Follicum

CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

A randomised, double-blind, placebo-controlled phase 2 trial of FOL-005 to investigate efficacy on hair growth on scalp skin in healthy volunteers

Trial code:	FCS-002	**Trial development phase:**	Phase 2
EudraCT number:	2017-003809-17	**Investigational medicinal product:**	FOL-005 solution for injection
Version:	1.0	**Date:**	07 November 2017

Coordinating Investigator: Prof. Dr. Ulrike Blume-Peytavi

Sponsor Signatory: Jan Alenfall, PhD, CEO

<table>
<tr><td>Name of Company:

Name of Active Ingredient:</td><td>Individual trial table</td><td>(For national authority use only)</td></tr>
<tr><td colspan="2">Name of Investigational Products: FOL-005
Solution for injection
Placebo solution for injection</td><td>Trial under an IND:
No</td></tr>
<tr><td colspan="3">Title of trial:
A randomised, double-blind, placebo-controlled phase 2 trial of FOL-005 to investigate efficacy on hair growth on scalp skin in healthy volunteers</td></tr>
<tr><td colspan="2">Planned trial period:
January 2018 – June 2018</td><td>Phase of development:
Phase 2</td></tr>
<tr><td colspan="3">Objectives:

Primary objective:
The primary objective of this trial is to evaluate the efficacy of FOL-005 on scalp hair density in healthy male subjects when applied intradermally three times weekly for 12 weeks.

Secondary objectives are:
The secondary objective of this trial is to evaluate the efficacy of FOL-005 on scalp hair density in healthy male subjects when applied intradermally three times a week for 8 weeks and to evaluate the safety and tolerability of 12 weeks of treatment with FOL-005 in healthy male subjects.</td></tr>
</table>

Methodology:
The trial is a multicentre, randomised, double-blind, placebo controlled phase 2 trial

60 healthy bald male subjects diagnosed with androgenic alopecia (Norwood/Hamilton grade 3V to 4/4a), who are between 18 and 55 years old and provide written informed consent will be eligible for inclusion.

The trial period will consist of a screening period of up to 1 week followed by 12 weeks of dosing, three times per week. Each subject will receive two doses of the four trial treatment doses (0.00625, 0.025, 0.050, and 0.100 µg respectively) and the placebo dose. On each volunteer, two treatment areas will be selected on the head and the two selected doses will be allocated to the respective treatment areas according to the randomisation scheme. The treatment areas will be selected on the border between the bald surface and the surface with hair.

The subjects will be screened for eligibility at the screening visit where a physical examination and assessment of vital signs will be performed. Blood samples for safety and laboratory assessment will be taken. The subjects will return to the clinic for the inclusion visit (visit 1, day 1) 3 to 21 days later. If the subject is eligible for inclusion, the 2 treatment areas will be shaved and the centre of each treatment area where the trial treatments will be applied will be marked with a tattooed dot.

At visit 2, day 5, the first trial treatment application will be performed after TrichoScan imaging of the treatment areas. Subjects will then return to the clinic for treatment application three times per week with at least one day in between.

All subjects who have received at least one dose of trial drug will go through the procedures for safety and efficacy assessments at last visit (EOT, visit 38).

All adverse events will be followed until resolved or stabilised. Procedures for removal of subjects from therapy or assessments are described in Section 8.7.

Number of subjects:
A total of 60 healthy male subjects will be included.
Each subject will be treated at two sites. Each site will be treated with different treatments.
Thus, a total of 120 treatment areas will be available for treatment on the 60 subjects

Inclusion criteria:
The subjects must meet all of the following criteria to be eligible to enter the trial:

1. Healthy male, aged 18-55 years
2. Androgenetic alopecia (AGA)) – Norwood/Hamilton grade 3V to 4/4a [1]
3. Caucasian, skin type I – IV according to Fitzpatrick's classification [2]
4. Willing to have treatment areas shaved for TrichoScan® measurement marked with small semi-permanent dot tattoos
5. Willing and able to comply with scheduled visits
6. Willing to maintain the same hygiene products and skin cleansing habits during the trial period.
7. Willing to continue to use the currently used shampoo throughout the course of the trial.

8. Following verbal and written information about the trial, the subject has to provide signed and dated informed consent before any trial related activity is carried out.

Exclusion criteria:
Subjects meeting any of the following criteria will not be permitted to enter the trial:

1. Damaged skin in or around test sites including sunburn, uneven skin tones, tattoos, scars or other disfiguration of the test sites risking interfering with investigational evaluations
2. Any dermatological disorders of the scalp which might interfere with the application of IMP or examination method, such as fungal or bacterial infections, seborrheic dermatitis, psoriasis, eczema, folliculitis or scalp atrophy
3. Any skin pathology (e.g. scar, nevus) or general condition (e.g. uncontrolled thyroid diseases) that in the investigator's opinion can interfere with the evaluation of the treatment areas or requires topical or systemic therapy
4. History of active hair loss due to alopecia areata, scarring alopecia, diffuse telogen effluvium or conditions other than androgenetic alopecia
5. Use of or planned use of any shampoo with expected medicinal effect on the scalp (e.g. but not limited to antifungal or anti-dandruff shampoo, shampoo containing urea, caffeine or acetylsalicylic acid, etc.) during the course of the trial
6. Known or suspected allergy or sensitisation to any of the IPs or excipients
7. Immunological disorders such as alopecia areata, and systemic lupus erythematosus and other systemic known autoimmune disorders
8. Diabetes mellitus
9. Topical treatments for hair growth (minoxidil, anti-androgens or other agents known to affect hair growth) in the last 6 months
10. Topical scalp over-the-counter (OTC) or cosmetic treatments including shampoos known to affect hair growth in the last 4 weeks
11. Topical treatments of the scalp including corticosteroids, tacrolimus, retinoids in the last 2 months or other treatments that may affect hair growth
12. Platelet rich plasma (PRP) treatment on scalp during the last 12 months
13. Systemic therapy using retinoids, cyclosporine within the last 3 months
14. Systemic treatment with beta blockers or corticosteroids, scalp procedures e.g. surgery, laser, light, micro-needling within the last 6 months
15. Finasterid (e.g. Propecia®) or Dutasteride intake in the last 12 months, or any systemic hair therapy medication in the last 12 months
16. Other systemic therapy which in the opinion of the investigator might affect hair growth
17. Known needle fear or loss of consciousness while having blood sample taken or receiving injections
18. History of any acute (e.g. acute infections) or chronic illness (e.g. psoriasis, atopic dermatitis, porphyria) or known skin cancer that in the opinion of the investigators might confound the results of the trial
19. History or clinical signs of keloids or hypertrophic scars

20. Positive HIV-Antibody, HBs-Antigen or HCV-Antibody-Test at screening
21. Elevated values for vital signs:
    - blood pressure: systolic above 160 mmHg, diastolic above 95 mmHg
    - heart rate: above 100 beats/min.
22. Current or within 2 weeks prior to first dosing use of vasodilating drugs (e.g. Pentoxifyllin, nitroglycerine) or anticoagulating drugs (e.g. heparine, cumarines, new oral anticoagulants, regular intake of acetylsalicylic acid)
23. Current or within 3 months prior to first dosing use of anti-inflammatory medication (ibuprofen, paracetamol is permitted), corticosteroids (nose drops, eye drops and/or inhalers are permitted) or immunosuppressive drugs taken for more than 2 consecutive weeks
24. Current or within the last 6 months history of severe dietary or weight changes
25. Hair transplantation at any time
26. Known sensitization to cosmetic hair dyes or hypersensitivity to ingredients of the IMP or tattoo ink.
27. Planned or scheduled subject surgery or hospitalisation during the course of the trial
28. Any condition for which the investigator determines that the subject could be placed under undue risk.
29. Participation in any clinical trial within the last four weeks
30. Previously randomised in this trial
31. Subject is institutionalized because of legal or regulatory order
32. Close affiliation with the investigator (e.g. a close relative) or persons working at the trial site, or subject that is an employee of sponsor
33. In the opinion of the investigator unlikely to comply with the clinical trial protocol

Investigational products, dose and mode of administration:

The trial treatments will consist of three times per week application of:

- FOL-005 0.00625 µg solution, or
- FOL-005 0.025 µg, or
- FOL-005 0.050 µg, or
- FOL-005 0.100 µg, or
- FOL-005 placebo.

The treatment will be randomized to the 120 treatment areas in the ratio of: 5:5:5:5:4, i.e. 5 of each active treatment and 4 of placebo.

The investigational products will be administered as a local intradermal injection of 50 µl solution into the skin.

Treatment areas
Two mini-zones (circle of 1.5 cm diameter), located on 2 contra-lateral zones, the right and left sides of the frontal areas of the scalp. Areas should be located in a transitional area of hair loss. The middle of each treatment area will be identified by a dot micro-tattoo, to ensure that the same area is treated, documented and evaluated throughout the study.

Duration of treatment:

In total 12 weeks of dosing three times weekly

Assessments
Efficacy assessment:

- Hair growth parameters on treatment areas using TrichoScan® software at Baseline and weeks 8 and 12.

Safety
assessments:

- Adverse events
- Local tolerability
- Vital signs including supine systolic and diastolic blood pressure (mmHg), supine heart rate (beats per minute), body temperature
- Physical examination including general appearance, mouth and throat, ears (left and right), lungs, abdomen, neurological
- Blood and Urine sampling

Criteria for evaluation:

Efficacy variables:

- Cumulative hair thickness (mm/cm²)
- Hair thickness (µm/cm², mean median)
- Hair length (mm/cm^2; mean, median)
- Total hair density (n/cm^2)
- Terminal hair density (n/cm^2)
- Vellus hair (<40µm thick) density (n/cm^2)
- Total hair growth (µm/day/cm^2)
- Hair growth (µm/day/cm^2, mean median)
- Anagen hair density (n/cm^2)
- Telogen hair density (n/cm^2)

Safety and tolerability variables:

- Any adverse events reported (including change in vital signs, physical examination and safety laboratory parameters)
- Any adverse drug reaction reported (including change in vital signs, physical examination and safety laboratory parameters)
- The reasons for withdrawal from the study
- Local tolerability; Erythema, Haematoma, dyspigmentation, induration and pain/discomfort will be assessed on a 4-graded scale (none, mild, moderate and severe)

Endpoints:

Primary endpoint:
Change from baseline of total hair density (No. of hairs per cm^2) on the scalp after 12 weeks of treatment

Secondary endpoints are:
Change from baseline of total hair density (No. of hairs per cm^2) on the scalp after 8 weeks of treatment

Change from baseline of hair growth parameters after 8 and after 12 weeks of treatment:
- Cumulative hair thickness (mm/cm^2)
- Hair thickness ($\mu m/cm^2$, mean median)
- Hair length (mm/cm^2; mean, median)
- Terminal hair density (n/cm^2)
- Vellus hair (<40µm thick) density (n/cm^2)
- Total hair growth ($\mu m/day/cm^2$)
- Hair growth ($\mu m/day/cm^2$, mean median)
- TrichoScan Anagen/Telogen ratio
- Proportion of anagen hairs (%)
- Proportion of telogen hairs (%)
- Proportion of vellus hair (%)

To evaluate the safety based on:
- Any adverse events and adverse drug reactions reported
- Local tolerability assessments
- Vital signs and physical examination
- Abnormal safety laboratory parameters

Statistical methods:
Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, efficacy variables, and safety variables.
Continuous variables will be presented by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for each treatment dose, if applicable.
Descriptive summaries by study center will be presented for the primary efficacy endpoint.

