

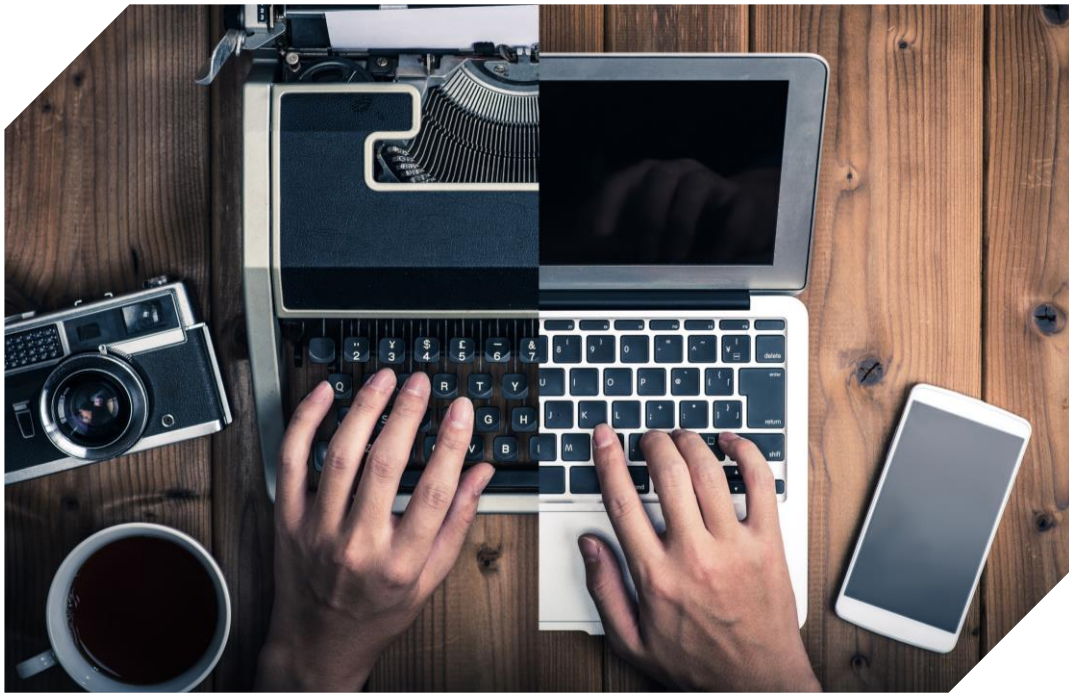
REMASTERED

COL-FRAG™

A NEW COLLAGEN ERA

The **classics** beyond trends

Timeless classics have become **must-haves** because they are **trustworthy** thanks to their record of **quality** and **efficacy**. They seldom follow the trends. The classics set trends by inspiring higher levels of **excellence, technology & comfort**.



Collagen: when the classic becomes essential



The confidence in collagen's **exceptional antiaging** properties has been passed down for generations. Consumers **trust** in this ingredient for its **efficacy** and as a **habit, becoming loyal** to those products containing collagen.

Collagen evolution

Consumers also look for innovation combined with the high efficacy of its traditional hero ingredients.

TRADITIONAL COLLAGEN

- ❖ Collagen sources: animals (e.g. cows, pigs, fishes)
- ❖ Collagen types:
 - ✓ native form
 - ✓ partially hydrolyzed
 - ✓ amino acids

Hydrolysates and amino acids act as building blocks for collagen formation and to stimulate collagen synthesis in fibroblasts.

CURRENT COLLAGEN IN THE MARKET

New sustainable and animal-friendly sources:

- ✓ synthetic collagen
- ✓ biomimetical molecules
- ✓ recombinant collagen obtained through bacteria, yeast or plant-cell cultures

Yeasts and bacteria cannot perform post-translational hydroxylations (key for triple helix stabilization). Hence, the resulting collagen is **not fully functional**.

Collagen: **remastering** the classic

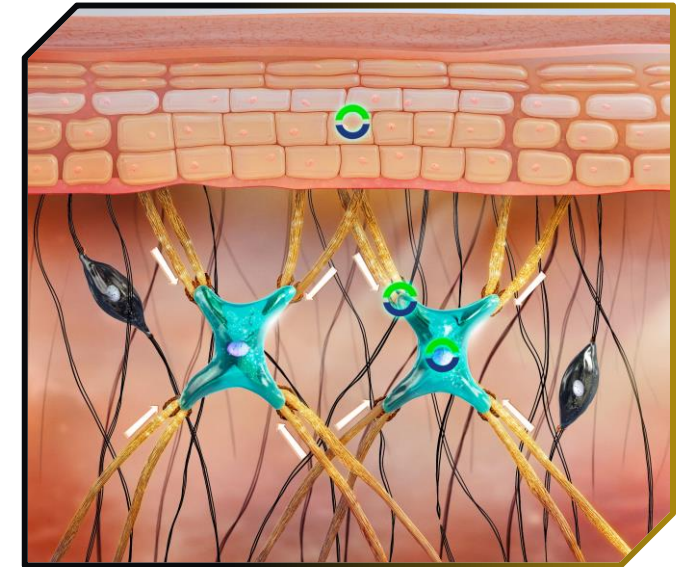
Col-Frag remastered™ is a **plant-based fragment of human type I collagen** transiently expressed through the Wild plants as biofactories technology.



EXPRESSION IN WILD PLANTS.



SUSTAINABLE COLLAGEN.



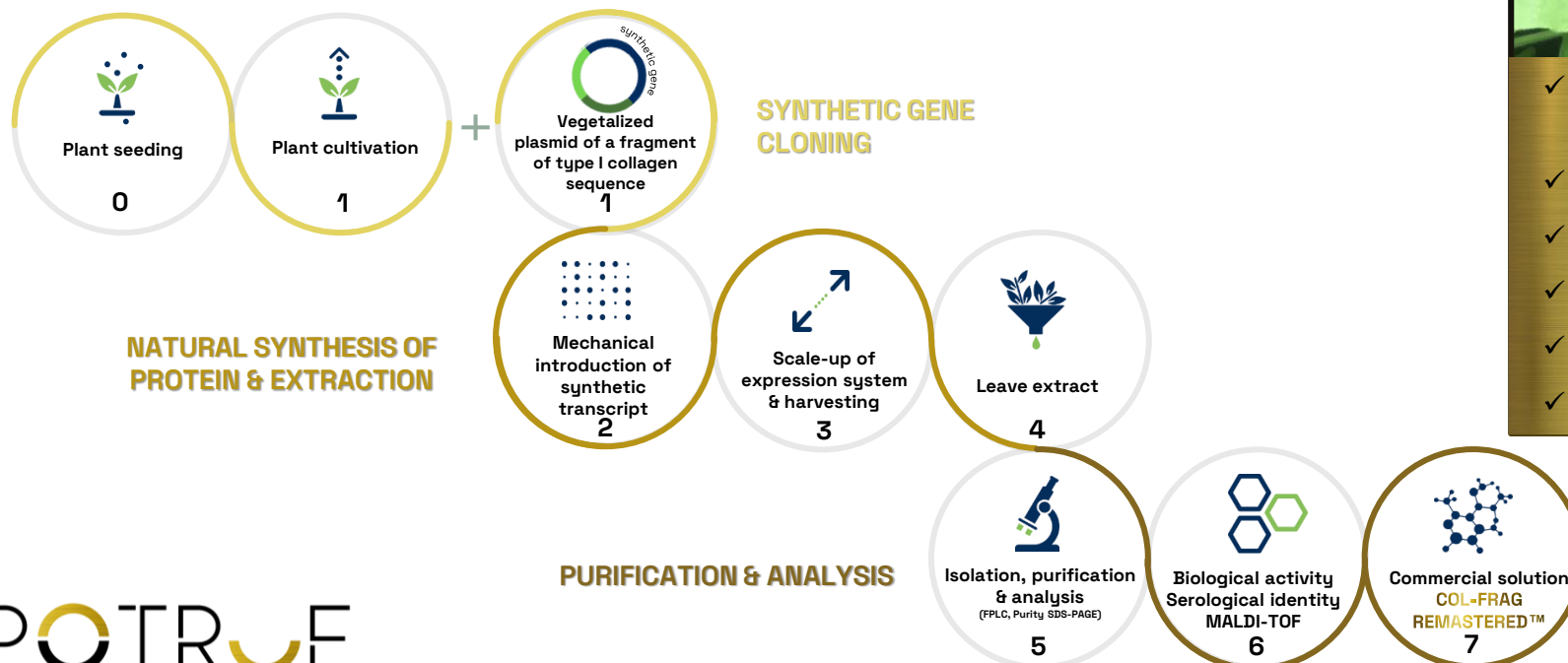
REMASTERED EFFICACY.

Expression in wild plants

N. benthamiana is a plant model system for the **transient expression** of peptides, polypeptides and proteins (50-380 aa).

TRANSIENT EXPRESSION.

Synthetic fragment of **human type I collagen** cloned into an expression vector, transcribed *in vitro* into mRNA and inserted through the leaves into the cytoplasm of vegetal cells while nuclei remains untouched (natural plant expression system).



Sustainable collagen

CONTROLLED-ENVIRONMENT AGRICULTURE.

