00~96.00	
	Visit6	63	74.54±8.72	75.00	47.00~93.00	
	DIFF(Visit2-Visit6)	63	-0.19±9.93	-2.00	-35.00~25.00	0.879*
Pulse rate [bpm]	Visit2	65	78.85±10.48	79.00	56.00~110.00	
	Visit3	65	77.88±10.08	77.00	57.00~104.00	
	Visit4	65	79.12±13.83	78.00	60.00~134.00	
	Visit5	64	79.22±12.26	76.50	56.00~117.00	
	Visit6	63	80.03±10.80	78.00	63.00~119.00	
	DIFF(Visit2-Visit6)	63	-0.97±10.65	-1.00	-31.00~24.00	0.473*
Body temperature (℃)	Visit2	65	36.64±0.42	36.70	36.00~37.60	
	Visit3	65	36.57±0.34	36.50	36.00~37.30	
	Visit4	65	36.54±0.40	36.50	36.00~37.50	
	Visit5	64	36.50±0.45	36.40	36.00~37.50	
	Visit6	63	36.41±0.32	36.30	36.00~37.20	
	DIFF(Visit2-Visit6)	63	0.25±0.46	0.30	-0.70~1.20	p<0.0001*

1) paired t-test

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6

Physical examinations were conducted for normal or abnormal on General Appearance, Head, Chest, Abdomen, Urogenital Organ, Shoulder and Back, Extremities, Lymph nodes, Mental Status, Allergy and Others. The results showed that all subjects had normal values at both Visit 1 and 6 (Table 44).

Table 44. Physical Examination

Organs, n(%)	Visit1 \ Visit6	Normal	Abnormal NCS†	Abnormal CS‡
General Appearance	Normal	63(100)	0(0)	0(0)

Organs, n(%)	Visit1 \ Visit6	Normal	Abnormal NCS†	Abnormal CS‡
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Head	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Chest	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Abdomen	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Urogenital Organ	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Shoulder and Back	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Extremities	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Lymph Nodes	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Mental Status	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)
Allergy	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)

Organs, n(%)	Visit1 \ Visit6	Normal	Abnormal NCS†	Abnormal CS‡
	Abnormal CS‡	0(0)	0(0)	0(0)
Other	Normal	63(100)	0(0)	0(0)
	Abnormal NCS†	0(0)	0(0)	0(0)
	Abnormal CS‡	0(0)	0(0)	0(0)

Abnormal CS‡: Clinically Significant

Abnormal NCS†: Not Clinically Significant

※ A total of 63 subjects due to the 2 withdrawn subjects(R01-01, R01-16) at Visit 6

11.7 Concomitant Medications and Therapy

All 65 subjects (100%) received concomitant medications during the clinical trial period, and in total there were 193 cases of concomitant medication usage. The number of concomitant medication use per subject was therefore 2.97. All concomitant medications were classified into Level 1 and 2 according to the ATC code in the WHO Drug Dictionary. All 65 subjects (100%) used concomitant medications for the Nervous system, which included the following 112 cases: there were 100 cases of Anesthetics used on all 65 subjects (100%), and there were 3 cases of Analgesics used on 3 subjects (4.62%) and 4 cases each of Antiepileptics and Psychoanaleptics used on 2 subjects (3.08%). Also, there were 18 cases of Alimentary tract and metabolism used on 13 subjects (20.00%), 11 cases of Sensory organs used on 8 subjects (12.31%), 9 cases of Musculo-skeletal system used on 7 subjects (10.77%) and 6 cases of Systemic hormonal preparations, excl. sex hormones and insulins used on 6 subjects (9.23%). The details regarding concomitant medication used after the application of the investigational devices are presented in Table 45. Among them, the number of cases who had taken the disallowed concomitant medications was 4 cases in 4 subjects (6.15%). The results of the classification for the disallowed concomitant medications are presented in Table 46, and the list of the subjects who had taken disallowed concomitant medications is provided in Table 47.