Hypothesis
Since this is an exploratory trial no formal hypotheses are postulated. Comparisons by means of p-values will be interpreted in a descriptive manner.

Efficacy analysis:
Statistical analyses will be performed using two-sided tests and confidence intervals, as appropriate. The primary efficacy endpoint, the change from baseline for hair density on the scalp after 12 weeks, will be analysed using the exact Wilcoxon signed rank test to test versus zero. The secondary efficacy endpoints will be analysed using the same methodology as in the analysis of the primary efficacy endpoint.

Safety analysis:
All AEs reported during the trial period will be listed, documenting course, severity, investigator assessment of the relationship to the IP, and outcome. AEs will be coded using the MedDRA mapping system and tabulated by system organ class (SOC) and by preferred term. Listings of serious adverse events (SAE) and subjects who prematurely discontinued treatment due to AEs will be given.
Safety laboratory parameter (hematology, clinical chemistry) and vital signs will be

summarized descriptively, including changes from baseline. Urinalysis outcomes and outcomes of local tolerability assessments will be summarized by frequency counts.

Analysis populations:
Safety summaries will be performed on the safety analysis set. The Per-protocol set will be considered the primary efficacy subset of subjects. The Full analysis set will be used for a sensitivity analysis of the primary efficacy variable only.

1.1 Trial flow chart

		Treatment period									
Visit number	**Screening[a)]**	**1**	**2**	**3 - 21**	**22**	**23**	**24**	**25 - 36**	**37**	**38**	**EoT[i)]**
Week	-3 to -1	1 - 12									
Day	-21 to -3	1	3	5 - 48	50	52	54	57 - 82	85	87	NA
Visit window (+/- days) with at least 1 day interval			1	1	1	1	1	1	1	1	1
Informed consent	X										
Physical examination [b)]	X	X								X	X
Inclusion/exclusion criteria	X	X									
Demographic data	X	X									
Medical and surgical history	X										
Vital signs [c)]	X	X								X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Determ. of investing. Areas [d)]		X									
Marking of test areas		X									
Randomisation			X								
Dot tattoo [e)]	X			X [e)]				X [e)]			
IP/ Placebo administration			X	X	X		X	X			
Shaving of treatment areas		X				X				X	
TrichoScan		X [f)]	X			X [f)]	X		X [f)]	X	
Safety assessment/ local tol.		X	X	X	X	X	X	X	X	X	X
Blood sampling (haem. and clin chem)[g)]	X									X	X
Blood sampling (Hep B, Hep C, HIV)	X										
Urine sampling [h)]	X									X	X
Recording of AEs/SAEs		X	X	X	X	X	X	X	X	X	X

a) The screening period is defined as the time between visit 0 and visit 1. The screening period will vary in length to accommodate flexibility in the planning of subject visit schedule.

b) The physical examination will include: General appearance, mouth and throat, ears (left and right), lungs, abdomen, neurological

c) Vital signs will include: Systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and body temperature

d) The treatment areas will be evenly placed on the scalp

e) The dot tattoo will be repeated if necessary during the course of the trial. Ensure that this performed at least 6 days prior to the next TrichoScan assessment.

f) TrichoScan imaging will be performed without hair dye

g) Haematology: haemoglobin, white blood cell count including differential cell count, red blood cell count, platelet count, coagulation (partial thromboplastin time and prothrombin time); Clinical Chemistry: Glucose, creatinine, total bilirubin, gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), Electrolytes (Na, K), lactate dehydrogenase (LDH), C-reactive protein (CRP), total cholesterol

h) Urine analysis (urine qualitatively): blood, ketones, glucose, protein, pH, nitrites, leucocytes, microscopy if results are positive for blood or protein

i) End of Treatment (EoT) procedures should as far as possible be completed for all subject.

2 THE TABLE OF CONTENTS

Section **Page**

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 List of Abbreviations

AE	Adverse Event
ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CA	Competent Authority
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicines Agency
EoT	End of Treatment
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification Data
IEC	Independent Ethics Committee
IP	Investigational Product(s)
MD	multiple dose
PPS	Per-Protocol Set
Q1	First quartile
Q3	Third quartile
SAD	single ascending dose
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual Analogue Scale
VASI	Visual Analogue Scale for Itching

3.2 Definition of Terms

Competent Authority	A government body or government appointed body that has legal authority to approve or disapprove clinical trials

4 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

PRINCIPAL INVESTIGATOR

Name: Prof. Dr. Ulrike Blume-Peytavi
Address: Klinik für Dermatologie, Venerologie und Allergologie, Charité-Universitätsmedizin Berlin
Charitéplatz 1 - 10117 Berlin
Phone: +49 (0)30 450 518 122
E-mail: crc-office@charite.de; ulrike.peytavi@charite.de

SPONSOR'S TRIAL DIRECTOR

Name: Jan Alenfall
Address: Follicum AB
Scheelevägen 22
SE-223 63 Lund
Sweden
Phone: +46 (0)46 19 21 97
+46 (0)709 31 51 15
E-mail: jan.alenfall@follicum.com

CONTRACT RESEARCH ORGANISATION

Name: Dr. Anke Müller
Address: bioskin GmbH
Burchardstr. 17
20095 Hamburg
GermanyPhone:+43 40 60689755
Fax: +43 40 60689730
E-mail: anke.mueller@bioskincro.com

LABORATORY FOR SAFETY PARAMETER ANALYSIS

Name: LKF- Laboratorium für Klinische Forschung GmbH
Address: Lise-Meitner-Straße 25-29
24223 Schwentinental
Germany
Phone: +49 4307 8276 0
Fax: +49 4307 8276 79
E-mail: project@lkf-kiel.de

TRICHOLOG ASSESSMENT

Name: Prof. Dr. Rolf Hoffmann
Address: TRICHOLOG GmbH
In den Eschmatten 24
79117 Freiburg i. Brsg.
Germany
Phone: +49 761 6800112
Fax: +49 761 6800113
E-mail: info@tricholog.de

PROJECT LEADER

Name: Johan Quensel
Address: Follicum AB
Scheelevägen 22
SE-223 63 Lund
Sweden
Phone: +46 (0)760 46 67 44

E-mail: johan.quensel@follicum.com

BIOSTATISTICIAN

Name: Maciej Hoffman-Wecker
Address: bioskin GmbH
Burchardstr. 17
20095 Hamburg
Germany
Phone: +43 40 60689737
Fax: +43 40 60689730
E-mail: maciej.hoffman-wecker@bioskincro.com

PHARMCOVIGILANCE/ SAFETY MEDICAL MONITOR

Name: Dr. Monika Storm
Address: FGK Clinical Research GmbH
Heimeranstr. 35
80339 Munich
GermanyPhone: +49 4340 702 9992
E-mail: monika.storm@fgk-cro.de

Serious Adverse Event Reporting

E-mail: safety@fgk-cro.com
FAX: +49 89 893 119 180

5 INTRODUCTION

5.1 Background

Hair follicle morphogenesis and growth is controlled by a complex network of sequential activation and inactivation of autocrine, paracrine and endocrine signalling pathways [3]. The regulation and molecules involved are not yet fully known. There are three phases of the hair cycle: a growth phase (anagen), a regression phase (catagen), and a resting phase (telogen). The duration of the phases depends on the type and localization of the hair follicle. For instance body hair follicles remain for a shorter period in anagen leading to shorter hair shaft length as compared to scalp hair follicles [4].

Follicum AB develops peptides derived from human osteopontin with a focus on local application for modulation of hair growth. Osteopontin is a 32 kDa extracellular matrix glycoprotein with diverse immunomodulatory functions and has been associated with inflammation and fibrosis. Its synthesis is stimulated by calcitriol (1,25-dihydroxy- vitamin D3).

Follicum's initial finding was that a modified form of the glycoprotein osteopontin (OPN) induces hair growth in young mice, where the follicles are in telogen phase, after subcutaneous administration. There are reports on OPN to be present in hair follicles in a hair cycle dependant manner [5]. The first candidate drug is a synthetic peptide named FOL-005. This candidate peptide is comprised of 15 amino acids with a free N and C- terminal; the molecular weight is 1672 Da and the molecular formula $C_{74}H_{114}N_{18}O_{26}$. Except for hair growth promoting activity, it is considered that Follicum's drug candidate FOL-005 does not possess any of osteopontin's mentioned effects, as major functional parts of OPN have been deleted in the FOL-005 peptide.

A possible link to the mode of action of FOL-005 could come from integrins. The modification of OPN was done in the region where the integrin binding sequence in OPN is located. The importance of a modified RGD sequence (specific 3 amino acid sequence in osteopontin) in hair growth may reveal an affinity to other receptors or other mechanisms than previously known. However, in Follicum's compounds the RDG site is disrupted and the cryptic integrin-binding site may become more active leading to a stronger interaction to these receptors. This may be the explanation for the better activity shown by the peptides compared to the full-length

Trial Rationale

In non-clinical *in vivo* studies in C57Bl/6 mice, treatment with low doses of FOL-005 showed significant anagen hair growth induction and complete hair growth was observed in almost all treated animals.

Distribution of immune labelled FOL-005 and its binding properties has been studied in mice and human tissues. Subcutaneously injected FOL-005 was indicated to diffuse rapidly from the site of injection, and into deeper skin levels [6]. FOL-005 binding was mainly present in the Outer Root Sheet (ORS), being relatively dominating close to the base of the follicles, both in mice and human tissues [6, 7]. The strongest binding was detected in the anagen phase of hair growth. The FOL-005 peptide C-terminal and central amino-acid regions appears to be most important for its binding [7].

FOL-005 has been studied in a Phase I study in healthy male volunteers. FOL-005 was administered as intradermal injections in specified skin areas on the forefront of the thighs. After a single ascending dose phase, safety and efficacy was studied during 12 weeks in a multiple dose phase. In the multiple dose phase, four different doses of FOL-005 and placebo were injected 2 or 3 times weekly for 12 weeks.

A statistically significant up-regulation of hair growth with bell-shaped dose-response, with maximum effect at 0.025µg of FOL-005, was observed after twice or 3 times weekly administration for 12 weeks. No serious adverse events or other safety issues were recorded; FOL-005 was well tolerated [8].

5.2 Potential Risks and Benefits

No direct benefit is expected for subjects participating in early clinical trials.

Preclinical toxicity studies have not shown any clinically visible changes or histological changes after subcutaneous injections to indicate any tolerability issue.

In the First in Man (FIM) clinical trial, FOL-005 was well tolerated. No Serious Adverse Events were reported during the trial and no subject withdrew from treatment or had the treatment interrupted due to AEs. No severe AEs were reported. Local tolerability events, mostly assessed as procedure related, contributed to a majority of the reported events. These were almost exclusively of mild severity; only 2 injection site haematomas of moderate severity were reported.

There were no differences in local AE frequency between doses, ranging from 0.005 to 0.500 µg of FOL-005 or, between FOL-005 and placebo treatment. Neither were there any increases in frequency of AEs or in AE severity during treatment. In contrast, the frequency of reported local tolerance AEs decreased over time [8].

