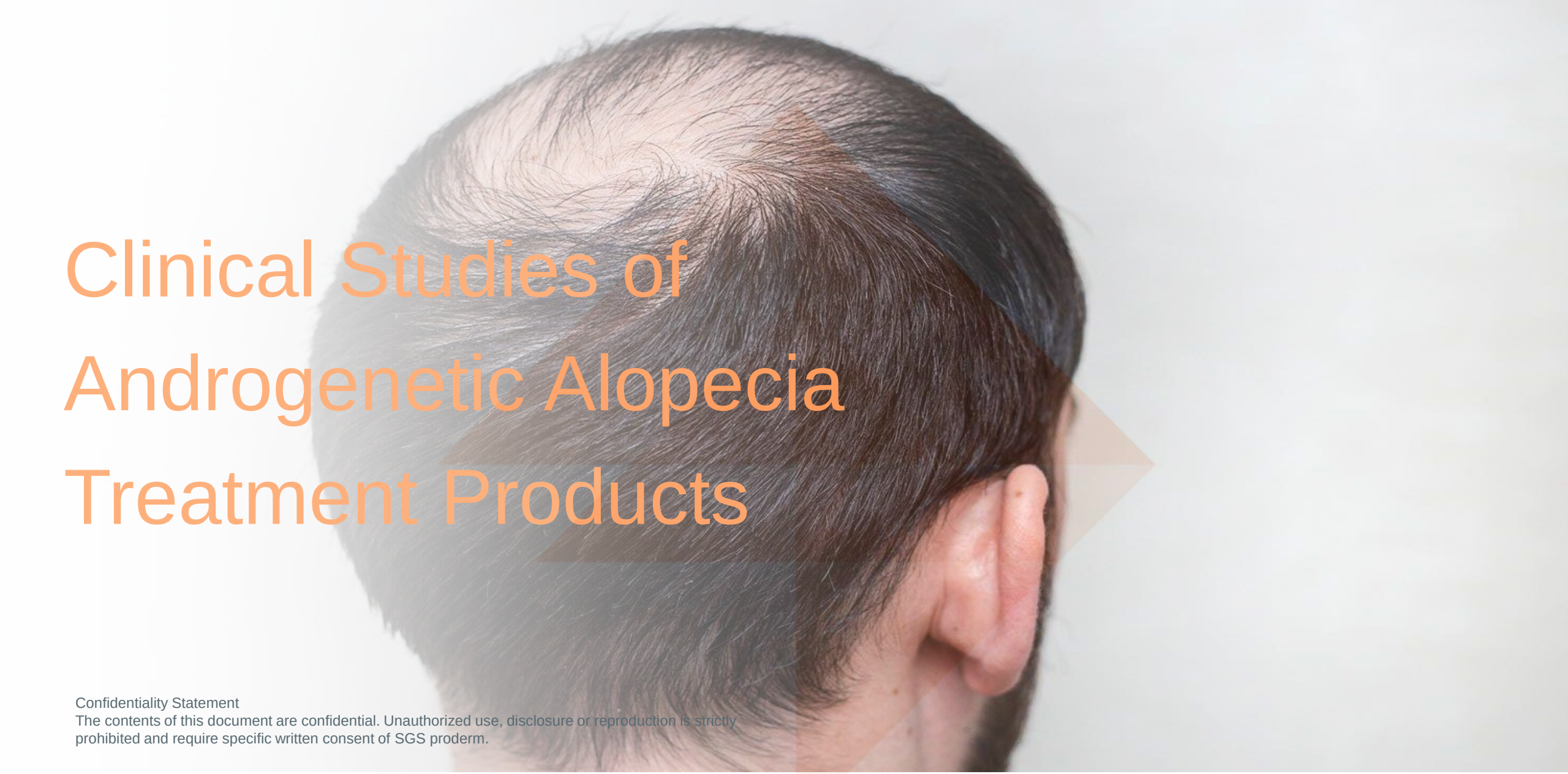

Clinical Studies of Androgenetic Alopecia Treatment Products

Sandra Bleckwenn | Matthias Seise | Michal Kasprzak | November 09, 2023

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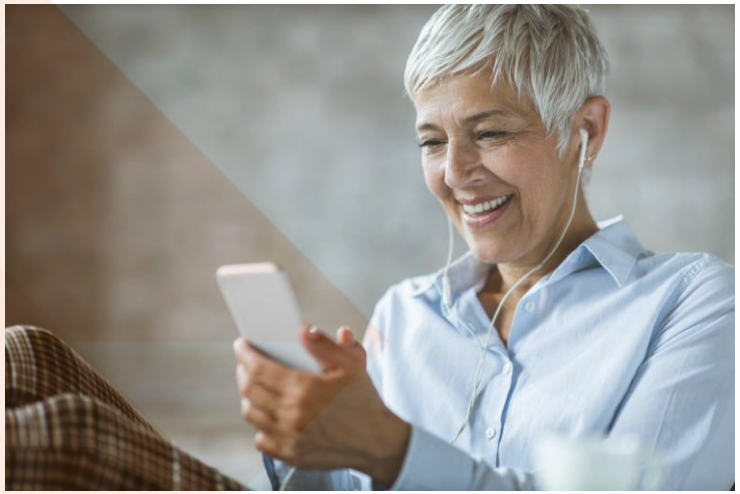
Overview of the Webinar - Agenda

- What kind of products?
- Regulatory background
- Anatomy human scalp & hair
- What is Androgenetic Alopecia?
- Clinical study design
- Inclusion criteria
- Objective & subjective evaluation
- Methods & devices
- Possible claims
- Questions & answers



Product Categories

- **Cosmetic products:**
  - Caffein, Cannabidiol, Biotin, Plant-based Oils, Niacin derivates, Redensyl
- **Food supplements:**
  - Vitamins , Minerals, Nutraceuticals
- **Medical devices:**
  - Advanced Laser Treatment (LLLT), Microneedling
- **Medicinal products:**
  - Minoxidil, Finasterid, (Dutasteride), Diasteride, Pyrilutamide, Spironolactone etc.
  - Botulinum Toxin, Platelet-rich-plasma (PRP), Stemm Cell Therapy etc.

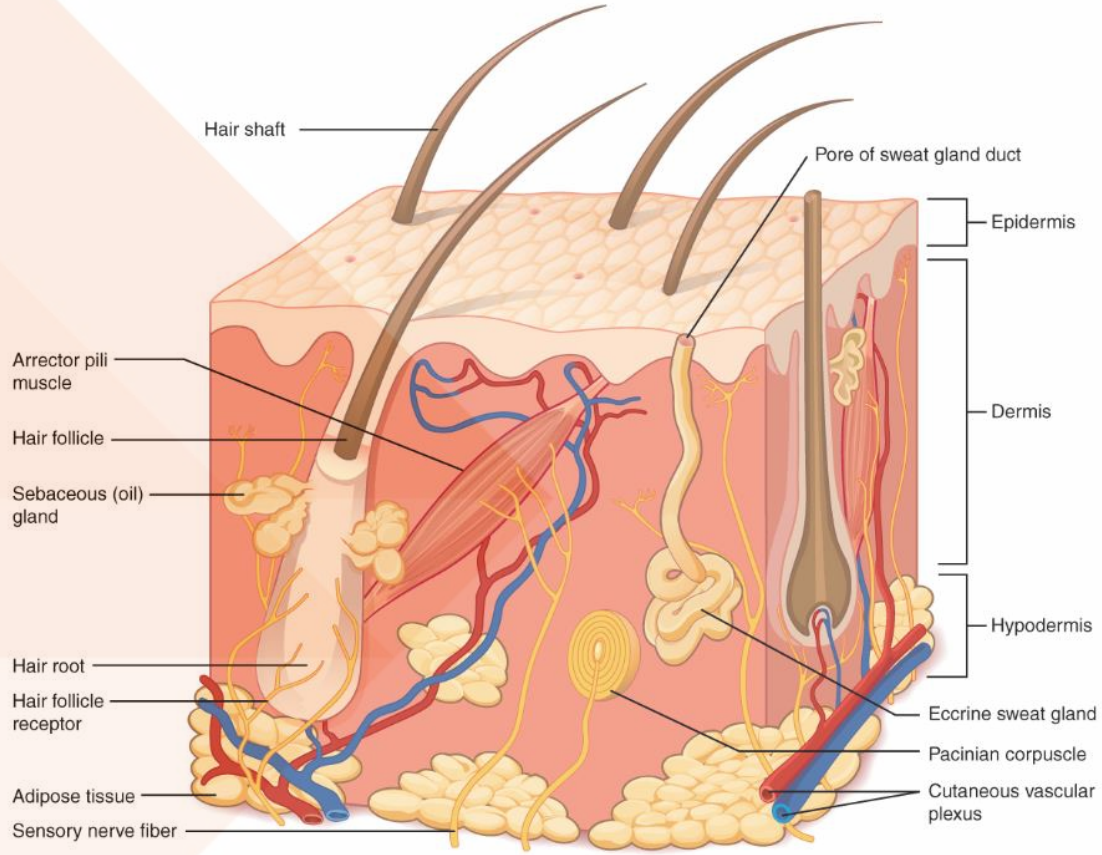
Regulatory Background

§

- Cosmetic products according to **Cosmetic Product Regulation (EC) No 1223/2009**
- Food supplements - Beauty & Health Claims **EFSA**
- Medical devices **: MDR (EU) 2017/ 745 directive 93/42/EEC, ISO 14 155, MDCG guidances**
- Medicinal products : **CTR : (EU) No 536/2014** and relevant ICH and EMA guidelines:

