Clinical Study Report

Clinical study for safety and effectiveness about improvement of both nasolabial wrinkles using SkinPlus-Hyal as tissue augmentation materials

Investigator	Prof.Jang Hak, Dept.of Plastic Surgery ,SNUH
	Prof.Hu Chan Young,Dept of Plastic Surgery,SNUH(Bundang)
Test Client	Bioplus Co Ltd.
Name	Skin-Plus-Hyal
CSR Version	1.0
Protocol No.	Skin-Plus-Hyal
Stage of the clinical test	Clinical Test for approval
Start	2013.06.18
End	2014.03.14
Submission Date	2014.07.21

Confidential

<u>Cover</u>

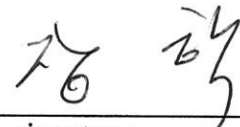|	
Title	Clinical test of safety and effectiveness evaluation of Skinplus-Hyal
Medical device	Skin-Plus-Hyal
Target disease	Subjects who want improvement of both nasolabial wrinkles.
Test client	Hyun-Kyu Jung, CEO of Bioplus Co Ltd (Tel:02-521-1898)
Number of test plan & date of approval	SkinPlus-Hyal version 1.1(date of approval: 2012.02.15) SkinPlus-Hyal version 1.4(date of approval: 2013.06.12) SkinPlus-Hyal version 2.0(date of approval: 2013.12.24) SkinPlus-Hyal version 3.0(MFDS under application change))
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Start(date)	2013.06.18
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Submission Date	2014.07.21

signature page

Medical writer:

MEDICAL WRITER(S):   오준환

NAME OF COMPANY: HamiltonCS

_____   2014/7/21
signature   date

Co-ordinating Investigator signature

C-ordinating
INVESTIGATOR: 장   학

_____   2014/7/21
signature   date

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_____   2014/7/21
Signature   date

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. **Synopsis**

Test Client : Bioplus Co.Ltd.	**Report Volume**
Name : SkinPlus-Hyal	: Total 65 pages
Material: Hyaluronic acid	

Title:Clinical test for safety and effectiveness about improvement of both nasolabial Wrinkles using Skinplus- Hyal : Single blind study,randomization, matched pairs design,clinical comparison	
Manager:	Prof.Jang Hak, Dept.of Plastic Surgery, SNUH Prof.Hu Chan Young,Dept of Plastic Surgery,SNUH(Bundang)

Period of test2013.06.18 ~ 2014.03.14	**Stage :**Clinical test for approval

Purpose:Skinplus Hyal is, HA is injected into subcutaneous tissue and use for temporarily improvement of wrinkles, for replacement & repairof skin tissue when occurs wrinkles due to accident and other problems.
And verify that this product has not inferiority compared with other HA products for improvement of nasolabial wrinkles in the market.
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Method of test
Randomization,blind trial of subjects & assessor, matched pairs design,clinical comparison

Number of subjects
○Planned subjects
- Randomization: 129
- Effective analysis: 120
○Number of included in analysis
- Subjects of randomization:129
- Subjects of safety analysis: 123
- Subjects of FAS analysis:120
- Subjects of PP analysis: 113

Target disease: Subjects who want improvement of both nasolabial wrinkles

Standard of selection & exemption

Selection
1. Volunteers who signed the agreement of subjects.
2. Men & women over 20 years old.
3. Both nasolabial wrinkles are visual symmetry , as level is between 3 & 4 points classified by 5 stages(WSRS)
4. Women who agree contraception during period of clinical trials.

Exemption

1. Subjects who can not follow the requirement of clinical trials plan.
2. Under 20 years old.
3. Person who has anaphylaxis about hyaluronic acid sodium
4. Person who has anaphylaxis about allergy.
5. Has eczema,psoriasis,rosacea,scleroderma, infection , severe acne.
6. Person who has disease on site of both nasolabial wrinkles
7. Diabetes,thrombokinesis,desmoplastic disorder,lipodystrophy,disease affect whole body
8. Person who has herpes labialis.
9. Infected HIV or under treatment of immunosuppressive.
10. Not passed 18 months, after injection of tissue augmentation material
11. Person who implant permanent tissue on site of both lasolabial wrinkles..
12. Not passed 3 months, after particiapation of clinical trials for medical device..
13. During this clinical trials, plan to participate another trials(botox.   etc.)
14. During clinical trials, plan to undergo a plastic surgery.
15. Drug addicts and alcoholics..
16. During clinical trials, subjects who not want to agree the contraception.
17. Person who has a history of metal illness.
18. Person who directly related to this clinical trials.
19. Person who want to treat trauma as purpose.
20. Person who is suitable for 1,2,5 as wrinkle is specified under 5 stages(WSRS)
21. Person who use Retin-A(prevention of wrinkles) within 1 month from trials..
22. Have experienced botox procedure within 6 months from trials..
23. Have experienced laser peeling within 12 months from trials.
24. Have experienced anaphylaxis and complex allergy.
25. Person who has hypertrophic scar and keloid history.
26. Hepatitis carrier
27. Person who has permanent implants on site of nasolabial wrinkles
28. Person who takes antithrombotic within 2 weeks from the screening.
29. Person who is restricted participation for scientific and ethical reason.

Use &dose of medical device for clinical trials

Dose

e of once is limited as 1.5ml.

Use 1.5ml /1 procedure for test & control group.But changeable and record the dose..

Test Client : Bioplus Co.Ltd.	Report Volume
Name : SkinPlus-Hyal	: Total 65 pages
Material: Hyaluronic acid	

Method of use

1) Open box and check the product in 1.00cc syringe..

2) Check 2 pcs of the product by sterile package and 1/2(27) gauge needle.

3) .Select suitable needle for site of injection(not be contaminated) and link the needle.

4) Definitely injected into the dermis.

5) Needle heads to skin and inject to middle and bottom of the dermis.

6) After using the product by selection of user, dispose of the rest.

Observation:Application is 1 time as randomization & observation is 24 weeks.

Method of statistical analysis:

Analysis of effectiveness is done by FAS & PPS and main is result of FAS analysis.Demographic material is FAS and material for safety is Safety Set.

Evaluation of effectiveness

1. Primary end point

: After 24 weeks from final application,test group of wrinkles that specified 5 stages(WSRS) evaluated by indepent valuer is at least over -1 of rate of subject is non inferiority compared with control group.

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2. Secondary end point

① After 2, 6, 12 weeks from final application,the values of wrinkles by 5 stages (Wrinkle Severity Rating Scale) evaluated by indepent valuerof level of change is evaluated between test & control group.

② After 2,6,12,24 weeks from final application,the values of wrinkles by 5 stages by tester of level of change from baseline is evaluated between test & control group.

③ After 2,6,12,24 weeks from final application, level of change of Global Aesthetic Improvement by tester is evaluated between test & control group.

④ After 2,6,12,24 weeks from final application,level of GAI by subject is evaluated between test & control group.

⑤ After 24 weeks from final application,level of change specified 5 stages(WSRS) evaluated by tester is at least over -1 of rate of subject is evaluated between test & control group.

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Evaluation of safety

Analyze the trends of items between before test of experiment results & after test (24 weeks)

Check & record about abnormal local reaction on site of application for 30 minutes, after application.

After application, record abnormalreaction of face of incidence & loss for 2 weeks.Evaluate

non inferiority compared with control group.Analysis of safety is conducted by two-tail test(level of

significance 5 %)

Summary & conclusion   (1)Primary end point

Result of effectiveness :After 24 weeks from final application,rate of improvement of wrinkles between test & control group. In FAS improvement ratio of WSRS(test) is 34. 179 %,control is 36.67 & gap(2.5%)97.5% of difference rate of improvement of wrinkles &lower limit of confidence of interval is -9.60%.So,bigger than -20%(allowable limit of non inferiority)Test group is non inferiority VS control group.

Also,In PP rate of improvement(test) is 35.40%(40/113person)control is 38.05%(43/113)Difference is abt 2.65%.97.5% of difference of rate of improvement of wrinkles & lower limit of confidence of interval is -9.91%.So, bigger than -20% (allowable limit of non inferiority) Even in PP,Test group is non inferiority VS control group.

(2) Secondary end point

- **After 2,6,12,weeks from final application,the values of wrinkles by 5 stages by tester of lever of change from baseline.**
  In FAS,after 2weeks from final application,average variation is -0.53+_0.69 in test group.-0.54+_0.82 in control. No gap statistically(p=0.9034)
  After 6 weeks from final application,variation is -0.58+_0.69 in test group,-0.54+_ 0.80 in control.No gap statistically(p=0.6296)
  After 12 weeks from final application,variation is -0.29+_0.84 in test group, average -0.33+_0.89 in control.No gap statistically (p=0.5606)
  Between 2 groups , there is no difference statistically.

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- **After 2,6,12,24 weeks from final application,the values of wrinkles by 5 stages by tester of lever of change from baseline.**
  In FAS,after 2 weeks from final application,average variation is -1.22+_0.87 -1.21+_0.90 in control. No gap statistically(p=0.8283)
  After 6 weeks from final application,average variation is -1.16+_0.81 in test group ,-1.16+_0.79 in control. No gap statistically(p=1.000
  After 12 weeks from final application,average variation is -1.09+_0.79 in test group, -1.07+_0.73 in control.No gap statistically(p=0.4409)
  After 24 weeks from final application,average variation is -1.04+_073 in test group, -1.04+_0.73 in control. No gap statistically(p=0.4675)
  Between 2 groups(PP & FAS group), there is no difference statistically.

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- **After 2,6,12,24 weeks from final application,level of change of GAI by tester.**
  In FAS,after 2 weeks, Global Aesthetic Improvement(GAI) by tester(upgrade, much, very much) is 99.16% in test group &98.32 in control.After 6 weeks,97.39 % ,99.13 % each. After 12 weeks,95.41 %, 92.66%each.After 24 weeks,91.30 %,92.17 %eachBetween 2 groups no gap statistically.Also,the result of PP is similar with FAS. GAI by tester between 2 groups is no difference statistically.

- **After 2,6,12,24 weeks from final application,level of GAI by subject**
  In FAS,after 2 weeks,GAI by subject(upgrade,much,very much) is 94.12%in test group &92.44%in control.After 6 weeks,93.91%,93.91%each.After12weeks 88.07% 85.32%each,After 24 weeks,83.48%,82.61%each.Between 2 groups no gap statistically.Also,the result of PP is similar with FAS. GAI by subject between 2 groups is no difference statistically.