Considering the safety results in the FIM study, the foreseeable risks to the subjects of any FOL-005 related reactions are very low.

The duration of trial FCS-002, will be identical to the FIM trial and the maximum dose (single doses as well as accumulated dose) will be lower than in the FIM trial. The application areas differ however between the trials; in the FIM trial administrations were performed on the thighs and in trial FCS-002 administrations will be performed on the scalp.

The foreseeable risks of the subjects related to the trial procedures include allergic or hypersensitivity reactions to the tattoo or the disinfectants, and mild pain and local discomforts (e.g. haematoma) related to the intradermal injection of the peptide and blood samplings.

The dot tattoos on the skin, which are required for high-level standardization, may cause transient local bleeding. Rarely, inflammation, injury or irritation of nerves occurs. The dye applied may cause sensitization e.g. contact eczema which occurs within hours or days after the application. The most common manifestations are pruritus, predominant oedema unlike typical eczema lesions (erythema associated with vesicles). This reaction progresses to a dry skin with desquamations and often requires the administration of a topical treatment. If tattoos do not fade within 3 months after trial end, the subject will be offered a free laser removal of the dot tattoo.

The intradermal injection of the peptide as well as blood sampling may cause a short pain and mostly immediate local discomforts during the puncture. Occasionally a bruise may appear when a small amount of blood gets into the surrounding tissues. This normally disappears within a few days. Possible other side effects like thrombosis, infection, damage of nerves or surrounding tissues are very rare and almost negligible since only trained staff is involved in the trial.

6 TRIAL OBJECTIVES

6.1 Primary Objective

The primary objective of this trial is to evaluate the efficacy of FOL-005 on scalp hair density in healthy male subjects when applied intradermally three times a week for 12 weeks.

6.2 Secondary Objective

The secondary objective of this trial is to evaluate the efficacy of FOL-005 on scalp hair density in healthy male subjects when applied intradermally three times weekly for 8 weeks and to evaluate the safety and tolerability of 12 weeks of treatment with FOL-005 in healthy male subjects.

7 INVESTIGATIONAL PLAN

7.1 Trial Design and Plan-Description

The trial is a multicentre, randomized, double-blind, placebo controlled phase 2 trial.

The trial centres will screen a sufficient number of subjects (approximately n = 90) to include 60 eligible male subjects. Subjects withdrawn for IMP-unrelated reasons will be replaced if treatment was performed for less than 4 weeks.

60 healthy male subjects, who are 18 to 55 years old and provide written informed consent will be included

The trial period will consist of a screening period of up to 3 weeks followed by 12 weeks of dosing. Each subject will receive their first doses at visit 2 (day 5). Subjects will then return to the clinic for treatment application 3 times per week with at least one day in between**.** 4 active dose strengths and one placebo dose will be used in the trial and each subject will be randomly assigned two of these 5 treatments. Thus, all 60 subjects will receive 2 doses.

The subjects will be screened for eligibility at the screening visit where a physical examination and assessment of vital signs will be performed. Blood samples for HIV/Hep-b/Hep-c, safety and laboratory assessment will be taken. The subjects will return to the clinic for the inclusion visit (visit 1, day 1) 3 to 21 days later. If the subject is eligible for inclusion, the 2 treatment areas will be shaved and the centre of each treatment area where the trial treatments will be applied will be marked with a tattooed dot.

At visit 2, day 3, the first TrichoScan imaging of dyed hair for determination of baseline total hair density per cm^2 and the first trial treatment application will be performed on the treatment areas. Subjects will then return to the clinic for treatment application three times per week with at least one day in between.

All subjects who have at least received one dose of trial drug will go through the procedures at the Follow up safety and efficacy assessments at the EoT visit.
All adverse events will be followed until resolved or stabilised. Procedures for removal of subjects from therapy or assessments are described in Section 8.7.

Trial Treatments

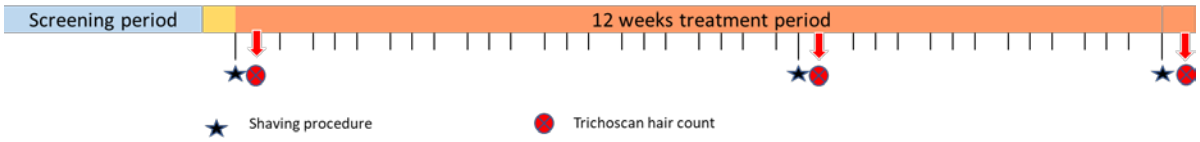
50 µl of the trial treatments will be applied intradermally at each treatment site in the centre marked with a tattooed dot. The dilutions and preparation of vials will be performed at the centre, by blinded personnel.

The trial treatments will consist of three times per week application of:

- FOL-005 0.00625 µg solution, or
- FOL-005 0.025 µg, or
- FOL-005 0.050 µg, or
- FOL-005 0.100 µg, or
- FOL-005 placebo.

Each subject will receive 2 trial treatments. The trial treatments will be randomised and a subject can receive any combination of the above 5 trial treatments except two of the same treatment. The expected duration of participation in the trial will be maximum 87 days for each subject.

Figure 1 Trial Design



7.2 Trial Procedures

7.2.1 Schedule of Trial Events

The trial assessments described in the sections below are presented in detail in Section 10.2 (efficacy assessments), Section 10.3 (demographic data and baseline characteristics) and Section 10.4 (safety assessments). Recording and reporting of AEs are described in detail in Section 11.

The timing of all trial events is shown in Tables 1 - Trial Flow Chart

Table 1 Trial flow chart

		Treatment period									
Visit number	**Screening[a)]**	**1**	**2**	**3 - 21**	**22**	**23**	**24**	**25 - 36**	**37**	**38**	**EoT[i)]**
Week	-3 to -1	1 - 12									
Day	-21 to -3	1	3	5 - 48	50	52	54	57 - 82	85	87	NA
Visit window (+/- days) with at least 1 day interval			1	1	1	1	1	1	1	1	1
Informed consent	X										
Physical examination [b)]	X	X								X	X
Inclusion/exclusion criteria	X	X									
Demographic data	X	X									
Medical and surgical history	X										
Vital signs [c)]	X	X								X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Determ. of investing. Areas [d)]		X									
Marking of test areas		X									
Randomisation			X								
Dot tattoo [e)]	X			X [e)]				X [e)]			
IP/ Placebo administration			X	X	X		X	X			
Shaving of treatment areas		X				X				X	
TrichoScan		X [f)]	X			X [f)]	X		X [f)]	X	
Safety assessment/ local tol.		X	X	X	X	X	X	X	X	X	X
Blood sampling (haem. and clin chem)[g)]	X									X	X
Blood sampling (Hep B, Hep C, HIV)	X										
Urine sampling [h)]	X									X	X
Recording of AEs/SAEs		X	X	X	X	X	X	X	X	X	X

a) The screening period is defined as the time between visit 0 and visit 1. The screening period will vary in length to accommodate flexibility in the planning of subject visit schedule.

b) The physical examination will include: General appearance, mouth and throat, ears (left and right), lungs, abdomen, neurological

c) Vital signs will include: Systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and body temperature

d) The treatment areas will be evenly placed on the scalp

e) The dot tattoo will be repeated if necessary during the course of the trial. Ensure that this performed at least 6 days prior to the next TrichoScan assessment.

f) TrichoScan imaging will be performed without hair dye

g) Haematology: haemoglobin, white blood cell count including differential cell count, red blood cell count, platelet count, coagulation (partial thromboplastin time and prothrombin time); Clinical Chemistry: Glucose, creatinine, total bilirubin, gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), Electrolytes (Na, K), lactate dehydrogenase (LDH), C-reactive protein (CRP), total cholesterol

h) Urine analysis (urine qualitatively): blood, ketones, glucose, protein, pH, nitrites, leucocytes, microscopy if results are positive for blood or protein

i) End of Treatment (EoT) procedures should as far as possible be completed for all subject.

7.3 Discussion of Trial Design, Including the Choice of Control Groups

A randomised controlled blinded design is used. Such a design is most suitable to prevent and/or to minimize selection, performance, attrition, and detection bias.

The primary objective of this trial is to evaluate the effect of FOL-005 on scalp hair growth in healthy male subjects.

The TrichoScan is a reliable, well-validated phototrichogram method assessing the biological parameters of hair growth by combining dermoscopy with automatic digital image analysis for the measurement of human hair in situ. The TrichoScan system is designed to take reproducible images from shaved areas on the scalp. A good correlation between TrichoScan and manual evaluation of hair counts has been demonstrated [9, 10].

Safety and tolerability will be evaluated as secondary objectives. FOL-005 was considered safe and well tolerated in a previous phase 1 trial, FCS-001, as described in the investigator's brochure.

Each subject will have 2 treatment areas, A and B, evenly located on the scalp, at least 5 cm apart from each other. Treatment areas will be treated with either one of the following treatments: 0.00625 µg, 0.025 µg, 0.050 µg, 0.100 µg and placebo according to the randomisation schedule.

7.4 Trial Period

The trial is planned to start in January 2018 and be completed in June 2018.

7.5 End of Trial

The end of trial is defined as the date of the last subject's last visit.

8 SELECTION OF TRIAL POPULATION

8.1 Subject recruitment

Subjects will be recruited from subject databases and advertisements.

8.2 Number of Subjects

The trial is planned to include in total 60 male subjects. Subjects withdrawn for IMP-unrelated reasons will be replaced if treatment was performed for less than 4 weeks.

8.3 Inclusion Criteria

The subjects have to meet all of the following criteria to be eligible to enter the trial:

1. Healthy male, aged 18-55 years
2. Androgenetic alopecia (AGA)) – Norwood/Hamilton grade 3V to 4/4a [1]
3. Caucasian, skin type I – IV according to Fitzpatrick's classification [2]
4. Willing to have treatment areas shaved for TrichoScan® measurement marked with small semi-permanent dot tattoos
5. Willing and able to comply with scheduled visits
6. Willing to maintain the same hygiene products and skin cleansing habits during the trial period.
7. Willing to continue to use the currently used shampoo throughout the course of the trial.
8. Following verbal and written information about the trial, the subject has to provide signed and dated informed consent before any trial related activity is carried out.