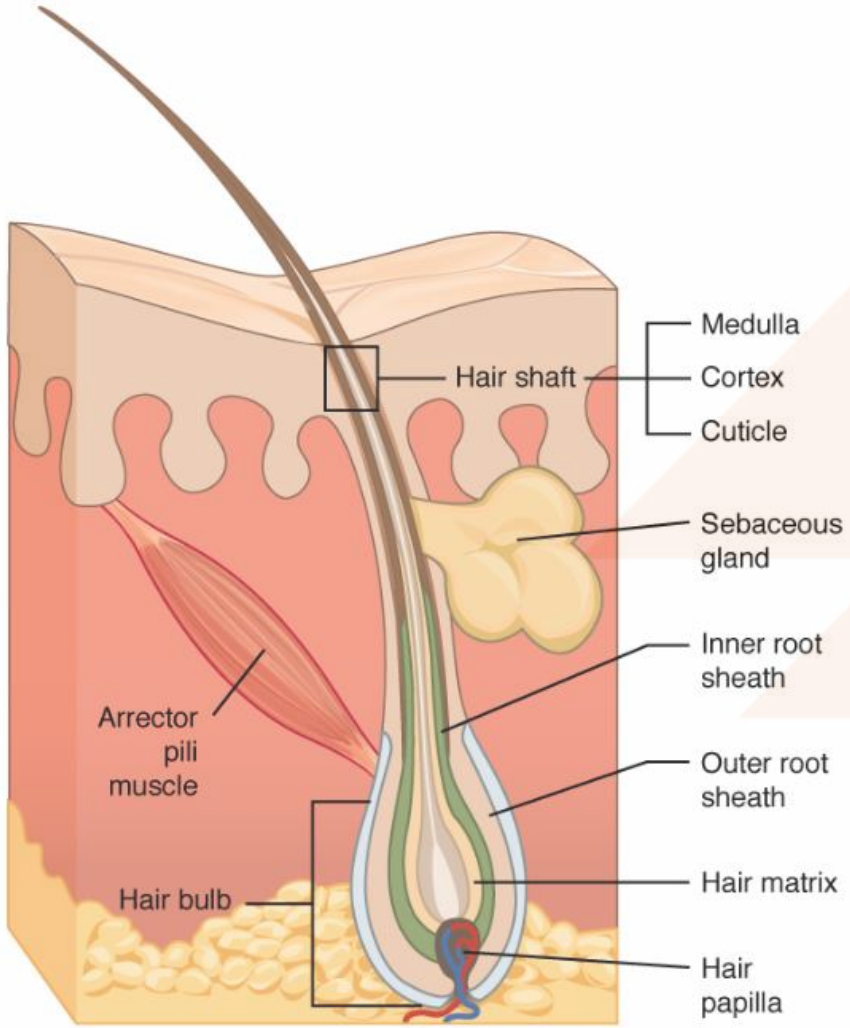
Anatomy of the Scalp

- Epidermis
- Dermis
- Hair & Hair Folicle
- Sebacous Glands
- Blood vessels



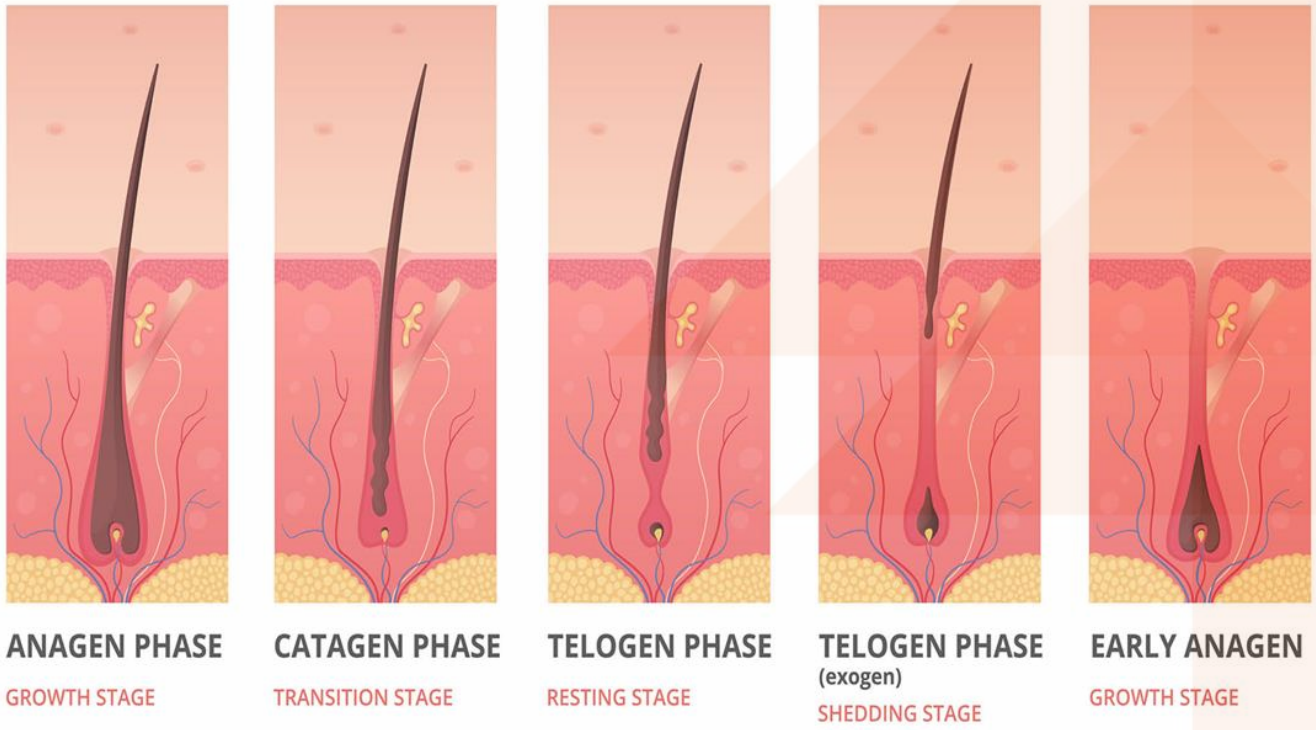
Betts, et al.; No changes made; https://ecampusontario.pressbooks.pub/medicalterminology/chapter/integumentary-system/#Figure6.1id

Hair Follicle Structure



- Hair shaft - Medulla, Cortex, Cuticle
- IRS - Henle's layer, Huxley's layer, Cuticle
- ORS - outer root sheath
- Hair buldge region – between sebaceous gland and arrector pili muscle
- Hair bulb - hair matrix, hair papilla

Hair Cycle



Phases

- Anagen: Growth - Proliferation - 2 to 7 years
- Catagen: Transition - Apoptosis - 2 weeks
- Telogen : Resting - Hair removal - 12 weeks
  Shedding
- Anagen: Growth stage of the new hair

Hair Loss – Effluvium

is a symptom and not a diagnosis

- Functional or structural disorders
- >100 hairs fall out per day
- Hair follicle damage
- Cancer treatment (Chemotherapy/ Radiotherapy)
- Hormonal and nutritional disorders
- Stress etc

110.000 hairs
600 cm ^{2}
50-100 hairs/day

- Alopezia Areata (AA) - patchy hair loss
- Androgenetic Alopecia (AGA) – pattern hair loss

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Androgenetic Alopecia (AGA)

- Hair Loss in male or female pattern
- Anagen phase shorter
- More telogen hairs
- Less anagen hairs
- Hairs tend to miniaturize
- Decrease of hair density on the scalp

Clinical Studies

- Scientific Credibility
- Standardization
- Ethical Requirements
- Good Clinical Practice (GCP)
- Compliance & Follow up
- Adverse Events & Safety

