An evaluator-blinded multi-center study of combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster as compared to single treatment with either Azzalure/Dysport alone or Restylane/Emervel filler alone

Q-Med /Galderma Products:	Dermal fillers (Medical devices) Restylane®Lidocaine, Restylane®Perlane Lidocaine, Emervel®Classic Lidocaine, Emervel®Deep Lidocaine Restylane Skinboosters (Medical device) Restylane® Vital Lidocaine (Europe) Restylane® Vital (Brazil) Botulinum toxin (Medicinal product) Azzalure® (Europe) Dysport® (Brazil)
Q-Med /Galderma Substance:	Dermal fillers and Restylane Skinboosters Stabilised hyaluronic acid of non-animal origin containing lidocaine hydrochloride Botulinum toxin Clostridium botulinum toxin type A
Clinical Trial Number:	05PDF1401 (Study 2)
EudraCT Number:	2014-001202-17
Sponsor:	Q-Med AB [redacted]

1 Signed Agreement of the Study Protocol

1.1 Investigator statement

Clinical Trial Number: 05PDF1401 (Study 2)
EudraCT Number: 2014-001202-17

Study title: An evaluator-blinded multi-center study of combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster as compared to single treatment with either Azzalure/Dysport alone or Restylane/Emervel filler alone

We, the undersigned, have read and understand the protocol specified above, and agree on the contents. The study protocol, the Clinical Trial Agreement and the additional information given in the Instructions for Use and Summary of Product Characteristics will serve as a basis for co-operation in this study.

Principal Investigator

Print Dr Name, Site _____ Signature _____ Date

1.2 Signature page

Head of Medical Affairs, Q-Med [redacted]	Electronically signed in the document management system within Q-Med quality management system
Study Director, Q-Med [redacted]	Electronically signed in the document management system within Q-Med quality management system
Study Statistician, Q-Med [redacted]	Electronically signed in the document management system within Q-Med quality management system

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2 Abbreviations and definitions of terms

AE	Adverse event
Azzalure/Dysport	Botulinum toxin A
CE	Conformité Européene
CRF	Case Report Form
CTA	Clinical Trial Agreement
DMP	Data Management Plan
eCRF	Electronic Case Report Form
[redacted]	[redacted]
GCP	Good Clinical Practice
HA	Hyaluronic acid
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
NLF	Nasolabial fold
NSAID	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-counter
PP	Per protocol
QA	Quality Assurance
SAE	Serious Adverse Event
s.U	Speywood Unit
WHO	World Health Organization
Co-ordinating Investigator	An Investigator assigned the responsibility for the coordination of Investigators at different sites participating in a multicenter study
Institution	Any public or private entity or agency or medical or dental facility where clinical studies are conducted.
Investigator	The Principal Investigator or other qualified person, i.e. subinvestigator, designated and supervised by the Principal Investigator at a study site to perform critical study-related procedures and/or make important study-related decisions as specified on the delegation log.
Investigator File	Essential documents relating to a clinical study as defined in ICH-GCP guidance document and maintained by the Investigator.
Sponsor File	Essential documents relating to a clinical study as defined in ICH-GCP guidance document and maintained by the Sponsor.
Study product	Investigational product (study drug and study medical device)

3 General Information/Study Administrative Structure

Co-ordinating Investigator	[redacted]
Sponsor	Q-Med AB [redacted]
Chief Medical Officer, Head of Medical Affairs	[redacted]
Sponsor's Medical Expert	[redacted]
Study Director	[redacted]
Study Statistician	[redacted]

Further details on the complete study administrative structure are found in the Sponsor File. Administrative changes are to be documented in the Sponsor File without requiring a formal protocol amendment.

4 Clinical Study Protocol Synopsis

Title of study:	An evaluator-blinded multi-center study of combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster as compared to single treatment with Azzalure/Dysport alone or Restylane/Emervel filler alone.
Clinical Trial Number:	05PDF1401 (Study 2)
EudraCT Number:	2014-001202-17
Countries involved, number of sites/country, number of subjects	Approximately 60 subjects from 4-6 sites in Europe and Brazil will be involved in this study.
Clinical Study Objectives	The **primary objective** of this study is to evaluate if superior global facial aesthetic appearance can be achieved by combined treatment compared to single treatment. Comparisons are made between treatment results at 1 month after single treatment with treatment results at 1 month after first combined treatment in the same individual. Treatment result will be assessed by blinded evaluation of photographs. • single treatment is either Azzalure/Dysport* alone or Restylane/Emervel filler alone, • combined treatment consists of Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster. *Azzalure will be used in European countries and Dysport in Brazil. The **secondary objectives** of this study are to evaluate : • If superior global facial aesthetic appearance is achieved [redacted], as assessed by blinded evaluation of photographs. • [redacted] • First impression and perceived age assessment [redacted] y blinded evaluation of photographs. • [redacted] • Subject satisfaction [redacted] • Investigator satisfaction [redacted] • [redacted] • Injected filler volume [redacted] • Safety by assessment of adverse events (AEs) throughout the study period.

Study Design:	This is an evaluator-blinded, within-group comparative, multi-center study of the efficacy and safety of combined treatment with Azzalure/Dysport, Restylane/Emervel fillers and Restylane skinbooster as compared to single treatment with either Azzalure/Dysport alone or Restylane/Emervel filler alone. Approximately 60 subjects aged 35-50 years old with the intention to undergo facial aesthetic treatment of upper face, NLFs and/or cheeks and facial skin rejuvenation will be asked to participate in the study. Subjects will be randomised 1:1 to either Group A or Group B. The only difference between the two groups is the assignment of single treatment at baseline. Both groups will receive the same combined treatments at 6 months and 12 months thereafter. All subjects will be followed for 18 months. <u>Single treatment at baseline:</u> Subjects in Group A will receive a single treatment with Azzalure/Dysport injection of at least two of the following upper facial lines including glabellar lines, crow´s feet and forehead lines [redacted] Subjects in Group B will receive a single treatment with Restylane or Emervel filler injection [redacted] <u>Combined treatment and follow-up:</u> At 6 months and from 6 months onwards, both Group A and Group B will receive the same combined treatments as follows: At 6 months, the first combined treatment consisting of Azzalure/Dysport injection of at least two of the following facial lines including glabellar lines, crow´s feet and forehead lines, Restylane/Emervel filler injection of NLFs and/or cheeks and other facial areas as required if there is product left, and a Restylane skinbooster treatment of the face. [redacted] At 12 months, a second combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster similar to the first combined treatment. [redacted] For all treatments additional local anaesthesia may be used. In addition to treatment visits at baseline, 6 months and 12 months with optional touch up visits at 2 weeks following each Azzalure/Dysport treatment; follow-up visits are scheduled at 1 month, 3 months, 9 months, 15 months and 18 months. <u>Assessments:</u> Assessments will be made following the single treatment, the first combined treatment and the second combined treatment. Analysis will be made by comparing results following these three treatments. Photographs will be taken according to standardised settings. The parameters below will be analysed. Superior global facial aesthetic appearance, first impression and perceived age of subjects will be assessed by blinded evaluation of photographs. Global aesthetic improvement will be assessed by the subject, the investigator and by blinded evaluation. Wrinkle severity scores of glabellar lines, crow´s feet and forehead lines will be evaluated by the investigator. Subject and investigator satisfaction will be evaluated by questionnaires. Filler volume injected in NLFs and cheeks will be evaluated at each treatment session. Safety will be followed by adverse event reporting throughout the study.

Inclusion criteria:	1. Subjects aged 35 to 50 years old. 2. Subjects with the intention to undergo facial aesthetic treatment and who are likely to benefit from a combination of injection treatments and the benefit can be shown by improvements in their global facial aesthetic appearance and satisfaction. [redacted] 3. Subjects with nasolabial folds assessed as mild or moderate. 4. Subjects with upper facial lines to be treated (at least two of glabellar lines, crow´s feet and/or forehead lines) assessed as moderate or severe, when the severity of the lines has an important psychological impact on the subject. 5. Subjects with signed informed consent.
Exclusion criteria:	**Current facial conditions** 1. Obvious facial sagging (major loss of facial fat/volume). 2. Signs or symptoms of eyelid ptosis or signs of compensatory frontalis muscle activity. 3. Heavily scarred or sun-damaged facial skin. 4. Active skin disease, inflammation or related conditions, such as infection, psoriasis and herpes zoster near or on the areas to be treated. 5. Cancerous or pre-cancerous lesions in the areas to be treated. **Previous facial/dermatological procedures** 6. Facial tissue augmenting therapy or revitalization treatment with hyaluronic acid (HA) or collagen, or botulinum toxin treatment during the last 12 months. 7. Procedures or treatments inducing an active dermal response such as laser, Intense Pulsed Light, chemical peeling, microdermabrasion, retinoids within the last 6 months. 8. Any aesthetic surgery of the face. 9. Permanent implant or aesthetic treatment with non-HA or non-collagen products in the face. **Medical history and current health/medications** 10. History of severe keloids and/or hypertrophic scars. 11. Neuromuscular junctional disorders (e.g. myasthenia gravis, Eaton Lambert syndrome or amyotrophic lateral sclerosis) or history of dysphagia and aspiration. 12. Known hypersensitivity to hyaluronic acid, botulinum toxin, lidocaine hydrochloride or other amide-type anesthetics. 13. History of autoimmune diseases. 14. Any medical condition that in the opinion of the investigator would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may affect the general condition or may require frequent medical treatment). 15. Concomitant anticoagulant therapy and therapy with inhibitors of platelet aggregation (e.g. aspirin or other nonsteroidal anti-inflammatory drugs [NSAIDs]), Omega-3 or vitamin E within 10 days before study treatment, or a history of bleeding disorders. 16. Immunosuppressive therapy, chemotherapy, or systemic corticosteroids within the last 3 months prior to baseline visit. 17. Female subjects who are pregnant or plan to become pregnant within the study timeframe, or who are nursing. [redacted]