8.4 Exclusion Criteria

Subjects meeting any of the following criteria will not be permitted to enter the trial:

1. Damaged skin in or around test sites including sunburn, uneven skin tones, tattoos, scars or other disfiguration of the test sites risking interfering with investigational evaluations
2. Any dermatological disorders of the scalp which might interfere with the application of IMP or examination method, such as fungal or bacterial infections, seborrheic dermatitis, psoriasis, eczema, folliculitis or scalp atrophy
3. Any skin pathology (e.g. scar, nevus) or general condition (e.g. uncontrolled thyroid diseases) that in the investigator's opinion can interfere with the evaluation of the treatment areas or requires topical or systemic therapy
4. History of active hair loss due to alopecia areata, scarring alopecia, diffuse telogen effluvium or conditions other than androgenetic alopecia
5. Use of or planned use of any shampoo with expected medicinal effect on the scalp (e.g. but not limited to antifungal or anti-dandruff shampoo, shampoo containing urea, caffeine or acetylsalicylic acid, etc.) during the course of the trial
6. Known or suspected allergy or sensitisation to any of the IPs or excipients

7. Immunological disorders such as alopecia areata, and systemic lupus erythematosus and other systemic known autoimmune disorders
8. Diabetes mellitus
9. Topical treatments for hair growth (minoxidil, anti-androgens or other agents known to affect hair growth in the last 6 months
10. Topical scalp over-the-counter (OTC) or cosmetic treatments including shampoos known to affect hair growth in the last 4 weeks
11. Topical treatments of the scalp including corticosteroids, tacrolimus, retinoids in the last 2 months or other treatments that may affect hair growth
12. Platelet rich plasma (PRP) treatment on scalp during the last 12 months
13. Systemic therapy using retinoids, cyclosporine within the last 3 months
14. Systemic treatment with beta blockers or corticosteroids, scalp procedures e.g. surgery, laser, light, micro-needling within the last 6 months
15. Finasterid (e.g. Propecia®) or Dutasteride intake in the last 12 months, or any systemic hair therapy medication in the last 12 months
16. Other systemic therapy which in the opinion of the investigator might affect hair growth
17. Known needle fear or loss of consciousness while having blood sample taken or receiving injections
18. History of any acute (e.g. acute infections) or chronic illness (e.g. psoriasis, atopic dermatitis, porphyria) or known skin cancer that in the opinion of the investigators might confound the results of the trial
19. History or clinical signs of keloids or hypertrophic scars
20. Positive HIV-Antibody, HBs-Antigen or HCV-Antibody-Test at screening
21. Elevated values for vital signs:
    - blood pressure: systolic above 160 mmHg, diastolic above 95 mmHg
    - heart rate: above 100 beats/min.
22. Current or within 2 weeks prior to first dosing use of vasodilating drugs (e.g. Pentoxifyllin, nitroglycerine) or anticoagulating drugs (e.g. heparine, cumarines, new oral anticoagulants, regular intake of acetylsalicylic acid)
23. Current or within 3 months prior to first dosing use of anti-inflammatory medication (ibuprofen, paracetamol is permitted), corticosteroids (nose drops, eye drops and/or inhalers are permitted) or immunosuppressive drugs taken for more than 2 consecutive weeks
24. Current or within the last 6 months history of severe dietary or weight changes
25. Hair transplantation at any time
26. Known sensitization to cosmetic hair dyes or hypersensitivity to ingredients of the IMP or tattoo ink.
27. Planned or scheduled subject surgery or hospitalisation during the course of the trial
28. Any condition for which the investigator determines that the subject could be placed under undue risk.
29. Participation in any clinical trial within the last four weeks

30. Previously randomised in this trial
31. Subject is institutionalized because of legal or regulatory order
32. Close affiliation with the investigator (e.g. a close relative) or persons working at the trial site, or subject that is an employee of sponsor
33. In the opinion of the investigator unlikely to comply with the clinical trial protocol

8.5 Subject Screening Log

A screening log will be kept at the trial centres for all subjects seen during the enrolment period. Each screened subject will be allocated a unique screening number. In the subjects screening log, the screening number, the date of screening, age, and reason for non-inclusion should be stated.

8.6 Subject Randomisation

Subjects will be given a unique randomisation number at the first treatment visit (Visit 1). The randomisation number is a unique subject identifier used throughout the trial, in lieu of the subject's name.

8.7 Removal of Subjects from Therapy or Assessment

Subjects are free to discontinue their participation in the trial at any time. Withdrawal from the trial will not affect or prejudice the subject's further care or treatment. Subjects may be withdrawn from trial treatment and assessments at any time, if deemed necessary by the Investigator.

Mandatory discontinuation criteria:

- Withdrawn consent
- Adverse events, which bring the subject at risk or might confound the result of the trial;
- Occurrence of local intolerance according to specification in section 10.5
- 4 consecutive treatments and/or in total 7 missed treatments
- Un-blinding
- Trial terminated by Sponsor

Additional reasons that may result in withdrawal of subjects from this trial are:

- Physicians' decision;
- Start of medication in the subject which is susceptible to interfere with hair growth or with further study performance (e.g. 5a reductase inhibitor, anti-coagulative therapy, systemic immune suppression);
- Any appearance of exclusion criteria during the trial;
- Protocol deviations/violation;

The reason and date the subject is withdrawn from the trial will be documented in the eCRF.

If a subject is withdrawn from further treatment with the IP, the investigator should attempt to complete the EoT visit. All adverse events should be followed up according to Section 11.2.

If a subject is withdrawn from the trial, all data collected until the time of withdrawal will be used in the analyses.

8.8 Premature Termination of the Trial

The Investigator or the Sponsor may terminate this trial prematurely for any reasonable cause. In this case the Ethics Committee (EC) and Competent Authority (CA) should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the trial, or potential trial subjects
- A decision on the part of the Sponsor to suspend or discontinue development of the IP.

If the CA obtains information that raises doubts about the safety or scientific validity of the clinical trial, the CA can suspend or prohibit the trial. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the Sponsor and/or the investigator for their opinion, to be delivered within one week (Directive 2001/20/EC, Article 12, Section 1).

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects and should assure appropriate therapy and follow-up for the subjects.

9 TREATMENT OF SUBJECTS

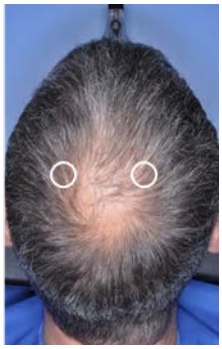
9.1 Investigational Products

9.1.1 Treatment Regimens

FOL-005 solution and placebo of FOL-005 solution will be administered at the trial centre. The solutions are intended for local intradermal injection into the skin. With each injection a volume of 50µl will be administered. The treatment areas will have a dot tattoo in the centre, edges will be drawn as dots with a skin marker, maximum once per week (Figure 2).

Each subject will have 2 treatment areas, A and B, evenly located on the scalp, at least 5 cm apart from each other. Treatment areas will be treated with either of the following treatments: 0.00625 µg, 0.025 µg, 0.050 µg, 0.100 µg and placebo according to the randomisation schedule.

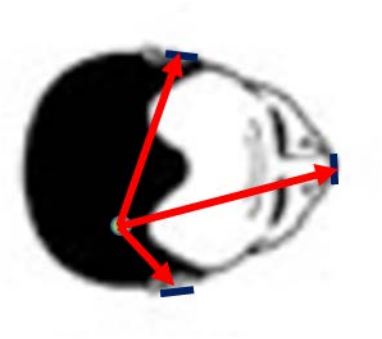
Figure 2 Treatment areas



Treatment areas will be on the balding scalp. Treatment sites have to be free of scars, tattoos or dermatological defects that might impair measurements. Treatment areas (1.5 cm diameter) are located on the scalp in the hair recession area of the frontotemporal and vertex regions and will be marked with a red dot tattoo in the middle, as depicted. Edges will be marked as dots using a skin temporary marker.
To help relocate the tattoo dot the following distances should be documented:

- R: Distance between the tattoo and the middle of the right tragus
- L: Distance between the tattoo and the middle of the left tragus
- N: Distance between the tattoo and the tip of the nose.

Figure 3 Schematic picture of distance measurements



The minimal distance between treatment areas should be 5 cm.

Instructions for Application

Before clinical examination of the subject's treatment areas and subsequent application of FOL-005, the treatment areas will be cleansed by the investigator or trial personnel using a standard skin disinfectant.

The application of IP should be performed according to the following instructions:

1. Inject 50 µl to the treatment area according to the subject's specific randomisation list. Care should be taken to avoid injections at the very same spot on every visit.
2. Discard injection device.
3. Document injection.

This procedure is repeated for each treatment area.

9.1.2 Identity of Investigational Products

The active ingredient, FOL-005, is a chemically synthesised 15 amino acid peptide, which is based on an endogenous part of osteopontin. The sequence is H-Val-Asp-Thr-Tyr-Asp-Gly-Asp-Ile-Ser-Val-Val-Tyr-Gly- Leu-Arg. Each vial of the IP FOL-005, solution for injection contains 9 mL, 10 µg/mL of FOL-005. It further contains sodium chloride, sodium hydrogen phosphate, hydrogen chloride, sodium hydroxide and purified water. The placebo product contains diluent only and is identical in appearance to the active product.

9.1.3 Packaging and Labelling of Investigational Products

FOL-005, 10 µg/mL solution for injection, is manufactured and released for the trial by Recipharm Pharmaceutical Development AB, Solna, Sweden.

All manufacturing is performed in accordance with current Good Manufacturing Practice (cGMP).

The labelling of FOL-005, solution for injection, the diluent and the dilution vials will be according to §5, GCP-V.

9.1.4 Storage and Handling of Investigational Products

The FOL-005 solution for injection must be stored in a freezer at a temperature of <-20°C. The temperature of the freezer will be logged.

The IP will be stored at the trial site as required by local regulations and laws for the participating site.

The IP, FOL-005, solution for injection will be thawed and reconstituted by dilution with isotonic phosphate buffer pH 7.4 into the following concentrations: 0.125, 0.5, 1.0, and 2.0 µg/mL, as described in the study specific IP dilution manual. A schematic overview of the IMP dilution manual is found in Appendix 1. The handling of placebo is also described in the study specific dilution manual. Lab personnel not otherwise involved in assessment procedures will handle the preparation of vials.

9.2 Method of Assigning Treatment areas

Two of the 5 investigational treatments will be randomly assigned to the 2 treatment areas 1 and 2 according to the randomisation list for each subject. The treatment areas 1 and 2 will receive the same treatment throughout the trial period.

9.3 Selection of Doses in the Trial

The rationale for the choice of dose in the present trial is based on previous results from the phase I/IIa trial FCS-001

In FCS-001 the subjects were dosed twice or three times per week at four individual areas of the thighs with injections of 50 µL resulting in 0.005 to 0.250 µg of FOL-005. The maximum efficacy measured both as increase in hair density as well as in percentage of responders, was found at 0.025 µg and the effect was more prominent after three administration times per week as compared to two times per week. FOL-005 was well tolerated at all tested doses and local tolerability AEs due to the injection procedure contributed to the majority of the reported events. Moreover, there was no detectable systemic absorption of FOL-005 at either of the doses.

In the present study 50 µL of FOL-005 will be injected into two separate areas on the scalp. The scalp has a higher density of hair follicles than the thighs and the hair cycle intervals generally have a longer duration on the head, Therefore, it cannot be ruled out that the hair follicle on the scalp responds different to FOL-005 than hair follicles on the thighs The doses strengths in the present trial have therefore been selected to cover a range below and over the optimal dose strength identified in FCS-001, i.e. 0.025 µg. The selected doses are 0.00625, 0.025, 0.050 and 0.10 µg and each subject will receive different doses at the two separate areas, or one dose and placebo. The total maximal dose given to one individual subject in this trial - 0.150 µg for the subjects receiving the 0.050 and 0.100 µg doses - is well below the maximum dose given in the previous trial where each subject received four active doses, a total of 0.405 µg at each occasion.
Based on clinical safety data from the previous study and the selection of doses in the present study, it is assumed that this design provides a minimized potential risk and a high probability to estimate possible effects of FOL-005.