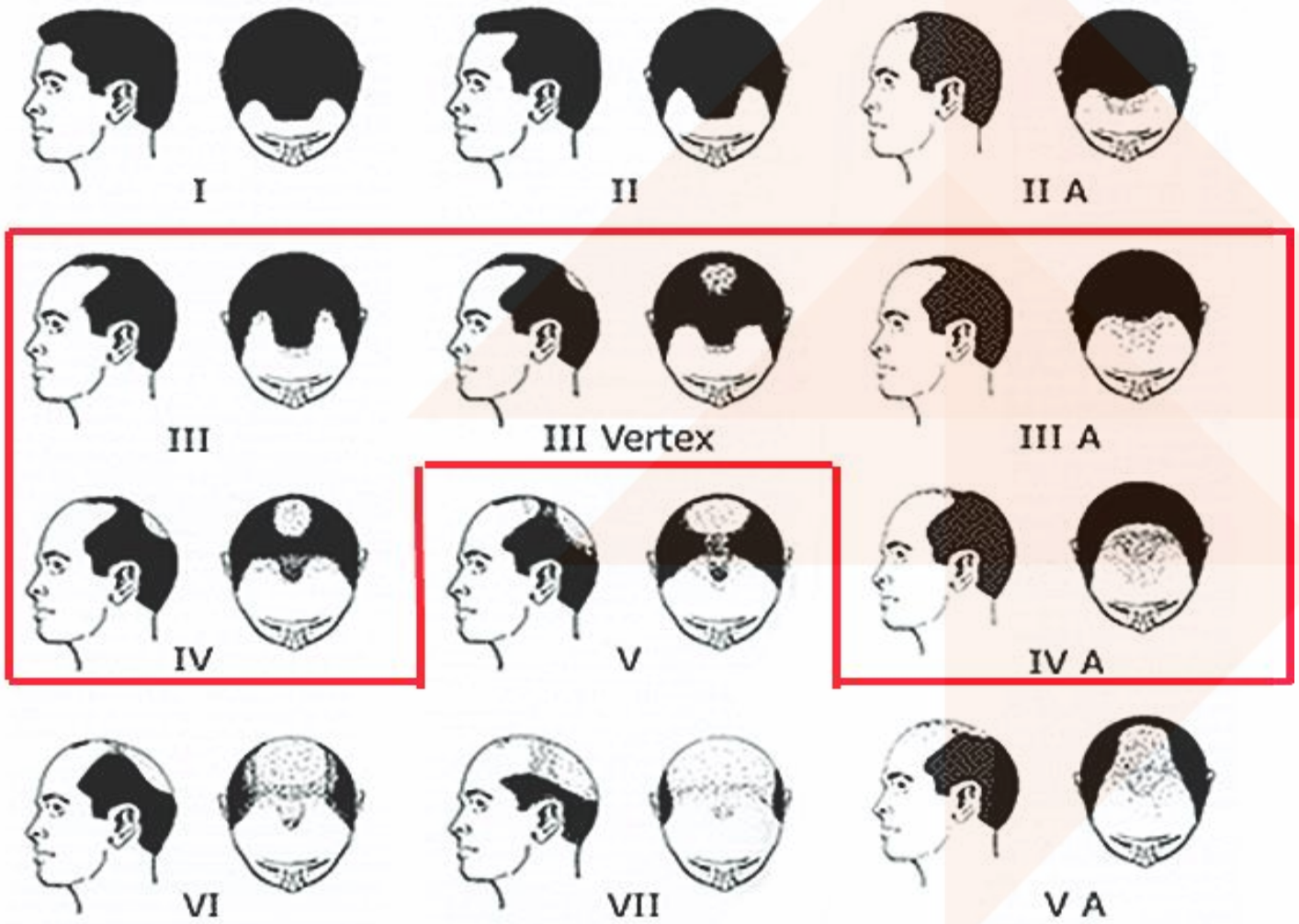
Clinical Study Design

- Prospective – not retrospective
- Randomization – treatment & control groups
- Blinding – patients & observer
- Controlled – placebo, controls, untreated
- Confirmatory or exploratory

Clinical Study Design

- Study duration – active in dermis: 3 months or longer
- Sample size – statistical power
- Participant selection - In- / exclusion criteria
- Endpoints - safety & efficacy
- Objective & subjective assessments
- Methods & measurements

Hamilton Score



Male participants

Inclusion according to scheme, III to IV

Ludwig Scale

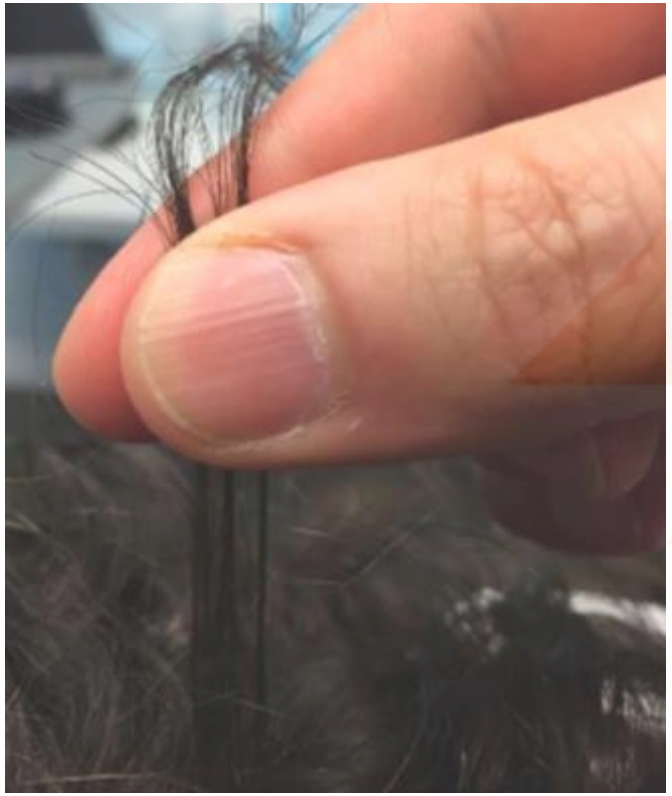
- Erich Ludwig's female pattern baldness classification system
- I: Visible thinning of the hair on the top of the head
- II: More extensive thinning of the hair than in I
- III: Full baldness

Savin Score

Female participants

Inclusion according to score -> 2 to 4

Pull Test



- Grasping 40 to 60 hairs between the thumb and index-finger and applying steady traction
- In general, only a few hairs can be plucked in this fashion
- < 10% normal
- >10% indicative of a pathologic process

Blume-Peytavi, U., Hillmann, K., & Guarrera, M. (2008). Hair growth assessment techniques *Hair pull test* (pp. 130-131). Springer, Berlin, Heidelberg

Treatment

- Topical
  - Shampoos and hair waters
  - Scalp lotions, creams and sera
  - Foams, sprays
  - Advances laser treatment
  - Injections of PRP, MSCs cells etc.
  - Microneedling
- Systemic
  - Tablets
  - Capsules
  - Fluids
  - Powders

- Application
  - Dose
  - Procedure
  - Duration (each time & overall)
  - Frequency

Parameters

- Vertex images (full head)
- Images of the test area for analysis (test area)
- Ranking of images (trained grader/ lay raters/ participants)
- Counting of combed-out hairs (trained technician/subjects)

- Objective (trained grader/ dermatologist) & subjective evaluation (participants):
  Hair densitiy, volume, length, growth, strength, thickness and hair quality,,

- Quality of Life [Subjects]
- Product acceptance questionnaire (Subjects)
- Assessment of tolerance (trained grader/dermatologist and participant)

Study Design – Phototrichogram

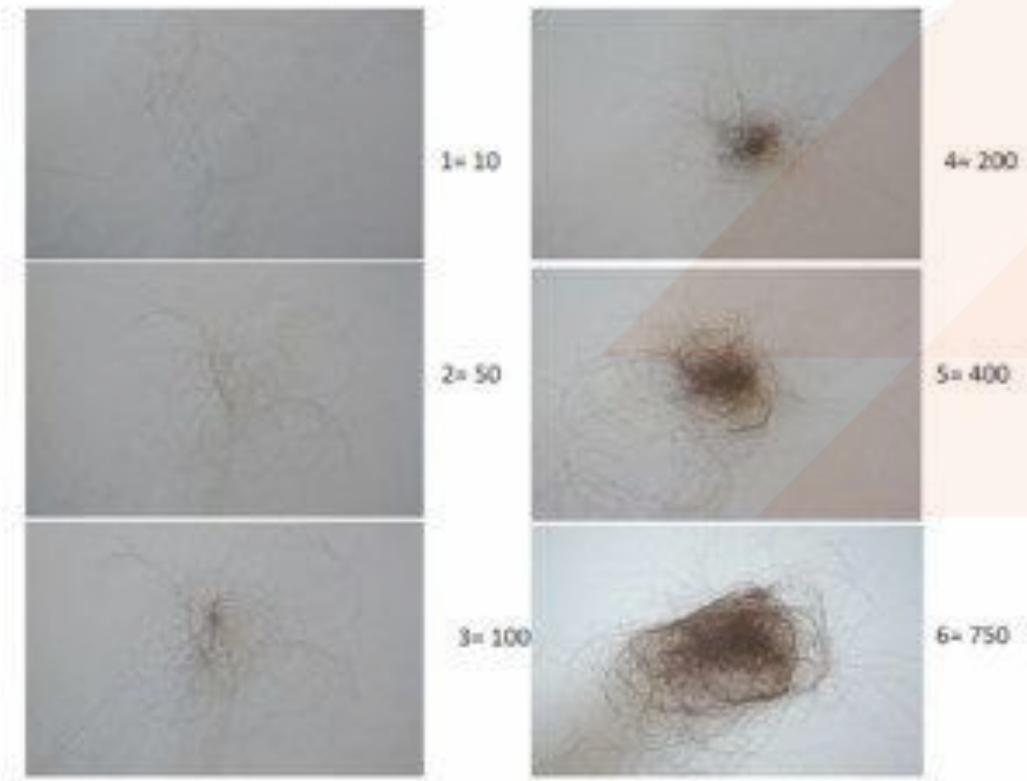
- Inclusion; according to Hamilton Score (male) or Savin Score (female),
  Pull test (pull of telogen hairs) or according to self-estimation (weaker)