	[redacted]
Investigational product, dose and mode of administration:	**Medicinal products** Azzalure®/Dysport® (botulinum toxin A) treatment * Azzalure: A vial with 125 s.U of Azzalure powder is to be reconstituted in 0.63 mL NaCl 0.9% before injection (10 U per 0.05 mL of reconstituted solution). • Treatment areas and recommended doses: o Glabellar lines, 50 s.U according to SmPC o Crow´s feet, 60U, 30 s.U/side, 3 points/side o Forehead lines, 20-60 s.U, 4-6 points, 5-10 s.U per point • Touch-up treatment can be administered (optional) • No treatment of other areas is allowed **For Brazil Dysport is used instead of Azzalure:* *Dysport: A vial with 300 s.U of Dysport powder is to be reconstituted in 1.5 mL NaCl 0.9% before injection (10 s.U per 0.05 mL of reconstituted solution).Maximum 125 s.U is allowed to be used.* **Medical device products** Restylane or Emervel filler treatment Each subject will receive filler treatment from either the Restylane range or the Emervel range and the same range is to be used throughout the study. At each treatment occasion choice of filler product will be based on investigator preference after discussion with the subject. Restylane range of filler products includes Restylane Lidocaine, and Restylane Perlane Lidocaine Emervel range of filler products includes Emervel Classic Lidocaine, and Emervel Deep Lidocaine For subjects in Group B: Maximum 1 mL (one syringe) of Restylane or Emervel filler can be administered at initial treatment at baseline and maximum 2 mL (two syringes) at each of the two combined treatments. • If a subject receives a Restylane filler at baseline, products within the Restylane range should be used at both subsequent combined treatments. The investigator is free to choose between products within the Restylane range. • If a subject receives an Emervel product at baseline, products within the Emervel range should be used at both subsequent combined treatments. The investigator is free to choose between products within the Emervel range. • Treatment of nasolabial folds and/or cheeks are mandatory at initial single treatment and the first and second combined treatments. At the first and second combined treatments other facial areas can be treated as required if there is product left in the syringe(s) after treatment of mandatory areas. • No touch-up treatments using fillers is allowed. For subject in Group A: Maximum 2 mL (two syringes) of fillers from either the Restylane or Emervel ranges can be used at each of the two combined treatments. • If a subject receives a Restylane filler at the first combined treatment, products within the Restylane range should be used at the second combined treatment. The investigator is free to choose between products within the Restylane range. • If a subject receives an Emervel product at the first combined treatment, products within the Emervel range should be used at the second combined treatment. The investigator is free to choose between products within the Emervel range.

	• Treatment of nasolabial folds and/or cheeks are mandatory at the first and second combined treatments. At the first and second combined treatments other facial areas can be treated as required if there is product left in the syringe(s) after treatment of mandatory areas. • No touch-up treatments using fillers is allowed. Restylane skinbooster treatment as part of both combined treatments in both Group A and Group B Restylane skinbooster product refers to Restylane Vital Lidocaine (Europe) and Restylane Vital (Brazil). • Maximum 1 mL (one syringe) of Restylane skinbooster can be administered at each treatment. • Facial skin rejuvenation treatment. ***Note:*** Individual treatment areas cannot be injected with both Azzalure and filler or both Azzalure and Restylane skinbooster at the same treatment occasion.
Reference therapy, dose and mode of administration	NA
Treatment schedule:	**Treatment** At baseline (visit 2) The first injections will be performed. • Group A will receive Azzalure/Dysport [redacted] • Group B will receive Restylane or Emervel filler injection of NLFs and/or cheeks [redacted] 2 weeks after baseline (visit 2b) Group A will receive an optional touch-up treatment [redacted] 6 months after baseline (visit 5) Both groups will receive a combined treatment with Azzalure/Dysport injection [redacted] 2 weeks after first combined treatment (visit 5b) Both groups will receive an optional touch-up treatment with Azzalure/Dysport [redacted] 12 months after baseline (visit 8) Both groups will receive a second combined treatment with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster. [redacted] 2 weeks after second combined treatment (visit 8b) Both groups will receive an optional touch-up treatment with Azzalure/Dysport [redacted] **Follow-up** Each subject will participate for a period of approximately 18 months. Up to 14 study visits are scheduled for each subject.

Efficacy Assessment:	**Primary efficacy assessment:** "Global facial aesthetic *appearance"* [redacted] will be compared by a blinded evaluator who will review a set of photographs taken from each of the two visits and then choose the set of photographs that show superior global facial aesthetic *appearance*. **Secondary efficacy assessments:** • "Global facial aesthetic *appearance"* [redacted] by a blinded evaluator that will review photographs from the visits and chose at which set of photographs the subject shows superior global facial aesthetic *appearance*. • [redacted] • First impression and perceived age of subjects will be assesses by a blinded evaluator reviewing photographs [redacted] • [redacted] • Subject satisfaction will be assessed a[redacted] • Investigator satisfaction will be assessed at follow-up visits (at 1, 7, 12, 13 and 18 months). • Wrinkle severity scores of treated glabellar lines [redacted] • Injected filler volume [redacted]
Safety Assessment:	• Safety by assessment of AEs by the investigator throughout the study period.
Statistical Methods:	[redacted]

5 Background Information

5.1 Indication Description

5.2 Product Description

[redacted]

5.3 Justification for the design of the clinical study

[redacted]

[redacted]

5.4 Risks and benefits of the study products and the clinical study

[redacted]

[redacted]

[redacted]

5.5 Study Rationale

[redacted]

[redacted]

[redacted]

[redacted]

5.6 Compliance Statement

The study will be conducted in compliance with the Clinical Trial Agreement (CTA), the study protocol, Good Clinical Practice (GCP) and applicable regulatory requirements. The international standards for GCP, intended for medical devices ISO 14155:2011 and intended for pharmaceuticals ICH GCP E6, will be followed. The provision of informed consent and review by Independent Ethics Committees (IEC) or Institutional Review Boards (IRB) as required by e.g. the Declaration of Helsinki (Appendix1) will also be followed. The collection, access to, processing and transfer of protected health information and/or sensitive personal data will be carried out in accordance with applicable rules and regulations.

6 Study Objectives

6.1 Primary Objective

The **primary objective** of this study is to evaluate if superior global facial aesthetic appearance can be achieved by combined treatment compared to single treatment. Comparisons are made between treatment results at 1 month after single treatment with treatment results at 1 month after first combined treatment in the same individual. Treatment result will be assessed by blinded evaluation of photographs.

- single treatment is either Azzalure/Dysport* alone or Restylane/Emervel filler alone,
- combined treatment consists of Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster.

*Azzalure will be used in European countries and Dysport in Brazil.

6.2 Secondary Objectives

The **secondary objectives** of this study are to evaluate:

- If superior global facial aesthetic appearance is achieved [redacted]
- [redacted]
- First impression and perceived age assessment [redacted] by blinded evaluation of photographs.
- [redacted]
- Subject satisfaction [redacted]
- Investigator satisfaction [redacted]
- [redacted]
- Injected filler volume [redacted]
- Safety by assessment of adverse events (AEs) throughout the study period.

7 Study Design

7.1 Study Outline

This is an evaluator-blinded, within-group comparative, multi-center study of the efficacy and safety of combined treatment with Azzalure/Dysport, Restylane/Emervel fillers and Restylane skinbooster as compared to single treatment with either Azzalure/Dysport alone or Restylane/Emervel filler alone.

Approximately 60 subjects aged 35-50 years old with the intention to undergo facial aesthetic treatment of upper face, NLFs and/or cheeks and facial skin rejuvenation will be asked to participate in the study.

Subjects will be randomised 1:1 to either Group A or Group B. The only difference between the two groups is the assignment of single treatment at baseline. Both groups will receive the same combined treatments at 6 months and 12 months thereafter. All subjects will be followed for 18 months.

At baseline subjects in **Group A** will receive a single treatment with Azzalure/Dysport injection [redacted]

At 6 months and from 6 months onwards, both Group A and Group B will receive the same combined treatments as follows:

At 6 months, the first combined treatment is administered consisting of Azzalure/Dysport injection [redacted] Restylane/Emervel filler injection [redacted], and a Restylane skinbooster treatment of the face. [redacted]

At 12 months, a second combined treatment is administered with Azzalure/Dysport, Restylane/Emervel filler and Restylane skinbooster similar to the first combined treatment. [redacted]

For all treatments additional local anaesthesia may be used.

In addition to treatment visits at baseline, 6 months and 12 months with optional touch up visits at 2 weeks following each Azzalure/Dysport treatment; follow-up visits are scheduled at 1 month, 3 months, 9 months, 15 months and 18 months.

Assessments will be made following the single treatment, the first combined treatment and the second combined treatment. Analysis will be made by comparing results following these three treatments. Photographs will be taken according to standardised settings. The parameters below will be analysed.

Superior global facial aesthetic appearance, first impression and perceived age of subjects will be assessed by blinded evaluation of photographs. Global aesthetic improvement will be assessed by the subject, the investigator and by blinded evaluation. Wrinkle severity scores of glabellar lines, crow´s feet and forehead lines will be evaluated by the investigator. Subject and investigator

satisfaction will be evaluated by questionnaires. Filler volume injected in NLFs and cheeks will be evaluated at each treatment session.

Safety will be followed by adverse event reporting throughout the study.

7.2 Number of Subjects

Approximately 60 subjects (30 subjects in group A and 30 in group B) will be recruited from 4-6 sites in Europe and Brazil.