9.4 Selection and Timing of Dose for Each Subject

The dose regime in the study, 3 times per week, is selected based on the results in the phase I/IIa trial FCS-001 where the subjects were treated 2 or 3 times per week. The efficacy measured both as increase in hair density as well as in percentage of responders, was more prominent after administration three times per week as compared to two times per week. FOL-005 was well tolerated at all tested doses and there was no detectable systemic absorption of FOL-005 at either of the dosing regimens. Injection related AEs such as haematomas and erythema, were more frequent in the group treated 3 times per week as

compared to the group treated 2 times. This is considered to be a result of the injection procedure and not the active ingredient. No increase in systemic AEs was found with the more frequent dosing.

Detailed descriptions of the treatment regimen and instructions for application of the IP are given in Section 9.1.1.

Restrictions to follow during the treatment period are described in Section 9.8.1.

9.5 Blinding

This trial will be double-blinded, meaning that neither the subject nor the Investigator will know which treatment areas will receive which treatment (actives or placebo). The appearance of the IP does not differ between the placebo and the active treatments.

The treatment of the subject's treatment areas will be randomised as described in Section 9.2 and the subjects will receive a subject and random number. .

In order to ensure the double blindness in the trial, dilution of the IP will be done according to the Study Specific Laboratory Manual (see Appendix 1), by persons not otherwise involved in the trial.

9.6 Randomisation

Each randomised subject will be treated with 2 of the 5 trial treatments on the two treatment areas on the scalp. The two treatment areas (1 and 2) will be symmetrical placed on the scalp (see figure 2)

Thus, the subject will be randomised to receive any of the following 10 treatment combinations:

A:	• FOL-005 placebo: • FOL-005 0.00625 µg:
B	• FOL-005 placebo: • FOL-005 0.025 µg:
C	• FOL-005 placebo: • FOL-005 0.050 µg:
D	• FOL-005 placebo: • FOL-005 0.100 µg:
E	• FOL-005 0.00625 µg: • FOL-005 0.025 µg:
F	• FOL-005 0.00625 µg: • FOL-005 0.050 µg:
G	• FOL-005 0.00625 µg: • FOL-005 0.100 µg:
H	• FOL-005 0.025 µg • FOL-005 0.050 µg:

I	• FOL-005 0.025 µg • FOL-005 0.100 µg:
J	• FOL-005 0.050 µg: • FOL-005 0.025 µg

Each of these 10 combinations may be allocated in two ways: First treatment on area 1 and second treatment on area 2 or vice visa.

The total allocation ratio of treatments will be 5:5:5:5:4 where 4 depicts placebo.

In general, computer generated randomisation lists will be created containing one randomisation scheme per subject.

Upon signature of informed consent (screening period) each subject receives a 5-digit patient identification number, which is composed of:

Digits 1 and 2: trial center (01, 02, 03, etc.)

Digits 3, 4 and 5: individual screening number within the center (consecutively in the order of screening within the center: 001, 002, etc.)

Subjects who are eligible for enrollment into the trial will obtain a random number (501, 502, 503, etc.) The random number will not be reused if a subject discontinues the trial.

Subjects discontinued from the trial for IMP-unrelated reasons with treatment for less than 4 weeks will be replaced (see section 7.1). The replacement subject will receive the same treatments as the discontinued subject. The original randomization number will be replaced by a new randomization number generated by the last two digits of the original number preceded by 6 (e.g. original random number is 553; replacement random number is 653).

In order to further avoid bias of the results, the trial biostatistician will also be blinded and the preparation of the randomisation lists and envelopes are therefore performed by psy consult scientific services, Frankfurt, Germany, not directly involved in the study.

9.7 Breaking the Randomisation Code

9.7.1 Un-blinding of Individual Subject Treatment

The trial sites will receive sealed envelopes containing a list of individual treatment codes. The envelopes will be kept by unblinded staff members at the trial site.

The unblinded staff will keep the envelopes in a secure, limited access location to prevent inadvertent breaking of the blind of the investigator. The double blindness must be maintained throughout the trial.

Suspected unexpected serious adverse reactions (SUSARs) will be unblinded for reporting to regulatory agencies and ethics committees. The pharmacovigilance team at FGK Clinical Research GmbH, Munich, Germany will be supplied with sealed envelopes of the randomization list to break the trial blind as required for regulatory reporting purposes. However, the investigator, sponsor, and blinded trial team will be kept blinded to treatment allocation. The information with regards to unblinding will be stored in a secure environment accessible only to pharmacovigilance team.

If the code has been broken for a subject, the subject will be withdrawn from the trial and procedures accompanying withdrawal are to be performed.

9.8 Prior and Concomitant Therapy

The use of prior medication used up to 4 weeks before study start and all concomitant medication (including Over the Counter and herbal medicines) by the subject will be recorded in the appropriate section of the eCRF up to the End of Trial Visit.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator. However, concomitant medication administered during the trial may lead to withdrawal of the subject from the trial (see Section 8.7) or subsequent exclusion form the PP analysis population if considered to be compromising the trial outcome.

9.8.1 Disallowed Concomitant Therapy and Procedures

The following treatments and/or procedures are prohibited during the trial:

- Prolonged UV exposition and UV tanning beds; subjects are advised to wear hats/caps while outside
- Sauna will not be permitted during the trial
- Use of any topical drug on the treatment area(s) except for subject's usual shampoo and hair care/cosmetic products as long as they do not claim to increase hair growth
- Use of any washes using alcohol, vinegar or other astringents, including peeling agents on the treatment areas
- Hair removal on skin treatment areas, e.g. waxing and shaving

The following should be avoided during the trial:

- More than once per day bathing/swimming
- Normal washing/showering of the head / scalp is allowed but a 2 hour free interval before or after injection should be respected

9.9 Treatment Compliance

Application of IP in the treatment areas will be performed only at the trial centre by qualified medical staff of the trial team. Compliance of the subject regarding concomitant therapies and the use of cosmetics in the treatment areas will be documented throughout the trial.

9.10 Drug Accountability

All IP supplied for this trial must be stored in a secure place. The Investigator or designated personnel at the trial site will keep a record of the inventory and dispensing of all IP. The Investigator is responsible for the drug accountability.

The monitor will perform a final drug accountability at the site before the used IP can be destroyed or shipped back to Sponsor (unused IP).

Study drug accountability, i.e., documentation of delivery, inventory, and return of IP will be maintained. Forms for documentation of the dilution procedures will be provided with the study specific IMP dilution manual.

10 TRIAL ASSESSMENTS AND PROCEDURES

10.1 Endpoints

Primary endpoint:
Change from baseline of total hair density (No. of hairs per cm2) on the scalp after 12 weeks of treatment

Secondary endpoints are:
Change from baseline of total hair density (No. of hairs per cm2) on the scalp after 8 weeks of treatment

Change from baseline of hair growth parameters after 8 and 12 weeks of treatment:
- Cumulative hair thickness (mm/cm²)
- Hair thickness (µm/cm², mean median)
- Hair length (mm/cm^2; mean, median)
- Terminal hair density (n/cm^2)
- Vellus hair (<40µm thick) density (n/cm^2)
- Total hair growth (µm/day/cm^2)
- Hair growth (µm/day/cm^2, mean median)
- TrichoScan Anagen/Telogen ratio
- Proportion of anagen hairs (%)
- Proportion of telogen hairs (%)
- Proportion of vellus hair (%)

To evaluate **the** safety based on:
- Any adverse events and adverse drug reactions reported
- Local tolerability assessments
- Vital signs and physical examination
- Abnormal safety laboratory parameters

10.2 Efficacy Assessments

10.2.1 Efficacy Variables

- Cumulative hair thickness (mm/cm²)
- Hair thickness (µm/cm², mean median)
- Hair length (mm/cm^2; mean, median)
- Total hair density (n/cm^2)
- Terminal hair density (n/cm^2)
- Vellus hair (<40µm thick) density (n/cm^2)
- Total hair growth (µm/day/cm^2)
- Hair growth (µm/day/cm^2, mean median)
- Anagen hair density (n/cm^2)
- Telogen hair density (n/cm^2)

10.2.2 Methods for Efficacy Assessments: TrichoScan imaging and measurement

10.2.2.1 Determination of Clinical Response to Investigational Product

Photos of the treatment areas will be taken, and assessment of hair growth (hair count and hair density) calculated based on TrichoScan images. The analysis of the images will be performed centrally by a unit independent of the investigators. The analysis of the images will be performed while keeping the blind with regard to the treatment assignment. Assessment of hair growth will be performed as follows:

At Screening:

1. Treatment areas will be trimmed over a large area to achieve a hair length of 1mm;
2. Treatment areas (1.5 cm in diameter) will be selected and marked by a dot tattoo;

At visit 1 (day 1):

1. Selected treatment areas (1.5 cm in diameter) will be identified;
2. Selected treatment areas will be trimmed over a large area to achieve a hair length of 1mm;
3. A TrichoScan image is taken without hair dye with the TrichoScan camera/optics system held always in the same position;

At visit 2 (day 3):

1. Selected treatment areas (1.5 cm in diameter) will be identified;
2. A TrichoScan image is taken after hair dye with the TrichoScan camera/optics system held always in the same position **prior to IMP treatment**;

The procedures of visit 1 are repeated for visits 23 and 35. The procedures for visit 2 are repeated for visits 24 and 36.

For details of the TrichoScan imaging please refer to the TrichoScan manual.

10.3 Demographic and Other Baseline Characteristics

10.3.1 Demographic and Baseline Data

Demographic and baseline data will be collected at Visit 1. The following data will be collected:

- Date of birth
- Weight and height

10.3.2 Medical History

For the documentation of the medical history, **relevant** previous and concomitant diseases, allergies and familiar predispositions during the last year before the screening will be documented in the source data and the eCRF.
The medical history will be obtained by asking the subject and by inspecting his/her medical records. Relevant medical and surgical history will be recorded at visit 1.

10.3.3 Prior Medication

Any medication taken by a subject within 12 month before the clinical trial is considered as prior medication.
Use of prior medication will be recorded in the source data and the eCRF at Visit 1.

10.3.4 Concomitant Medication

Any medication taken by a subject during the clinical trial apart from the trial medication is considered as concomitant medication.
Use of concomitant medication will be recorded in the source data and the eCRF at Visit 1 and during the whole trial period if changed.

10.4 Safety Assessments

10.4.1 Safety Variables

The following safety variables will be measured:

- Adverse Events (nature and incidence) (see Section 11.2)
- Physical examination
- Vital signs (blood pressure [11], heart rate and body temperature) in sitting position
- Laboratory safety assessments (haematology, clinical chemistry and urinalysis)
- Local tolerability, as defined in section 10.4.6

All local tolerability assessments must be performed by an investigator with dermatological expertise. As far as possible the same investigator shall assess a subject at all assessment. Safety of the IP after the first application of the single dose will be assessed by AE documentation approximately 15 minutes after injection, as well as throughout the whole trial. The assessing investigator will be identified in the source data at each visit.

10.4.2 Adverse Events

AEs will be recorded at Visit 1 and until the End of Trial.

For further information of definitions and reporting of AEs and SAEs, see Section 10.5.

10.4.3 Physical Examination

Standard physical examinations will be performed at Screening, Visits 0, 36 and EoT visit.