- Conduct : 8 weeks, 3, 4 or 6 to 12 month with compliance visits every 4 weeks

  - Day 1 Clipping of small Area on the Scalp, relocation of areas with microtattoos
  - Day 3 Images 2 days after clipping for phototrichogram Analysis
  - Image Analysis: hair density, rates of anagen and telogen hairs, anagen hair density, telogen hair density, anagen/telogen ratio, cumulative hair thickness, hair growth rate

- Test area : Full head , ½ or defined part of the scalp

Combing, Counting Of Combed-Out Hairs



- Combing of hair
- Manual counting of combed out hairs

Vertex Images

- Subjective rating by lay persons , same panel

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Vertex Images

- Subjective rating by lay persons , same panel
- Objective evaluation by hair dresser or other experts

(Recommendation in “S3 - European Dermatology Forum Guideline for the Treatment of Androgenetic Alopecia in Women and in Men”)

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High Resolution Full Head Images

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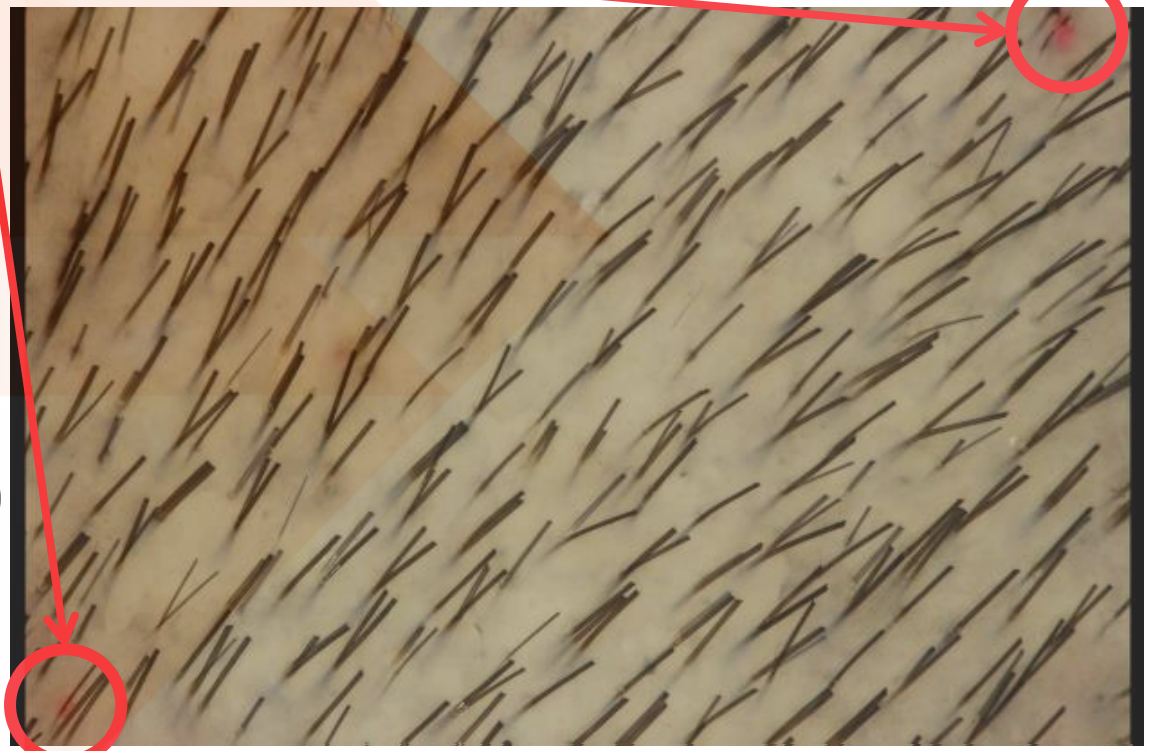
Phototrichogram method

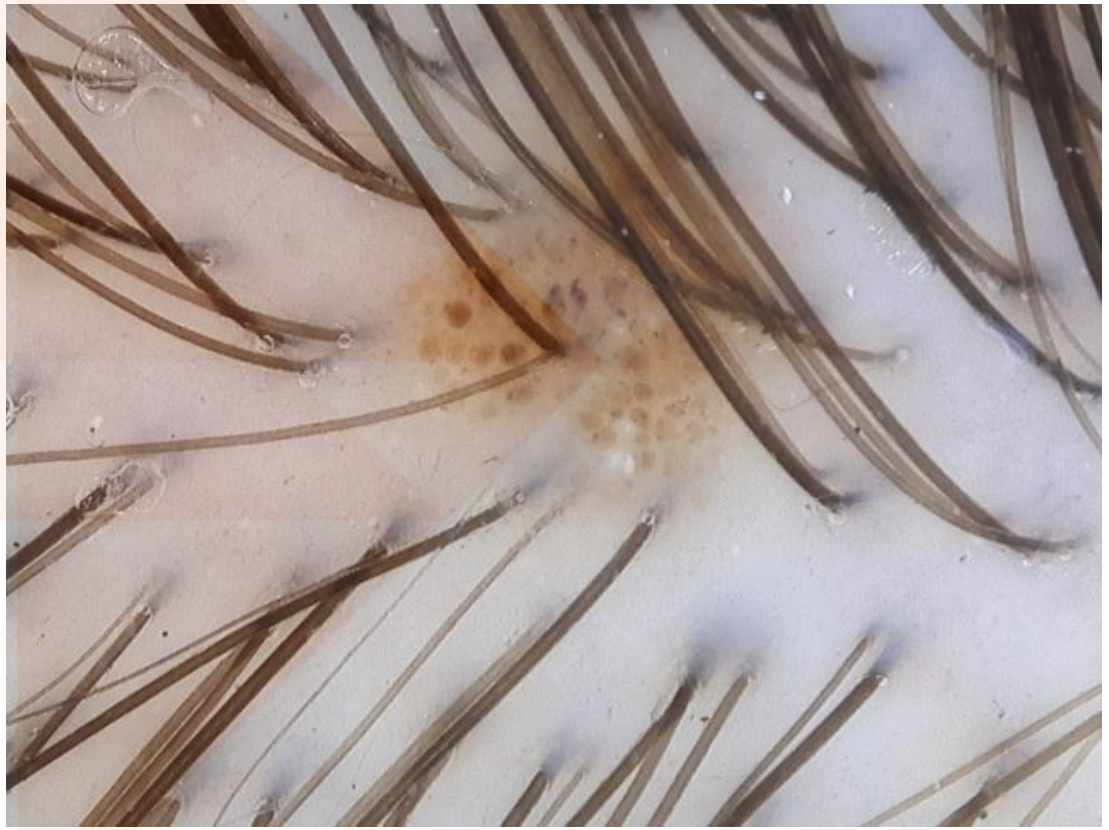
- Clipping of hair in a small area on scalp
- Photo by Leviacam to check the shaving quality and visibility of microtattoos
- 2 days regrowth of hair
- Dying the hair

Phototrichogram method

- Relocation of areas with microtattoos
- Photo by Leviacam, analysed for
  - hair density (hairs/cm²),
  - rate of anagen/telogen hairs (%),
  - ratio of anagen rate/telogen rate
  - growth rate (mm/day)
  - cumulative hair thickness (mm/cm²)
- Same procedure at further timepoints



How to identify the same spot on scalp?



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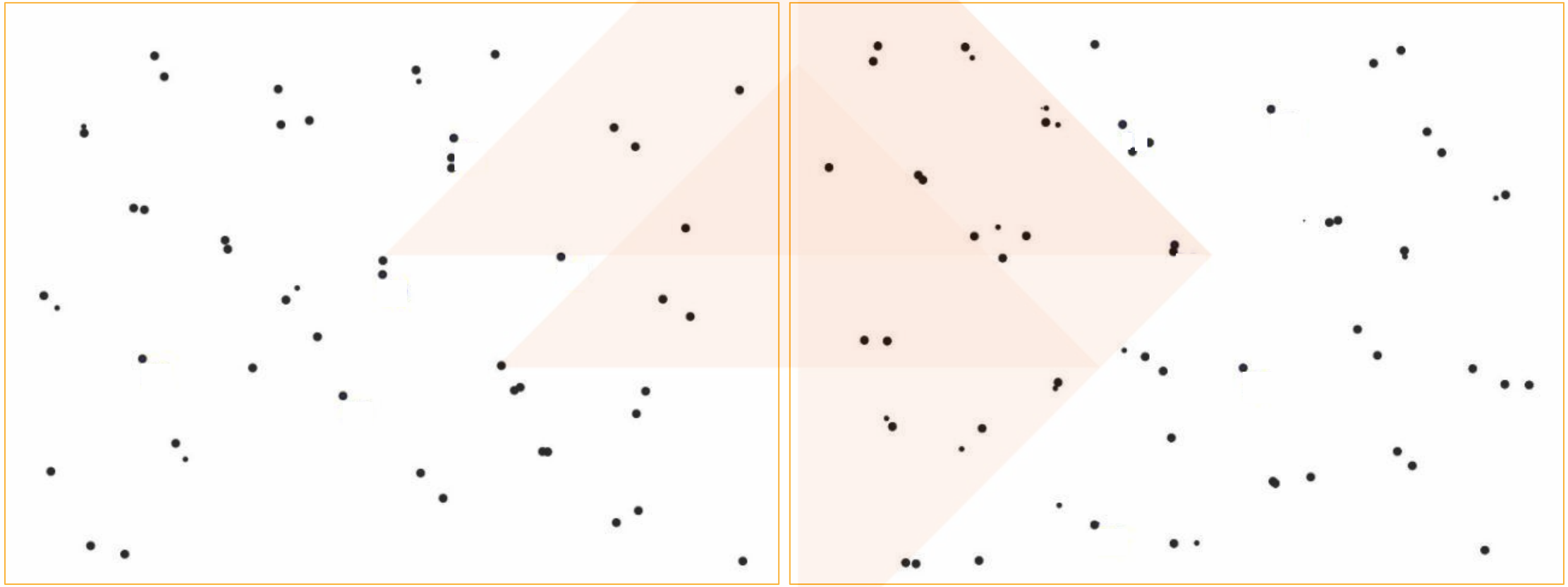
Remove hair & characteristic skin lesions from the image