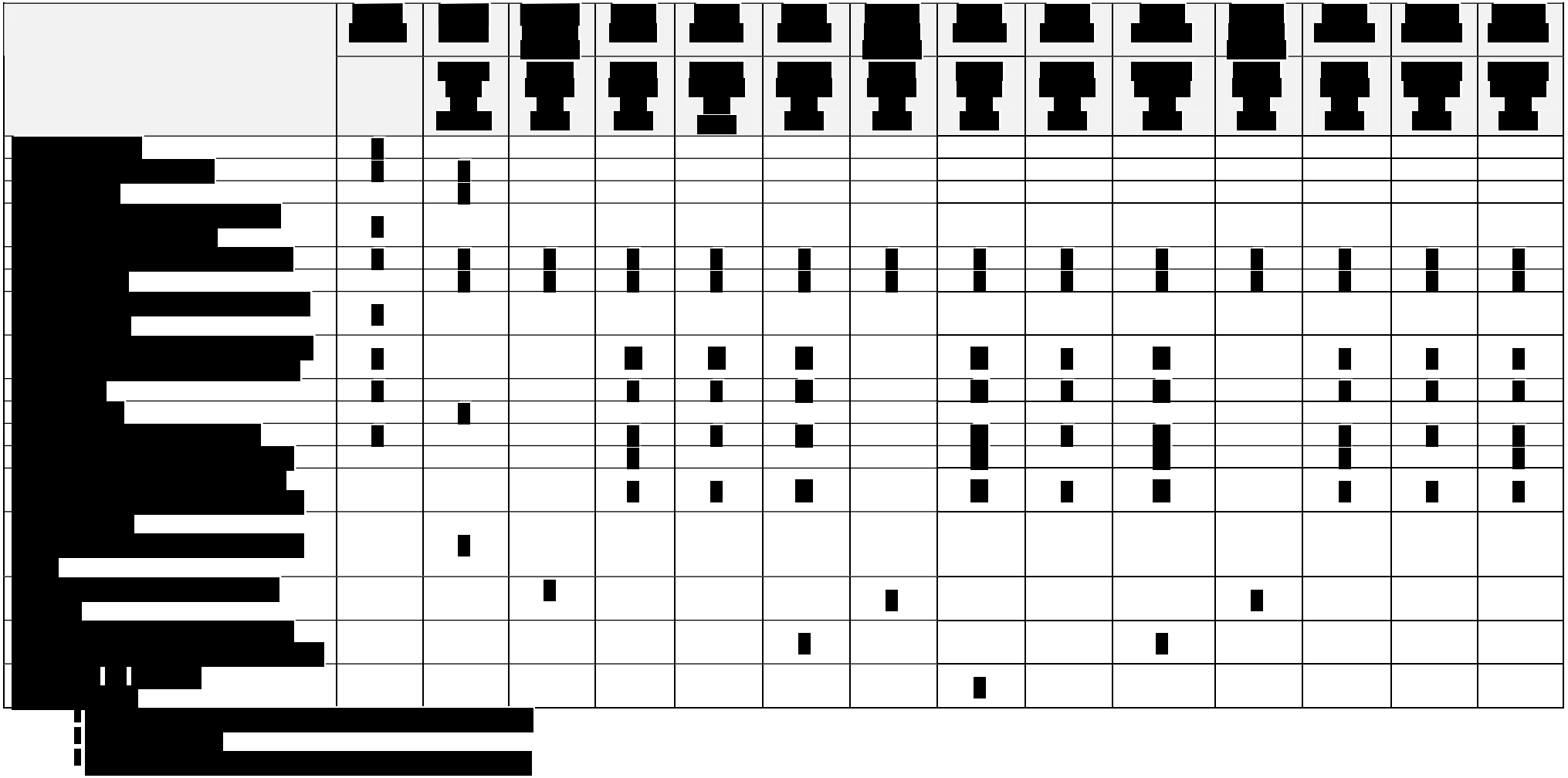
7.3 Duration of the Study and Subject Participation

A subject will be involved in the study for approximately 18 months.

7.4 Schedule of Events

The assessments to be done at each visit are presented in Table 1. The corresponding electronic Case Report Forms (eCRFs) should be completed and signed by the Investigator for each visit. In case of a withdrawal (subject dropout before completion of the intended follow-up period), the Study Termination Section in the eCRF should be completed.

Table 1 Schedule of Events



[redacted]

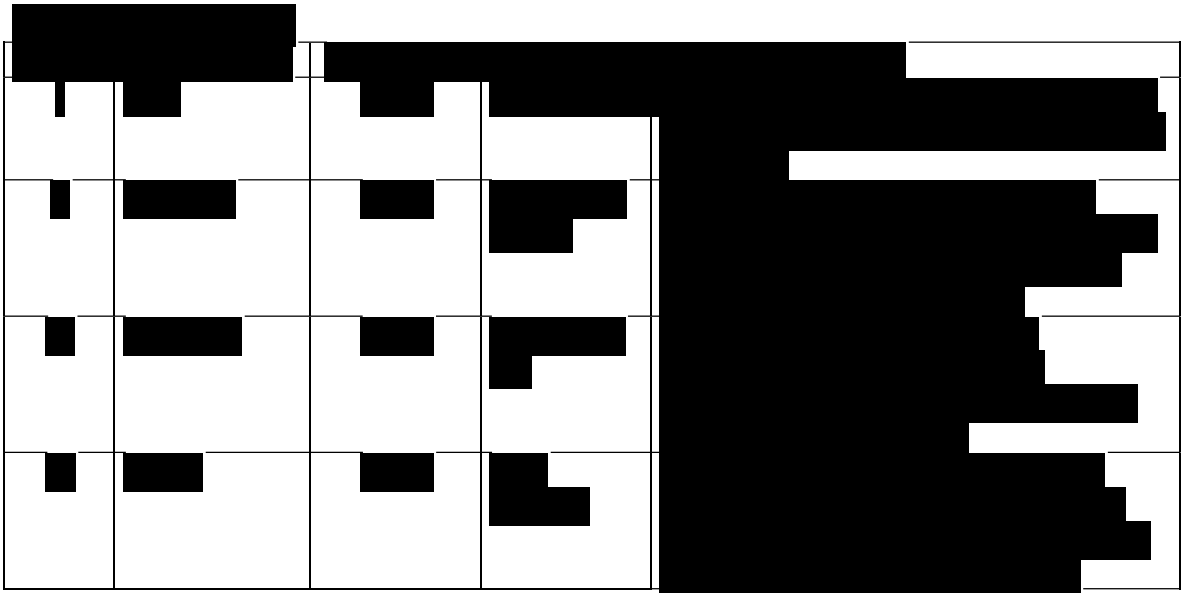
[redacted]

7.5 Demographics and Baseline Assessments at Screening Visit

Demographics and baseline assessments include:

- Informed consent
- Subject initials (collected only if accepted by national regulations)
- Date of birth (collected only if accepted by national regulations)
- Age
- Gender
- Ethnic origin (collected only if accepted by national regulations)
- Inclusion and exclusion criteria
- Relevant medical history/concurrent diseases
- Previous facial dermatological/surgical procedures performed, areas treated and products used (e.g. fillers, neurotoxins, Restylane skinbooster)
- Smoking history (yes/no; if no, stopped within the last 12 months before treatment)
- Concomitant medications and procedures
- [redacted]
- Assessment of face skin condition (sun-damaged skin [yes/no] and skin elasticity [elastic/non-elastic]) and skin type [redacted]

[redacted]



8 Selection and Withdrawal of Subject

8.1 Subject Inclusion Criteria

1. Subjects aged 35 to 50 years old.
2. Subjects with the intention to undergo facial aesthetic treatment and who are likely to benefit from a combination of injection treatments and the benefit can be shown by improvements in their global facial aesthetic appearance and satisfaction.
3. Subjects with nasolabial folds assessed as mild or moderate.
4. Subjects with upper facial lines to be treated (at least two of glabellar lines, crow´s feet and/or forehead lines) assessed as moderate or severe, when the severity of the lines has an important psychological impact on the subject.
5. Subjects with signed informed consent.

8.2 Subject Exclusion Criteria

Current facial conditions

1. Obvious facial sagging (major loss of facial fat/volume).
2. Signs or symptoms of eyelid ptosis or signs of compensatory frontalis muscle activity.
3. Heavily scarred or sun-damaged facial skin.
4. Active skin disease, inflammation or related conditions, such as infection, psoriasis and herpes zoster near or on the areas to be treated.
5. Cancerous or pre-cancerous lesions in the areas to be treated.

Previous facial/dermatological procedures

6. Facial tissue augmenting therapy or revitalization treatment with hyaluronic acid (HA) or collagen, or botulinum toxin treatment during the last 12 months.
7. Procedures or treatments inducing an active dermal response such as laser, Intense Pulsed Light, chemical peeling, microdermabrasion, retinoids within the last 6 months.
8. Any aesthetic surgery of the face.
9. Permanent implant or aesthetic treatment with non-HA or non-collagen products in the face.

Medical history and current health/medications

10. History of severe keloids and/or hypertrophic scars.
11. Neuromuscular junctional disorders (e.g. myasthenia gravis, Eaton Lambert syndrome or amyotrophic lateral sclerosis) or history of dysphagia and aspiration.
12. Known hypersensitivity to hyaluronic acid, botulinum toxin, lidocaine hydrochloride or other amide-type anesthetics.
13. History of autoimmune diseases.
14. Any medical condition that in the opinion of the investigator would make the subject unsuitable for inclusion (e.g. a chronic, relapsing or hereditary disease that may affect the general condition or may require frequent medical treatment).
15. Concomitant anticoagulant therapy and therapy with inhibitors of platelet aggregation (e.g. aspirin or other nonsteroidal anti-inflammatory drugs [NSAIDs]), Omega-3 or vitamin E within 10 days before study treatment, or a history of bleeding disorders.
16. Immunosuppressive therapy, chemotherapy, or systemic corticosteroids within the last 3 months prior to baseline visit.
17. Female subjects who are pregnant or plan to become pregnant within the study timeframe, or who are nursing.