- Protected greenhouse
- Optimization of water, energy & space (indoor vertical farming)
- Controlled temperature, light (LED lights) & ventilation
- No pesticides
- Recycling of used soil (sterilization for use in conventional crops or gardens)

GREEN CHEMISTRY.

- Water consumption reduction & recycling after treatment for irrigation and agricultural & industrial purposes
- Waste management improvement: reduction & recycling
- Energy consumption reduction
- Protein synthesis optimization: less energy, resources & waste

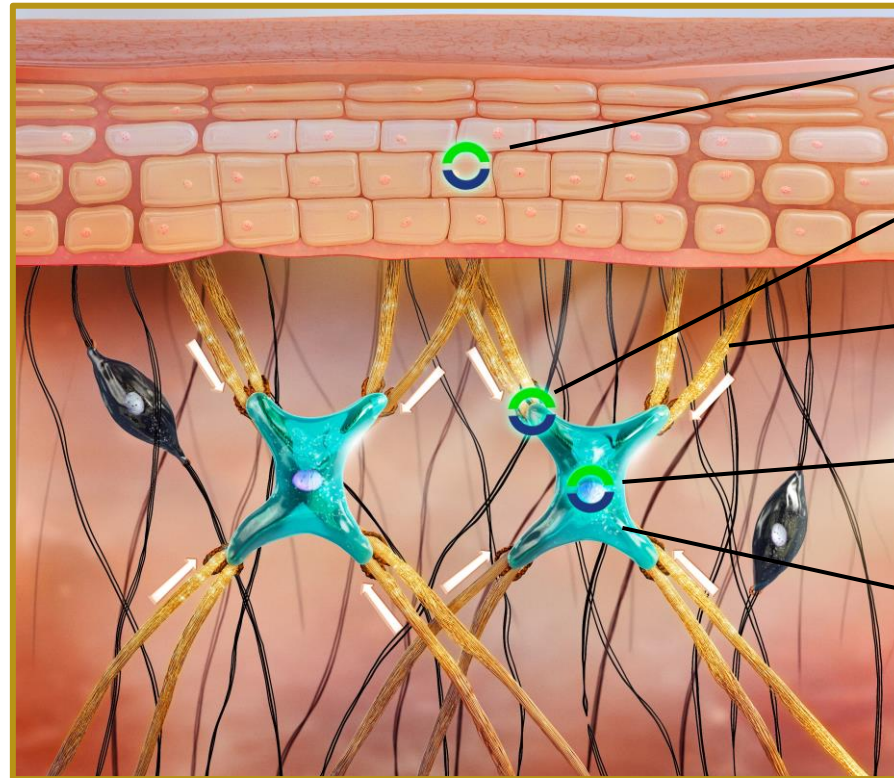


- ✓ **PLANT-BASED**
- ✓ **SUSTAINABLE SOURCE**
- ✓ **NON-GMO**

Remastered efficacy

Plant-based human collagen type I fragment with:

- **Integrin-binding motifs & cell-attachment** binding sequences.
- **Prolines & hydroxyprolines** which help biosynthesis, function & stabilization of collagen.
- **Human** collagen type I activity.



Fibroblasts attach to collagen fibrils to form adhesion complexes (through integrins), exerting contractile forces in the cytoskeleton that induces gene expression (↑ collagen and ↓ MMPs).

Collagen degradation due to aging causes loss of attachment sites (↓ integrins).

Skin fibroblasts senescence results in ↓ collagen and ↑ MMPs.

EPIDERMAL COMPACTNESS.

- ↑ cell adhesion
- Surface tension

BINDING SITES REINFORCEMENT.

- ↑ integrins

COLLAGEN FIBERS TENSION (LIFTING).

- ECM contractility

COLLAGEN SYNTHESIS.

- Procollagen type I synthesis
- Building blocks
- Collagen synthesis & stabilization

DERMAL REJUVENATION.

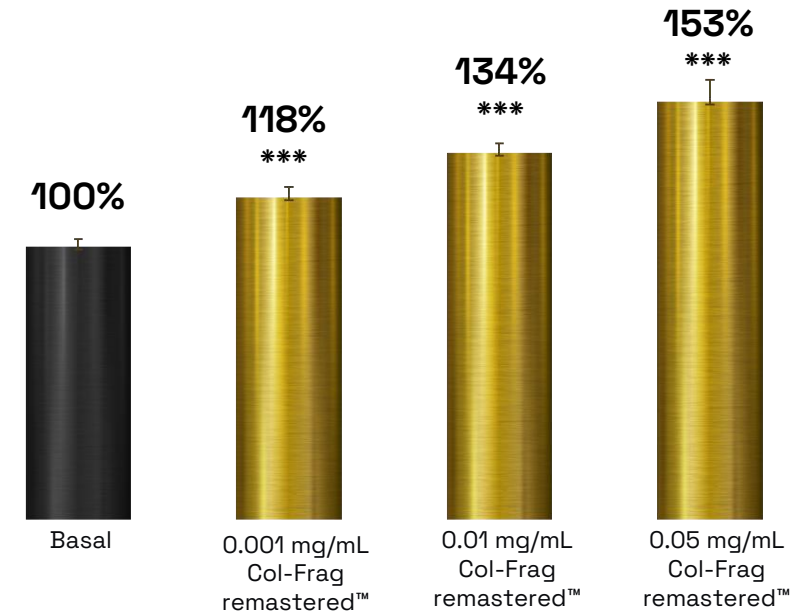
- Dermal renewal (fibroblast turnover)
- ↑ collagen ↓ MMPs genes expression
- ↓ dermal senescence

Epidermal compactness



Cell-cell adhesion in the epidermis is involved in epidermal structural integrity and barrier formation.

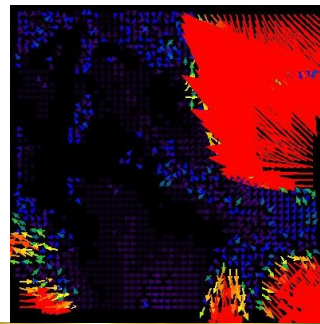
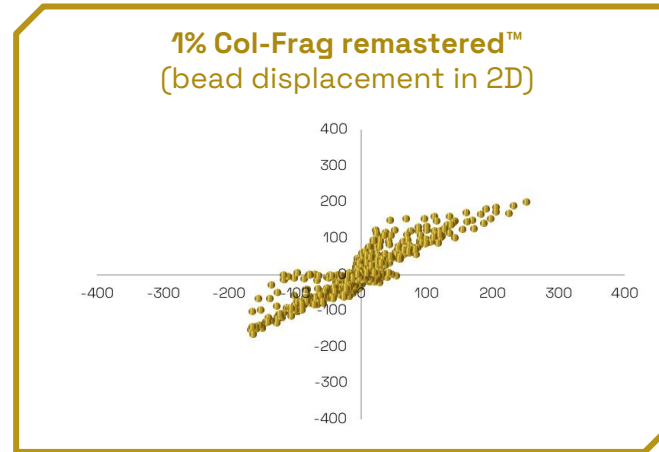
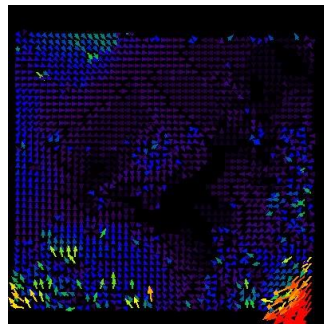
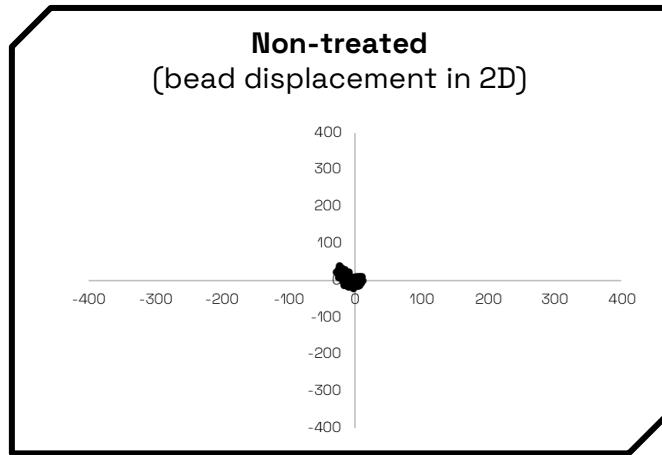
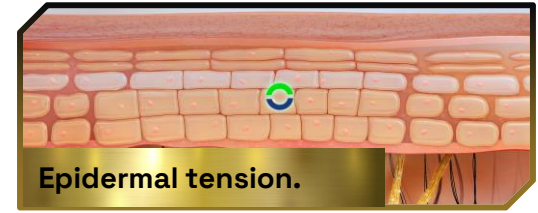
Epidermal adhesion (%)



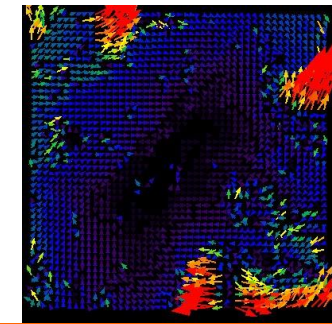
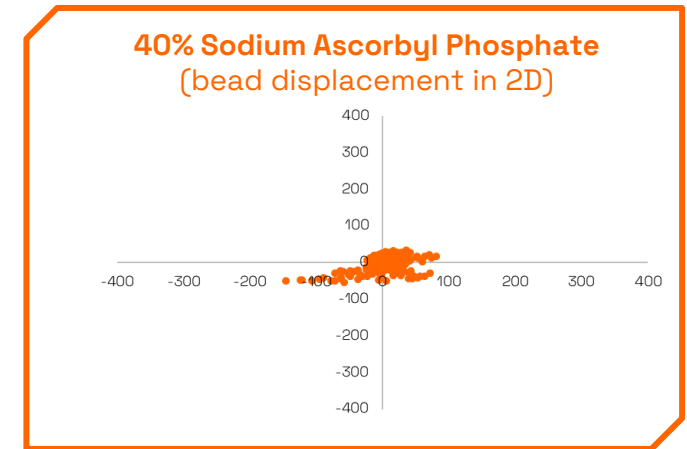
Epidermal tension



The tensor effect on skin surface was analyzed through fluorescent beads' movements. The more the vectorial arrow is close to red, the higher the displacement.