The physical examination will include:

- General appearance
- mouth and throat
- ears (left and right)
- heart
- lungs
- abdomen
- neurological (rough inspection of strength and touch sensation)
- axillary and inguinal lymph node palpation

The parameters will be assessed as “normal” or “abnormal”. Abnormal findings will be specified and assessed as “clinically significant” or “not clinically significant”.

Clinically significant abnormal findings at Visit 0 will be recorded in the source data and on the medical and surgical history page in the eCRF. New or worsening clinically significant abnormal findings at all subsequent visits will be recorded in the source data and on the AE page in the eCRF.

10.4.4 Vital Signs

Vital signs will be recorded at screening, visit 1, visit 36 and EoT visit.
The following vital signs will be monitored as safety variables in a comfortable seated individual after 5 minutes:

- Supine systolic and diastolic blood pressure (mmHg)
- Supine heart rate (beats per minute)

- Body temperature measured in degrees Celsius (°C) according to site specific methods

The observed values will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

Clinically significant abnormal findings at Visit 1 will be recorded in the source data and on the medical and surgical history page in the eCRF. New or worsening clinically significant abnormal findings at all subsequent visits will be recorded in the source data and on the AE page in the eCRF.

10.4.5 Laboratory Assessments

A safety screen including standard safety laboratory parameters will be performed. Blood and urine samples for clinical chemistry and haematology evaluations will be collected at screening, 36 and at EoT visit. Serology samples will be taken at the screening visit and the result should be available at visit 1 before inclusion and randomisation. The samples will be analysed at the central laboratory LKF - Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany.

The observed values will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

Clinically significant abnormal findings at Visit 1 will be recorded in the source data and on the medical and surgical history page in the eCRF. New or worsening clinically significant abnormal findings at following visits will be recorded in the source data and on the AE page in the eCRF.

The following laboratory parameters will be measured (Table 2):

Table 2 Laboratory parameters

Category	Laboratory Parameter
Haematology	haemoglobin, white blood cell count including differential cell count, red blood cell count, platelet count, coagulation (partial thromboplastin time and prothrombin time)
Clinical Chemistry (blood serum)	Glucose (random), creatinine, total bilirubin, gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), Electrolytes (Na, K,), lactate dehydrogenase (LDH), total cholesterol
Urinalysis	blood, ketones, glucose, protein, pH, nitrites, leucocytes, microscopy if results are positive for blood or protein
Serology (at Screening visits only)	Hepatitis B (HBsAg, HB core antibody), hepatitis C, and HIV (anti-HIV).

10.4.6 Local tolerability

At each visit, the investigator will assess the local tolerability using a 4-point local tolerability / safety assessment scale (Table 3).
Local Tolerability will be reported as an AE if the local tolerability signs and/or symptoms results in temporarily or permanently stopping of further administration of trial treatment or if it is stopped at the request of the subject.
The outcome will have to be followed until resolution, steady state or until evidence that the investigational products and/or the subject’s participation in the trial are not responsible for the event.

Table 3 Local skin tolerance/ side effects

ERYTHEMA		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No evidence of erythema present
1	Mild	Slight pink discoloration
2	Moderate	Definite redness, easily recognized
3	Severe	Marked erythema, bright red to dusky dark red in color
HAEMATOMA		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No haematoma
1	Mild	Slight haematoma inside the treatment area
2	Moderate	Definite haematoma of strong color inside the treatment area
3	Severe	Marked haematoma, covering the whole treatment area
DYSPIGMENTATION (HYPER- AND HYPOPIGMENTATION)		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No signs of dyspigmentation
1	Mild	Slight dyspigmentation of small definite area
2	Moderate	Marked dyspigmentation inside the treatment area
3	Severe	Dyspigmentation of the treatment area including areas not injected
INDURATION		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No induration
1	Mild	Barely perceptible induration
2	Moderate	Induration palpable
3	Severe	Marked induration
PAIN/ DISCOMFORT		
SCORE	**GRADE**	**DESCRIPTION**
0	None	No pain or discomfort
1	Mild	Slight pain, not really bothersome
2	Moderate	Definite pain that is somewhat bothersome
3	Severe	Intense pain that may interrupt daily activities and/or pain Strong paraesthesia of the treatment area

For subjective scoring, the subject should be questioned with regard to the period after the last and prior to the next injection procedures scheduled for the respective day.

10.5 Procedures

10.5.1 Screening period (Day -21 to -1)

Within the three weeks prior to the first visit, the volunteers will come to the sites for the initial screening (including documentation of demographic data). Screening assessments will be performed after the volunteer has agreed to participate and has signed and dated the informed consent form.

The following examinations will be performed:

- Documentation of relevant relevant medical and surgical history (last 1 year)
- Documentation of demographic data;
- Documentation of relevant previous medication (last 12 months);
- Check in-/exclusion criteria (see section 8.2 and 8.4);
- Physical examination of general appearance, mouth and throat, ears (left and right), lungs, abdomen, neurological (see section 10.4.3);

- Vital signs: systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and body temperature (see section10.4.4);
- Blood and urine sampling for assessment of safety laboratory parameters, HIV/hepatitis;
- Determination of treatment areas;
- Marking of test areas;
- Shaving of test areas;
- Tatooing of test area;

10.5.2 Experimental phase

Visit 1

- Re-check of the inclusion and exclusion criteria (see section 8.2 and 8.4);
- Physical examination (see section 10.4.3);
- Vital signs (see section 10.4.4);
- Documentation of demographic data;
- Update of previous and concomitant medication;
- Recording of AEs/SAEs;
- Identification of treatment areas;
- Marking of test areas;
- Shaving of test areas;
- TrichoScan imaging without hair dye;
- Safety assessment and local tolerance assessment (see section 10.4);

Visit 2

- Update of previous and concomitant medication;
- Recording of AEs/SAEs (record potential AEs also 15 min after first application);
- Safety assessment and local tolerance assessment (see section 10.4);
- Randomisation
- Identification of selected treatment areas;
- Marking of selected treatment areas;
- TrichoScan imaging including hair dye
- IP application

Visit 3 - 21

- Update of previous and concomitant medication;
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Optinal: repeat of tattooing, if necessary;
- Identification of selected treatment areas;
- IP application

Visit 22

- Update of previous and concomitant medication;
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Identification of selected treatment areas;
- IP application

Visit 23

- Update of previous and concomitant medication;
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Identification of selected treatment areas;
- Marking of selected treatment areas;
- Shaving ot test areas
- TrichoScan Image without hair dye

Visit 24

- Update of previous and concomitant medication;
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Identification of selected treatment areas;
- Marking of selected treatment areas;
- TrichoScan imaging including hair dye
- IP application

Visit 25 - 36

- Update of previous and concomitant medication;
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Optinal: repeat of tattooing, if necessary;
- Identification of selected treatment areas;
- IP application

Visit 37

- Update of previous and concomitant medication;
- Recording of AEs/SAEs;

- Safety assessment and local tolerance assessment (see section 10.4);
- Identification of selected treatment areas
- Shaving ot test areas;
- TrichoScan imaging without hair dye;

Visit 38

- Update of previous and concomitant medication;
- Physical examination (see section 10.4.3);
- Vital signs (see section 10.4.4);
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Blood and urine sampling for assessment of safety laboratory parameters;
- TrichoScan imaging including hair dye

EoT visit (if not identical with Visit 38 due to early discontinuation)

- Update of previous and concomitant medication;
- Physical examination (see section 10.4.3);
- Vital signs (see section 10.4.4);
- Recording of AEs/SAEs;
- Safety assessment and local tolerance assessment (see section 10.4);
- Blood and urine sampling for assessment of safety laboratory parameters;

Subjects should refer to the clinical site three times a week at an interval of at least 1 day.

10.6 Criteria for discontinuation of subject due to local intolerance and further proceedings

In case of adverse events, which bring the subject at risk or might confound the results of the trial the subject should be discontinued. The subject should be referred to his private practitioner for further diagnostics.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

Any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

11.1.2 Adverse Reaction

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Comment: All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorised IP or summary of product characteristics for an authorised product).

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

11.1.4 Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- May not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Comments: Life-threatening in the definition of an SAE or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

11.2 Reporting of Adverse Events

All trial subjects will be carefully monitored for the occurrence of AEs during the trial period, from intake of the first dose of IP until the last dose of IP for each subject. Previously reported AEs will be followed up and assessed as “recovered” or “not recovered”. The Investigator will collect AEs with a non-leading question such as “have you experienced any new health problems or worsening of existing conditions” as well as reporting events directly observed or spontaneously volunteered by subjects.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the subject, or reported in answer to an open question by the Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the source data and the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding trial treatment
- Opinion on causality
- Seriousness
- Outcome

Severity

Severity describes the intensity of an event, and will be assessed as:

Mild

The AE does not interfere in a significant manner with the subject’s normal functioning level. It may be an annoyance.

Moderate

The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe

The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.

If an AE changes in severity, the worst severity should be reported.

Causality

Causality will be assessed as:

Probable

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or

chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.

Possible

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely

A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Follow-up of Subjects after Adverse Events

Ongoing AEs will not be followed after the date of trial termination for a subject, unless the Investigator assesses the AE as relevant to follow from a trial perspective. The date when the Investigator considers one of these outcomes to have occurred for the last ongoing AE for a subject will be considered the last visit for this subject, and the outcome should be recorded in the source data and the eCRF.

Abnormal Laboratory Values/Vital Signs

An asymptomatic abnormal laboratory/vital sign finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE or if it causes the subject to discontinue the trial.

Clinically significant abnormal findings at Visit 1 will be recorded in the source data and on the medical and surgical history page in the eCRF. New or worsening clinically significant abnormal findings at all Visits will be recorded in the source data and on the AE page in the eCRF.

If an abnormal laboratory/vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory/vital sign result should be considered additional information.

11.3 Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported immediately, by e-mail (preferred) or fax, but in any case no later than 24 hours of any site staff becoming aware of the event.

Initial notification should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify subjects by unique code numbers assigned in the trial and not by the subjects' names, personal identification numbers, and/or addresses. The following information is **mandatory** for the initial report:

- Subject trial identification data (ID)
- Trial treatment (blinded, if applicable)
- Start date (time, if relevant) of the trial treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria

- Causality assessment

For reported deaths, the Investigator should supply the Sponsor and the IEC (if applicable) with any additional requested information (e.g. autopsy reports and terminal medical reports).

SAE REPORTING CONTACT DETAILS

Dr. Monika Storm

FGK Drug Safety

E-mail: safety@fgk-cro.com
FAX: +49 89 893 119 180

In addition please notify the bioskin CTM (Anke Müller, anke.mueller@bioskin CRO.com). The FGK pharmacovigilance team takes over the Sponsor's task of informing the Competent Authorities and the European Medicines Agency (EMA) of any individual case reports of SAEs that are determined to be reportable by the sponsor (i.e. adverse events considered as serious, related and unexpected [SUSARs]). SUSARs will be distributed within 7/15 working days to the EMA (EudraVigilance) and concerned Competent Authorities and the Ethics Committees, according to local regulations. The investigator will be notified by FGK of safety issues/SUSARs according to current legislation.

11.4 Precautions/Overdose

Since all study treatments are administered by trained trial personnel and are applied intradermally, the risk of overdose is minimal.

11.5 Pregnancy

Not applicable.