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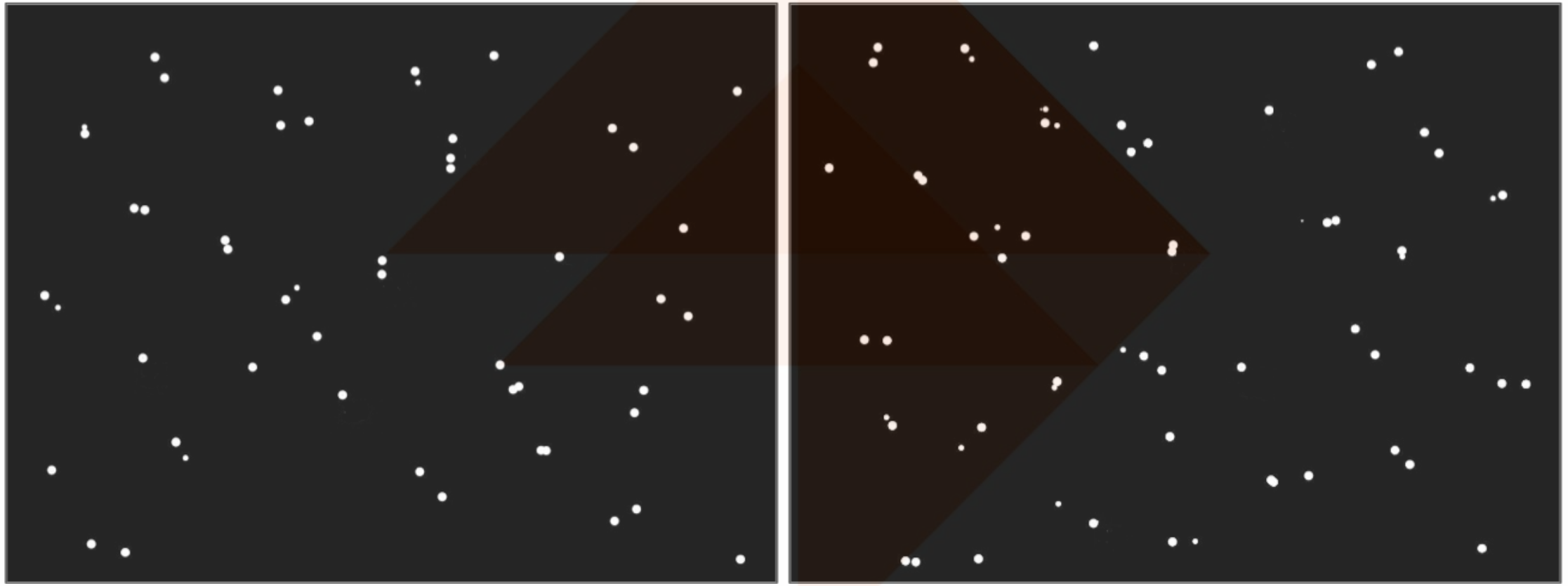
…looks like sky at night



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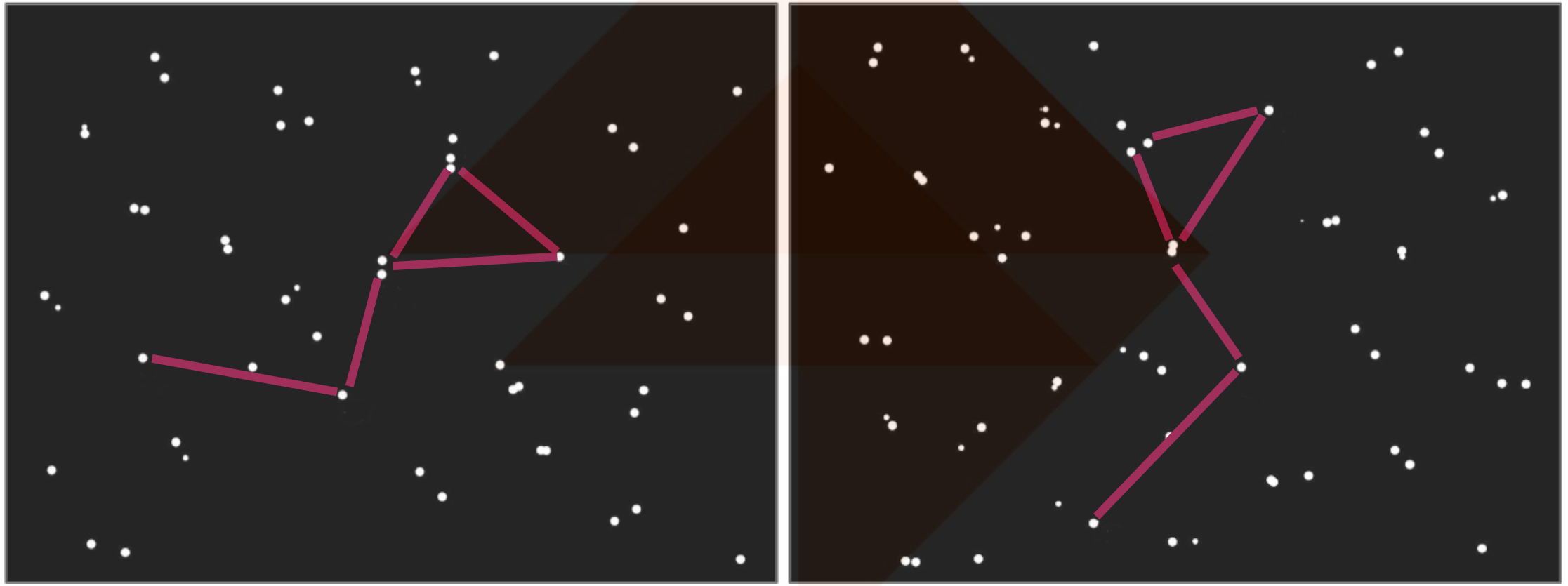
Astronomy approach:



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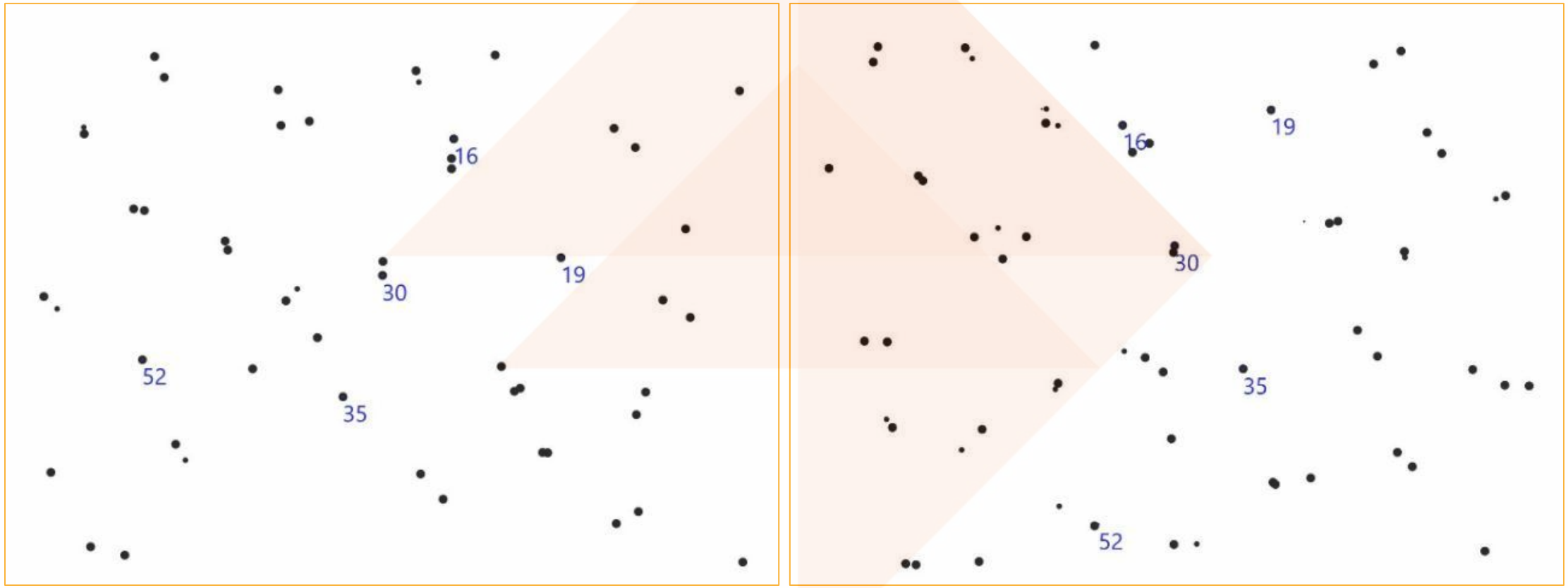