+200% bead displacement**



+151%* bead displacement

- ✓ Human skin explants (woman, 59 years old)
- ✓ Cream with 1% Col-Frag remastered™
- ✓ Positive control & benchmark: Sodium Ascorbyl Phosphate (Vitamin C derivative)
- ✓ 24 h
- ✓ Tracking of fluorescent beads movement after treatment
- ✓ Confocal microscopy
- ✓ **p<0.01 vs non-treated, *p<0.05 vs non-treated

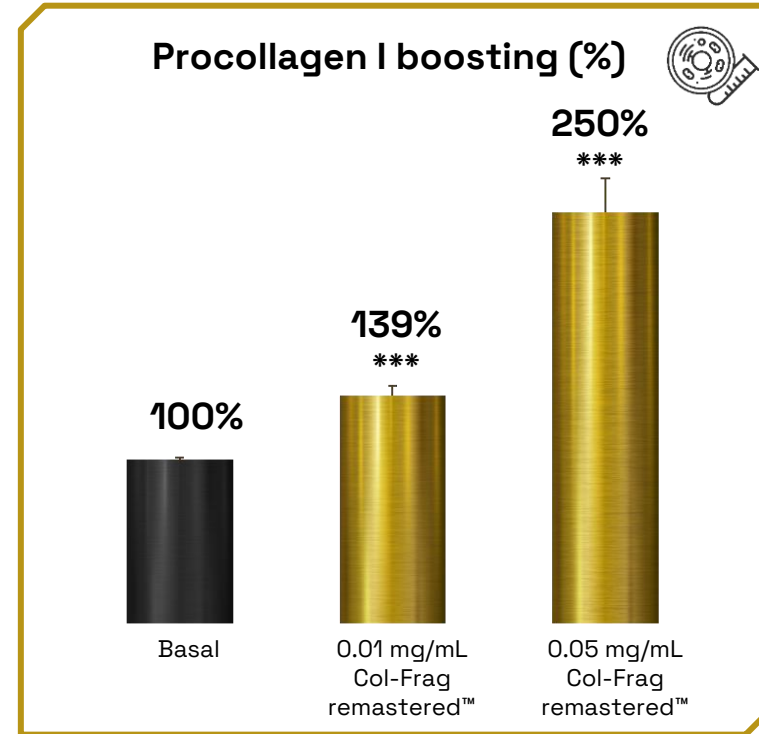
Collagen building



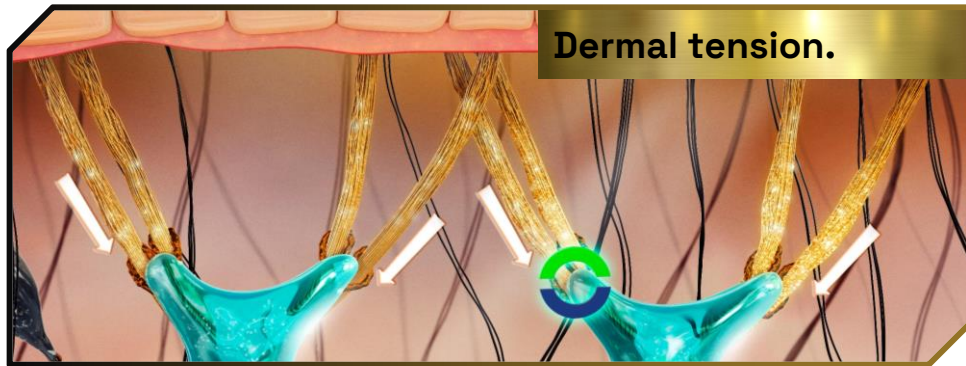
Collagen booster.

Human fragments of type I collagen can be used as building blocks to synthesize new collagen.

Reinforcement of collagen network induces collagen synthesis through integrins.



Collagen-fibroblasts binding site reinforcement



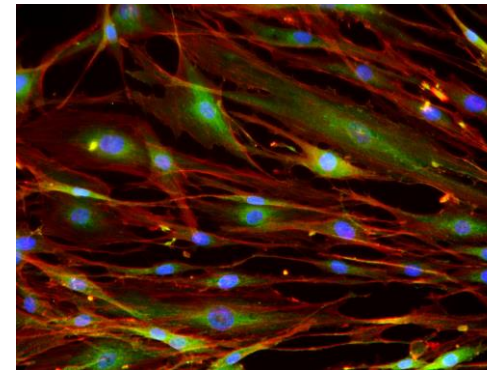
Fibroblasts interact with ECM constituents via integrins.

Integrin $\alpha 2 \beta 1$ mediates ECM contraction, regulates collagen and MMP-1 expression and is key for fibroblast cytoskeleton tension.

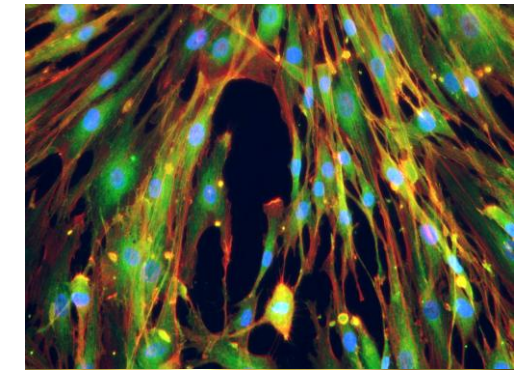
Simultaneous function of both subunits of integrin $\alpha 2 \beta 1$ on fibroblasts regulates dermal collagen network.

+1.4x SMARTDATA
inside
ITGB1 in HDFa

Basal
(integrin $\beta 1$ in green)

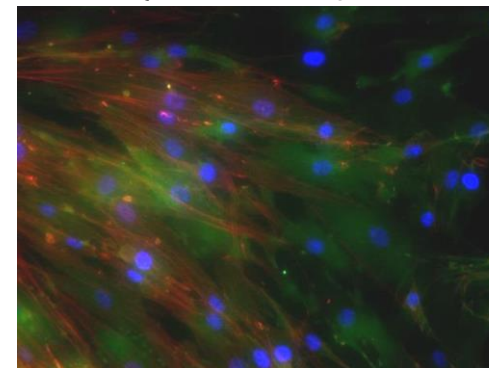


Col-Frag remastered™
(integrin $\beta 1$ in green)

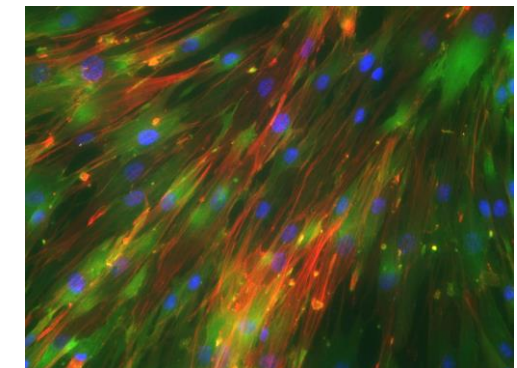


+15%* integrin $\beta 1$

Basal
(integrin $\alpha 2$ in green)



Col-Frag remastered™
(integrin $\alpha 2$ in green)