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 Statistical and Analytical Plans

Before unblinding the trial data, a separate statistical analysis plan (SAP), may be prepared.

12.1.1 Data Sets to be Analysed

The subject population sets are defined as follows:

Safety analysis set (SAS): All randomised subjects who received at least 1 dose of IP. Subjects will be analysed according to actual treatment received.

Full analysis set (FAS): All correctly included (i.e. fulfilling all the entry criteria) and randomised subjects with at least one post baseline measurement of the primary efficacy variable and having received at least one dose of the study medication. Subjects will be analysed according to the randomised treatment irrespective of actual treatment received.

Per-protocol set (PPS): All subjects included in the FAS and who have:

- taken the correct treatment throughout the trial (single treatment errors will be evaluated individually prior to un-blinding)
- no major protocol violations that could interfere with the objectives of this trial.

Further exclusion of subjects and/or subject data will be decided upon during the blind review of the data, focusing on concomitant medication and also considering compliance.

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented (on an individual level) at the clean file meeting before breaking the randomisation code.

Safety summaries will be performed on the safety analysis set. The safety analysis set will be considered the primary analysis population for the safety variables.

The PPS will be considered the primary efficacy subset of subjects. The FAS will be used for a sensitivity analysis of the primary efficacy variable only.

12.1.2 Definitions

Baseline — A baseline measurement refers to the last non-missing assessment made before the first administration of IP (at the screening and baseline visit). This is valid where a change from baseline is derived.

12.1.3 Statistical Issues

Handling of dropouts and missing data

Outliers will be included in summary tables and listings, and will not be handled separately. If a subject is withdrawn from the trial, all data collected until the time of withdrawal will be used in the analyses. Missing data will not be imputed.

Level of significance, multiple comparisons and multiplicity

Since this is an exploratory trial no formal hypotheses are postulated. Comparisons by means of p-values will be interpreted in a descriptive manner, nominal p-values and confidence intervals will be presented.

12.1.4 Summary Statistics

Data will be summarised by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum median and maximum value. Categorical data will be presented as counts and percentages. The data will be presented for each dose level.

Descriptive summaries by study center will be presented for the primary efficacy endpoint only.

12.1.5 Efficacy Analyses

The primary efficacy objective is to evaluate the hair density (No. of hairs per cm^2) on the scalp after 12 weeks of treatment as compared to baseline. The relative change will be used, i.e. after 12 weeks of − Baseline

The hypothesis that the relative change from baseline is equal to zero will be analysed using the exact Wilcoxon signed rank test.

The secondary efficacy objectives will be analysed using the same methodology as in the analysis of the primary efficacy objective.

12.1.6 Demographic and Other Baseline Characteristics

Demographic and other baseline data will be presented using summary statistics.

12.1.7 Exposure to Treatment

Exposure to treatment (number of injections divided by planned number of injections) with IP will be presented using summary statistics for each dose.

12.1.8 Prior and Concomitant Treatment

Prior and Concomitant medication will be summarised as number of subjects being treated with each type of medication/therapy classified according to Anatomical Therapeutic Chemical (ATC) level 3 and World Health Organization (WHO) Drug Dictionary preferred term.

12.1.9 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and by preferred term.

The total number of subjects with at least 1 AE, at least one treatment emergent AE (TEAE) and the total number of AEs and TEAEs will be presented.

The number of subjects, percentage and the number of TEAEs will be tabulated by SOC and by preferred term. TEAEs will also be tabulated by severity and by relationship to treatment. In this table, subjects with TEAEs will be counted only once within a SOC or a preferred term by using the event with the worst severity or the closest causal relationship, respectively, within each category. AEs due to local tolerance issues will be presented by dose administered to the respective treatment areas.

12.1.10 Medical History

All previous and concomitant diseases will be coded with MedDRA.

12.1.11 Other Safety Assessments

Physical Examination

Physical examination will be presented in a shift table. The shift table will show the number of subjects who changed (compared to visit 1) from “normal” or “abnormal” at baseline to “normal” or “abnormal” at each time of assessment.

Vital Signs

Vital signs will be summarised by treatment combination, together with changes from baseline, by visit.

Laboratory Safety Assessments

For laboratory data, summary statistics will be produced for observed values and for changes from baseline to each visit. In addition, the number of abnormal and clinically significant observations will be tabulated for each treatment combination by visit. Abnormal values will be flagged in listings.

Shift tables will show the number of subjects who changed from below, within or above the reference range at baseline to below, within or above the reference range at each time of assessment.

For laboratory values which are below the limit of quantification, the value corresponding to the limit of quantification will be used when summarising data (e.g. if the result is <x.x then the value x.x will be used in the statistical analysis).

Local Tolerance Assessments

Local tolerance assessments will be summarised by dose administered to the respective treatment areas.

12.2 Determination of Sample Size

The change from baseline until end of the treatment period (delta) is the primary efficacy endpoint and the base for the sample size estimation.
The expected standard deviation for delta is 23.0 based on data published by Olsen EA et. al [12]. The expected change in hair density from baseline is 8 % which is 13.6 hairs/cm^2 assuming the baseline hair density is 170 hairs/cm^2.
Using a statistical power of 80 % and a two-sided significance level on 5 % the number of fully evaluable subject on the dose of interest is 23. Assuming a dropout rate of 10 % results in a need to include 26 subjects whom all are given the dose of interest.

12.3 Justification for the sample size

12.3.1 Introduction

The assumptions for the design and power calculations are:

- The variable the powering is based on is Hair Density (HD, number of hair per cm^2) and absolute change from baseline
- The hypotheses to be tested will be two-sided, i.e. no assumptions on the direction of the effect
- The estimation of the expected baseline hair density and expected standard deviation is based on the Olsen EA et. al [12]

12.3.2 Expected baseline hair density and expected standard deviation

The expected baseline hair density is presented in Table 1 in Olsen EA et. al [12]. In the patients randomised to get placebo the mean hair density is 168.9 hairs/cm^2 and in the patients randomised to receive active treatment the baseline hair density is 170.8 hairs/cm^2. In the sample size calculations it is then estimated that the mean hair density at baseline is 170 hairs/cm^2.
The minimum increase in hair density expected to be needed from a marketing perspective is 8%, i.e. a mean increase of 13.6 hairs/cm^2. In the sample size calculations an increase of 13.0 is used in order to be conservative.
In Table II in Olsen EA et. al [12] the observed standard deviation for the change in hair density from baseline until 16 weeks post baseline is given. The observed standard deviation for patients given placebo is 19.7 and for patients given active treatment it is 22.5. In the sample size calculations a standard deviation of 23.0 is used in order to be conservative.

12.3.3 Sample size Formula

The following hypothesis is to be tested:

$$H_0: \mu = 0$$
$$H_1: \mu \neq 0$$

Where μ is the expected value in the group (i.e. the mean in an infinite group) implying that μ is the expected absolute change over time within a certain dose level.
The following formula has been used to calculate the number of patients needed [13] (n=number of patients on the dose of interest):

$$n = \frac{\sigma^2 \times \left(\lambda_\alpha + \lambda_\beta\right)^2}{(\mu)^2}$$

In the formula above σ is the expected standard deviation, λ_α is the $1-\alpha$ percentile of the standardized normal distribution and λ_β is the $1-\beta$ percentile of the standardized normal distribution. If the test is two-sided and the significance level is 0.0500 then $\lambda_\alpha = 1.9600$. If the power is 80% then $\lambda_\beta = 0.8416$ and if the power is 90% then $\lambda_\beta = 1.2816$.

12.3.4 Results

Table 4 Number of fully evaluable subjects needed in order to get 80 % probability to get a two-sided p-value less than 5 % by some values for the expected standard deviation and by some differences in hair counts from baseline until end of treatment.

Delta	Standard deviation									
	18.00	19.00	19.70	20.00	21.00	22.00	22.50	23.00	24.00	25.00
10.00	26	29	31	32	35	38	40	42	46	50
11.00	22	24	26	26	29	32	33	35	38	41
12.00	18	20	22	22	25	27	28	29	32	35
13.00	16	17	19	19	21	23	24	25	27	30
13.60	14	16	17	17	19	21	22	23	25	27
14.00	13	15	16	17	18	20	21	22	24	26
15.00	12	13	14	14	16	17	18	19	21	22
16.00	10	12	12	13	14	15	16	17	18	20

12.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Any important deviation(s) from the originally planned statistical analysis (as described in the trial protocol) will be described and justified in a protocol amendment, in the statistical analysis plan and/or in the final report, as appropriate.

13 INVESTIGATOR/SPONSOR RESPONSIBILITIES

13.1 Ethics

13.1.1 Independent Ethics Committee (IEC)

This protocol and any amendments will be submitted to a properly constituted EC, in accordance with the International Conference on Harmonisation (ICH) guidelines, the applicable European Directives and local legal requirements, for approval/favourable opinion of the trial. Approval/favourable opinion must be obtained in written form before the first subject can be recruited.

13.1.2 Ethical Conduct of the Trial

The trial will be conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

13.1.3 Subject Information and Consent

All subjects will receive written and verbal information regarding the trial before any trial-related procedures are performed. This information will emphasise that participation in the trial is voluntary and that the subject may withdraw from the trial at any time and for any reason. All subjects will be given the opportunity to ask questions about the trial and will be given sufficient time to decide whether to participate in the trial.

Informed consent must be obtained before any trial-related procedures at screening visit.

The following will thus be required for participation in the present trial:

Subjects ≥18 years: informed consent form signed and personally dated by the subject **and** by the person who conducted the informed consent discussion

The consent includes information that data will be recorded, collected, processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the trial.

A copy of the subject information including the signed informed consent form will be provided to the subject, for their records.

13.2 Regulatory Authority

This protocol and any amendments will be submitted to the responsible regulatory authority for approval of the trial. Approval must be obtained in written form before the first subject can be recruited.

13.3 Subject Data Protection

All information containing personal data will be handled in accordance with German data protection legislation and with the EU Data Protection Directive (95/46/EC).

13.4 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties: Regulatory Authorities, Investigators and ECs.

A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent.

13.5 Good Clinical Practice

13.5.1 Legal Preconditions

This clinical trial is carried out according to the current and valid guidelines of and in agreement with:

- ICH efficacy guidelines and “Guidelines for Good Clinical Practice” (GCP) (2002)
- Declaration of Helsinki, revised 2013;
- Statute in dealing with pharmaceuticals, German drug law (AMG), in version of 12.12.2005, Article 1 changed most recently on 02.09.2015 (BGBl. I S. 1571);
- GCP-regulation: Decree in pursuance on Good Clinical Practice in conduction of human clinical drug trials from 09.08.2004, article 8 changed most recently on 19.10.2012 (BGBl. I S. 2192);
- Directive 2001/20/EG of the European parliament and of the council from 04.04.2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;
- Directive 2005/28/EG from 08.04.2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products;
- ENTR/F2/BL D (2003): Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (October 2005);
- ENTR/CT 2: Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (February 2006).

13.5.2 Protocol conformity

Protocol deviations are any discrepancy from the procedures defined in the trial protocol, such as skipping tests or examinations, not permitted concomitant medication, improper handling of the investigational product(s). After inclusion of a subject, it is the responsibility of the investigator/sponsor to avoid protocol deviations.