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- **After 24 weeks from final application,values of level of change by 5 stages by tester is at least -1 over of rate of subject**
  In FAS,rate of improvement (WSRS) is 77.50% in test group &77.50% in control. No gap statistically(p-value=1.0000) In PP,79.65% in test group &79.65% in control.No gap statistically(p-value=0.8101)

<u>Result of safety</u>

Presenting rate of case of abnormal reaction is 66.67% during period of trials& related material of clinical trials of presenting rate of case(Over possible) is 62.60% And important abnormal reaction is 1.63%.Among 252 of abnormal reaction, mild symptom is 227, middle is 23 & severe is 2.

In Causality,Definite is 197, unrelated is 39,possible is 6,probable is 6,unknown is 4.In treatment of abnormal reaction,No is 246,stop is 3.In result of reaction, recovery is 238,under recovery is 14.

In abnormal reaction of 252,abnormal of injection site is 182 among 75 persons,abnormal of skin is 23 among 16,abnormal of respilatory is 11 among 9.In details,bruising of site of injection is 69 among 52,edema of site of application is 38 among 31,tenderness is 39 among 27.

During clinical trials,important abnormal reaction is 2(bursting of sinew,breast cancer) This reaction is due to extension of admission & Unrelatedto medical device of clinical trials.Confirmed abnormal reaction of procedure of the day is 3 in 1 person. Types are vertigo,flare of visual field,nausea (each 1 case) Casual relationship with medical device is definite.

Test Client : Bioplus Co.Ltd.	Report Volume
Name : SkinPlus-Hyal	: Total 65 pages
Material: Hyaluronic acid	

Conclusion

After 24 weeks from final application,the result for improvement of wrinkles,difference about rate of improvement between test & control group is abt.25 %.97.5% of difference rate of improvement of wrinkles &lower limit of confidence of interval is-9.60 % So,bigger than -20%(allowable limit of non inferiority)Confirm that test group is non inferiority VS control group.Also, clinically there is no abnormal reaction and clinically there is no problem in evaluation of safety.Therefore,results of clinical trials,come to the conclusion that SkinPlus-Hyal has a safety and has a effectiveness about improvement of nasolabial wrinkles.

Reporting date: Jun 25, 2014

2. Table of contents

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3. Abbreviation & Term

ALT : ALanine Transaminase

ALP : Alkaline Phosphatase

AST : ASpartate Transaminase

BUN : Blood Urea Nitrogen

CRF : Case Report Form

FAS : Full Analysis Set

IRB : Institute Review Board

LCL : Lateral Canthal Line

LOCF : Last Observation Carried Forward

PP : Per Protocol

PT : Prothrombin Time

PTT : Activated Partial Thromboplastin Time

RBC : Red Blood Cell

WBC : White Blood Cell

WHOART : World Health Organization Adverse Reactions Terminology

WHO ATC : World Health Organization Anatomical Therapeutic Chemical Classification System

γ-GT : Gamma Glutamyl Transferase

Appendx

4. Ethical consideration

This trials was done according to standard of management of clinical trials & proceeded according to Declaration of Helsinki of right & safety of subject

The plan of clinical trials,agreement of subject and relative matters were approved KFDA & IRB of administration of clinical trials. And changed matters were approved KFDA & IRB before doing.

Before, consent of subject for trials about safety ,contents of trials & others was received And signed.Before consent, it was not proceeded.

The name of subject was kept secret and relative material was in computer. Also, done confidentially. The agreement was kept by pointed person.

After approval of plan of clinical trials, begin to do clinical trials on Apr 30, 2013
(First approval date: Sept 5, 2011)

5. Tester & supporting organization

5.1 Name and title of investigator & person in charge

Investigator

SNUH	Dept of plastic surgery	Prof. Jang Hak
SNUH(Bundang)		Prof.Huh Chan Young

Person in charge

SNUH(Bundang)	Plastic surgery	Full time Dr	Lim Hyung Woo
SNUH(Bundang)	Plastic surgery	Full time Dr	Park Chang Sik
SNUH(Bundang)	Plastic surgery	Associate Prof.	Jung Jae Hoon
SNUH(Bundang)	Plastic surgery	Research nurse	Shin Pil Gyun
SNUH(Bundang)	Plastic surgery	Research nurse	Lee Dam On
SNUH	Plastic surgery	Full time Dr	Lee Jung Min
SNUH	Plastic surgery	Research nurse	Lee Ryun Sook
SNUH	Plastic surgery	Research nurse	Jang Young Eun

5.2 Name & title of manager for medical device

Manager

SNUH(Bundang)	Plastic surgery	Yoon Hye Kyung
SNUH(Bundang)	Plastic surgery	Kang Yoon Ki
SNUH	Plastic surgery	Lee Jong Hee

5.3 Client & others

(1) Client

Bioplus Co Ltd(CEO, Jung Hyun Kyu)

Add:Rm403 60 339 Gil Nambusunhwanro Seocho Gu Seoul Korea

(2) Agency

Hamilton CS , Oh Joon Hwan

Add:Rm1713 A Samhomulsan 83 Nohyunro Seocho Gu Seoul Korea

(3) Independent valuer

Korea University(Anam Hospital)	Plastic surgery	Yoon Eul Sik
Korea University(Anam Hospital)	Plastic surgery	Yoo Hee Jin
Korea University(Anam Hospital)	Plasitc surgery	Kim Hyun Seok

(4) Auditor

Taewoong Medical Min Young Ran

6.Introduction

Restylane that uses hyaluronic acid is compared with SkinPlus-Hyal and judged the effectiveness & safety. Restylane was approved by EU in Sept.1996. After that,approved additionally in 27 countries .Restylane proved effective & safe.Therefore, have a plan for clinical trials to confirm performance & get approval of product as verification of inferiority compared with Restylane.

7. Purpose of trials

SkinPlus-Hyal using HA compared with Restylane and verify inferiority about improvement of nasolabial wrinkles.

8. Plan of clinical trials

8.1 Method

Before 2 weeks ,do examination and after 2 weeks from examination,
randomize from baseline and apply the device on both nasolabial wrinkles.Also, takes a picture. If the result is confirmed at the same day of screening, apply the device.According to reseracherer ,uses LIDOCINE.Same tester is involved in the procedure and could know each site of application of the device as randomization.The subject is examined during 30 minutes wherther abnormal reaction occurs or not and record abnormal reaction in report during 2 weeks. After 2 weeks the subject visit to the hospital and return to the report.
After 2,6,12,24 weeks from baseline all subject visit to hospital of clinical trials.Including Baseline, effectiveness & safety are evaluated.The pictures are numbered as randomization by Independent Expert Reviewer.The picture of subject was sent to independent valuer without Information and the picture is evaluated to level of evaluation under clinical trial. Independent evaluation is proceeded in the third party.

Time table

Phase	Screening	Period of trials				
Phase	visit 1 -2week	visit 2 baseline	visit 3 +2week (± 4day)	visit4 +6week (± 7day)	visit5 +12week (± 7day)	visit 6 +24week (± 7day)
Agreement of subject						
Demographical information	●					
Search of medical history	●					
Check (banned combined drug	●	●	●	●	●	●
Standard of selection/exemption	●					
Check(laboratory)	●					●
Check site of injection		●				
Randomization		●				
Application of device		●				
Return to report of subject			●			
Take a picture		●	●	●	●	●
WSRS –Indepentent tester		●	●	●	●	●

		•	•	•	•	•
WSRS - Tester		•	•	•	•	•
GAI - Tester			•	•	•	•
GAI - Subject			•	•	•	•
Abnormal reaction		•	•	•	•	•

8.2   Selection of subject

8.2.1   Standard of selection

1. Person who signed agreement of subject and want to join
2. Men & Women (Over 20 years old).

3.Visual symmetry of both nasolabial wrinkles and score 3-4 of level of wrinkles by 5 stages.

3. Among fertile women,   women who agree contraception..

8.2.2   Standard of exemption

1. Subjects who can not follow the requirement of clinical trials plan.
2. Under 20 years old.
3. Person who has anaphylaxis about hyaluronic acid sodium
4. Person who has anaphylaxis about allergy
5. Has eczema,psoriasis,rosacea,sclerodema,infection,severe acne.
6. Person who has disease on site of both nasolabial wrinkles
7. Diabetes,thrombokinesis,desmoplastic disorder,lipodystrophy,disease affect whole body
8. Person who has herpes labialis
9. Infected HIV or under treatment of immunosuppressive.
10. Not passed 18 months,after injection of tissue augmentation material.
11. Person who implant permanent tissue on site of both lasolabial wrinkles.
12. Not passed 3 months,after participation of clinical trials for medical device
13. During this clinical trials,plan to participate another trials(botox….etc)

14. During clinical trials,plan to undergo a plastic surgery
15. .Drug addicts and alcoholics
16. During clinical trials,subjects who not want to agree the contraception.
17. Person who has a history of mental illness
18. Person who directly related to this clinical trials.
19. Person who want to treat trauma as purpose.

20. Person who is suitable for1,2,5, as wrinkle is specified under 5 stages(WSRS)

21. .Person who use Retin-A(prevention of wrinkles)within 1 month from trials.

22. Have experienced botox procedure within 6 months from trials.

23. Have experienced laser peeling within 12 months from trials

24. Have experienced anaphylaxis and complex allergy.

25. Person who has hypertrophic scar and keloid history.

26. Hepatitis carrier

27 Person who has permanent implants on site of nasolabial wrinkles.

28 Person who takes antithrombotic within 2 weeks from the screening.

29 Person who is restricted participation for scientific and ethical reason.

8.3   Start of clinical trials

8.3.1   Use & dose

Dose

Dose of once is limited as 1.5ml.

Use 1.5ml/1 procedure for test & control group.But changeable and record the dose.

Method of use

1) Open box and check the product in 1.00cc syringe.

2) Check 2 pcs of the product by sterile package and 1/2(27) gauge needle.

3) Select suitable needle for site of injection(not be contaminated) and link the needle.

4) Definitely injected into the dermis.

5) Needle heads to skin and inject to middle and bottom of the dermis.

6) After using the product by selection of user, dispose of the rest.

8.3.2 Combination therapy

No use local anesthetics between surgery

No combined drug

Drug as ban in combination

    1) After application, do not use until 1 week.

     - Vitamin E

     - NSAID

    2) During trials, please do not use following drugs & procedure on facial region..

     - Supplement:Colagen,Hydroxyl,Apatide,Hyaluronic acid,Silicon,Polymethylmethacylate
      PTFE.

     - Therapy of wrinkles by botulinum

     - Decortication

     - Noninvasive skin reproduction(laser)

     - Removal of retinoid

     - Steroid

    3) During trials, please do not use following drugs.