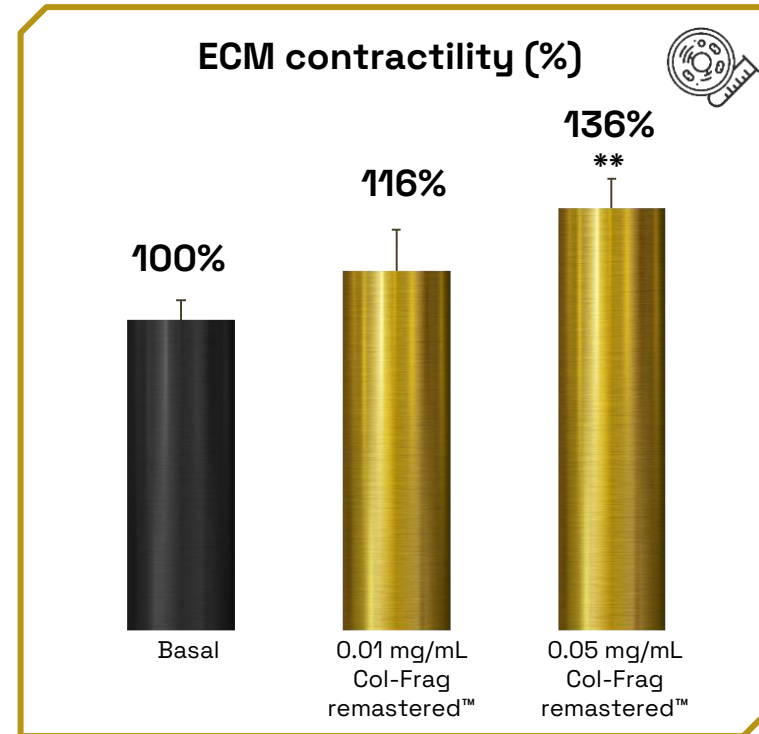
+39%* integrin $\alpha 2$



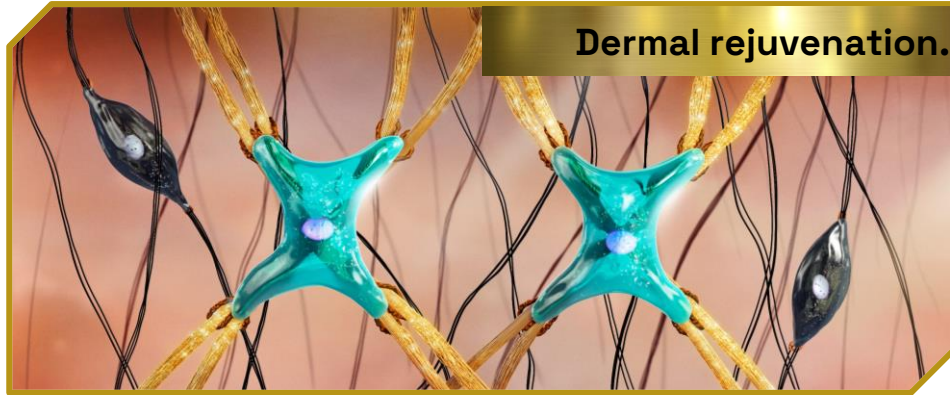


Collagen fibers tension (lifting)

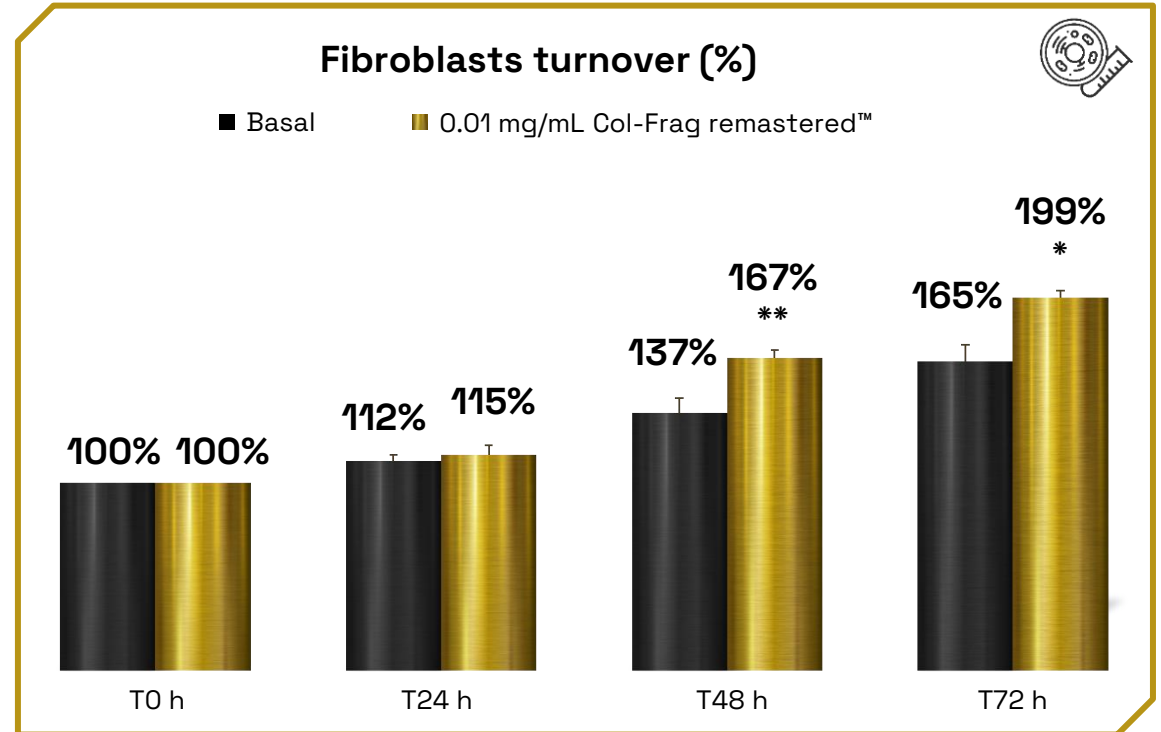
Integrin $\alpha 2\beta 1$ mediates ECM contraction, helping collagen fibers tension which may result in a visible firmer and lifted skin.



Dermal renewal



Fibroblasts turnover helps to improve the turnover of the ECM, renewing the dermis with new components.





Reverting senescence

Skin fibroblasts senescence results in
 ↓ collagen and ↑ MMPs.

Oxidation of cells induce senescence. Protecting cells from
 senescence helps to prevent skin aging.



+1.3x

COL3A1 in HDFa

-1.4x

MMP1 in HDFa

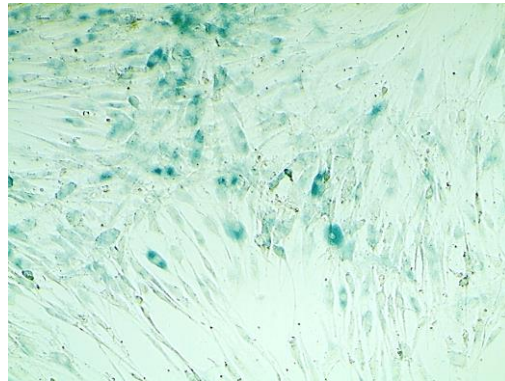
+1.2x

COL1A1 in HDFa

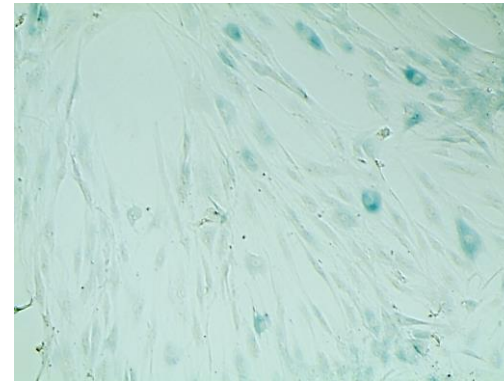
-1.3x

MMP2 in HDFa

50 μ M H₂O₂
 (β-Galactosidase positive cells in blue)

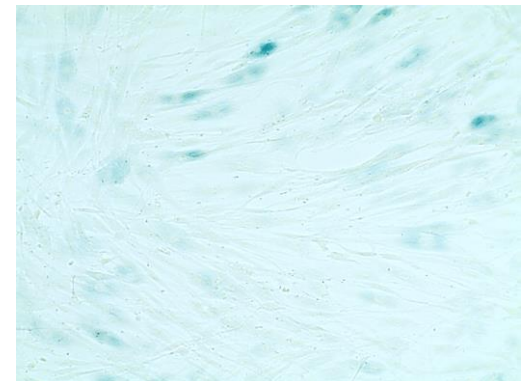


50 μ M H₂O₂ +
 Col-Frag remastered™
 (β-Galactosidase positive cells in blue)



-36.4%* senescent cells**

Basal
 (β-Galactosidase positive cells in blue)