Table 45. Concomitant Medications after the Application of the Investigational Device (Safety)

Current Concomitant Medications	Institution		Total N=65
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	
Subjects with Current Concomitant Medications	32(100)	33(100)	65(100)

Current Concomitant Medications	Institution		Total N=65
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	
95%CI	-	-	-
Total Cases	76	117	193
Cases per Subject	2.38	3.55	2.97
Level 1*			
Level 2*			
Nervous system	32(100.0),[39]	33(100.0),[73]	65(100.0),[112]
· Anesthetics	32(100.0),[33]	33(100.0),[67]	65(100.0),[100]
· Analgesics	1(3.13),[1]	2(6.06),[2]	3(4.62),[3]
· Antiepileptics	1(3.13),[2]	1(3.03),[2]	2(3.08),[4]
· Psychoanaleptics	1(3.13),[3]	1(3.03),[1]	2(3.08),[4]
· Psycholeptics	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Alimentary tract and metabolism	6(18.75),[7]	7(21.21),[11]	13(20.00),[18]
· Drugs for acid related disorders	4(12.50),[5]	4(12.12),[6]	8(12.31),[11]
· Mineral supplements	1(3.13),[1]	1(3.03),[1]	2(3.08),[2]
· Vitamins	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Digestives, incl. enzymes	1(3.13),[1]	0(0.0),[0]	1(1.54),[1]
· Drugs for constipation	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
· Drugs for functional gastrointestinal disorders	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Sensory organs	4(12.50),[6]	4(12.12),[5]	8(12.31),[11]
· Ophthalmologicals	4(12.50),[6]	3(9.09),[4]	7(10.77),[10]
· Otologicals	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Musculo-skeletal system	3(9.38),[4]	4(12.12),[5]	7(10.77),[9]
· Antiinflammatory and antirheumatic products	3(9.38),[4]	3(9.09),[3]	6(9.23),[7]
· Muscle relaxants	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
Systemic hormonal preparations, excl. sex hormones and insulins	1(3.13),[1]	5(15.15),[5]	6(9.23),[6]
· Corticosteroids for systemic use	0(0.0),[0]	3(9.09),[3]	3(4.62),[3]

Current Concomitant Medications	Institution		Total N=65
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	
· Thyroid therapy	1(3.13),[1]	2(6.06),[2]	3(4.62),[3]
Cardiovascular system	1(3.13),[1]	4(12.12),[7]	5(7.69),[8]
· Agents acting on the renin-angiotensin system	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Lipid modifying agents	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Vasoprotectives	0(0.0),[0]	1(3.03),[2]	1(1.54),[2]
· Cardiac therapy	1(3.13),[1]	0(0.0),[0]	1(1.54),[1]
· Diuretics	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
Respiratory system	2(6.25),[8]	2(6.06),[4]	4(6.15),[12]
· Drugs for obstructive airway diseases	2(6.25),[2]	2(6.06),[2]	4(6.15),[4]
· Antihistamines for systemic use	2(6.25),[3]	1(3.03),[1]	3(4.62),[4]
· Nasal preparations	1(3.13),[1]	1(3.03),[1]	2(3.08),[2]
· Cough and cold preparations	1(3.13),[2]	0(0.0),[0]	1(1.54),[2]
Antiinfectives for systemic use	3(9.38),[6]	1(3.03),[1]	4(6.15),[7]
· Antibacterials for systemic use	3(9.38),[4]	1(3.03),[1]	4(6.15),[5]
· Immune sera and immunoglobulins	1(3.13),[1]	0(0.0),[0]	1(1.54),[1]
· Vaccines	1(3.13),[1]	0(0.0),[0]	1(1.54),[1]
Blood and blood forming organs	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Antithrombotic agents	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
Genito urinary system and sex hormones	1(3.13),[1]	1(3.03),[1]	2(3.08),[2]
· Sex hormones and modulators of the genital system	1(3.13),[1]	1(3.03),[1]	2(3.08),[2]
Unknown	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
· Unknown	0(0.0),[0]	2(6.06),[2]	2(3.08),[2]
Antineoplastic and immunomodulating agents	1(3.13),[3]	0(0.0),[0]	1(1.54),[3]
· Antineoplastic agents	1(3.13),[3]	0(0.0),[0]	1(1.54),[3]
Dermatologicals	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]
· Corticosteroids, dermatological preparations	0(0.0),[0]	1(3.03),[1]	1(1.54),[1]

*ATC code 2013

n(%), [case]

Table 46. Disallowed Concomitant Medications after the Application of the Investigational Device (Safety)

Disallowed Concomitant Medications	Institution		Total
	Seoul National University Hospital n1=32	Keimyung University Dongsan Medical Center n2=33	N=65
Subjects with Disallowed Concomitant Medications	-	4(12.12)	4(6.15)
95%CI	-	0.99-23.26	0.31-12.00
Total Cases	-	4	4
Cases per Subject	-	1.00	1.00
Level 1*			
Level 2*			
Sensory organs	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
· Otologicals	0(0.0), [0]	1(3.03), [1]	1(1.54), [1]
Systemic hormonal preparations, excl. sex hormones and insulins	0(0.0), [0]	3(9.09), [3]	3(4.62), [3]
· Corticosteroids for systemic use	0(0.0), [0]	3(9.09), [3]	3(4.62), [3]