8.3 Assigning Screening and Subject Numbers

Each study participant who has signed the Informed Consent Form will be assigned a screening number and should be listed on a Screening and Inclusion Log. The reason for excluding a subject from entering the study should be specified in each case.

When the Investigator has confirmed that all inclusion criteria and no exclusion criteria are met, each study participant will be assigned a subject number consisting of the centre number followed by a consecutive number starting with 01 at each centre. The subject number, subject name and other information sufficient to link the eCRF to the medical records (e.g. social security number, chart number, etc.) should be recorded on a Subject Identification List.

8.4 Withdrawal of Subjects

A subject can be withdrawn from the study if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject. If a subject does not return for a scheduled visit, every effort should be made to contact that subject. In any circumstance, every effort should be made to perform follow-up assessments of subjects and to document subject outcome for all study assessments (primary and secondary variables), if possible.

The reason for withdrawal should be clearly described on the Study Termination Form, and, when possible, an explanatory comment should be added to further explain the reason for withdrawal.

A withdrawn subject should not be replaced or re-entered in the study.

If an AE, which according to the investigator's assessment is related to the use of any of the study products, is still ongoing at the time of the withdrawal, the subject should be followed up until the AE resolves or is assessed by the investigator to be chronic or stable, or for at least 3 months (Section 11.1.6).

A "screening failure" is not defined as a subject being withdrawn from the study. A screening failure is a subject who signed the Informed Consent Form but failed any of the inclusion or exclusion criteria and never received treatment with the study product. For screening failures, the screening visit eCRFs should be completed to an extent which makes it clear which assessments have been made and the reason why the subject did not fulfil the eligibility criteria.

9 Study Products and Treatment of Subjects

The term "study product" refers to Azzalure and Dysport (study drug) and Restylane and Emervel fillers and Restylane skinbooster (study device). All study products will be provided by Q-Med AB. The study products are for single use only.

[redacted]

[redacted]

[redacted]

[redacted]

9.2 Reference Product

No reference product will be used in this clinical study.

9.3 Additional Products and Material

The sponsor will provide blunt cannulas and photo material as needed to the clinics. Pregnancy tests (U-HCG) and Sodium Chloride 9 mg/mL (0.9%) solution for injection (for reconstitution of Azzalure®/Dysport® powder), will be ordered by each clinic and the cost will be taken by the sponsor.

The investigator will provide anaesthetics for the treatment sessions and adequate equipment in case of emergency.

9.4 Packaging, Labelling and Storage

Standard commercially available Azzalure®, Dysport®, Restylane®Lidocaine, Restylane® Perlane Lidocaine, Emervel®Classic Lidocaine, Emervel®Deep Lidocaine, Restylane® Vital Lidocaine and Restylane® Vital will be used.

In addition to the standard labelling of the products, an additional labelling for clinical trial use as required by Good Manufacturing Practice, Good Clinical Practice will be attached to the boxes according to national regulations.

[redacted]

9.5 Treatment with Study Product

9.5.1 Treatment Procedure

The study products are reserved for use by doctors who have been trained in the appropriate injection techniques.

All traces of cosmetics should be removed prior to any injection. The treatment site should be cleaned with a suitable antiseptic solution (extend at least 5 cm around the injection site). Good aseptic technique should be observed at all times including the use of disposable gloves during the injection procedure.

Before injections, local anesthetics may be used at the discretion of the investigator.

Individual treatment areas cannot be injected with both Azzalure and filler or both Azzalure and Restylane skinbooster at the same treatment occasion.

[redacted]

[redacted]

eCRF recording

The local anaesthetic (if applicable), study product used, injection technique, injected volume or injected dose and type and size of cannula/needle should be recorded for each treatment area in the eCRF.

[redacted]

9.6 Randomisation and Blinding

9.6.1 Randomisation

Prior to study start, a statistician from Q-Med or designee will generate a randomisation list by using the SAS® system or applicable eCRF system.

Each subject will be assigned a consecutive subject number by the eCRF system at the treatment visit when all inclusion criteria and exclusion criteria have been verified. Each subject number is linked to Group A or Group B according to the randomization list.

9.6.2 Blinding

External blinded evaluator(s) will perform all blinded evaluations retrospectively by using photographs. The blinded evaluator(s) will not have any access to documents with information on individual study treatment.

The site personnel and subjects will not be blinded during the study. Neither will the sponsor and sponsor representative at site be blinded during the study.

9.7 Compliance to the Study Treatment

The investigational products are administered by the investigator and the details of the administration are recorded in the eCRF.

- Azzalure/Dysport (Study drug): the volume for reconstitution as well as the injected dose will be reported in the eCRF for each treatment area.
- Restylane and Emervel fillers and Restylane Skinbooster (Study devices): the injected volume of each product will be reported in the eCRF for each injected area.

No other measurements of treatment compliance will be made.

9.8 Continuation of Treatment

No additional treatment will be provided after the last treatment at the 12-month visit and optional touch-up visit at 2 weeks after the 12-month visit. Subjects should be informed that continued treatment after study end is provided by aesthetic clinics.

9.9 Product Accountability

The products will be released to the Principal Investigator after approval of the protocol has been obtained from the IRB/IEC and RA, if applicable, and the CTAs have been finalised and signed at the sites.

The Principal Investigator must ensure that the study products (study drugs and study devices) are kept in a secure location, with access limited to those authorised by the Principal Investigator.

The study products must be traceable from the manufacturer to their use in subjects, and it is therefore important that the Principal Investigator maintains accurate product accountability records, i.e. documentation of deliveries and return of study products between the Sponsor and the Principal Investigator, and documentation of administration of product to the subject. A log will be kept of all study products received from the Sponsor, including date received, batch number, expiration date and amount received.

In addition, dispensing logs will be maintained for each specific study product batch, including the date, the number of study products (study drug vials or medical device syringes) used and the subject receiving the study products.

The used study products will be destroyed at site. During the study all unused study products will be inventoried by the sponsor representative at site (study monitor).

When the study is completed, all unused study product at each study site will be returned to Sponsor or designee for destruction or be destroyed locally at the site, with proper documentation.

Products deliberately and/or accidentally destroyed during shipment or at a study site should be accounted for and documented. Used study products should be destroyed according to standard procedures at the clinic. Disposal of hazardous material, i.e. syringes/vials and needles must conform to applicable laws and regulations. The study products must not be used outside the study.

9.10 Concomitant Medication, Treatment and Procedure

Except as noted below, concomitant medications or other treatments or procedures may be utilized when the investigator or delegated personnel deems it medically necessary. Any concomitant medications, including over-the-counter medications (OTC), administered during the study are to be recorded in the eCRFs. The generic name or trade name of the relevant concomitant medication or a description of the concomitant procedure and the reason for its use should also be entered in the eCRF.

[redacted]

If a subject has used any of the above prohibited medications or procedures, she or he should, for safety reasons, continue in the study for the scheduled follow-up visits.

The subject will be instructed to remove any make-up at the clinic prior to assessments and photographs, or alternatively remove the make-up prior to arrival at the clinic.

10 Efficacy Assessments

10.1 General Information

The methods for collecting efficacy data include photography, assessment of superior global facial aesthetic appearance, [redacted] score, first impression and perceived age, wrinkle assessment [redacted] subject satisfaction questionnaire and investigator satisfaction questionnaire, in addition to assessment of injected filler volume.

Throughout the study, efficacy assessments for each individual subject should be performed by the same person at site (investigator or co-investigator). If it is not possible to use the same person to follow the subject, then evaluations should overlap for at least one visit in order to examine the subject together and discuss findings.

At visits when injections are performed, the efficacy assessments should be done prior to the injections.

The subjects should be instructed to remove any make-up prior to arriving to the clinic or to remove it before any assessments are done or photographs are taken.

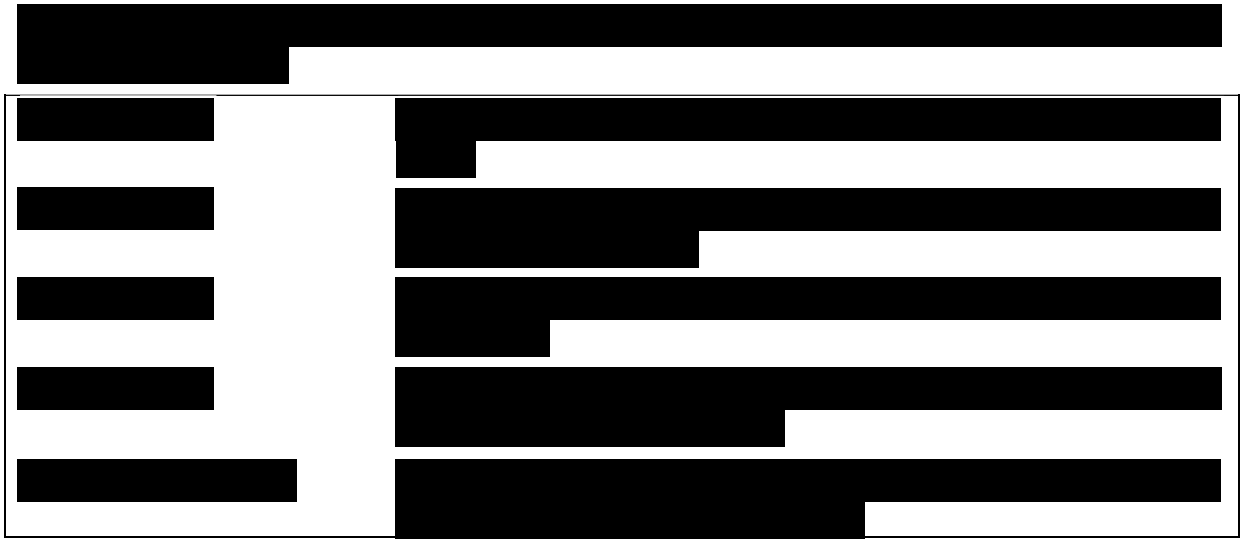
10.2 Photography

Photographs will be taken by the Investigator or study staff before first treatment and at follow-up visits (except touch-up visit 2b, 5b and 8b).