     - Blood coagulants(exemption:Aspirin 100mg,300mg/day)

     - Steriod(whole body),Anabolic steroid

8.3.3 Medical device for clinical trials

(1) Test

    1)   Number of approval: N/A

    2)   Name of product: Tissue augmentation material

    3)   Name of model: SkinPlus-Hyal

    4)   Manufacturer: Bioplus Co Ltd

(2) Device for control

    Restylane of Q-med Company

1) Number of approval:04-1163
2) Nmae of product: Tissue augmentation material
3) Name of model:RESTYLANE
4) Manufacturer: Q-Med
5) Importer:Contac Korea Corp.

8.3.4 Standard of stop & exemption (subject)

Standard of stop

1) Trials could be a early termination & a pause by client,investigator,IRB and KFDA.
2) In case of hard status,investigator can stop the trial by decision of IRB.
3) Client can stop the trial due to safety &others,after permission of IRB..
4) Temporally stopped due to abnormal reaction of subject, to investigate.

Treatment of stop

1) Inform relative administration & submit a statement of reasons.

1)Investigator inform subject the reasons & treat and monitor.

2)in case of stop,investigator give report of case and status of trial to client.Also,all relative materials are returned to client.Administration keeps the copies.

3)Until the time of end,materials of subject can be used in statistics for effectiveness & safety

Standard of exemption

1) Subject ask to stop clinical trials
2) Subject who is not followed and can not keep the agreement
3) Occurs important abnormal reaction
4) During trial, exemption is decided.
5) During trial, is pregnant
6) Tester decide that it is difficult to proceed clinical trials

Treatment of exemption

1) In harfway dropouts,relative materials are recorded and kept.
2) Halfway dropouts of materials are included in statistics
3) Data obtained from trilas sets to data. if there is missing data, it is anylized after Adjustment.

8.4 Evaluation items of safety & effectiveness

8.4.1 Evaluation items of effectiveness

8.4.1.1 Primary end point

After 24 weeks from final application,level of change of WSRS

8.4.1.2 Secondary end point

① After 2,6,12weeks from final application,the values of wrinkles by 5 stages by valuer of lever of change from baseline.

② After 2,6,12,24 weeks from final application,the values of wrinkles by 5 stages by tester of level of change from baseline.

③ After 2,6,12,24 weeks from final application,level of change of GAI by tester.

④ After 2,6,12,24 weeks from final application,level of change of GAI by subject

⑤ After 24 weeks from final application,values of level of change by 5stages by tester is at least -1 over of rate of subject.

8.4.1.3 End point for safety

Abnormal reaction & test as type of laboratory were evaluated.

8.4.2 Method & level of evaluation of safety & Method of analysis

8.4.2.1 Subject of evaluation

Safety Set: At least one more application of subject as randomization of datas are included

8.4.2.2 Method of evaluation

1. Adverse Event(AE) is not intended sign,symptom & disease of subject But,not surely related casuality of device.
2. Adverse Device Effect is abnormal reaction related to medical device
3. Serious AE/ADE is following cases..

A Causing death & threat life

  B Admission & extension of it

  C Causing malfunction & disabilitry

  DCausing congenital deformity

8.4.2.3 Level of evaluation

1) Level of abnormal reaction

Side effect & level of abnormal reaction are evaluated according to the followings

    1) Mild:not interfere daily life of subject

    2) Moderate:Interfere slightly

    3) Severe:Interfere significantly

2) Casuality with medical device

  Tester evaluate according to the following level and describe opinion of tester.

    1) Definitely related

      a.Timing order of expression of abnormal reaction is reasonable.

      b.Abnormal reaction by device concerned rather than others.

      c.When stop, disappear the abnormal reaction.

      d.Result of reuse is positive

      e.Abnormal reaction of information is same as equal type of device

    2) Probably related

aEvidence of using device

bTiming order of expression of abnormal reaction is reasonable.

c.Abnormal reaction by device concerned rather than others

d When stop, disappear the abnormal reaction.

3) Possibly related

a Evidence of using device

bTiming order of expression of abnormal reaction is reasonable.

c.Abnormal reaction is caused by device(same level of other causes)

e.When stop,disappear the abnormal reaction

4) Probably not related

a.Evidence of using device

b.There is another possible cause

c.Result of stop is negative and uncertain

e.Reuse of device is negative and uncertain.

5) Definitely not related

a.Device was not used by subject

b.Timing order of expression of abnormal reaction is not reasonable.

c.There is other obvious cause.

6) Unknown

a. Can not decide due to insufficient information & verify.

b.

8.4.2.6 Method of report

When occurs important abnormal reaction, follow the rule of report.

1) Duty of IRB : Recommand to stop the trial to the investigator.

2) Duty of tester:In sevre reaction,inform client with report.(within 24 hrs)

3) Duty of client:client inform IRB & Tester about severe &unexpected reaction.

a.In case of causing death, inform within 7 days & added report within 8 days.

b.Regarding other severe & unexpected reaction inform within 15 days.

8.5 Quality assurance

According to standard of management of trials,fulfill & management was conducted.Before start, plan of trial was approved through review of KFDA & IRB and all process was monitored.
To check to compare data of trials with data of basis,verify and conduct according to standard of management of trial,visit to tester &monitor.When monitor,check scope of nomal value of test as type of laboratory and if normal value is changed, have it in writing.

Audit was carried out by independent organization in Feb.25 &26,2014 and checked quality of clinical trials(Reference: audit report 17.1.6)

8.6 Method of statistical analysis

8.6.1 Statistical analysis

8.6.1.1 Definition of analysis group

Datas are FAS(Full Analysis Set),PP(Per Protocol) & SafetyAnd Main population is FAS
Additional is PP & Data of safety is Safety groupAfter comparison with all groups, in case of
difference of result,suggest the result of each method of analysis & explain the reason.
Including test of non inferiority of primary end point, analysis of effectiveness & safety are
Conducted by two-tail test.

FAS group

After randomization,subject who applied device more than 1 time& at least 1 time checked
effectiveness end point was included FAS is according to rule of intention-to-treat.

PP group

  PP is group that finished trials according to plan of trials among subject of FAS analysis
Following subjects are exempted.

   1) Halfway dropouts of subject

   2) Subject of medication of prohibited combined drug &having therapy of ban of
combination.
   3) Subject who violated the standard of inclusion & exemption
   4) In case of important violation of plan of trials.

Safety group

Subject who applied(device)once as randomization.In analysis of data of safety using
safety group subject is included in treatment group corresponds to used device.
In most subject, they can be treatment group as randomization.

Treatment of missing data

  Missing data was substituted using Worst observation carried forward.

8.6.1.2 Method of statistical analysis

Demographic &basic information

Descriptive statistics was calculated about demographic information & test in Lab. for subject. All data of subject is evaluated using descriptive satistics.Continuous data is summarized using average ,standard deviation,mini./max.value & categoritical data suggest descriptive satistics using absolute frequency & percentage.

Analysis of effectiveness

First analyisis

After 24 weeks from final application,values of level of change by 5 stages by valuer is at least -1over of rate of subject.To show test group is non inferiority VS control, check the gap of rate of improvement between 2 groups.

2x2 contingency table for result of device for test & control

Device for control Device for test	O(1)	X(0)	Total
Success(1)	$x_{11}\ (p_{11})$	$x_{10}\ (p_{10})$	$x_t\ (p_t)$
Failure(0)	$x_{01}\ (p_{01})$	$x_{00}\ (p_{00})$	$n-x_t\ (1-p_t)$
Total	$x_r\ (p_r)$	$n-x_r\ (1-p_r)$	n

$x_{10}\ (p_{10})$(Result of test=S,Result of control=F)number of observation(probability

$x_{01}\ (p_{01})$(Result of test=F,Result of control=S)(Probability)Pt is success of test Pr is success of control of device.

$p_t - p_r = (p_{11} + p_{10}) - (p_{11} + p_{01}) = p_{10} - p_{01}$ is result of non inferiority. $p_{10}\ p_{01}$of

estimator. $\widehat{p_{10}} = \dfrac{x_{10}}{n}$, $\widehat{p_{01}} = \dfrac{x_{01}}{n}$.

A null hypothesis & alternative hypothesis about check of non inferiority.

$H_0 : p_t - p_r \le -\delta\ (\delta > 0),\quad vs \quad H_1 : p_t - p_r > -\delta$

$\hat{\sigma}^2(\hat{\theta}) = \dfrac{(\widehat{p_{01}} + \widehat{p_{10}}) - \hat{\theta}^2}{n}$ $\theta = p_t - p_r = p_{10} - p_{01}$ $\hat{\theta}$ $\hat{\theta} = \widehat{p_t} - \widehat{p_r} = \widehat{p_{10}} - \widehat{p_{01}} = \dfrac{x_{10}}{n} - \dfrac{x_{01}}{n}$.,

$\hat{\theta} - AN(-\delta, \hat{\sigma}^2(\hat{\theta}))$So,one-tail test of Wald type asymptotic is as bellows.

$$Z = \frac{\hat{\theta}-(-\delta)}{\hat{\sigma}(\hat{\theta})} = \frac{(\widehat{p_{10}}-\widehat{p_{01}})+\delta}{\left\{\left[(\widehat{p_{01}}+\widehat{p_{10}})-(\widehat{p_{10}}-\widehat{p_{01}})^2\right]/n\right\}^{\frac{1}{2}}} = \frac{x_{10}-x_{01}+n\delta}{\sqrt{(x_{01}+x_{10})-\frac{1}{n}(x_{10}-x_{01})^2}} \quad Z > z_\alpha$$

$$(\widehat{p_{10}}-\widehat{p_{01}})-z_\alpha\left\{\left[(\widehat{p_{01}}+\widehat{p_{10}})-(\widehat{p_{10}}-\widehat{p_{01}})^2\right]/n\right\}^{\frac{1}{2}} > -\delta \quad (\widehat{p_{10}}-\widehat{p_{01}}) \ 100\times(1-\alpha)\% \ H_0$$

is rejected. Under ICH E9 use $z_{\alpha/2}$. If confidence interval is
bigger than $-\delta$

$$(\widehat{p_{10}}-\widehat{p_{01}})-z_{\alpha/2}\left\{\left[(\widehat{p_{01}}+\widehat{p_{10}})-(\widehat{p_{10}}-\widehat{p_{01}})^2\right]/n\right\}^{\frac{1}{2}} > -\delta \ H_0$$ is rejected.Decided non
Inferiority(Liu et al:2002)

In order to check the difference of rate of improvement for device of test & device of control between organizations of trial,use marginal model by generalized estimating equations and analyzed.If there is a gap between organizations,write the reason and use the difference in analysis.

Second analysis

Statistical analysis of end point considers matched pairs design.After 2,6,12,24 weeks from final application,comparison of WSRS of level of change frombaseline or comparison of GAI is analyzed by paired t-test or Wilcoxon signed rank test.

  Method of analysis per end point is as bellows:

.