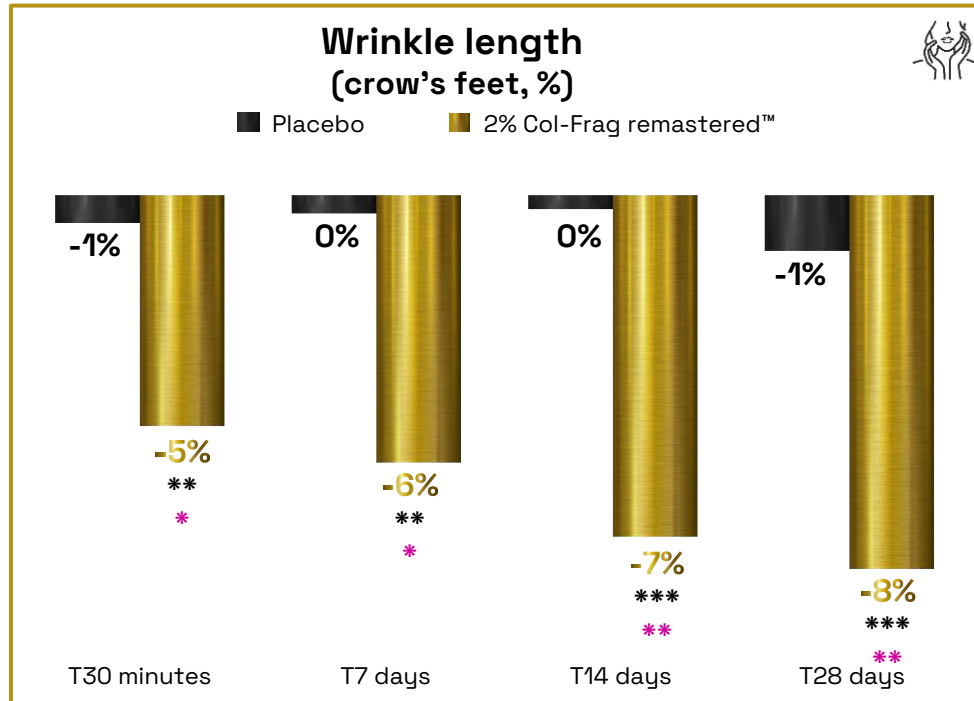


- ✓ HDFa
- ✓ Col-frag remastered™ active ingredient (0.0005 or 0.001 mg/mL)
- ✓ qPCR (quantitative PCR)
- ✓ 24 h
- ✓ COL3A1 (Collagen type III alpha 1 chain)
- ✓ COL1A1 (Collagen type I alpha 1 chain)
- ✓ MMP1 (Matrix metalloproteinase 1)
- ✓ MMP2 (Matrix metalloproteinase 2)

- ✓ HDFa
- ✓ H₂O₂ to induce oxidative stress
- ✓ 0.05 mg/mL Col-Frag remastered™ active ingredient in presence of oxidative stress
- ✓ 4 days
- ✓ B-Galactosidase activity is a marker of senescence
- ✓ Staining & microscopy
- ✓ ***p<0.001 vs H₂O₂

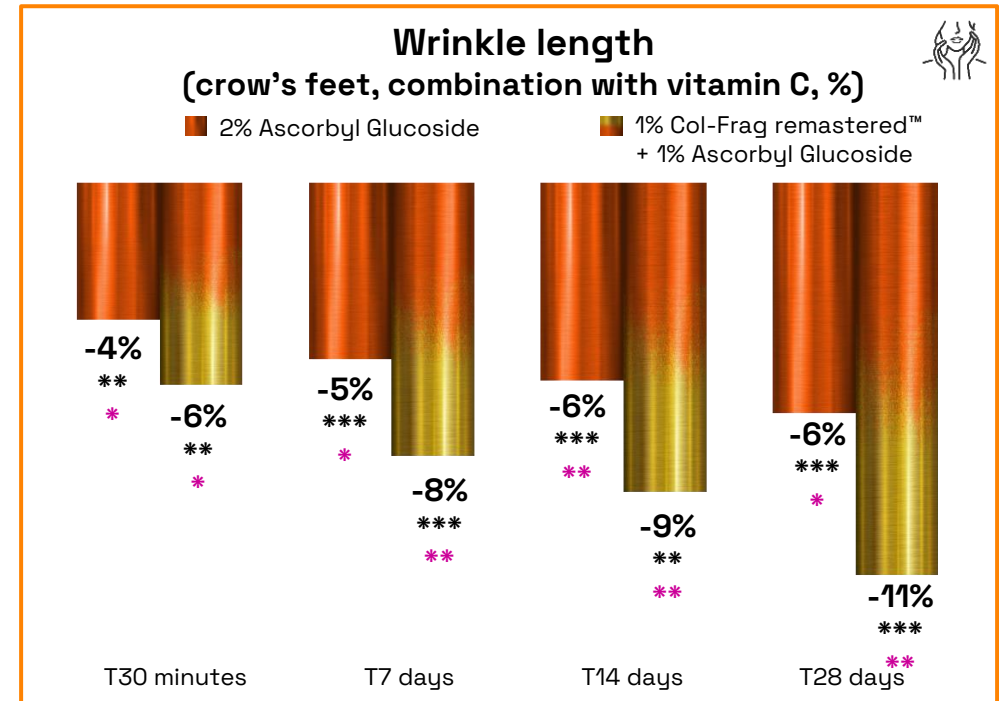
A new collagen era

Ascorbyl Glucoside is a stabilized form of vitamin C which is known for inducing collagen synthesis and is used as wrinkle smoother.



-7% after 30 minutes in 80% volunteers

Up to:
-21% in 30 min
-21% in 28 days



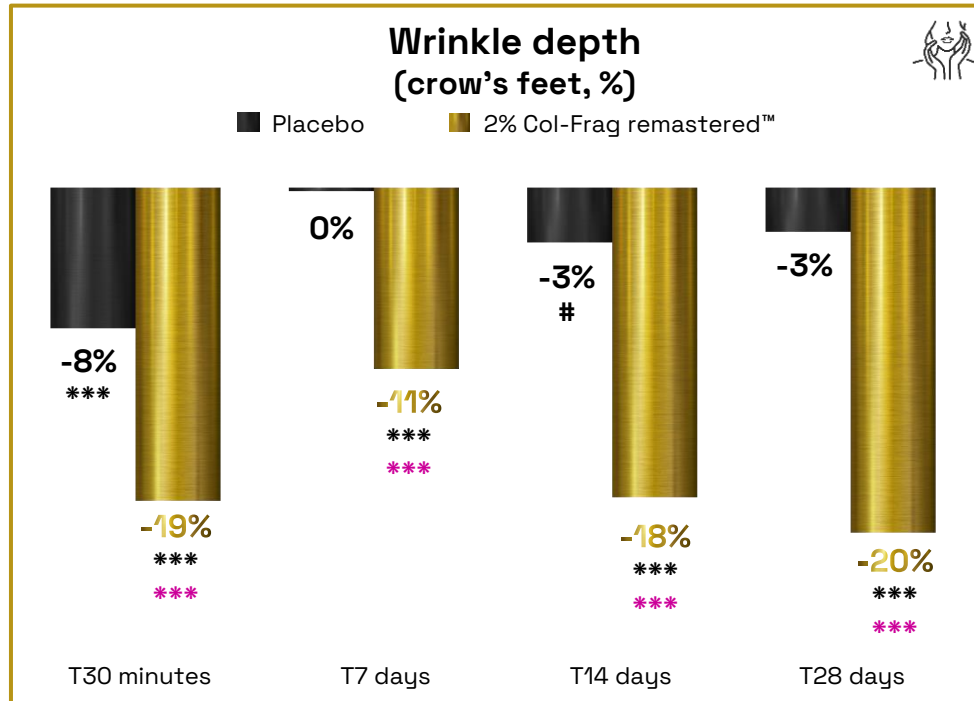
Up to:
-19% in 30 min
-26% in 28 days

-8% after 30 minutes in 80% volunteers

- ✓ 20 women (50-62 years old)
- ✓ Cream with 2% Col-Frag remastered™ vs placebo
- ✓ Twice a day for 28 days, half face
- ✓ Primos 3D
- ✓ ***p<0.001 vs T0, **p<0.01 vs T0
- ✓ **p<0.01 vs placebo, *p<0.05 vs placebo

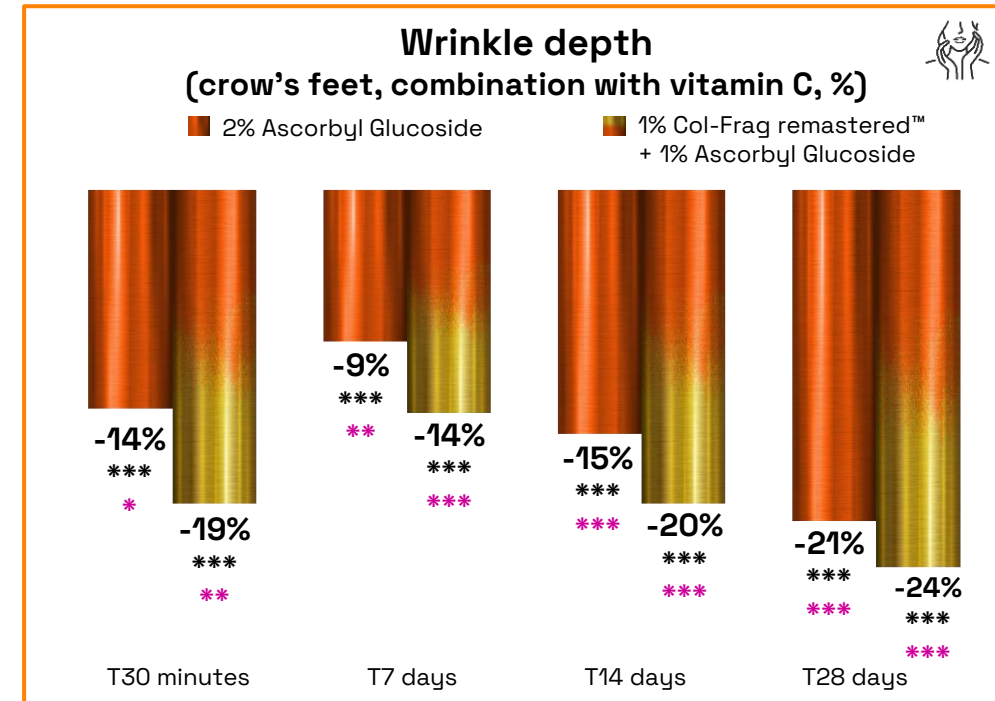
- ✓ 20 women (47-62 years old)
- ✓ Cream with 2% Ascorbyl Glucoside vs 1% Col-Frag remastered™ + 1% Ascorbyl Glucoside
- ✓ Twice a day for 28 days, half face
- ✓ Primos 3D
- ✓ ***p<0.001 vs T0, **p<0.01 vs T0
- ✓ **p<0.01 vs placebo, *p<0.05 vs placebo