*ATC code 2013
n(%), [case]

Table 47. List of the Subjects with Disallowed Concomitant Medications (Safety)

Institution	Subject No.	Gender	Age	Name of medications	Level 1	Level 2	Dosage per day(Unit)	Freguency	Application route	Date of start	Date of discontinuence	Purpose of application
Keimyung University Dongsan Medical Center	S2-28	Female	43	ciprocin otic susp7ml	Sensory organs	Otologicals	Tablets	BID(Twice daily)	Other(Specify)	2013/11/29	2013/12/05	Medical History

Institution	Subject No.	Gender	Age	Name of medications	Level 1	Level 2	Dosage per day(Unit)	Freguency	Application route	Date of start	Date of discontinuence	Purpose of application
Keimyung University Dongsan Medical Center	S2-24	Female	44	Solondo 5mg	Systemic hormonal preparations, excl. sex hormones and insulins	Corticosteroids for systemic use	Tablets	BID(Twice daily)	PO(Per Oral)	2013/07/24	2013/08/02	Medical History
Keimyung University Dongsan Medical Center	S2-29	Female	49	Triamcinolne inj 40mg	Systemic hormonal preparations, excl. sex hormones and insulins	Corticosteroids for systemic use	Tablets	Stat(Single, immediate dose)	SC(Subcutaneous)	2013/10/31	2013/10/31	Medical History
Keimyung University Dongsan Medical Center	S2-33	Female	43	Dexamethasone	Systemic hormonal preparations, excl. sex hormones and insulins	Corticosteroids for systemic use	Tablets	Stat(Single, immediate dose)	IV(Intravenous)	2013/08/14	2013/08/14	Medical History

There was 1 subject (1.54%) with 2 cases that had taken the concomitant therapy after the application of the investigational devices, which were Burn dressing and Laser therapy.

Table 48. Concomitant Therapy after the Application of the Investigational Device (Safety)

Current Concomitant Therapy	Institution		Total
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	N=65
Subjects with Disallowed Concomitant Medications	-	1(3.03)	1(1.54)
95%CI	-	0.00-8.88	0.00-4.53
Total Cases	-	2	2
Cases per Subject	-	2.00	2.00
System Organ Class*			
Preferred Term*			
Surgical and medical procedures	0(0), [0]	1(3.03), [2]	1(1.54), [2]
· Burn dressing	0(0), [0]	1(3.03), [1]	1(1.54), [1]

Current Concomitant Therapy	Institution		Total
	Seoul National University Hospital n_1=32	Keimyung University Dongsan Medical Center n_2=33	N=65
· Laser therapy	0(0), [0]	1(3.03), [1]	1(1.54), [1]

*MedDRA 16.0
n(%), [case]

11.8 Safety Conclusion

The safety evaluation for this clinical trial was conducted with 65 subjects in the Safety Set. However, the results of Visit 6 were analysed for 63 subjects except for the 2 withdrawn subjects who had no data for the test at Visit 6, and it was analysed for 33 subjects except for the subjects who had missed the test at Visit 1 in some parts of laboratory tests. 18 subjects (27.69%) experienced one or more adverse events during the clinical trial period and the total number of adverse events was 24 cases. The mean incidence per person was 1.33. Among them, none of cases had ADE, SAE and withdrawal for AE. The outcomes of adverse events for each subject evaluated at the last visit were as follows: there were 15 subjects (62.50%) of full recovery, 8 subjects (33.33%) in the progress of recovery, and 1 subject (4.17%) of recovery but left after effects. As for the severity of the adverse events, 23 cases (95.83%) were mild and the remaining 1 case (4.17%) was moderate.
Among the whole adverse events, the most number of cases was 7 with Infections and infestations in 7 subjects (10.77%). Then, there were 4 cases of Musculoskeletal and connective tissue disorders in 4 subjects (6.15%), 3 cases of Gastrointestinal disorders in 3 subjects (4.62%) and other events occurred in 1 or 2 subjects.
Among the adverse events, 1 case was adverse device event related to the investigational device or reference device, which was Injection site induration with mild, but it recovered at the day. None of SAE was reported during this clinical trial.

In laboratory tests such as the hematology test, blood chemistry test, blood coagulation test, and urine test, there were no cases in which a subject who had been in a normal or NCS state prior to the application and became CS in Week 24 (Visit 6) after the final application of investigational device.
As for the vital signs, the mean values of all temperature, systolic/diastolic blood pressure and pulse rate measurements taken before and after the application of the investigational device stayed within the normal range. The physical examinations found that all values were normal at both Visit 2 and 6.