At visits when injections are performed, the photographs should be taken prior to the injections.

Subjects should not ware any make-up on the photographs.

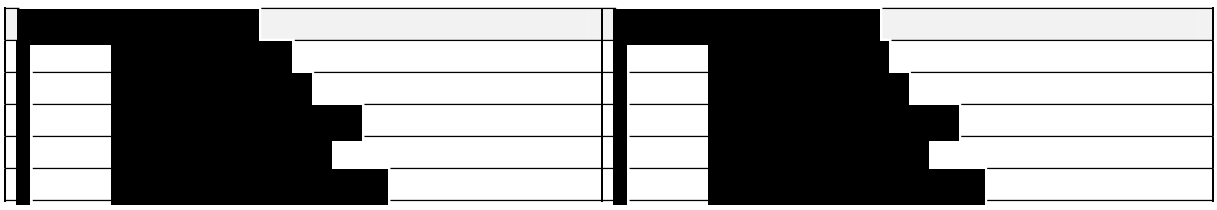
The 2D-photographs should be taken in a standardised way regarding equipment, photographic settings and light conditions at each visit. The photographs should be taken against a neutral background.



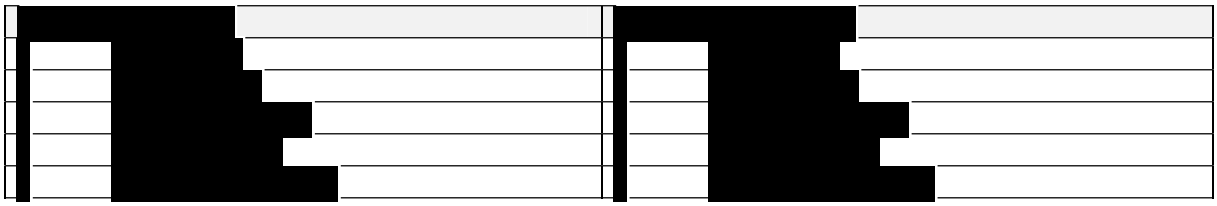
Each photograph should be linked to the subject number and the date and visit number of the photograph.

Training of the study staff on how to use the camera will be performed prior to the start of the study. Photography instruction guidelines will be provided to the sites.

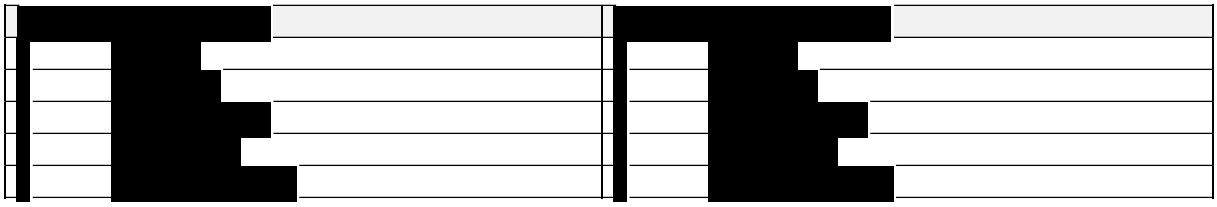
[redacted]



[redacted]



[redacted]



[redacted]

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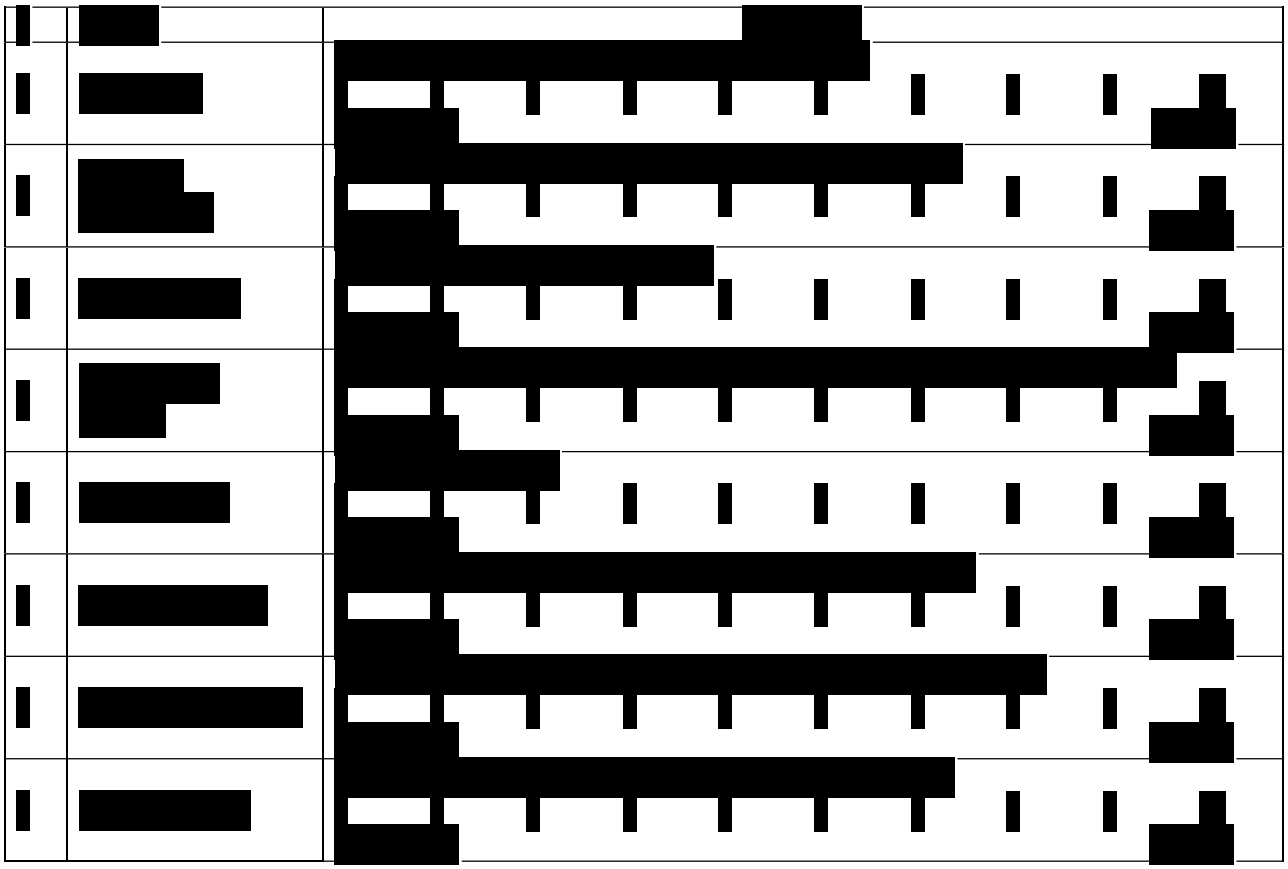
[redacted]



[redacted]

11 Safety Assessments

The methods for collecting safety data include assessments of Adverse Events (Section 11.1) and Device Deficiency (Section 11.2).

11.1 Adverse Events

11.1.1 Definition of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product/investigational product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can be any unfavourable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal/investigational product, whether or not related to the study products or to the study procedures.

Thus any new sign, symptom or disease, or clinically significant increase in the intensity of an existing sign, symptom or disease, should be considered as an adverse event.

Notes:

- Clinically significant worsening of the disease/condition being evaluated, which occurs during the study, is considered an adverse event,
- Any new sign or symptoms suffered by the subject which appear after accidental or intentional overdose or misuse should also be reported as an adverse event.

11.1.2 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is an Adverse Event that

- results in death,
- is life-threatening*,
- requires inpatient hospitalization** or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly or birth defect

And also:

- Other important medical events that jeopardize the subject or require intervention to prevent one of the outcomes listed above

* Life threatening means that the subject was at immediate risk of death from the Adverse Event as it occurred, or it is suspected that the use or continued use of the study product would result in the subject's death. Life threatening does not mean that had an Adverse Event occurred in a more severe form it might have caused death.

** Hospitalisation requires over-night stay at the hospital. Out-patient treatment in an emergency room, and hospitalization solely for the purpose of diagnostic tests, even if related to an adverse event, is not itself a Serious Adverse Event. Hospital admission and operations planned before or during a study are not considered Serious Adverse Events, if the illness or disease existed before the subject was enrolled in the study, unless it deteriorates in an unexpected way during the study.

In cases of doubt of whether an Adverse Event fulfils a criterion for a Serious Adverse Event or not, it should be reported as a Serious Adverse Event (Section 11.1.5).

11.1.3 Recording Instructions

Each subject will be questioned about Adverse Events at each clinical visit following the screening visit. The question asked will be "Since your last clinical visit have you had any health problems?" Information on Adverse Events can also be obtained from signs and symptoms detected during each examination, observations by the study personnel or spontaneous reports from the subjects.