A new collagen era



-22% after 28 days in 95% volunteers

Up to:
-34% in 30 min
-34% in 28 days



Up to:
-46% in 30 min
-39% in 28 days

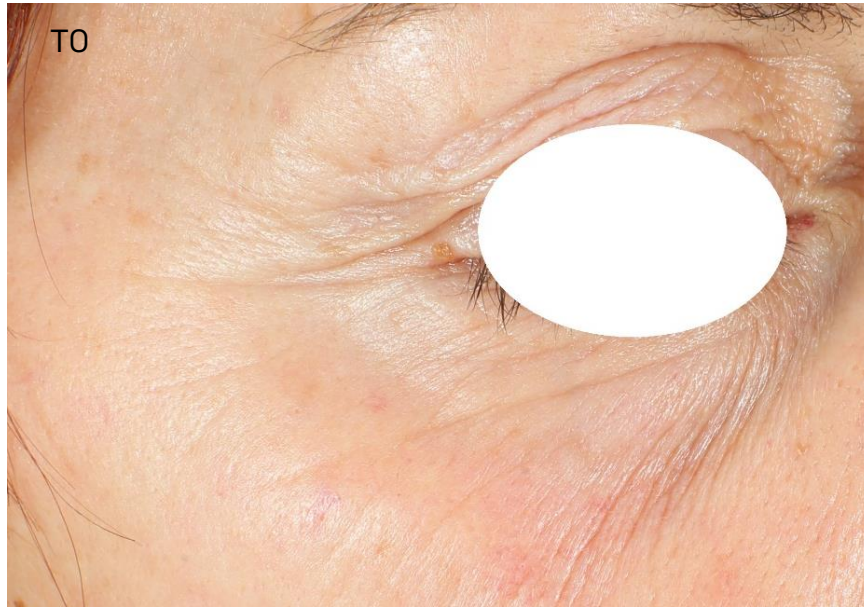
-24% after 28 days in 100% volunteers

- ✓ 20 women (50-62 years old)
- ✓ Cream with 2% Col-Frag remastered™ vs placebo
- ✓ Twice a day for 28 days, half face
- ✓ Primos 3D
- ✓ ***p<0.001 vs T0, #p<0.1 vs T0
- ✓ **p<0.01 vs placebo

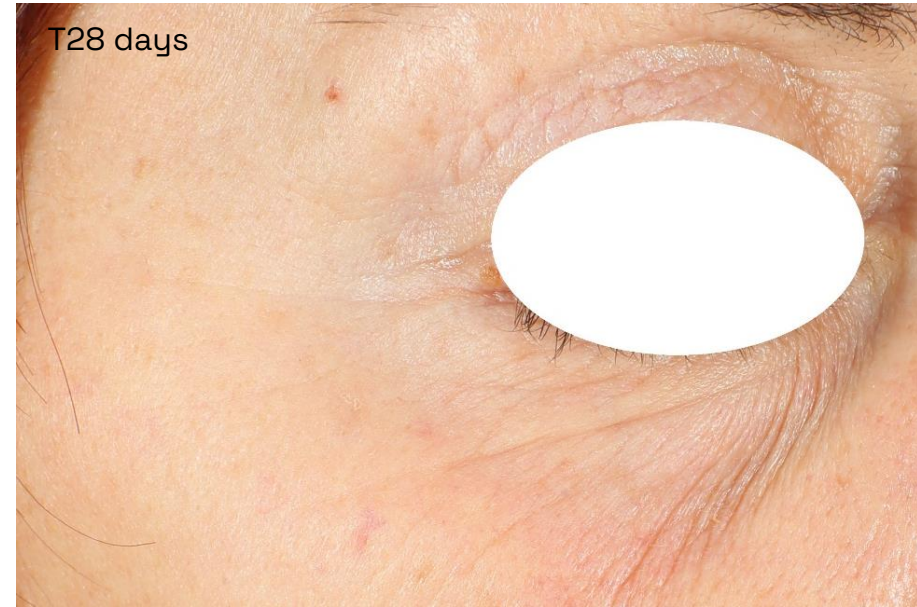
- ✓ 20 women (47-62 years old)
- ✓ Cream with 2% Ascorbyl Glucoside vs 1% Col-Frag remastered™ + 1% Ascorbyl Glucoside
- ✓ Twice a day for 28 days, half face
- ✓ Primos 3D
- ✓ ***p<0.001 vs T0
- ✓ ***p<0.001 vs placebo, **p<0.01 vs placebo, *p<0.05 vs placebo

A new collagen era

2% Col-Frag remastered™



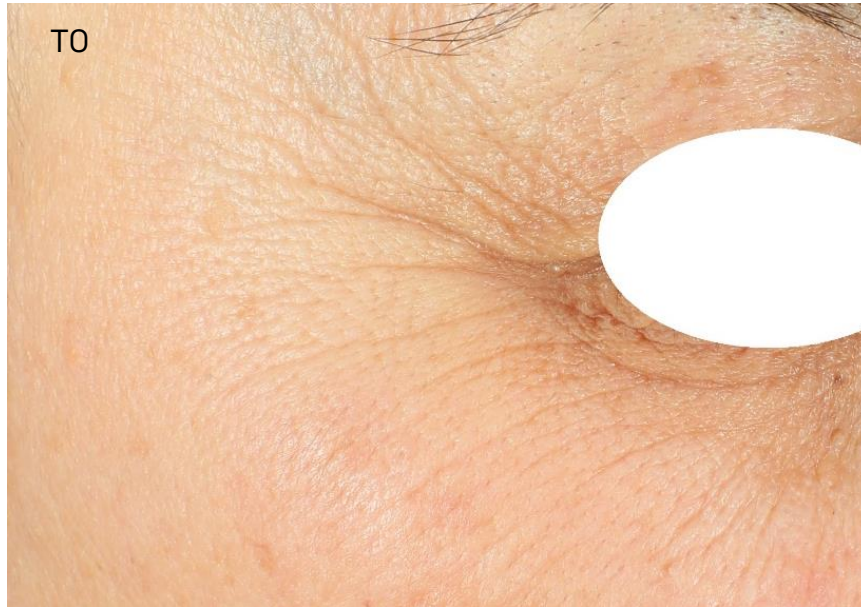
Vol 5 (55 years old)



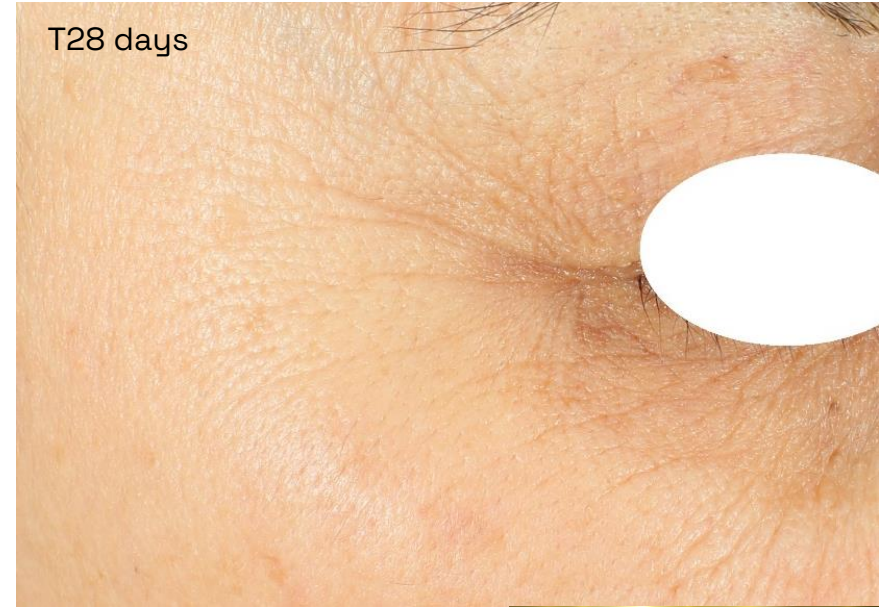
-15.4% wrinkle depth
-20.7% wrinkle length