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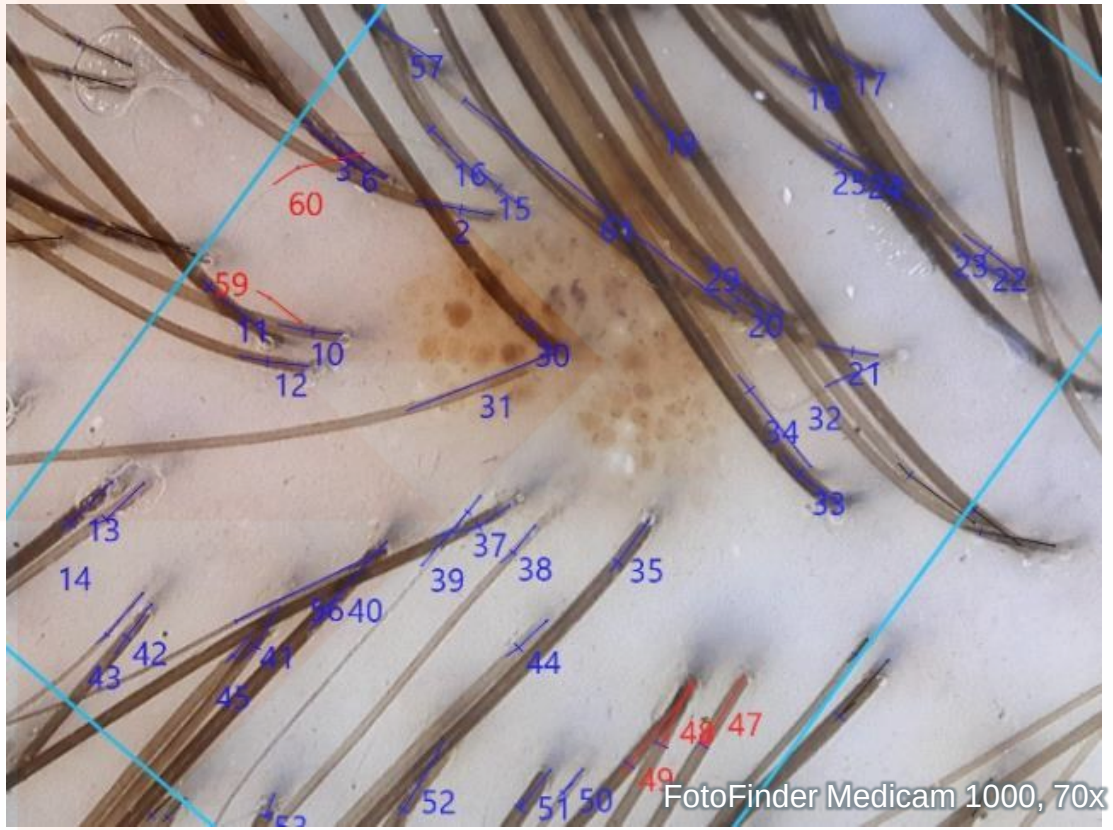
And back to trichoscopy



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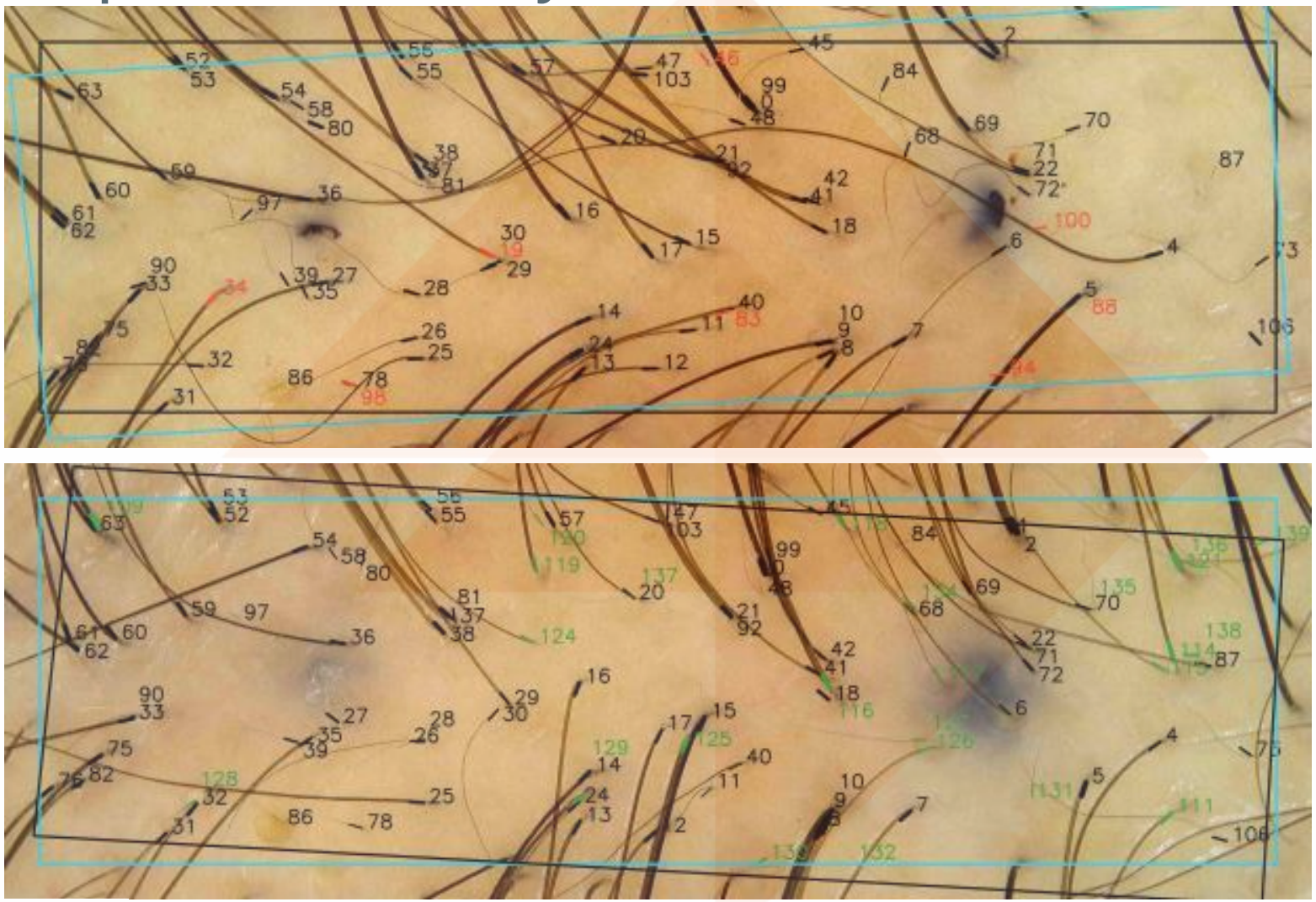
Make a comparison hair-by-hair – the H2H matching