Investigators, or other study personnel, shall record all Adverse Events in the eCRF, including:

- Event term (recorded in standard medical terminology and avoiding abbreviations)
- Affected area
- Start date (first day with symptoms)
- Stop date (last day with symptoms)
- Intensity (mild, moderate or severe)
- Seriousness (serious or not serious, according to definition in Section 11.1.2.)
- Causal relationship to study treatment (study product and study product injection procedure) (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment, other procedures/tests, subject withdrawn)
- Outcome of the Adverse Event (recovered, recovered with sequelae, death, chronic/stable, ongoing)

The AE Form in the eCRF must be signed and dated by the investigator.

11.1.3.1 *Intensity*

For each reported Adverse Event, the intensity will be recorded. The following definitions of intensity are to be used:

Mild:	Awareness of symptoms or signs, but easily tolerated (acceptable).
Moderate:	Enough discomfort to interfere with usual activity (disturbing).
Severe:	Incapacity to work or to do usual activity (unacceptable).

If the intensity changes over time, the maximum intensity of the Adverse Event during the course of the event should be recorded.

11.1.3.2 *Causal Relationship and Seriousness*

Each Adverse Event, serious as well as non-serious, will be assessed by the Investigator for a reasonable causal relationship with the study treatment (study product and study product injection procedure) and for seriousness (yes or no) of the event.

A two-point scale (Yes or No) will be used for causality assessments. Investigators are asked to indicate “Yes” or “No” in response to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?

For the Adverse Events considered to be reasonable related to the study treatment (causality assessment indicated Yes), the study product(s) (i.e. Azzalure/Dysport, Restylane/Emervel filler and/or Restylane skinbooster) involved with the Adverse Event will be specified by the Investigator.

Each Adverse Event will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

11.1.4 Reporting of Adverse Events

Adverse Event reporting shall start after each subject has signed the informed consent form. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All Adverse Events, non-serious as well as serious, are to be reported as an Adverse Event in the eCRF. In addition, **Serious Adverse Events** are to be reported as Serious Adverse Events in the eCRF (see section 11.1.5).

11.1.5 Reporting of Serious Adverse Events

Serious Adverse Events are to be reported by the Investigator to the Sponsor **immediately but not later than 24 hours of awareness** of the event. This initial report can be made via e-mail (electronically sent via eCRF system) or fax.

The initial report should preferably contain all information specified on the Serious Adverse Event form in the eCRF, even if some of it is regarded as preliminary data. This initial SAE report must contain the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- Study number (05PDF1401)
- Subject identification (age, gender, subject study number)
- Study product
- Adverse Event description
- Classification of seriousness (according to definition in Section 11.1.2.)
- Causal relationship to study treatment (study product and study product injection procedure) (yes or no)
- Onset date of Adverse Event and date event became serious
- Treatment specification
- Name of Investigator and original reporter (if other than Investigator)

Any follow-up information as specified on the Serious Adverse Event form in the eCRF should be reported to the Sponsor **immediately but not later than 24 hours of awareness**.

Supporting documentation to SAE report:

- Concomitant Medication form/list
- Concomitant Procedure/Treatment form/list
- Adverse Event form
- Medical History form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports, etc.)

The Sponsor has two affiliates for Serious Adverse Event handling. All SAE reports will be sent to both affiliates for assessment (e-mail addresses will be pre-programmed in the eCRF system):

	Affiliate 1 - Sweden	**Affiliate 2 – France**
E-mail:	[redacted]	[redacted]
Fax number:	[redacted]	[redacted]
Phone number:	[redacted])	[redacted]

If the 24-hour Serious Adverse Event report does not contain full information, or if it is made without using the Serious Adverse Event form, the fully completed and signed Serious Adverse Event form should be e-mailed or faxed to the Sponsor.

The SAE form must be signed and dated by the Investigator and a copy of the report shall be kept at the study site.

SAEs should, in addition, be reported by the Investigator to the responsible IRB/IEC without undue delay, if applicable and according to national regulations.

The Sponsor is responsible for reporting to the Competent Authority/Regulatory Authority, if applicable and according to national regulations.

11.1.6 Follow-up of Unresolved Events after study termination

All serious as well as non-serious Adverse Events with a causal relationship to the study product and/or its usage must continue to be followed even after the subject's participation in the study is finalised. Such events will be followed until resolved, assessed as chronic or stable, or for at least three months within the study. Final outcome after study end can be reported on the AE follow up form in the eCRF.

11.1.7 Pregnancy

Pregnancy itself is not regarded as an Adverse Event.

If there is a pregnancy during the study period the subject must be withdrawn from any following study treatment. The subject must continue to be followed within the study, and the outcome of pregnancy must be reported even if the expected date of delivery occurs after study completion.

If a woman is confirmed pregnant during the study period, the Investigator must fill in the Pregnancy Report Form(s). The initial report will be made in the eCRF system. E-mail, telephone or fax can be used if there are difficulties accessing the eCRF.

- Part A should be completed and submitted to the Sponsor immediately upon knowledge of the pregnancy.
- Part B should be completed and submitted to the Sponsor when the outcome of the pregnancy is known.

All Pregnancy Reports must be sent to the Sponsor (e-mail address will be pre-programmed in the eCRF system):

	Affiliate 1-Sweden
E-mail:	[redacted]
Fax number:	[redacted]
Phone number:	[redacted])

All congenital abnormalities/birth defects, spontaneous miscarriages and ectopic pregnancies shall be reported as **Serious Adverse Events according to section 11.1.5**.

Elective abortions without complications shall not be reported as Adverse Events.

11.1.8 Anticipated Adverse Events

For the **medicinal product**, the Adverse Events that might occur following treatment and are considered as anticipated Adverse Events are listed in the following Summary of Product Characteristics (SmPC):

- Azzalure – Appendix 5
- Dysport – Appendix 6

For the **medical device** products, the Adverse Events that might occur following treatment and are considered as anticipated Adverse Events are listed in the following Instructions for Use (IFU):

- Restylane Lidocaine – Appendix 7
- Restylane Perlane Lidocaine – Appendix 8
- Emervel Classic Lidocaine – Appendix 9
- Emervel Deep Lidocaine – Appendix 10
- Restylane Vital Lidocaine/Restylane Vital – Appendix 11

11.2 Device Deficiency

11.2.1 Definition of Device Deficiency

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety* or performance.

* Inadequacy of device safety refers to properties of the device which could have or have led to an Adverse Event.

11.2.2 Recording Instructions

When a Medical Device Deficiency is discovered, Part A of the Clinical Study Complaint Form (in the eCRF if applicable or on paper CRF) will be completed by the Investigator. The type of complaint will be described and injury to the subject or user and/or unintended exposure to study product will be reported as applicable.

If an injury has occurred, an AE Form should be completed and if applicable a SAE form (Section 11.1). All Serious Adverse Events that has occurred should be recorded according to section 11.1.5.

If no SAE was experienced as a result of the Device Deficiency, the Investigator will assess whether or not the Device Deficiency could have led to an SAE if:

- Suitable action had not been taken
- Intervention had not been made
- Circumstances had been less fortunate

In Part B of the Clinical Study Complaint Form, the Sponsor will make the same assessment.

11.2.3 Reporting Device Deficiency

The Investigator will send the completed Clinical Study Complaint Form to the Sponsor:

	Affiliate 1-Sweden
E-mail:	[redacted]
Fax number:	[redacted]
Phone number:	[redacted]

If an SAE has resulted from a Device Deficiency or if either the Investigator or the Sponsor assesses that the Device Deficiency could have led to an SAE the Sponsor is responsible for reporting the Device Deficiency to Regulatory Authorities and the Investigator is responsible for reporting it to the IEC/IRB, as applicable.

12 Statistics and Data Management

12.1 Data Management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routines include procedures for database set-up and management, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the Data Management Plan (DMP).

The database, the data entry screens and program will be designed in accordance with the study protocol and the eCRFs. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded according to WHODrug and MedDRA as specified in the DMP. SAEs in the clinical database will be reconciled with the safety databases.

When all efforts have been made to ensure that the data entered in the database is as correct and complete as possible, the clinical database will be locked. Study data is transferred to SAS® datasets which thereafter are write protected. Statistical analyses will be generated in SAS® using data from the write protected datasets.

12.2 Statistical Analysis

12.2.1 General Analysis Issues

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system. Confidence intervals and p-values will be 2-sided and performed at a significance level of 5%.

[redacted]

12.2.2 Baseline Values and Subject Characteristics

Baseline values and will be presented by treatment group (Group A and B) using descriptive statistics.

12.2.3 Analysis Populations

Two analysis population sets will be defined for this study:

Safety: [redacted]

Intention to treat (ITT): [redacted]

ITT is the primary population for all efficacy analyses. If there are any protocol deviations that may influence the primary endpoint evaluation considerably, a per protocol (PP) population excluding those subjects may be defined.

The disposition of subjects will be described in tables and/or figures as applicable. The number of included, treated, completed and withdrawn subjects will be presented.

[redacted]

12.2.6 Handling of Missing Data

No imputation of missing data will be performed.

12.2.7 Analysis of data during the study

A first analysis of study data is planned after 7 months of follow-up. The sponsor will compile a statistical report on all available data. All data included in the report will go through quality procedures prior to analysis.

12.2.8 Withdrawals

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal.

12.2.9 Data Monitoring Committee (DMC)

Not applicable.

12.3 Determination of Sample Size

[redacted]

[redacted]

13 Direct Access to Source Data/Documents

The Principal Investigator/Institution shall permit study-related monitoring, audits, IRB/IEC review and regulatory inspections, and shall provide direct access to the source data/medical record.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). During the monitoring, the data recorded in the eCRFs by the Investigator or delegated will be checked for consistency with the source documents/medical record by the study monitor (source data verification). In order to be able to perform source data verification, information about each subject's participation in the study has to be detailed in the medical record.