A new collagen era

2% Col-Frag remastered™



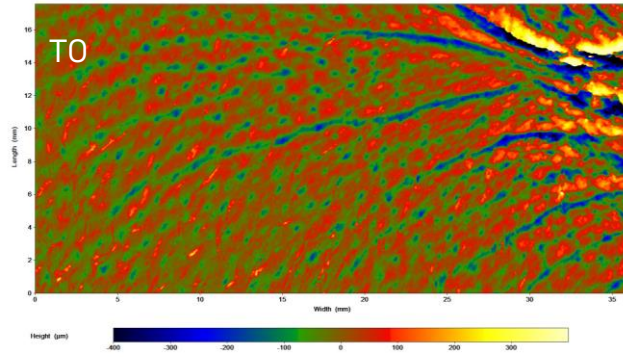
Vol 3 (58 years old)



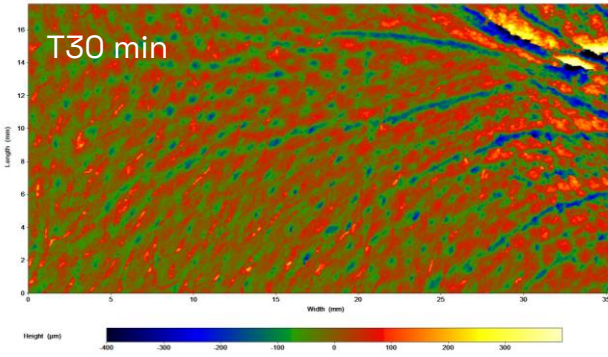
-32.8% wrinkle depth
-12% wrinkle length

A new collagen era

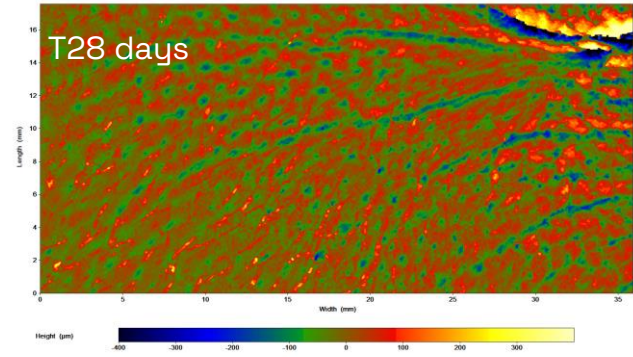
2% Col-Frag remastered™



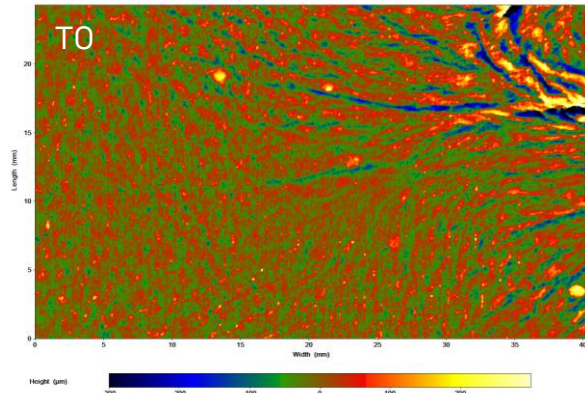
Vol 3 (58 years old)



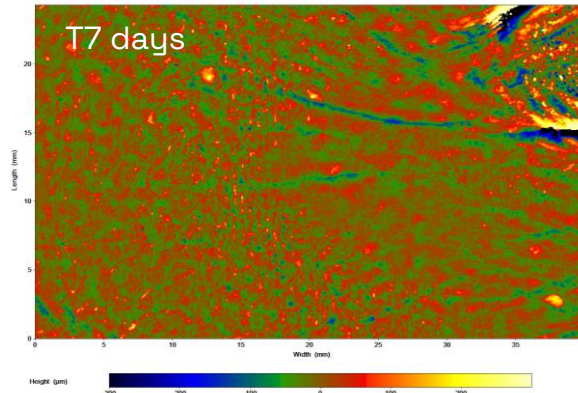
-10% wrinkle depth
-5.2% wrinkle length



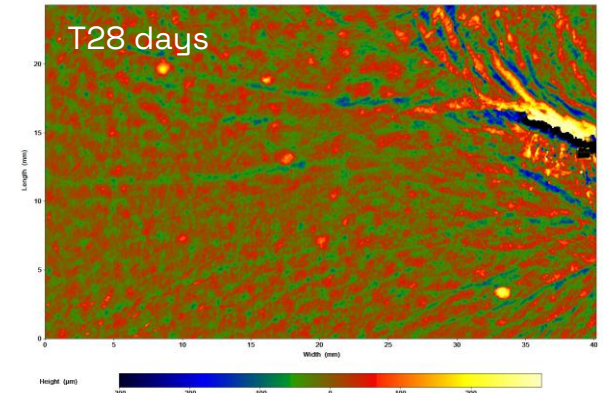
-32.8% wrinkle depth
-12.8% wrinkle length



Vol 14 (55 years old)



-17.9% wrinkle depth
-5.1% wrinkle length

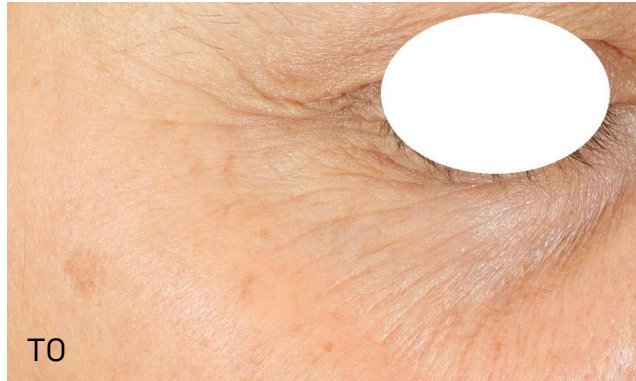


-29.2% wrinkle depth
-7.2% wrinkle length

- ✓ 20 women (50-62 years old)
- ✓ Cream with 2% Col-Frag remastered™ vs placebo
- ✓ Twice a day for 28 days, half face
- ✓ Primos 3D

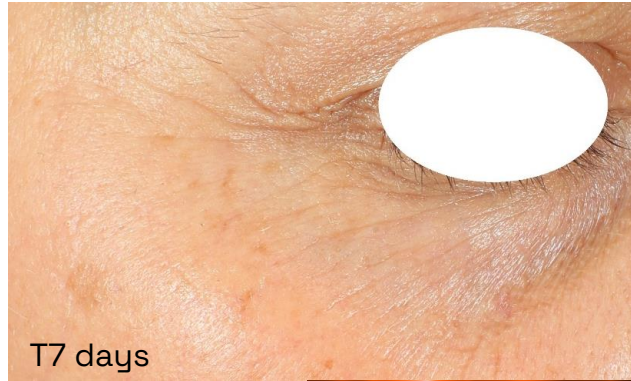
A new collagen era

2% Ascorbyl Glucoside



T0

Vol 39 (52 years old)



T7 days

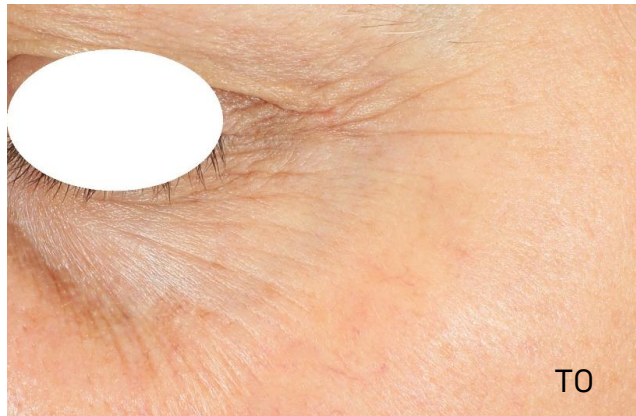
-17.7% wrinkle depth



T28 days

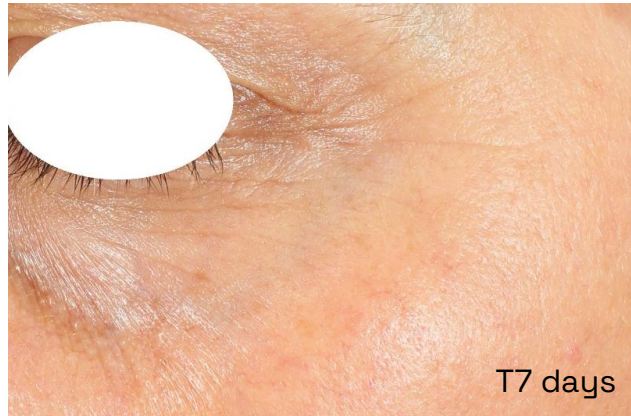
-17.3% wrinkle depth

1% Col-Frag remastered™ + 1% Ascorbyl Glucoside



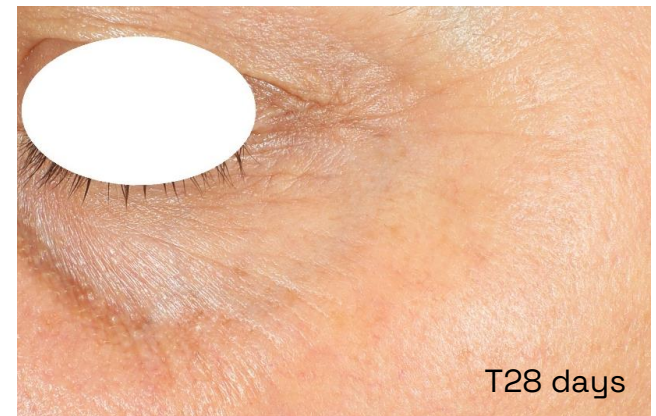
T0

Vol 39 (52 years old)