All 65 subjects (100%) (Safety Set) received concomitant medications during the clinical trial period, and in total there were 193 cases of concomitant medication usage. The number of concomitant medication use per subject was therefore 2.97. These medications were classified by organ systems. All 65 subjects used concomitant medications for the Nervous system, which included the following 112 cases: there were 100 cases of Anesthetics used on all 65 subjects and there were 3 cases of Analgesics used on 3 subjects (4.62%). Among these subjects, 4 subjects had taken the disallowed concomitant medications including Otologicals in 1 subject (1.54%) and Corticosteroids for systemic use in 3 subjects (4.62%). Also, there was 1 subject (1.54%) who had taken the concomitant therapy.

All the analysis results of the safety evaluation above demonstrate that GENOSS Filler is a safe medical device proven to be safe and effective in the in the human body when it applied to nasolabial folds, in comparison to Restylane®.

12. CONSIDERATIONS AND OVERALL CONCLUSION

GENOSS Filler, the investigational device used in this clinical trial, is a biomaterial for tissue repair composed of stabilized hyaluronic acid. The objective of the clinical trial was to verify that GENOSS Filler is not inferior to Restylane® in its efficacy and safety in the correction of nasolabial folds.

This clinical trial was conducted at a total of two institutions from July 10th, 2013 (the initial subject visit to Keimyung University Dongsan Medical Center) to January 22th, 2013 (the last subject visit to Seoul National University Hospital). A total of 66 subjects were enrolled in this clinical trial after signing the written informed consent form. All of 66 subjects were judged to be eligible for the study and randomized, however, as 1 subject violated the inclusion/ exclusion criteria, the remaining 65 subjects were received the application of investigational devices and included the FA Set. Among them, they were withdrawn from the study with 2 subjects for follow-up failure and 4 subjects for taking the disallowed concomitant medications, and the remaining total of 59 subjects were included in the PP Set. 65 subjects, who were randomized and applied with the investigational devices at least once, were included in the Safety Set.

For the primary efficacy endpoint, the GENOSS Filler group were compared with the Restylane® group in terms of the mean WSRS scores assessed at Week 24 after the final application of the investigational devices. The lower limit of the one-sided 97.5% confidence interval of the mean of differences was -0.24, and this result proved the non-inferiority of GENOSS Filler compared to

Restylane®, since the value was greater than the non-inferiority limit of -0.29 originally targeted in this clinical trial.

In regards to the secondary efficacy results, the mean of the WSRS scores assessed by the independent evaluator at Weeks 8 and 16 from the final application of the GENOSS Filler was higher than that of Restylane®; however, there was no significant difference. Also, the mean of the WSRS scores assessed by the investigator at Weeks 8, 16 and 24 from the final application of the investigational devices had no statistically significant differences between the groups. In addition, compared to the mean of the WSRS scores at screening, which were 3.58±0.50 in the GENOSS Filler group and 3.54±0.50 in the reference group, constituted a “3” rating indicating a “moderate” condition, the WSRS scores were found to have improved to the latter of “1” rating indicating an “absent” or the early “2” rating indicating an “mild” conditions for the GENOSS Filler group in regards to the degree of nasolabial folds.
The mean of the GAIS scores from both the GENOSS Filler group and the Restylane® group assessed by the investigator and subject at Weeks 8, 16, and 24 after the final application of investigational devices was compared to the condition prior to the initial application. As the results, the means of the GAIS score in the GENOSS Filler group were higher than that of the Restylane® group although there were no statistically significant differences between the groups.
The proportion of subjects whose WSRS scores decreased at least 1 level when assessed by the independent evaluator in Week 24 from the final application of the investigational device was 90.77 % in the GENOSS Filler group and was 93.85 % in the Restylane® group. These results, however, did not constitute a statistically significant difference between the two groups, and there were no differences between the groups as they were both 100%.

In the safety evaluation, 18 subjects (27.69%) experienced one or more adverse events during the clinical trial period and the total number of adverse events was 24 cases. The mean incidence per person was 1.33. Among the adverse events, 1 case was adverse device event related to the investigational device or reference device, which was Injection site induration with mild, but it recovered at the day. In addition, there was no subject who was normal or NSC before the application of the investigational devices and became CS at Week 24 from the final application in the vital signs, physical examinations and laboratory tests.

In conclusion, the clinical trial verified that GENOSS Filler is an effective and safe medical device for the correction of nasolabial folds.

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