1) After2,6,12,weeks from final application,comparison of 2 groupsof level of change from baseline of values of wrinkles by 5 stages by valuer is analyzed by paired t-test or Wilcoxon signed rank test.

2) After2,6,12,24weeks from final application,comparison of 2groups of level of change from baseline of values of wrinkles by 5 stages by tester is analyzed by paired t-test or Wilcoxon signed rank test.

3) After 2,6,12,24weeks from final application,,comparison of GAI by tester is analyzed by paired t-test or Wilcoxon signed rank test.

4) After 2,6,12,24weeks from final application,comparison of GAI by subject is analyzed By paired t-test or Wilcoxon signed rank test.

5) After 24 weeks from final application,level of change specified 5 stages evaluated by tester is at least over -1 of rate of subject is evaluated between 2 groups(Check non inferiority using confidence interval like 14.5.1 1st analysis of effectiveness for

comparison between 2 groups)

Evaluation of safety

 Abnormal reaction

a.List them with details and evaluate relation with device and record the frequency.

b.Show case & rate of abnormal reaction and 95 % of rate(confidence interval) is calculated

c.Paired‐t‐test ,Wilcoxon signed rank or generalized linear mixed model are used(For comparison of 2 groups)

 Test as type of Lab.

For test variable as type of Lab.,shows descriptive statistic quantity and gap of application of device(before & after) use paired t-test or Wilcoxon signed rank test.

Evaluation of abnormal reaction right after application of device

Get quantity of topical abnormal quantity within 30 minutes and comparison is analyzed using paired t-test or Wilcoxon signed rank test .As model based, use generalized linear mixed model or marginal model through GEE.

 Records of subject for facial reaction(2 weeks)

After application,get a day of abnormal reaction and comparison is analyzed using paired t-test or Wilcoxon signed rank test. And use generalized linear mixed model or marginal model through GEE.

8.6.2　Targeting number of subject & basis

Number of subject

Total : 123 persons(Cosideration of 30 % miss)

SNUH: 62 persons,　SNUH(Bundang) : 61 persons

All 123 persons of subject are registered and clinical trials is completed.

8.4. Basis of calculation

After 24 weeks from final application,values of level of change by WSRS by valuer is At leat −1over of rate of subject.Check the gap of rate of improvement.Suppose that Pt is rate of success of test device &Pr is rate of success of control,null hypothesis & alternative hypothesis are as bellows for check of non inferiority..

$$H_0 : p_t - p_r \leq -\delta \ (\delta > 0), \quad vs \quad H_1 : p_t - p_r > -\delta$$

Number of subject N is according to following formula in test of non inferiority

$$n\left(\delta - \frac{1}{2n}\right)^2 = 2\, p_{01}\left(z_{\alpha/2}/\overline{w} + z_\beta\right)^2$$

$$\overline{w} = \left(2\, p_{01}\right)^{\frac{1}{2}} / \left(2\, \overline{p}_{l,01} - \delta - \delta^2\right)^{\frac{1}{2}}$$

$$\overline{p}_{l,01} = \left\{-a_1 + \left(a_1^2 - 8b_1\right)^{\frac{1}{2}}\right\}/4$$

$$a_1 = -\theta_o(1-\delta) - 2(p_{01} + \delta)$$

$$b_1 = p_{01}\delta(1+\delta)$$

Suppose each items are like as bellows,calculate sample count.

α= 0.05, Alpha error

β= 0.2, Beta error

p_{01}= 0.2, No effect in test group & probability of effect in control group.

δ= 0.2, Clinically significant gap in rate of effect (non-inferiority margin)

$\theta_o = 0$, When calculates sample count,gap of rate of success based on 0.

$\overline{p}_{l,01}: p_{l,01}$ of asymptotic limit and θ, $p_{01}\delta$ of function.

Mock test of sample count,n=86,&sample count is86/07=123(Rate of miss: 30 %)

		non-inferiority test		equivalence test	
		Sample-b	RMLE-b	Sample-b	RMLE-b
0.05	0.20	25	39	27	39
	0.25	17	28	18	27
	0.30	12	21	13	20

0.10	0.20	45	53	48	56
	0.25	29	37	32	38
	0.30	21	27	23	28
0.15	0.20	64	69	70	74
	0.25	42	46	46	49
	0.30	30	33	32	35
0.20	**0.20**	84	**86**	91	93
	0.25	55	56	59	60
	0.30	39	40	42	43
0.25	0.20	104	103	112	112
	0.25	67	67	73	72
	0.30	47	47	51	51
0.30	0.20	123	121	134	132
	0.25	80	78	87	85
	0.30	56	54	61	59
0.35	0.20	143	140	155	153
	0.25	92	89	100	98
	0.30	65	62	70	68

8.6.3 Performance of trials & change

The plan of clinical trial was proceeded after approval of IRB & KFDA and revised 4 times by KFDA.For final plan of clinical trial(version 3.0), refer to appendix 17.1

Times	Approval date(MFDS)	Contents of change
1	2012.02.05 (Version 1.1)	Change of test method & person in charge
2	2013.06.12 (Version 1.4)	Client,item,agreement of subject
3.	2013.12.14 (Version2.0)	Name & address of client,method of evaluation(effectiveness)
4.	2014. 07 (Version3.0)	Investigator of SNUH(Bundang)

9. Subject

9.1 Status of joining of subject

```
                    ┌─────────────────────┐
                    │      N = 129        │
                    │      Screeing       │
                    └─────────────────────┘
                              │
                    ┌─────────────────────┐
                    │      N= 129         │
                    │   Randomization     │
                    └─────────────────────┘
                              │
                    ┌─────────────────────┐
                    │      N= 123         │
                    │      Safety         │         ┌─────────────────────┐
                    │ (Test,control each  │─────────│  Exemption(FAS)N=3   │
                    │       123)          │         └─────────────────────┘
                    └─────────────────────┘
                              │
                    ┌─────────────────────┐
                    │      N =120         │
                    │        FAS          │         ┌─────────────────────┐
                    │ (Test,control each  │─────────│  Exemption(PP)N=7    │
                    │       120)          │         │                      │
                    └─────────────────────┘         └─────────────────────┘
                              │
                    ┌─────────────────────┐
                    │      N=113          │
                    │        PP           │
                    │ (Test,control each  │
                    │       113)          │
                    └─────────────────────┘
```
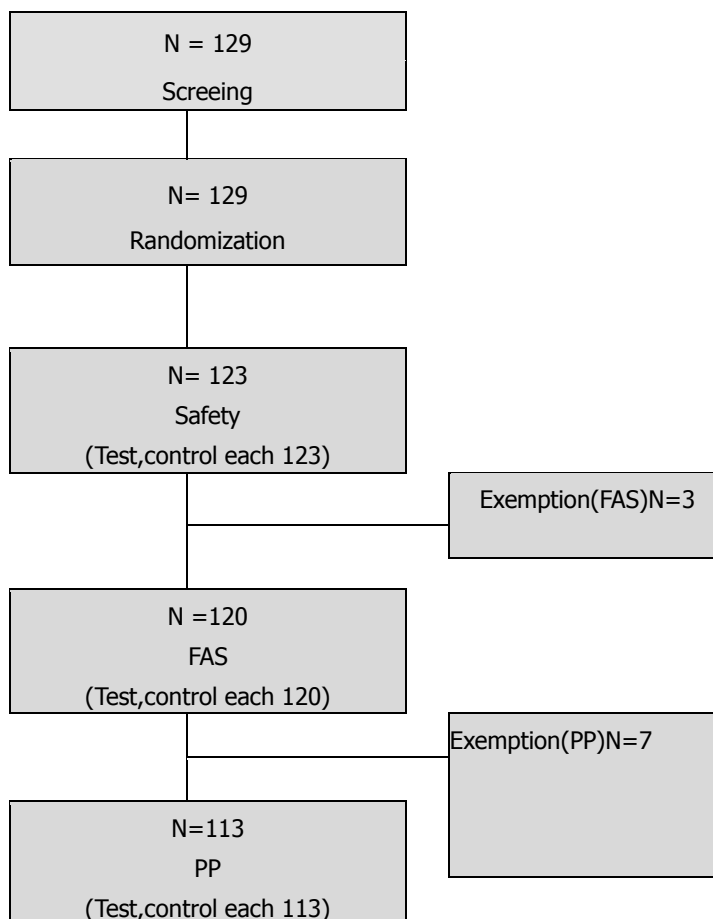
[Fig 1.   Status]

9.2 Protocol violation

Through period of screening and assigned person is 129.Safety is 123.Among Safety group, 3 is not recorded(primary end point) FAS is 120.Among FAS,request of stop is 3,rejection is 2exemption is 2.Completed is 113 as a plan of clinical trial(PP group)Specified as follows

<Protocol violation & distribution of halfway dropouts)

Division		Reason	(N=123) N(%)
Violation of FAS[)]		Total	3(2.44%)
		Not recorded(primary end point)	3(2.44%)
Violation of PP	Level of miss (PP)	Request of stop	3(2.44%)
		Rejection	3(2.44%)
		Exemption	2(1.63%)
		Total	7(5.69%)

10. Result of clinical trials

10.1 Selection of subject for analysisAmong listed subjects,suitable for selection as randomization,safety group is applied by device more than 1 time

And FAS is done test of primary end point for effectiveness more than 1 time(after application of medical device)PP is completed according to protocol(clinical trial plan) among FAS.

The subject for anylasis applied according to protocol. Safety group is used for evaluation of safety.FAS group is used for demographical basis data.FAS & PP are used for effectiveness and put priority on result of FAS.

10.2 Demographical information of subject & information of nature before trials

This trial is matched pair design and test & control groups are applied in one subject so, not specified with test & control about above informations..

10.2.1 Demographical basis data of subject

In FAS of 120,male is 6,female is 114,average age is 46.31+ _9.98(youngest 24,oldest 70.20) Over age 40,under 50 is 43, over age 50,under 60 is 39.Average height is 160.76+_5.64 츠 (smallest 149.90,tallest 182.00 cm)Average weight is 55.96+ _7.18kg(lightest 40.20 ,heaviest 76.00 kg)(table 1)

[Table 1. Demographical basis data, FAS]

Item		n(%)
Sex	male	6(5.00%)
	female	114(95.00%)
	Total	120(100.0%)
Age	N	120
	Mean±Std	46.31±9.98
	Median	47.00
	Min~Max	24.10~70.20
Age(scope)	20-30 (age)	11(9.17%)
	30-40	18(15.00%)
	40-50	43(35.83%)

Item		n(%)
	50-60	39(32.50%)
	Over 60	9(7.50%)
	Total	120(100.0%)
Height(cm)	N	120
	Mean±Std	160.76±5.64
	Median	160.4
	Min~Max	149.90~182.00
Weght(kg)	N	120
	Mean±Std	55.96±7.18
	Median	55.00
	Min~Max	40.20~76.00

10.2.2 Medical history of subject

Subject who has medical history is 42 of every 120(Table 2).