The Source data Location log specifies what data that should be available in the medical record. The Source data Location log should also specify the data for which the eCRF serves as the source document. Such data only need to be recorded into the eCRF and are typically associated with protocol-specific procedures and not with normal clinical care practice. For this type of study data the Investigator would not be expected to duplicate the information into the medical record.

14 Quality Control and Quality Assurance

Monitoring of the study will be arranged by the Sponsor according to GCP guidelines, by conducting monitoring visits regularly to the study sites during the study in order to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of consistency with data recorded on the eCRFs. Reporting and analysis of protocol deviations will be performed as described in the Study Monitoring Manual.

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate regulatory agencies. It is important that the Investigator and other relevant personnel are available during the monitoring visits and possible audits and inspections that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae or equivalent. The curriculum vitae shall give name, date/place of birth, address and place of work, and shall show the training, appointments and any other information that will confirm the suitability of the Principal Investigator to be responsible for the study. All Investigators and other responsible persons should be listed together with their function in the study on the signature and delegation log.

It is the responsibility of the Principal Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

15 Ethics

15.1 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Principal Investigator to obtain approval of the protocol/protocol amendments from the IEC. The Principal Investigator shall file all correspondence with the IEC in the Investigator File. Copies of the IEC approvals shall be forwarded to the Sponsor. The study product for this study will not be delivered to the study site until a copy of the IEC approval has been supplied by the Principal Investigator to the Sponsor.

The Principal Investigator is responsible for checking what reporting procedures are applicable for his/her IEC regarding Serious Adverse Events and final report of the outcome of the study, and to comply with such reporting procedures during the study period.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

15.3 Subject Information and Consent

It is the responsibility of the Principal Investigator or his/her designated representative, to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. If relevant new information is obtained during the study, the subjects should be informed about this.

The subject must be informed about his/her right to withdraw from the study at any time, and that such withdrawal will not affect his/her future medical care, treatment or benefits to which the subject is otherwise entitled. A copy of the written Subject Information must be given to each subject, to bring home. The Investigator, who gave the verbal and written information about the study to the subject, must sign the Informed Consent Form. See further section 16.4 regarding the protection of personal data. The Subject Information/Informed Consent Form may be revised by the Sponsor and/or the IEC before the start of the study. The Investigator must always use the IEC-approved Subject Information/Informed Consent Form and it must not be changed without prior discussion with the Sponsor and approval from the IEC.

Furthermore, it is the responsibility of the Investigator to obtain signed informed consent from all subjects prior to initiation of any study-related activity. The Investigator will confirm the receipt of informed consent from each subject by a recording in the eCRF. The signed Informed Consent forms shall be filed in the Investigator File for possible future audits and inspections.

15.4 Changes to the Study Protocol

The Principal Investigator should not implement any deviation from or changes to the protocol without agreement with the Sponsor and prior review and documented approval

from the IEC, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final protocol must be documented in a written protocol amendment. However, administrative changes are to be documented in the Sponsor File without requiring a formal protocol amendment.

15.5 Application to Competent Authorities/Regulatory Authorities

The study requires application for approval from the Competent Authority/Regulatory Authority. The study will not be started until receipt by the Sponsor of written approval or elapse of the statutory waiting period from the appropriate authority. The Sponsor should provide the Principal Investigator with a copy of the relevant document.

16 Data Handling and Record Keeping

16.1 Case Report Forms

An electronic data management system will be used to create, modify, maintain, archive, retrieve and transmit study data. An eCRF is required and shall be completed electronically for each screened (screening visit eCRF) and included subject (eCRF section for subsequent completed visits). The study data are the sole property of the Sponsor and shall not be made available in any form to third parties, except for authorised representatives of appropriate competent authorities/regulatory authorities, without written permission from the Sponsor. At study end, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the Investigator site as part of the Investigator File.

Any delegation of completion/entering of data should be specified in a Signature and Delegation Log. All information recorded by the Investigator (or delegated person) should be in English. The eCRFs must be signed and dated by the Investigator, who, by signing, takes responsibility for the accuracy, completeness and legibility of the data reported to the Sponsor in the eCRFs. Forms to be completed by the subject, e.g. Subject Satisfaction Questionnaire and GAIS should be translated into local language.

The name and address of the subjects must not be registered in the eCRFs or in the database. The subject's identity must always remain confidential.

16.2 Correction of Data Recorded in the eCRF

Corrections in the eCRF can be made by the Investigator (or delegated person) in the electronic system and any changes in the data are documented within the system, i.e. an audit trail is maintained within the system.

If discrepant data is detected during review of data either by study monitor or other Sponsor representative data queries will be generated in the system. The query should state the question or data to be changed and should be resolved in the system by the Investigator (or delegated person).

16.3 Record Keeping

To enable evaluations and/or inspections from Competent Authorities/Regulatory Authorities and audits from the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, i.e. eCRFs and medical record), all original signed Informed Consent Forms, copies of all eCRFs and

detailed records of study product accountability. The records should be retained by the Principal Investigators as required by local legislation and international guidelines.

16.4 Protection of Personal Data

The completion of the study involves the gathering and processing of Personal Data as specified in Directive 95/46 EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. For the purposes of the study, Sponsor will be considered the Data Controller, and Principal Investigator and Institution will both be considered Data Processors.

All processing of Personal Data must be carried out in accordance with national legislation concerning the protection of Personal Data. The Institution and Principal Investigator are responsible for complying with all requirements pursuant to national legislation in the country in which the Institution and Principal Investigator are located. The Sponsor will ensure that all requirements are complied with for data processing, which is carried out in Sweden by the Sponsor.

The Institution and Principal Investigator are jointly responsible for obtaining the appropriate informed consent of each subject for the processing of Personal Data required in order to complete the study. Such consent shall include the consent to the transfer of Personal Data to government authorities located in countries outside the European Union.

The Institution and Principal Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the study, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time. A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the study but the data collected until the consent was withdrawn may be used in the statistical analyses.

In territories outside the European Union, all collection, processing and analyses of protected health information, personal data or similar will be conducted in compliance with applicable local, national and international rules, regulations and guidelines.

17 Financing, Indemnification and Insurance

The CTA outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the protocol regarding certain rights and obligations the CTA is the prevailing document.

Q-Med agrees to assume liability for any product liability claim, which is not otherwise covered, arising out of a condition caused or allegedly caused by the study, provided that the study is performed in accordance with the provisions of the CTA, including, but not limited to, the protocol and, if required, the Statement of Investigator. Q-Med assumes no liability for any claim where the appropriate written, informed consent was not obtained. Q-Med will not accept responsibility for any loss, claims, and/or demands arising from injuries or damages incurred as a result of the negligence or willful malfeasance on the part of the Principal Investigator or the Principal Investigator’s agent, or claims resulting from activities not in

compliance with the provisions of the CTA, including the protocol. The Principal Investigator is obligated to notify Q-Med promptly upon receipt of any claim and to cooperate fully in the handling of the claim.

Q-Med's liabilities hereunder are covered by a Global Liability Insurance Policy. The insurance covers General Liability and Products Liability including clinical studies. A copy of an insurance certificate will be provided upon request. The Institution/Principal Investigator is obligated to maintain an equivalent insurance policy covering the Institution/Principal Investigator's liabilities under the CTA.

18 Publication Policy

The Principal Investigator's, Institution's and Q-Med's obligations regarding Intellectual Property and Confidentiality and Publication are described in detail in the CTA. They can be summarized as follows;

It is specifically agreed that all experience, knowledge or other information that is generated under the CTA or the study shall be the sole property of Q-Med.

As far as there are no other agreements or legal regulations, the Principal Investigator will treat all information regarding study product, Q-Med or the study as Q-Med's Confidential Information and will not disclose such Confidential Information to any third party or use the information for any other reason than the timely completion of this study. Excluded from this obligation is information that the Principal Investigator or Institution can prove is generally known via another manner than disclosure or other action by the Principal Investigator or Institution, or Information that was in the Principal Investigator's or Institution's possession prior to receipt of the information from Q-Med.

The Institution, Principal Investigator and his/her associates, colleagues and assistants involved in the study are obligated to refrain from participating in any form of publication of newsletters, scientific articles, or other disclosure regarding results of or information from the study without the prior written consent of Q-Med.

In accordance with the Principal Investigator's participation in a multicenter study, the Principal Investigator agrees that the first publication of the results of the study shall be co-operatively and that individual publications shall not be made prior to the first publication of the results of the multi-center study.

Everyone who is to be listed as an author of the results of the multicenter study should have made a substantial, direct, intellectual contribution to the work[1]. Authorship credit should be based on (1) contributions to conception and design, or acquisition of data, i.e., treatment of subjects and gathering of data, or analysis and interpretation of data; and (2); drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. To the greatest extent possible everyone who has made substantial intellectual contributions to the work should be listed as an author, and everyone else who has made other substantial contributions should be

[1] Uniform Requirements For Manuscripts Submitted To Biomedical Journals: Writing And Editing For Biomedical Publication, compiled by the International Committee of Medical Journal Editors (http://www.icmje.org)

acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med to take primary responsibility for the overall work as primary author.