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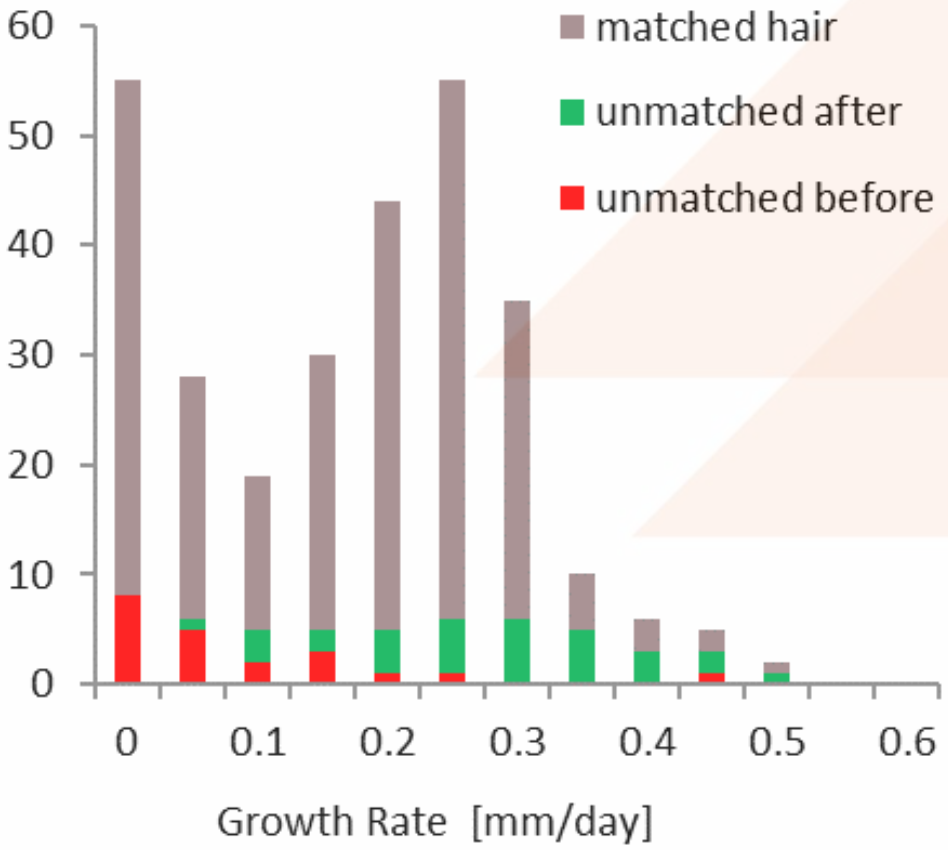
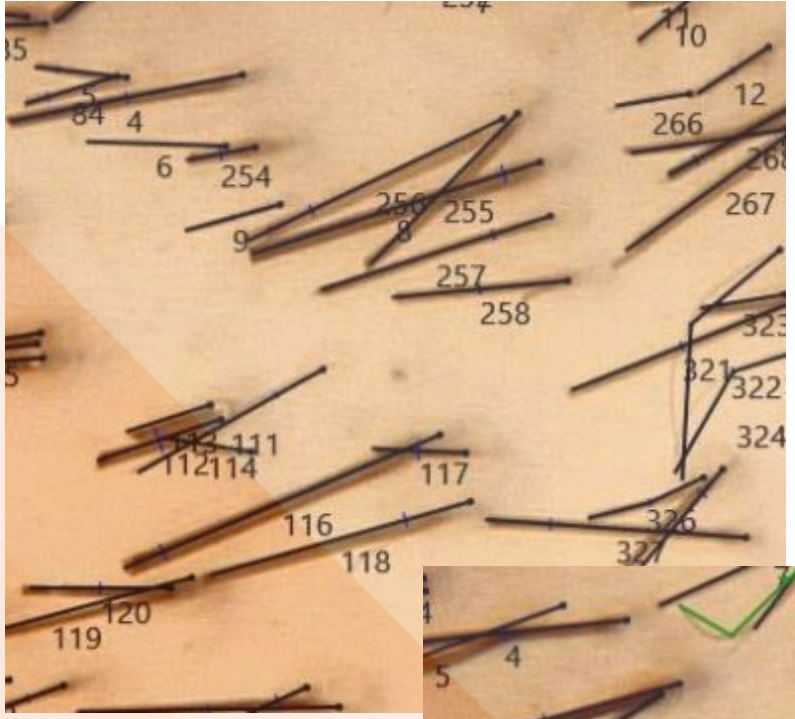
H2H matching of clipped hair





BEFORE TREATMENT

AFTER TREATMENT

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H2H matching validation project:

- Blinded, multi-site study with R.Grimalt clinic, Barcelona & R.Sinclair clinic, Melbourn
- Before-after difference in clipped & non-clipped hair count obtained with 3 methods:
  - automatic hair detection(TrichoScan)
  - manual corrected with standard TrichoLAB processing workflow
  - H2H matched
- H2H procedure enhanced with F-Mapping to recover information about hair that could not be detected in primary image from subsequent 2 images of the same spot
- Results:
  - automatic (clipped hair only): min ±12%
  - manual corrected: ±7% (clipped) and ±9% (non-clipped hair)
  - H2H matched: ±0.6% (clipped) and ±0.4% (non-clipped hair)

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Example: clinical trial planning

- Medication expected to trigger inactive hair follicles and increase hair density by minimum 3±3% in first 4 months
- Test procedure: Double blind with placebo control sample
- Examination procedure
  - First visit
    - Patient qualification
    - Clipping 1.5cm of scalp to c.a. 0.5mm hair length
    - Dying & tatooing
    - Image registration with m1000 20x (1mc2)
  - After 4 months
    - Cliping & Dying
    - Image taking with similar camera positioning
- Goal: prove therapeutic effect on P<5% Confidence Level

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Example: classical approach – pre-&post- haircount difference

Uncertainties & fluctuations of the result for one patient (assume average 100 hair in 1cm2)

- During 4 months 10 of hair will fall out and get replaced by new hair
  → expected fluctuation of ±6.0 hair in haircount difference in test sample, ±5.2 in control
- The pre- and post- image positioning precise to c.a. 0.5mm in X and Y so ca 90% of the image is the same but the remaining 10% - only similar
  → expected fluctuation of ±3.2 hair in haircount difference in remaining 10% of image area
- Pressing&manovering the camera stretches/tilts skin resulting in 10-20% area difference
  → expected fluctuation of ±3.9 hair in haircount difference
- Haircounting uncertainty → ±1 hair

→ Total expected fluctuation of ±7.9 hair (test) and ±7.3 hair (control)

→ At least **45 patients (net)**

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Example: H2H – difference in UNMATCHED hair count

Uncertainties & fluctuations of the result for one patient (assume average 100 hair in 1cm2)

- During 4 months 10 of hair will fall out and get replaced by new hair
  → expected fluctuation of ±6.0 hair in haircount difference in test sample, ±5.2 in control
- ~~The pre- and post- image positioning precise to c.a. 0.5mm in X and Y so ca 90% of the image is the same but the remaining 10% - only similar~~
  ~~→ expected fluctuation of ±3.2 hair in haircount difference in remaining 10% of image area~~
- ~~Pressing&manovering the camera stretches/tilts skin resulting in 10-20% area difference~~
  ~~→ expected fluctuation of ±3.9 hair in haircount difference~~
- Haircounting uncertainty → >±1 hair

→ Total expected fluctuation of ±6.1 hair (test) and ±5.4 hair (control)

→ At least **27 patients (net)**

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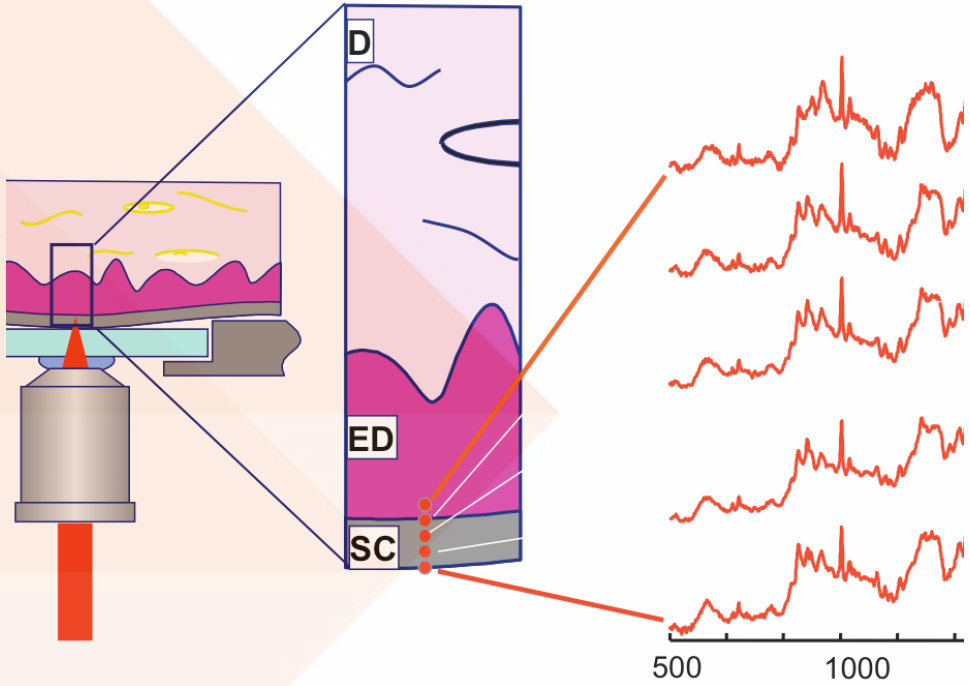
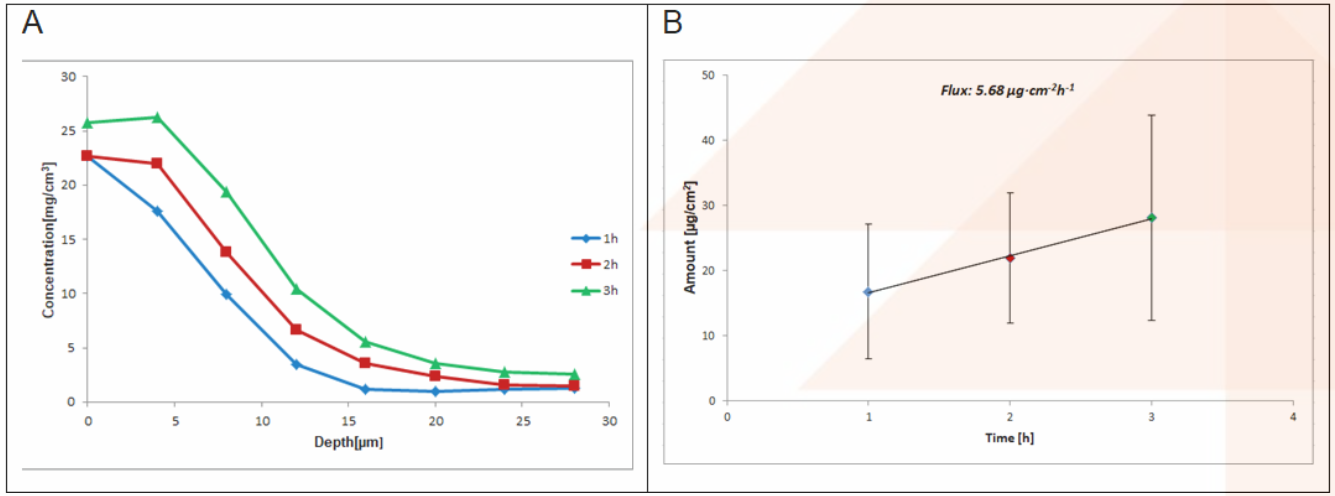
Confocal Raman Spectroscopy