[Table 2. Medical history, FAS]

Item		n(%)
Medical history	X	78(65.00%)
	O	42(35.00%)
	Total	120(100.0%)

Medical history is analyzed (big & small class) through WHO-ART(version 092)
Abnormality of endocrine is 9 among 9 persons, skin is 9 among 7,muscloskeletal is 7 among 6
Neogenesis is 6 among 6(Table 3)

[Table 3. Frequency of medcal history, FAS]

Big class(system organ class)	Small class(preferred term)	FAS, Medical history(N=42)		
		n	%	Freq
SECONDARY TERMS	Undrugged alergy	1	2.38%	1
	Nasal septum deviation	1	2.38%	1
	Hip surgery	1	2.38%	1
	Cesarean	1	2.38%	1
	Alveolar ridge angioplasty	1	2.38%	1
	All	5	11.90%	5
Abnormality of muscloskeletal	Arthritis	1	2.38%	1
	Osteoporosis	1	2.38%	1

	Fracture	1	2.38%	1
	Musculoskeltal pain	1	2.38%	1
	Syndrome of shoulder rotator	1	2.38%	1
	Ligament disorder	1	2.38%	1
	Sciatic neuralgia	1	2.38%	1
	All	6	14.29%	7
Abnormality of endocrine	Thyroidism	1	2.38%	1
	Goiter	1	2.38%	1
	Subthyroidism	3	7.14%	3
	Thyroid nodular	4	9.52%	4
	All	9	21.43%	9
Metabolism & nutrition	Dry eye	2	4.76%	2
	Hyperlipidemia	2	4.76%	2
	All	4	9.52%	4
Defence mechanism	Dry eye syndrome	1	2.38%	1
	Labial herpes	1	2.38%	1
	All	2	4.76%	2
Genital organ(female)	Adenomyosis	1	2.38%	1
	All	1	2.38%	1
Eye sight	Pigmentation	1	2.38%	1
	Blepharitis	1	2.38%	1
	All	2	4.76%	2
Neogenesis	Fibroadenoma	1	2.38%	1
	Neoplasm of breast	1	2.38%	1
	Breast cyst	1	2.38%	1
	Cervical polyp	1	2.38%	1
	Metrofibroma	1	2.38%	1
	Angioma	1	2.38%	1
	All	6	14.29%	6
Heartbeat	Palpitation	1	2.38%	1
	All	1	2.38%	1
Cardiovascular	Hypertension	5	11.90%	5
	All	5	11.90%	5
Gastric	Gastroesophageal reflux	1	2.38%	1
	Ulitis	1	2.38%	1
	Paradentitis	1	2.38%	1

	All	3	7.14%	3
Red blood cell	Anemia	1	2.38%	1
	Iron deficiency anemia	1	2.38%	1
	All	2	4.76%	2
Whole body	Carpal tunnel syndrome	1	2.38%	1
	All	1	2.38%	1
Central & peripheral	Drooped eyelid	1	2.38%	1
	On the verge of fainting	2	4.76%	2
	All	3	7.14%	3
Fetus	Deformed nose	1	2.38%	1
	Deformed teeth	2	4.76%	2
	All	3	7.14%	3
Specal organ	Fall of sense of smell	1	2.38%	1
	All	1	2.38%	1
Skin	Foot tinea	3	7.14%	3
	Nail mycoses	1	2.38%	1
	Eczema	1	2.38%	1
	Skin disease	2	4.76%	2
	Excess of sebaceous gland	1	2.38%	1
	Erythema exanthema	1	2.38%	1
	All	7	16.67%	9
Blood vessel(exclude heart)	Hemotelangiosis	1	2.38%	1
	All	1	2.38%	1
Respiratory	Atopic rhinitis	1	2.38%	1
	Mucus	1	2.38%	1
	Tonsillitis	2	4.76%	2
	Laryngitis	1	2.38%	1
	All	5	11.90%	5
Total				70

10.2.3 Combined drug

Before clinical trials, subject who take medication is 19 and trials with medication is 34 persons (Table 5)

Drugs are classified according to WHO ATC code.

Among preceding drug,high frequency of series,CARDIOVASCULAR SYSTEM is 7 among 6. ALIMENTARY TRACT & METABOLISM is 9 among 5.BLOOD & BLOOD FORMING ORGANS, SYSTEMIC HORMONAL PREPARATIONS,EXCL.SEX HORMONES & INSULINS are3 each among 3(Table 6)

Among combined drug,high frequency of series,ALIMENTARY TRACT &METABOLISM is 44 among 19NERVOUS SYSTEM is 20 among 14,MUSCULO-SKELETAL SYSTEM is 27among 13(Table 7)

[Table 5. Preceding/combined(yes, no)　FAS group

Item		n(%)
Preceding drug(yes, no)	No	101(84.17%)
	Yes	19(15.83%)
	Total	120(100.0%)
Combined drug(yes,no)	No	86(71.67%)
	Yes	34(28.33%)
	Total	120(100.0%)

[Table 6. Frequency of preceding drug, FAS]

Item	FAS Yes(N=19)		
	n	%	Freq
ALIMENTARY TRACT AND METABOLISM	5	26.32%	**9**
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	1	5.26%	1
DRUGS FOR ACID RELATED DISORDERS	3	15.79%	4
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	2	10.53%	3
MINERAL SUPPLEMENTS	1	5.26%	1
ANTIINFECTIVES FOR SYSTEMIC USE	1	5.26%	**1**
ANTIBACTERIALS FOR SYSTEMIC USE	1	5.26%	1
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	1	5.26%	**1**
ENDOCRINE THERAPY	1	5.26%	1
BLOOD AND BLOOD FORMING ORGANS	3	15.79%	**3**
ANTIANEMIC PREPARATIONS	1	5.26%	1
ANTITHROMBOTIC AGENTS	2	10.53%	2
CARDIOVASCULAR SYSTEM	6	31.58%	**7**
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	2	10.53%	3
CALCIUM CHANNEL BLOCKERS	2	10.53%	2
LIPID MODIFYING AGENTS	2	10.53%	2

	n	%	Freq
DERMATOLOGICALS	1	5.26%	**1**
ANTIFUNGALS FOR DERMATOLOGICAL USE	1	5.26%	1
MUSCULO-SKELETAL SYSTEM	2	10.53%	**3**
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	1	5.26%	1
MUSCLE RELAXANTS	1	5.26%	1
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	1	5.26%	1
NERVOUS SYSTEM	2	10.53%	**2**
OTHER ANALGESICS AND ANTIPYRETICS	1	5.26%	1
PSYCHOLEPTICS	1	5.26%	1
RESPIRATORY SYSTEM	1	5.26%	**1**
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	1	5.26%	1
SENSORY ORGANS	2	10.53%	**3**
OPHTHALMOLOGICALS	2	10.53%	3
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	3	15.79%	**3**
THYROID THERAPY	3	15.79%	3
VARIOUS	1	5.26%	**1**
ALL OTHER THERAPEUTIC PRODUCTS	1	5.26%	1
Total			**35**

[Table 7. Frequency of combined drug,FAS]

Item	FAS(N=70)		
	n	%	Freq
ALIMENTARY TRACT AND METABOLISM	19	55.88%	**44**
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	2	5.88%	2
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	1	2.94%	1
DIGESTIVES, INCL. ENZYMES	3	8.82%	3
DRUGS FOR ACID RELATED DISORDERS	10	29.41%	16
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	8	23.53%	13
MINERAL SUPPLEMENTS	2	5.88%	2
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	2	5.88%	2
STOMATOLOGICAL PREPARATIONS	5	14.71%	5
ANTIINFECTIVES FOR SYSTEMIC USE	7	20.59%	**14**
ANESTHETICS	1	2.94%	1
ANTIBACTERIALS FOR SYSTEMIC USE	7	20.59%	8
IMMUNE SERA AND IMMUNOGLOBULINS	2	5.88%	2
VACCINES	2	5.88%	3

ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	3	8.82%	**4**
ENDOCRINE THERAPY	2	5.88%	2
IMMUNOSUPPRESSANTS	1	2.94%	2
BLOOD AND BLOOD FORMING ORGANS	5	14.71%	**6**
ANTIANEMIC PREPARATIONS	1	2.94%	1
ANTITHROMBOTIC AGENTS	1	2.94%	1
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	3	8.82%	4
CARDIOVASCULAR SYSTEM	6	17.65%	**7**
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	2	5.88%	3
CALCIUM CHANNEL BLOCKERS	2	5.88%	2
LIPID MODIFYING AGENTS	2	5.88%	2
DERMATOLOGICALS	5	14.71%	**5**
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	1	2.94%	1
ANTIFUNGALS FOR DERMATOLOGICAL USE	1	2.94%	1
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	1	2.94%	1
OTHER DERMATOLOGICAL PREPARATIONS	1	2.94%	1
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	1	2.94%	1
GENITO URINARY SYSTEM AND SEX HORMONES	1	2.94%	**1**
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	1	2.94%	1
MUSCULO-SKELETAL SYSTEM	13	38.24%	**27**
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	12	35.29%	19
MUSCLE RELAXANTS	3	8.82%	4
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	2	5.88%	2
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	2	5.88%	2
NERVOUS SYSTEM	14	41.18%	**20**
ANALGESICS	3	8.82%	3
ANESTHETICS	5	14.71%	9
ANTIEPILEPTICS	1	2.94%	1
OTHER ANALGESICS AND ANTIPYRETICS	1	2.94%	1
PSYCHOLEPTICS	6	17.65%	6
RESPIRATORY SYSTEM	11	32.35%	**36**
ANTIHISTAMINES FOR SYSTEMIC USE	3	8.82%	6
COUGH AND COLD PREPARATIONS	6	17.65%	8
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	5	14.71%	9
NASAL PREPARATIONS	8	23.53%	10
THROAT PREPARATIONS	3	8.82%	3

SENSORY ORGANS	8	23.53%	**13**
OPHTHALMOLOGICALS	8	23.53%	13
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	4	11.76%	**9**
CORTICOSTEROIDS FOR SYSTEMIC USE	1	2.94%	6
THYROID THERAPY	3	8.82%	3
VARIOUS	3	8.82%	**3**
ALL OTHER THERAPEUTIC PRODUCTS	2	5.88%	2
DIAGNOSTIC AGENTS	1	2.94%	1
Total			**189**

10.3Evaluation of effectiveness

10.3.1 General principle
FAS Group & PP are target of analysis of effectiveness and main analysis is FAS Among halfway
Dropouts of materials, essential evaluation of effectiveness is using WOCF(Worst Observation
Carried Forward).