The Principal Investigator shall have the right to publish or present the results of his/her work conducted under the CTA, subject to providing Q-Med with the opportunity to review the contents of any proposed abstract of publication or presentation about its work, including any results of the study, in advance of any publication or presentation and, if necessary, to delay publication for a limited time in order to protect the confidentiality and proprietary nature of any information contained therein and to enable Q-Med to file such applications as are deemed necessary by Q-Med to achieve the protection envisioned in this Paragraph. Any publication or presentation by the Institution and/or Principal Investigator shall be submitted to Q-Med for review and comment no less than 60 days before submission for publication or presentation to allow Q-Med to determine whether any patentable invention or Confidential Information would be disclosed. Q-Med will provide any comments to the Institution and/or Principal Investigator within 30 days following receipt of the proposed publication or presentation. The Institution and/or Principal Investigator agree to consider, discuss and give reasonable considerations to comments by Q-Med relating to the submission. Q-Med may also request that the Company name (or that of a Q-Med employee) appear or does not appear in such publication.

19 Premature Termination of the Clinical Study

The Sponsor will terminate the study if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons as specified in the CTA.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrolment or non-compliance with the protocol, GCP or applicable regulatory requirements.

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21 Appendices

1. Declaration of Helsinki

Validated photonumeric grading scales

Instructions for Use / Summary of Product Characterisitcs

Validated photonumeric grading scales

Subject Questionnaire

Appendix 1

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004
59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

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13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must

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then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

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34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

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[1] **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**
The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review. 9.10.2004

Appendix 2

Validated photonumeric grading scale [redacted]

Appendix 3

Validated photonumeric grading scale – [redacted]

Appendix 4

Validated photonumeric grading scale – [redacted]

[redacted]

Appendix 5 - 11

Instructions for Use / Summary of Product Characteristics

[redacted]

Appendix 12

Validated photonumeric grading scale – [redacted]

Appendix 13

Validated photonumeric grading scale – [redacted]

Appendix 14

Validated photonumeric grading scale – [redacted]

Appendix 15

Validated photonumeric grading scale [redacted]

[redacted]

Appendix 16

Validated photonumeric grading scale – [redacted]

Appendix 17

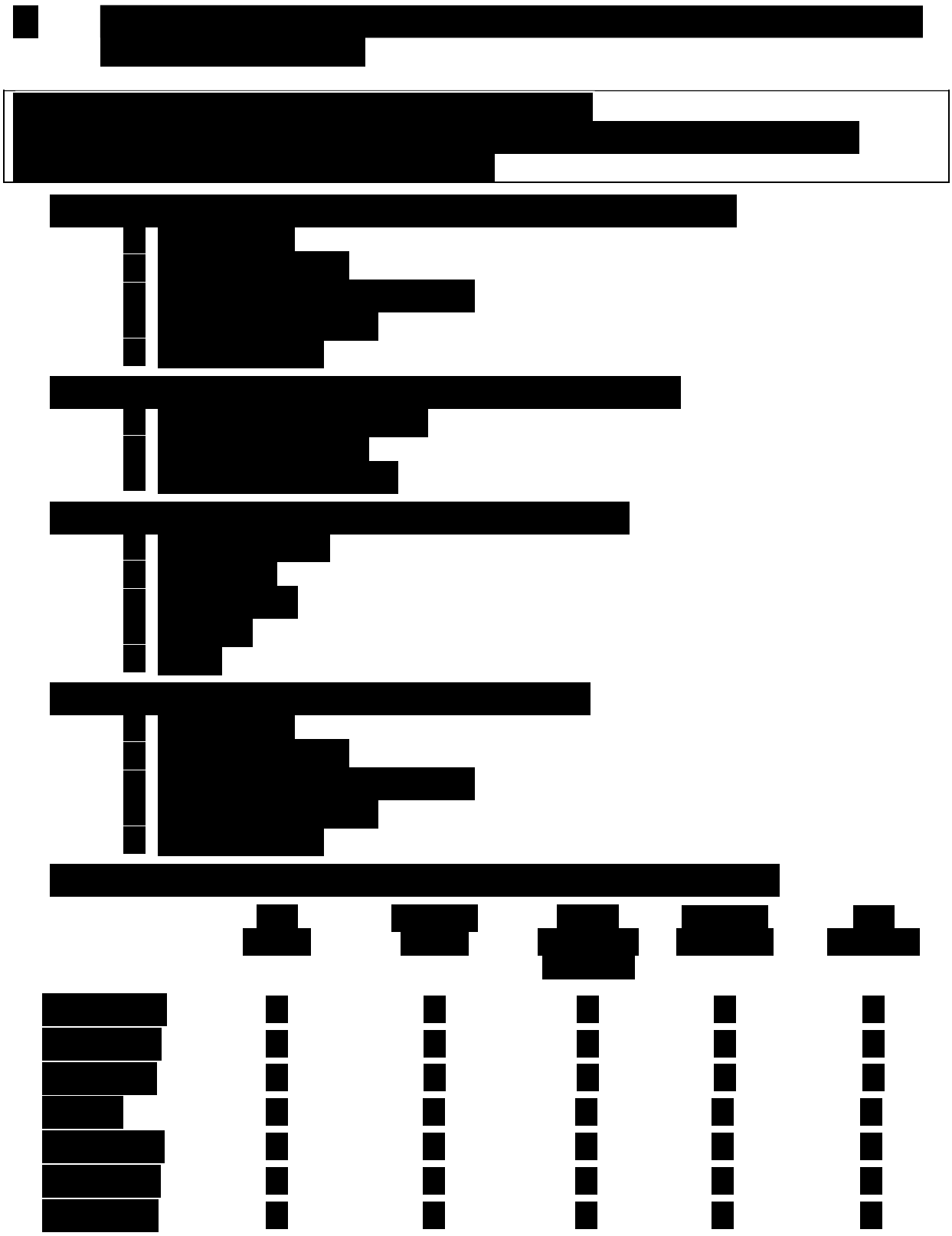
Validated photonumeric grading scale – [redacted]

Appendix 18

Subject satisfaction questionnaire

Appendix 18

Subject satisfaction questionnaire



Appendix 18

Subject satisfaction questionnaire

Appendix 18

Subject satisfaction questionnaire

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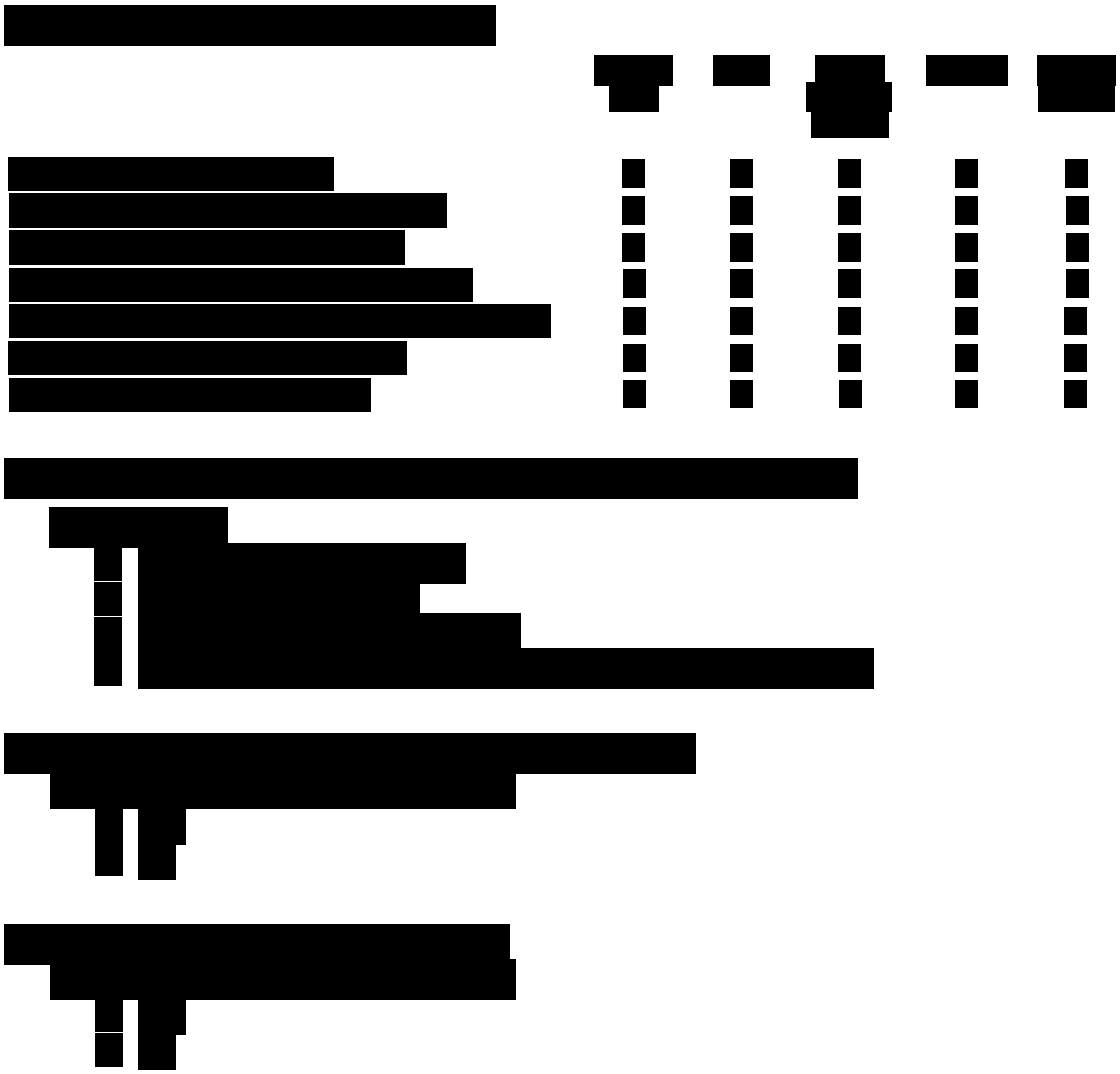
Subject satisfaction questionnaire



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