Deviations from the protocol will be assessed as “minor” or “major” on a case-by-case basis in cooperation with the Sponsor. This assessment will take place during a blind data review meeting. Major deviations from the protocol will lead to the exclusion of a subject from the per protocol analysis set.

Protocol deviations are specified in the 'Deviation Definition Document'. The Investigator shall make best efforts to collect the data exactly as specified in the protocol. Nevertheless small discrepancies can occur. These differences are to be noted and explained properly.

13.6 Subject Records and Source Data

Some data may be recorded directly in the eCRF and will then be considered source data. These data may include, but are not limited to, the following:

- height
- weight
- sex
- race

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the subject is in a clinical trial
- The identity of the trial e.g. Trial code
- Subject screening number and/or subject number
- That informed consent was obtained and the date
- Diagnosis
- Dates of all visits during the trial period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of trial termination
- Subject health service identification number

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the source data and the eCRFs. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Completed sections of eCRFs will be monitored on a regular basis as defined in the monitoring plan / monitoring manual.

13.7 Access to Source Data and Documentation

The Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the EC, if required.

13.8 Monitoring

The monitor will visit the trial sites before, during and after the trial to ensure that the trial is conducted and documented in accordance with this protocol, ICH-GCP guidelines, regulatory requirements and any trial specific documents such as eCRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The rights and well-being of human subjects are protected
- The investigational team is adhering to the trial protocol
- Informed consent has been obtained from all participants
- AEs have been reported as required
- Data are being accurately recorded in the eCRFs and are in accordance with source data
- IP is being stored correctly and drug accountability is being performed on an on-going basis
- IP is given to correct subject
- Facilities are, and remain, acceptable throughout the trial
- The Investigator and the site are receiving sufficient information and support throughout the trial

The eCRF data will be monitored on regular intervals. The monitoring will include source data verification (SDV) according to the SDV list and verification of data consistency over time. The Investigator and other relevant trial personnel should be available during the monitoring visits.

13.9 Data Management

An electronic CRF system will be used to capture data from the trial. The Investigator agrees to maintain accurate eCRF and source documentation as part of the research under this protocol. Each completed eCRF must be reviewed by the Investigator in a timely manner. Data management and handling of data will be conducted according to the trial specific Data Management Plan in accordance with ICH guidelines and the CROs standard operating procedures (SOPs).

Data entry will be performed by the trial site personnel. Validation and data queries will be handled by the CROs Data Management Team. The data will be subjected to validation according to the CROs SOPs in order to ensure accuracy in the collected eCRF data.

Changes to eCRF (if used) will be made at the site by the trial site personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Once all the queries are closed and data have been verified by the CRA, the eCRF will be signed (E-Signature) by the investigator and the database will be locked.

Before database closure, a reconciliation will be performed between the SAEs entered in the safety database and the trial database. After database closure, the database will be exported as SAS® data sets.

13.10 Quality Assurance and Audit

Audits or inspections, including source data verification, may be performed by the sponsor or its representatives, a CA and/or an EC.

13.11 Record Retention

The Investigator/institution should maintain essential documents for 15 years (as defined in ICH E6 GCP, Section 8) as required by the applicable regulatory requirement(s).

The Investigator/institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval.

It is the responsibility of the Sponsor to inform the Investigator/institution in writing as to when the documents no longer need to be retained.

13.12 Insurance

Every subject participating in the clinical trial will be insured in accordance with § 40 paragraph 3 of the German drug law against injuries to health which may occur during the trial.
Excluded from this however are injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the subject had not taken part in the clinical trial.
The insurance cover is jeopardized if the subject fails to report immediately to the investigator or responsible physician any injury to health which might have resulted from participation in the clinical trial, or if he/she undergoes any other medical treatment without their consent before the clinical trial has been completely finished - insofar as the individual subject is concerned.
Any injury to health which might have occurred as a result of participation in the clinical trial must be reported by the subject to the insurer without delay. The investigator is obliged to make such a report in any case.
The subject insurance will be arranged by bioskin GmbH on the basis of the final version of the subject information and informed consent form. The subject insurer is HDI-Gerling Industrie Versicherung AG", Überseering 10a, 22297 Hamburg, Tel. 040/36150-257, Fax 0511/645-1152305.

A travel insurance for the way to and from the site will be arranged.

13.13 Report and Publication

After completion of the trial, a clinical trial report will be prepared according to the ICH Guideline for Structure and Content of Clinical Trial Reports (ICH E3) by the Sponsor, to be defined in close collaboration with the Investigator and the Sponsor.

All publications and presentations must be based upon the clinical trial report.

All information supplied by the Sponsor in connection with this trial will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this trial.

If an Investigator wishes to publish results from this clinical trial, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this trial. If an Investigator is offered authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

14 REFERENCE LIST

1. Hamilton JB. Patterned loss of hair in man: Types and incidence. Ann N Y Acad Sci. 1951;53:708–28.
2. Fitzpatrick, T.B., The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol, 1988. 124(6): p. 869-71.
3. Paus, R. and G. Cotsarelis, The biology of hair follicles. N Engl J Med, 1999. 341(7): p. 491-7.
4. Vogt, A., K.J. McElwee, and U. Blume-Peytavi, Biology of the hair follicle, in Hair Growth and Disorders, U. Blume-Peytavi, D.A. Whiting, and R.M. Trüeb, Editors. 2008.
5. Yu, D.W., et al., Osteopontin gene is expressed in the dermal papilla of pelage follicles in a hair-cycle-dependent manner. J Invest Dermatol, 2001. 117(6): p. 1554-8.
6. Holmqvist H, (2016a), “Summary Report: Detection of FOL peptide in mouse skin after subcutaneous injection.” ImaGene-iT-SR (1)
7. Holmqvist H, (2016b), “Summary Report: Blocking of FOL005 peptide binding in human skin tissue.” ImaGene-iT-SR (2)
8. Edman K, (2017), “A randomised, double-blind, placebo-controlled trial of FOL-005 to investigate clinical safety and effect on hair growth in healthy volunteers.” Draft Trial Report FCS-001
9. Hoffmann R TrichoScan: Ein neues Werkzeug für die digitale Haarzählung. HAUTARZT. Dez 2002; 53:798-804
10. Hoffmann R TrichoScan: combining epiluminescence microscopy with digital image analysis for the measurement of hair growth in vivo. European Journal of Dermatology. Jul-Aug 2001; 4(11) 362-368
11. Alpert, B., et al., *Recommendations for blood pressure measurement in human and experimental animals; part 1: blood pressure measurement in humans.* Hypertension, 2006. 48(1): p. e3; author reply e5.
12. Elise A. Olsen, David Whiting, Wilma Bergfeld, Jeffrey Miller, Maria Hordinsky, Rita Wanser, Zhang and Bruce Kohut: “A multicenter, randomized, placebo-controlled, double-blind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men”. American Academy of Dermatology, Inc., 2007.
13. Lachin John M: Introduction to sample size determination and power analysis for clinical trials. Controlled Clinical Trials 2, 93-113, 1981.

15 SIGNATURE PAGES

Declaration of Sponsor

Title: A randomised, double-blind, placebo-controlled phase 2 trial of FOL-005 to investigate efficacy on hair growth on scalp skin in healthy volunteers.

This trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, revised 2013, and the guidelines on Good Clinical Practice (GCP).

_____ _____

Jan Alenfall, PhD, CEO
Follicum AB
Scheelevägen 22
Box 719
SE-220 07 Lund
Sweden
Phone: +46 709 31 51 15
E-Mail: jan.alenfall@follicum.com

Date

_____ _____

Johan Quensel, CEO
Q Clinical Research Consulting AB
Lärarvägen 12
SE-247 45 Torna Hällestad
Sweden
Phone: +46 760 46 97 44
E-Mail: johan.quensel@follicum.com

Date

Declaration of the Coordinating Investigator

Title: A randomised, double-blind, placebo-controlled phase 2 trial of FOL-005 to investigate efficacy on hair growth on scalp skin in healthy volunteers.

This trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, revised 2013, and the guidelines on Good Clinical Practice (GCP).

_____ _____

Signature Date
Prof. Dr. Ulrike Blume-Peytavi

Appendix 1

Schematic IP Dilution Manual for the FOL-005 IMP

Study Title: A randomised, double-blind, placebo-controlled phase 2 trial of FOL-005 to investigate efficacy on hair growth on scalp skin in healthy volunteers

Study Code: FCS-002

EudraCT: 2017-003809-17

IMP: FOL-005, 10 µg/mL, solution for injection, 9 mL

Other material: All needed material is delivered to site by the sponsor. This includes sterile, labelled dilution vials, sterile diluent, sterile syringes and needles needed for handling the dilution.

The dilution of IMP at site laboratory (or equivalent) is handled by personnel not otherwise involved in the study. A schematic description of the dilution of IMP in the clinical study is found below.

Dilution vials are marked with a vial code. The vial code number is predetermined and random and will remain the same throughout the study.

Please note that the order of the vial code numbers shown here are examples only and will be randomized and blinded in the study.

Vial code	**X**	**1**	**2**	**3**	**4**	**5**
FOL-005 (µg/mL)	5	2	1	0.5	0.125	Placebo
Given dose per 50 µL injection (µg)	-	0.100	0.050	0.025	0.00625	-

1) One vial, IMP (FOL-005, 10 µg/mL solution for injection) is thawed (precise thawing instruction will be provided)
2) Mark each dilution vial with preparation number and subject ID(s).
3) Equip each vial with a vented dispensing pin.
4) To each dilution vial (vial code 1-5 and X) transfer 3 mL of diluent.
5) Withdraw 3 mL from the thawed IMP and transfer to the vial marked “X”. Mix (precise mixing instruction will be provided)
6) Withdraw 2 mL from the vial marked “X” and transfer to the vial marked “1”. Mix
7) Withdraw 0.75 mL from the vial marked “X” and transfer to the vial marked “2”. Mix
8) Withdraw 0.75 mL from the vial marked “2” and discard.
9) Withdraw 2 mL from the vial marked “1”, discard 1 mL and transfer 1 mL to the vial marked “3”. Mix
10) Withdraw 1 mL from the vial marked “3” and transfer to the vial marked “4”. Mix.
11) Withdraw 1 mL from the vial marked “4” and discard.
12) Discard the vial marked “X”.

Each vial now contains 3 ml, and is marked with a vial code (random order). The vials are prepared at the study site daily. At the study site the investigator injects 50 µL from each vial in accordance with the patient specific randomization schedule.

Declaration of the Investigator

Title: A randomised, double-blind, placebo-controlled phase 2 trial of FOL-005 to investigate efficacy on hair growth on scalp skin in healthy volunteers.

All documentation for this trial that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this trial protocol, Investigator's Brochure, Case Report Forms (eCRFs), and other scientific data.

The trial will not be commenced without the prior written approval/favourable opinion of a properly constituted Ethics Committee (EC) and the regulatory authority. No changes will be made to the trial protocol without the prior written approval of the Sponsor, the EC and the regulatory authority, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

I confirm with my signature

- that I agree to conduct the trial in accordance with local law, the Declaration of Helsinki, ICH-GCP.
- that I have acquainted myself with the results of the pharmacological and toxicological trials of the investigational product and the results of other trials as described in the investigator’s brochure or other appropriate information.

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number