10.3.2 Effetiveness   end point

10.3.2.1   Primary end point

After 24 weeks from final application,level of change of WSRS of test & control group is at least
over -1 as rate of subject.In PP rate of improvement(test) is 35.4% control is 38.05%.Difference
is abt.2.65 %,97.5% of difference of rate of improvement of wrinkles & lower limit of
confidence of interval is -9.91% So,bigger than -20%(allowable limit of non inferiority) In PP,
test group is non inferiority VS control group(Table 8)

[Table 8.Primary end point,level of change of WSRS(FAS ,PPS)]

Test group	Control	Improvement		No		Total	
FAS	Yes	25	20.83%	16	13.33%	41	34.17%
	No	19	15.83%	60	50.00%	79	65.83%
	Total	44	36.67%	76	63.33%	120	100.00%
PPS	PPS	Improvement		No		Total	
	Yes	24	21.24%	16	14.16%	40	35.40%
	No	19	16.81%	54	47.79%	73	64.60%
	Total	43	38.05%	70	61.95%	113	100.00%

Item		Improvement	%	Gap	97.5% CI
FAS	Control	44/120	36.67%	2.50%	[-9.60,14.60]
	Test	41/120	34.17%		
PPS	Cotrol	43/113	38.05%	2.65%	[-9.91,15.22]
	Test	40/113	35.40%		

* Application of WOCF

10.3.2.2 Secondary end point

This is analyzed about 5 items for FAS,PP.Missing data is analyzed in application of WOCF.

① After 2,6,,12,24 weeks from final application,values of wrinkles by 5 stages evaluated by valuer of level of change from base line.

② After 2,6,12,24 weeks from final application,values of wrinkles by 5 stages evaluated by tester of level of change from base line.

③ After 2,6,12,24 weeks from final application,level of GAI evaluated by tester.

④ After 2,6,12,24 weeks from final application,level of GAI evaluated by subject.

⑤ After 24 weeks from final application,value11s of change specified 5 stages evaluated by tester is at least over -1 of rate of subject.

(1) After 2,6,12, weeks from final application,values of wrinkles by 5 stages evaluated by valuer of level of change from base line.

In FAS,after 2weeks from final application,average variation is -0.53+_0.69 in test group.-0.54+_0.82 in control. No gap statistically(p=0.9034)
After 6 weeks from final application,variation is -0.58+_0.69 in test group,-0.54+_ 0.80 in control.No gap statistically(p=0.6296)
After 12 weeks from final application,variation is -0.29+_0.84 in test group, average -0.33+_0.89 in control.No gap statistically (p=0.5606)
Between 2 groups , there is no difference statistically.

[Table 9. Secondary end point,After 2,6,12weeks,level of change of WSRS by valuer. FAS PP

ITEM(UNIT:SCORE)			TEST	CONTROL	P-value
FAS	Screening - Week2	N	120	120	0.9034
		Mean±Std	-0.53±0.69	-0.54±0.82	Paired t-test
		Median	-1.00	0.00	
		Min~Max	-2.00~1.00	-3.00~2.00	
	Screening – Week6	N	120	120	0.6296

ITEM(UNIT:SCORE)			TEST	CONTROL	P-value
		Mean±Std	-0.58±0.69	-0.54±0.80	Paired t-test
		Median	-1.00	2.00	
		Min~Max	-2.00~1.00	-3.00~1.00	
	Screening – Week12	N	120	120	0.5606
		Mean±Std	-0.29±0.84	-0.33±0.89	Paired t-test
		Median	0.00	0.00	
		Min~Max	-2.00~2.00	-3.00~2.00	
PPS	Screening - Week2	N	113	113	0.8008
		Mean±Std	-0.56±0.69	-0.58±0.80	Paired t-test
		Median	-1.00	0.00	
		Min~Max	-2.00~1.00	-3.00~1.00	
	Screening - Week4	N	113	113	0.6192
		Mean±Std	-0.60±0.69	-0.57±0.80	Paired t-test
		Median	-1.00	0.00	
		Min~Max	-2.00~1.00	-3.00~1.00	
	Screening – Week12	N	113	113	0.5553
		Mean±Std	-0.32±0.85	-0.36±0.88	Paired t-test
		Median	0.00	0.00	
		Min~Max	-2.00~2.00	-3.00~2.00	

- **After 2,6,12,24 weeks from final application,the values of wrinkles by 5 stages by tester of lever of change from baseline.**

  In FAS,after 2 weeks from final application,average variation is -1.22+_0.87

  -1.21+_0.90 in control. No gap statistically(p=0.8283)

  After 6 weeks from final application,average variation is -1.16+_0.81 in test group ,-1.16+_0.79 in control. No gap statistically(p=1.000

  After 12 weeks from final application,average variation is -1.09+_0.79 in test group,

  -1.07+_0.73 in control.No gap statistically(p=0.4409)

  After 24 weeks from final application,average variation is -1.04+_073 in test group,

  -1.04+_0.73 in control. No gap statistically(p=0.4675)

  Between 2 groups(PP & FAS group), there is no difference statistically.

[Table 10. Secondary end point After 2,6,12weeks,level of change of WSRS
By tester.FAS,PP

Item(Unit:Score)			Test group	Control	P-value
FAS	Screening - Week2	N	120	120	0.8283
		Mean±Std	-1.22±0.87	-1.21±0.90	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~-1.00	-3.00~1.00	
	Screening – Week6	N	120	120	1.0000
		Mean±Std	-1.16±0.81	-1.16±0.79	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~0.00	-3.00~0.00	
	Screening – Week12	N	120	120	0.4409
		Mean±Std	-1.09±0.79	-1.07±0.73	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~1.00	-3.00~0.00	
	Screening – Week24	N	120	120	0.4675
		Mean±Std	-1.04±0.73	-1.04±0.73	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~0.00	-3.00~0.00	
PPS	Screening - Week2	N	113	113	0.6567
		Mean±Std	-1.27±0.85	-1.26±0.87	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~-0.00	-3.00~0.00	
	Screening – Week6	N	113	113	1.0000
		Mean±Std	-1.20±0.80	-1.20±0.78	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~0.00	-3.00~0.00	
	Screening – Week12	N	113	113	0.2870
		Mean±Std	-1.14±0.77	-1.11±0.72	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~1.00	-3.00~0.00	
	Screening – Week24	N	113	113	0.3555
		Mean±Std	-1.12±0.81	-1.08±0.72	Paired t-test
		Median	-1.00	-1.00	
		Min~Max	-3.00~1.00	-3.00~0.00	

(3)

- **After 2,6,12,24 weeks from final application,level of change of GAI by tester.**

  In FAS,after 2 weeks, Global Aesthetic Improvement(GAI) by tester

  is 99.16% in test group &98.32 in control.After 6 weeks,97.39 %

  ,99.13 % each. After 12 weeks,95.41 %, 92.66%each.After 24

  weeks,91.30 %,92.17

  %eachBetween 2 groups no gap statistically.Also,the result of PP is similar with

  FAS.

  GAI by tester between 2 groups is no difference statistically.

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[Table 11. Secondaryend point-2,4,12,24weeks,bytester.GAI,FAS,PP

Item				Test		Control		P-value
				n	%	n	%	Fisher's exact test
FAS	WEEK2 (missing n=1)		Very much	31	26.05%	29	24.37%	0.9280
			Much	49	41.18%	47	39.50%	
			Upgrade	38	31.93%	41	34.45%	
			No change	1	0.84%	2	1.68%	
			Worse	0	0.00%	0	0.00%	
			Total	119	100.00%	119	100.00%	
	WEEK6 (missing n=5)		Very much	16	13.91%	16	13.91%	0.8379
			Much	50	43.48%	49	42.61%	
			Upgrade	46	40.00%	49	42.61%	
			No change	3	2.61%	1	0.87%	
			Worse	0	0.00%	0	0.00%	
			Total	115	100.00%	115	100.00%	
	WEEK12 (missing n=11)		Very much	9	8.26%	9	8.26%	0.8895
			Much	44	40.37%	43	39.45%	
			Upgrade	51	46.79%	49	44.95%	
			No Change	5	4.59%	8	7.34%	
		Worse		0	0.00%	0	0.00%	
			Total	109	100.00%	109	100.00%	

			Very much	4	3.48%	3	2.61%	0.7598
		WEEK24	Much	31	26.96%	25	21.74%	
		(missing n=5)	Uggrade	70	60.87%	78	67.83%	
			No change	10	8.70%	9	7.83%	
			Worse	0	0.00%	0	0.00%	
			Total	115	100.00%	115	100.00%	
PPS		WEEK2 (missing n=1)	Very much	31	27.68%	29	25.89%	0.9666
			Much	45	40.18%	44	39.29%	
			Upgrade	35	31.25%	37	33.04%	
			No change	1	0.89%	2	1.79%	
			Worse	0	0.00%	0	0.00%	
			Total	112	100.00%	112	100.00%	
		WEEK6 (missing n=4)	Very much	16	14.68%	16	14.68%	0.8543
			Much	47	43.12%	47	43.12%	
			Upgrade	43	39.45%	45	41.28%	
			No change	3	2.75%	1	0.92%	
			Worse	0	0.00%	0	0.00%	
			Total	109	100.00%	109	100.00%	
		WEEK12 (missing n=6)	Very much	9	8.41%	9	8.41%	0.8583
			Much	44	41.12%	43	40.19%	
			Upgrade	50	46.73%	48	44.86%	
			No change	4	3.74%	7	6.54%	
			Worse	0	0.00%	0	0.00%	
			Total	107	100.00%	107	100.00%	
		WEEK24 (missing n=0)	Very much	4	3.54%	3	2.65%	0.7569
			Much	30	26.55%	24	21.24%	
			Upgrade	69	61.06%	77	68.14%	
			No change	10	8.85%	9	7.96%	
			Worse	0	0.00%	0	0.00%	
			Total	113	100.00%	113	100.00%	

- **After 2,6,12,24 weeks from final application,level of GAI by subject**
  In FAS,after 2 weeks,GAI by subject(upgrade,much,very much) is 94.12%in test

group &92.44%in control.After 6 weeks,93.91%,93.91%each.After12weeks 88.07%

85.32%each,After 24 weeks,83.48%,82.61%each.Between 2 groups no gap statistically.Also,the result of PP is similar with FAS. GAI by subject between 2 groups is no difference statistically.