- Non-invasive method
- Using the „Raman methods“, light scattering to identify the molecules
- Allows to analyse the composition of the skin
- Can analyse multiple parameters in one measurement:
  - Thickness of Stratum Corneum
  - Water profile in epidermis
  - Natural Moisturizing Factors (NMF) & Barrier Lipids
  - Skin penetration of biomolecules, i.e. active ingredients, pharmacological products



Raman Measurements on the Scalp (Skin penetration of biomolecules)

Penetration of Caffeine 2% into Stratum Corneum
Application on 3 areas (volar forearm) for 1, 2, 3 hours,
n = 3

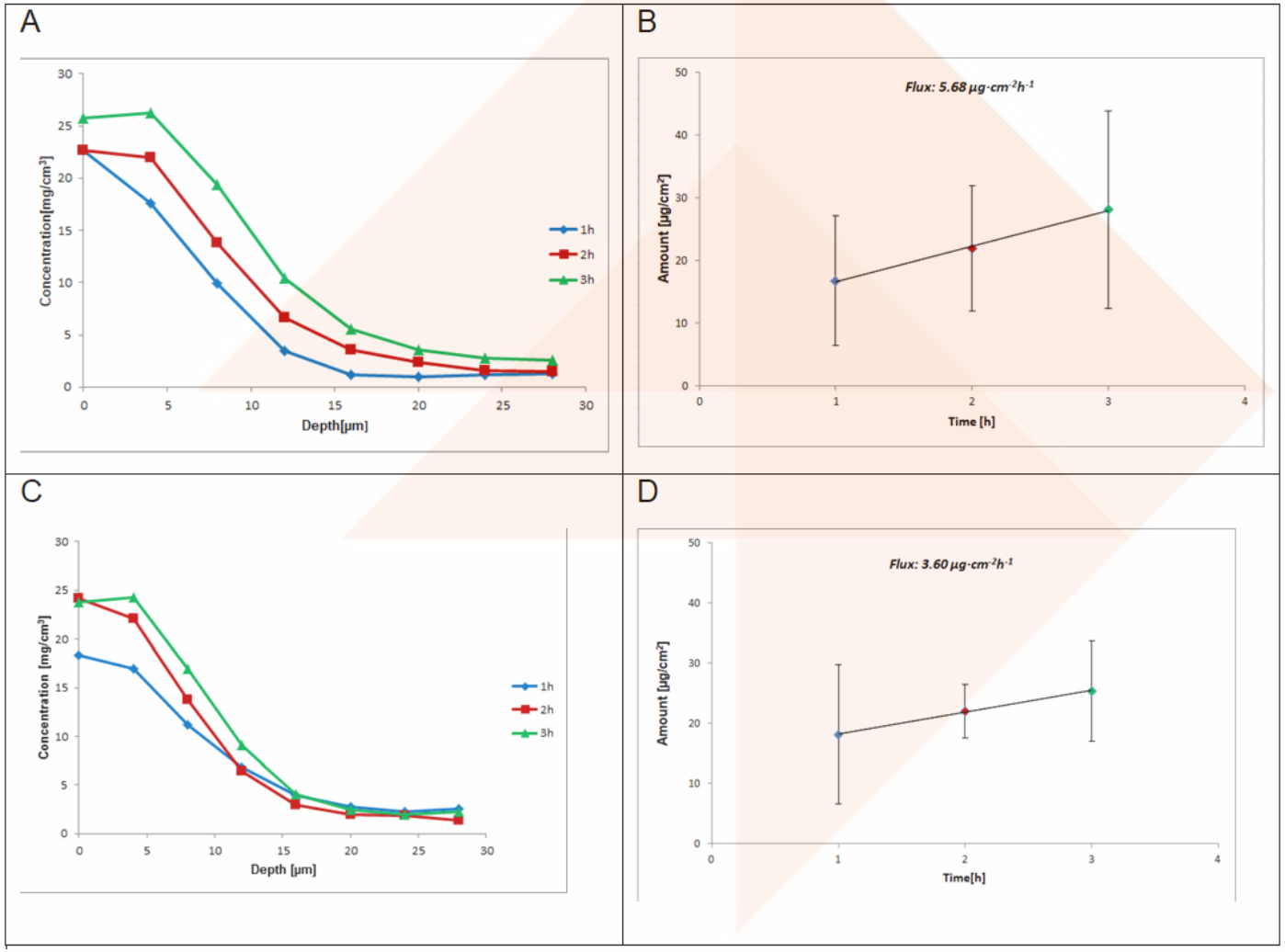


Penetration of Caffeine 2% into Stratum Corneum

Application on 3 areas (volar forearm) for 1, 2, 3 hours, n = 3

In water

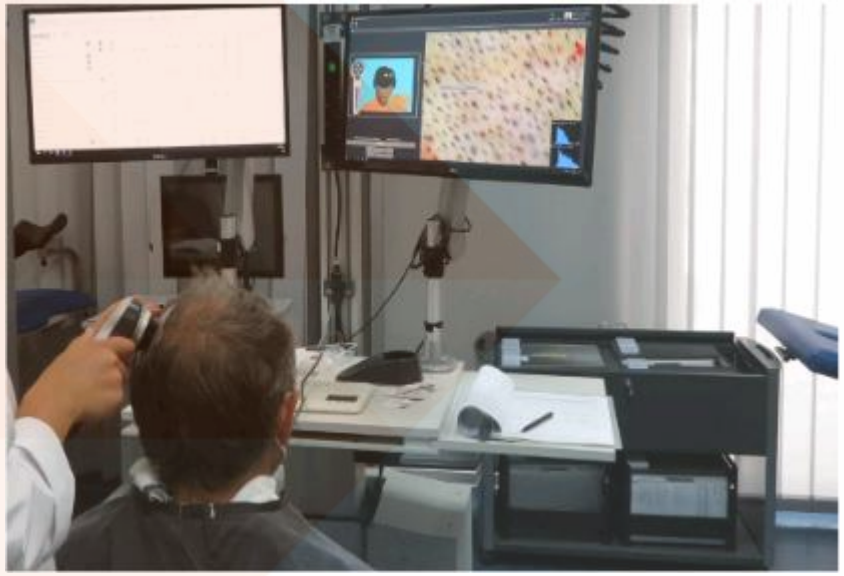
In water
+ penetration
enhancer



Medicinal Product Case Study

- Phase IIa study with 200+ patients to be enrolled with AGA according to the Hamilton-Norwood grade
- Multicenter- 3 Sites
- N= 210

- Full-service
  - Scientific Consulting
  - Project Management
  - Data Management & Statistics
  - Clinical & Medical Monitoring
  - Site &Vendor Management
  - Pharmacovigilance
  - Clinical Report Writing



Claims

- Relaunch hair growth, decrease hair loss
- Efficiency as alopecia hair loss treatment confirmed
- Visible results in xx weeks/ months
- Converse of hair follicles into the anagen phase
- Stronger and thicker hair
- Up to xx new hairs.
- High user satisfaction rate (+xx%)
- Tested under medical supervision
- Dermatologically approved tested
- Suitable for ‚sensitive scalp‘

Version July 2013

Guidelines to Commission Regulation (EU) No 655/2013

laying down common criteria for the justification of claims used

in relation to cosmetic products

Summary

Crucial aspect clinical study design with products for the Treatment of Androgenetic Alopecia:

- What kind of product is it? What is the mode of action?
- What is the purpose of the study?
- Which are the targeted Indications, claims/ marketing needs?
- ->
- Regulatory & ethical requirements, timelines, budget
- Study design, recruitment, parameters (safety & efficacy)
- Phototrichogram (H2H matching) is the ‚gold standard‘
- Double-blinded, placebo-controlled randomized trials and studies with direct comparisons between treatments are most scientifically meaningful

Questions?