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[Table 12. Secondary end pointAfter2,4,12,24weeks,evaluation of subjectGAI,FAS,PP

Item			Test		Control		P-value
			n	%	n	%	Fisher's exact test
FAS	WEEK2 (missing n=1)	Very much	31	26.05%	24	20.17%	0.8586
		Much	53	44.54%	57	47.90%	
		Upgrade	28	23.53%	29	24.37%	
		No change	6	5.04%	8	6.72%	
		Worse	1	0.84%	1	0.84%	
		Total	119	100.00%	119	100.00%	
	WEEK6 (missing n=5)	Very much	20	17.39%	19	16.52%	0.8641

		Much	41	35.65%	36	31.30%	
		Upgrade	47	40.87%	53	46.09%	
		No change	7	6.09%	7	6.09%	
		Worse	0	0.00%	0	0.00%	
		Total	115	100.00%	115	100.00%	
	WEEK12 (missing n=11)	Very much	16	14.68%	11	10.09%	0.7369
		Much	34	31.19%	36	33.03%	
		Upgrade	46	42.20%	46	42.20%	
		No Change	13	11.93%	16	14.68%	
		Worse	0	0.00%	0	0.00%	
		Total	109	100.00%	109	100.00%	
	WEEK24 (missing n=5)	Very much	17	14.78%	10	8.70%	0.5715
		Much	28	24.35%	31	26.96%	
		Upgrade	51	44.35%	54	46.96%	
		No change	19	16.52%	20	17.39%	
		Worse	0	0.00%	0	0.00%	
		Total	115	100.00%	115	100.00%	
PPS	WEEK2 (missing n=1)	Very much	31	27.68%	23	20.54%	0.8101
		Much	49	43.75%	54	48.21%	chi-square test
		Upgrade	26	23.21%	28	25.00%	
		No change	5	4.46%	6	5.36%	
		Worse	1	0.89%	1	0.89%	
		Total	112	100.00%	112	100.00%	
	WEEK6 (missing n=4)	Very much	20	18.35%	18	16.51%	0.8711
		Much	37	33.94%	33	30.28%	chi-square test
		Upgrade	45	41.28%	51	46.79%	
		No change	7	6.42%	7	6.42%	
		Worse	0	0.00%	0	0.00%	
		Total	109	100.00%	109	100.00%	
	WEEK12 (missing n=6)	Very much	16	14.95%	11	10.28%	0.7248
		Much	33	30.84%	35	32.71%	chi-square test
		Upgrade	46	42.99%	46	42.99%	
		No change	12	11.21%	15	14.02%	
		Worse	0	0.00%	0	0.00%	

			Test		Control		
				Total	107	100.00%	107	100.00%	

			n	%	n	%	
		Very much	17	15.04%	10	8.85%	0.7569
		Much	27	23.89%	30	26.55%	
WEEK24		Upgrade	51	45.13%	54	47.79%	
(missing n=0)		No change	18	15.93%	19	16.81%	
		Worse	0	0.00%	0	0.00%	
		Total	113	100.00%	113	100.00%	

(5)

- **After 24 weeks from final application,values of level of change by 5 stages by tester**

  is at least -1 over of rate of subject

  In FAS,rate of improvement (WSRS) is 77.50% in test group &77.50% in control. No gap statistically(p-value=1.0000) In PP,79.65% in test group &79.65% in control.No gap statistically(p-value=0.8101)

[Table 13.Secondary end point
-1 over of rate of WSRS by teter,FAS PP

Item			Test		Control		P-value
			n	%	n	%	chi-square test
FAS	WEEK24	Uggrade	93	77.50%	93	77.50%	1.0000
		No	27	22.50%	27	22.50%	
		Total	120	100.00%	120	100.00%	
PPS	WEEK24	Upgrade	90	79.65%	90	79.65%	0.8101
		No	23	20.35%	23	20.35%	
		Total	113	100.00%	113	100.00%	

11. Evaluation of safety

Evaluation of safety with abnormal reaction is suitable for standard of selection/exception as Randomization,the material gained from subject is anylized(Even 1 time of application of device).

11.1 Abnormal reaction

11.1.1 Summary of abnormal reaction

During trials,rate of expression of abnormal reaction is 66.67 %.Causality with medical device (possible) of rate of expression is 62.60%.Severe abnormal reaction is 1.63 %.

[Table 14. Rate of expression of abnormal reaction, Safety group

Item	Rate of onset(%)		95%confidenceinterval		No of onset(%)		Total
Abnormal reaction	82	66.67%	(58.34%,	75.00%)	252	204.88%	123
Abnormal by device	77	62.60%	(54.05%,	71.15%)	209	169.92%	123
Severe abnormal reaction	2	1.63%	(0.00%,	3.86%)	2	1.63%	123

11.1.2 Status of expression of abnormal reaction

(1) Level of abnormal reaction & result

Among 252 of abnormal reaction, mild symptom is 227, middle is 23 & severe is 2.
In Causality,Definite is 197, unrelated is 39,possible is 6,probable is 6,unknown is 4.In treatment of
abnormal reaction,No is 246,stop is 3.In result of reaction, recovery is 238,under recovery is 14

[Table 15. Level of abnormal reaction & result, Safety group

Item		TOTAL	
		No	%
Level	Mild	227	90.08%
	Middle	23	9.13%
	Severe	2	0.79%
	Total	252	100.00%
Casusality	Unknown	4	1.59%
	Unrelated	39	15.48%

	Possible	6	2.38%
	Probable	6	2.38%
	Definite	197	78.17%
	Total	252	100.00%
Treatment	Stop	3	1.19%
	Reduce	0	0.00%
	Increase	0	0.00%
	No change	3	1.19%
	Unknown	0	0.00%
	N/A	246	97.62%
	Total	252	100.00%
Result	Recovery	238	94.44%
	Under recovery	14	5.56%
	No recovery	0	0.00%
	Sequela	0	0.00%
	Death	0	0.00%
	Unknown	0	0.00%
	Total	252	100.00%

(2) Distribution of abnormal reaction

This is anylized using WHO-ART(version 092) by System Organ Class & Preferred Term

In abnormal reaction of 252,abnormal of injection site is 182 among 75 persons,abnormal of skin is 23 among 16,abnormal of respilatory is 11 among 9.In details,bruising of site of injection is 69 among 52,edema of site of application is 38 among 31,tenderness is 39 among 27.

[Table 16. Distribution of abnormal reaction, Safety group

Item(WHO-ART)	Test(N=72)		
	n	%	Freq
POISON SPECIFIC TERMS	**5**	**4.07%**	**6**
Mark of injection	5	4.07%	6
SECONDARY TERMS	**1**	**0.81%**	**1**
Avulsed wound	1	0.81%	1
Abnormal hepatobiliary	**1**	**0.81%**	**2**

Hepatosis	1	0.81%	2
Abnormality of musculoskeltal	**4**	**3.25%**	**4**
Pain of neck, shoulder	1	0.81%	1
Pain of body	1	0.81%	1
Abnormality of temporomandibular	1	0.81%	1
Bursting of sinew	1	0.81%	1
Cryptorrhea	**2**	**1.63%**	**2**
Nodal thyroid	1	0.81%	1
Hemorrhage of application site	1	0.81%	1
Abnormality of eye sight	**4**	**3.25%**	**6**
Conjunctivitis	1	0.81%	1
Flare of eye sight	1	0.81%	1
Stimulus of eyeball	1	0.81%	1
Eye-ache	1	0.81%	1
Allergic conjunctivitis	1	0.81%	1
Illacrimation	1	0.81%	1
Homeoplasia	**1**	**0.81%**	**1**
Breast cancer	1	0.81%	1
Abnormality of urinary tract	**1**	**0.81%**	**1**
Cystitis	1	0.81%	1
Abnormality of gastrointestinal tract	**5**	**4.07%**	**7**
Vomiting	1	0.81%	1
Dyspepsia	1	0.81%	1
Nausea	2	1.63%	2
Gastroesophageal reflux	1	0.81%	1
Gastric discomport	1	0.81%	1
Pain of gum	1	0.81%	1
Abnormality of erythrocyte	**1**	**0.81%**	**1**
Anemia	1	0.81%	1
Abnormality of whole body	**3**	**2.44%**	**3**
Chest pain	1	0.81%	1
Back pain	1	0.81%	1
Scar	1	0.81%	1
Abnormality of psychoneural	**1**	**0.81%**	**1**
Insomnia	1	0.81%	1
Abnormality of center & peripheral system	**1**	**0.81%**	**1**

Dizziness	1	0.81%	1
Abnormality of application site	**75**	**60.98%**	**182**
Rash	1	0.81%	1
Edema	31	25.20%	38
Stimulus	9	7.32%	14
Erythema	4	3.25%	4
Tenderness of injection site	27	21.95%	39
Bruising	52	42.28%	69
Erythema of injection site	1	0.81%	1
Bolus	13	10.57%	16
Abnormality of skin	**16**	**13.01%**	**23**
Fleckle	1	0.81%	1
Pruritus	12	9.76%	14
Simple erythema	1	0.81%	1
Hives	2	1.63%	2
Vesicle	1	0.81%	1
Purpuric eruption	1	0.81%	1
Wrinkles	3	2.44%	3
Abnormality of repiratory	**9**	**7.32%**	**11**
Common cold	5	4.07%	5
Cough	1	0.81%	1
Rhinitis	1	0.81%	1
URI	2	1.63%	2
Atopic dermatitis	1	0.81%	1
Pharyngitis	1	0.81%	1
Total			**252**

11.1.3 Important abnormal reaction

During clinical trials,important abnormal reaction is 2(bursting of sinew,breast cancer)(Table 17)

Details are in table 23.This reaction is due to extension of admission & unrelated to medical device of of clinical trials(Table 18)

[Table 17. Distribution of important abnormal reaction, Safety

Item(WHO-ART)	Test(N=123)		
	n	%	Freq
Abnormality of musculoskeltal	**1**	**0.81%**	**1**
Rupture of tendons	1	**0.81%**	1
Homeoplasia	**1**	**0.81%**	**1**
Breast cancer	1	0.81%	1

[Table 18. Important abnormal reaction] Safety group

Screening No	Reaction	Starting date	GRADE	Causality	Treat	Result	Importance
2-S06	Rotator tear	2013-10-05	Middle	Unrelated	N/A	Recovery	Admission/
2-S36	Breast cancer	2013-12-12	Severe	Unrelated	N/A	Recovery	Admission

11.1.4 Abnormal reaction of procedure of the day

During clinical trials,abnormal reaction of procedure of the day is 3 cases(1person) Types are vertigo,blurred vision and nausea each 1 case(Table 19).

Details are in table 23 . The causality with medical device is DEFINITE(all) (Table 20).

[Table 19. Distribution of abnormal reaction] Safety group

Item(WHO-ART)	Test(N=123)		
	n	%	Freq
Central & peripheral nervous system	**1**	**0.81%**	**1**
Vertigo	1	**0.81%**	1
Abnormality of eye sight	**1**	**0.81%**	**1**
Blurred vision	1	0.81%	1
Abnormality of gastric system	**1**	**0.81%**	**1**
Nausea	1	0.81%	1

[Table 20. Distribution of abnormal reaction]Safety group

Screening No	Reaction	Start	End	GRADE	Causality	Treat	Result	Severe
2-S42	Nausea	2013-09-04	2013-09-04	mild	Definite	Stop	Recovery	No

2-S42	Blurred vision	2013-09-04	2013-09-04	mild	Definite	Stop	Recovery	No
2-S42	,Vertigo	2013-09-04	2013-09-04	mild	Definite	Stop	Recovery/	No

11.2 Other evaluation of safety

11.2.1 Test as type of laboratoryIn test of type of laboratory, meaningful change of item of test as follows:W BC(P=0.0497)LDH(P=0.0008)Total Billirubin(p<0.0001)Gamma GT(p=0.0353)Na(P=0.0097)Ca(p=0.0497)

APTT(P=0.0178) PT(P=0.0461) But ,clinically no meaningful change.(Table 27)

[Table 21. Test as type of laboratory, Safety group]

Item			SAFETY(N=123)
WBC (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.29±1.54
		Median	-0.18
		Min~Max	-10.34 ~ 2.47
		Paired t-test	0.0497
RBC (missing N=8)	Screening – Week12	N	115
		Mean±Std	0±0.23
		Median	-0.02
		Min~Max	-0.69 ~ 0.98
		Paired t-test	0.9638
Hb (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.16±0.9
		Median	-0.2
		Min~Max	-3.3 ~ 4.2
		Paired t-test	0.0523
Hct (missing N=8)	Screening – Week12	N	115
		Mean±Std	0.05±2.45
		Median	0
		Min~Max	-8.2 ~ 11
		Paired t-test	0.8138

PLT (missing N=8)	Screening − Week12	N	115
		Mean±Std	-5.19±35.06
		Median	-6
		Min~Max	-93 ~ 225
		Paired t-test	0.1151
ALP (missing N=8)	Screening − Week12	N	115
		Mean±Std	-0.6±10.72
		Median	-1
		Min~Max	-48 ~ 43.9
		Paired t-test	0.5491
AST (missing N=8)	Screening − Week12	N	115
		Mean±Std	-0.5±7.04
		Median	0
		Min~Max	-54 ~ 19
		Paired t-test	0.4517
ALT (missing N=8)	Screening − Week12	N	115
		Mean±Std	-1.44±9.06
		Median	-1
		Min~Max	-60 ~ 27
		Paired t-test	0.0901
LDH (missing N=8)	Screening − Week12	N	115
		Mean±Std	7.58±23.48
		Median	7
		Min~Max	-77 ~ 96
		Paired t-test	0.0008
Total Bilirubin (missing N=8)	Screening − Week12	N	115
		Mean±Std	0.09±0.22
		Median	0.1
		Min~Max	-0.5 ~ 0.7
		Paired t-test	<0.0001
γ-GT (missing N=8)	Screening − Week12	N	115
		Mean±Std	-2.35±11.82
		Median	0
		Min~Max	-78 ~ 11
		Paired t-test	0.0353

Total Cholestero (missing N=8)l	Screening – Week12	N	115
		Mean±Std	0.53±23.13
		Median	1
		Min~Max	-74 ~ 116
		Paired t-test	0.8062
Glucose (missing N=9)	Screening – Week12	N	114
		Mean±Std	-0.03±19.59
		Median	-1
		Min~Max	-56 ~ 90
		Paired t-test	0.9886
Total Protein (missing N=12)	Screening – Week12	N	111
		Mean±Std	0.03±0.32
		Median	0.1
		Min~Max	-0.7 ~ 1
		Paired t-test	0.3022
Albumin (missing N=8)	Screening – Week12	N	115
		Mean±Std	0±0.22
		Median	0
		Min~Max	-0.5 ~ 0.7
		Paired t-test	0.9328
Triglyceride (missing N=8)	Screening – Week12	N	115
		Mean±Std	-6.98±72.57
		Median	-5.00
		Min~Max	-323 ~ 348
		Paired t-test	0.3043
Serum Creatinine (missing N=8)e	Screening – Week12	N	115
		Mean±Std	-0.02±0.57
		Median	0.03
		Min~Max	-5.98 ~ 0.32
		Paired t-test	0.7617
Na (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.42±1.7
		Median	0
		Min~Max	-4 ~ 5
		Paired t-test	0.0097

K (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.16±1.11
		Median	-0.1
		Min~Max	-11.3 ~ 1.6
		Paired t-test	0.1194
Cl (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.27±2.52
		Median	0
		Min~Max	-7 ~ 6
		Paired t-test	0.2540
Ca (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.5±2.7
		Median	-0.2
		Min~Max	-28.9 ~ 0.9
		Paired t-test	0.0497
aPTT (missing N=8)	Screening – Week12	N	115
		Mean±Std	-0.44±1.96
		Median	-0.5
		Min~Max	-5.3 ~ 8.3
		Paired t-test	0.0178
PT (missing N=8)	Screening – Week12	N	115
		Mean±Std	0.1±0.55
		Median	0.1
		Min~Max	-1.7 ~ 1.2
		Paired t-test	0.0461

12. Conclusion

This trials was proceeded ethically and scientifically according to KGCP & Helsinki Declaration. Also, proceeded according to approved protocol of KFDA & IRB.The trials was proceeded by written consent of all subject and process & material were controlled by monitor..

After 24 weeks from final application, test group of wrinkles that specified 5 stages (WSRS) is at least over -1 of rate of subject is non inferiority.

Result is summarized as bellows:

Firstly,subject as randomization through period of screening is 129 and applied device as over one time,safety group is 123.Among them,in primary end point 3 is not recorded so FAS group is 120.Among them, completed subject is 113 persons.

.Presenting rate of case of abnormal reaction is 66.67% during period of trials & related material of

clinical trials of presenting rate of case(Over possible) is 62.60% And important abnormal reaction is 1.63%.

Among 252 of abnormal reaction, mild symptom is 227, middle is 23 & severe is 2.
In Causality,Definite is 197, unrelated is 39,possible is 6,probable is 6,unknown is 4.In treatment of

abnormal reaction,No is 246,stop is 3.In result of reaction, recovery is 238,under recovery is 14.
In abnormal reaction of 252,abnormal of injection site is 182 among 75 persons,abnormal of skin is 23 among 16,abnormal of respilatory is 11 among 9.In details,bruising of site of injection is 69 among 52,edema of site of application is 38 among 31,tenderness is 39 among 27.
During clinical trials,important abnormal reaction is 2(bursting of sinew,breast cancer) This reaction
is due to extension of admission & Unrelated to medical device of clinical trials.Confirmed abnormal
reaction of procedure of the day is 3 in 1 person. Types are vertigo,flare of visual field,nausea (each 1 case) Casual relationship with medical device is definite.

After 24 weeks from final application,rate of improvement of wrinkles between test & control

group. In FAS improvement ratio of WSRS(test) is 34.179 %,control is 36.67 & gap(2.5%)97.5% of difference rate of improvement of wrinkles &lower limit of confidence of interval is -9.60%.So,bigger than -20%(allowable limit of non inferiority)Test group is non inferiority VS control group.

Also,In PP rate of improvement(test) is 35.40%(40/113person)control is 38.05%(43/113)Difference is abt 2.65%.97.5% of difference of rate of improvement of wrinkles & lower limit of confidence of interval is -9.91%.So, bigger than -20% (allowable limit of non inferiority) Even in PP,Test group is non inferiority VS control group.

Result of evaluation of Secondary End Point

- **After 2,6,12,weeks from final application,the values of wrinkles by 5 stages by tester of lever of change from baseline.**
  In FAS,after 2weeks from final application,average variation is -0.53+_0.69 in test
  group.-0.54+_0.82 in control. No gap statistically(p=0.9034)
  After 6 weeks from final application,variation is -0.58+_0.69 in test group,-0.54+_
  0.80 in control.No gap statistically(p=0.6296)
  After 12 weeks from final application,variation is -0.29+_0.84 in test group,
  average -0.33+_0.89 in control.No gap statistically (p=0.5606)
  Between 2 groups , there is no difference statistically.

- **After 2,6,12,24 weeks from final application,the values of wrinkles by 5 stages by tester of lever of change from baseline.**
  In FAS,after 2 weeks from final application,average variation is -1.22+_0.87
  -1.21+_0.90 in control. No gap statistically(p=0.8283)
  After 6 weeks from final application,average variation is -1.16+_0.81 in test group ,-1.16+_0.79 in control. No gap statistically(p=1.000
  After 12 weeks from final application,average variation is -1.09+_0.79 in test group,
  -1.07+_0.73 in control.No gap statistically(p=0.4409)

After 24 weeks from final application,average variation is -1.04+_073 in test group,

-1.04+_0.73 in control. No gap statistically(p=0.4675)

Between 2 groups(PP & FAS group), there is no difference statistically.

- After 2,6,12,24 weeks from final application,level of change of GAI by tester.

  In FAS,after 2 weeks, Global Aesthetic Improvement(GAI) by tester(upgrade, much, very much) is 99.16% in test group &98.32 in control.After 6 weeks,97.39 % ,99.13 % each. After 12 weeks,95.41 %, 92.66%each.After 24 weeks,91.30 %,92.17

  %eachBetween 2 groups no gap statistically.Also,the result of PP is similar with FAS.

  GAI by tester between 2 groups is no difference statistically.

- After 2,6,12,24 weeks from final application,level of GAI by subject

  In FAS,after 2 weeks,GAI by subject(upgrade,much,very much) is 94.12%in test group &92.44%in control.After 6 weeks,93.91%,93.91%each.After12weeks 88.07%

  85.32%each,After 24 weeks,83.48%,82.61%each.Between 2 groups no gap statistically.Also,the result of PP is similar with FAS. GAI by subject between 2 groups is no difference statistically.

- **After 24 weeks from final application,values of level of change by 5 stages by tester**

  is at least -1 over of rate of subject

  In FAS,rate of improvement (WSRS) is 77.50% in test group &77.50% in control. No gap statistically(p-value=1.0000) In PP,79.65% in test group &79.65% in control.No gap statistically(p-value=0.8101)

After 24 weeks from final application,the result for improvement of wrinkles,difference about rate of improvement between test & control group is abt.25 %.97.5% of difference rate of improvement of wrinkles &lower limit of confidence of interval is-9.60 % So,bigger than -20%(allowable limit of non inferiority)Confirm that test group is non inferiority VS control group.Also, clinically there is no abnormal reaction and clinically there is no problem in evaluation of safety.Therefore,results of clinical trials,come to the conclusion that SkinPlus-Hyal has a safety and has a effectiveness about improvement of nasolabial wrinkles.