T7 days

-21.2% wrinkle depth



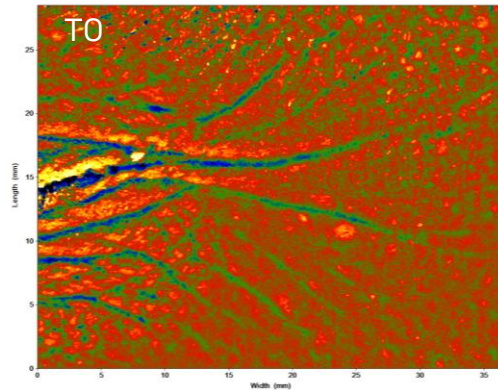
T28 days

-27.7% wrinkle depth

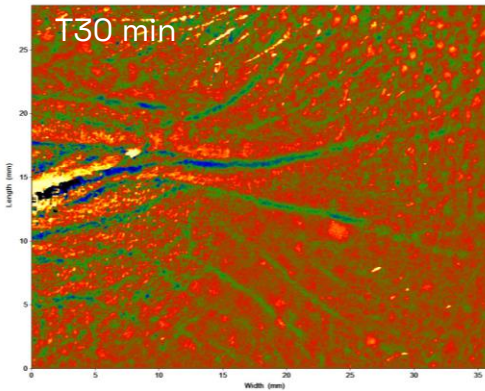
- ✓ 20 women (47-62 years old)
- ✓ Cream with 2% Ascorbyl Glucoside vs 1% Col-Frag remastered™ + 1% Ascorbyl Glucoside
- ✓ Twice a day for 28 days, half face
- ✓ Visia®-CR

A new collagen era

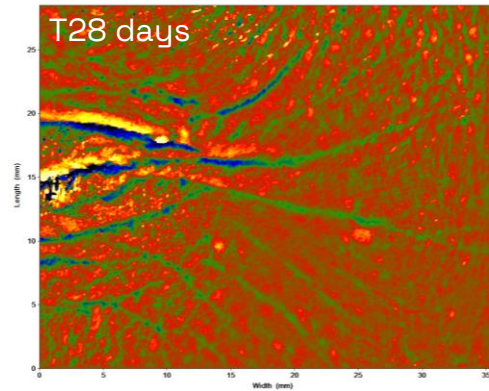
2% Ascorbyl Glucoside



Vol 27 (57 years old)

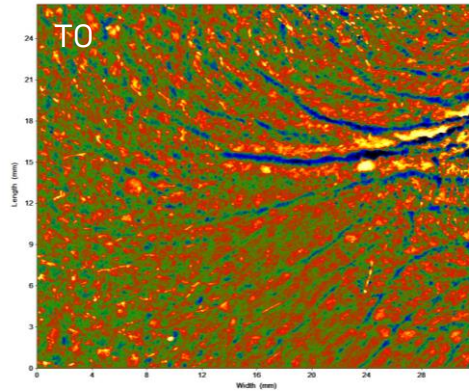


-19.8% wrinkle depth

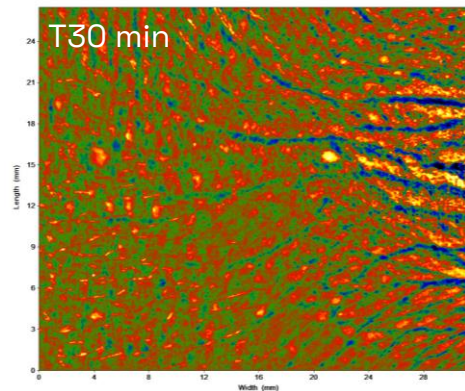


-21.7% wrinkle depth
-3.4% wrinkle length

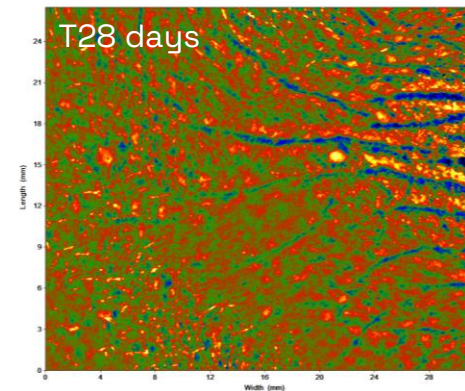
1% Col-Frag remastered™
+ 1% Ascorbyl Glucoside



Vol 27 (57 years old)

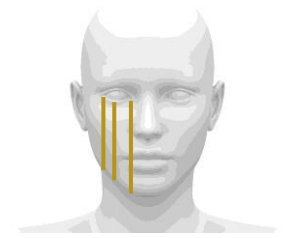


-45.7% wrinkle depth



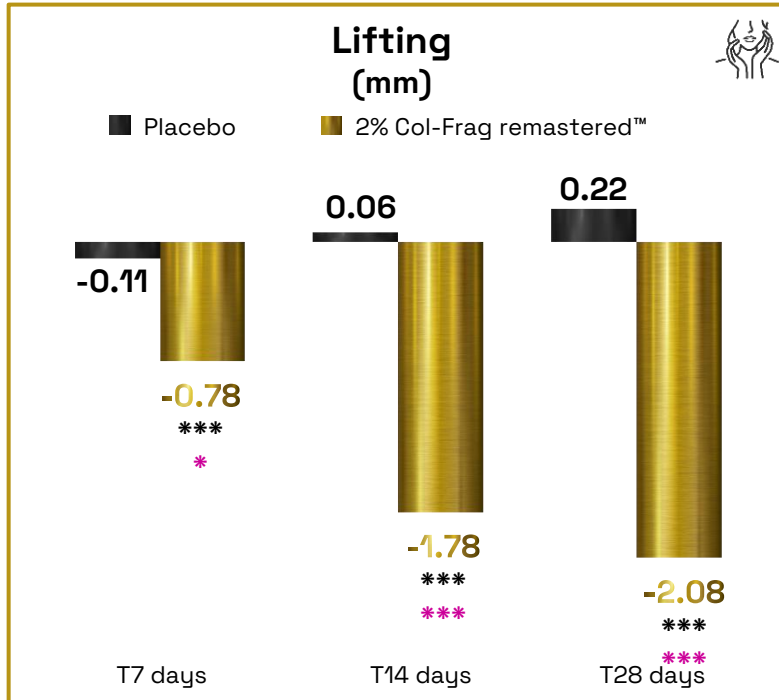
-38.8% wrinkle depth
-12.2% wrinkle length

- ✓ 20 women (47-62 years old)
- ✓ Cream with 2% Ascorbyl Glucoside vs 1% Col-Frag remastered™ + 1% Ascorbyl Glucoside
- ✓ Twice a day for 28 days, half face
- ✓ Primos 3D

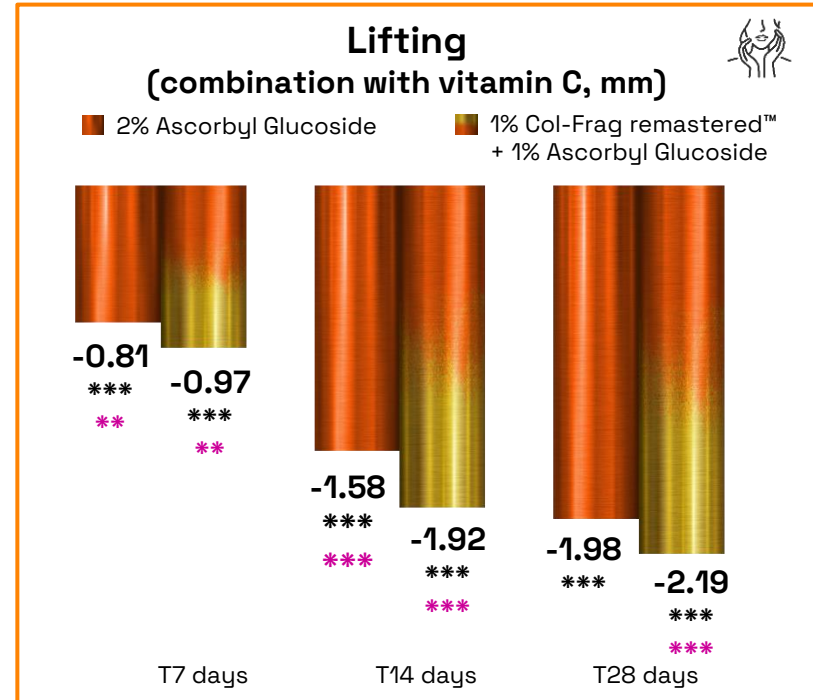


A new collagen era

-2.54 mm
after 28 days
in **85%**
volunteers



Up to:
-1.47 mm in 7 days
-3.16 mm in 28 days



Up to:
-1.62 mm in 7 days
-3.16 mm in 28 days

2.50 mm after 28 days
in **90%** volunteers

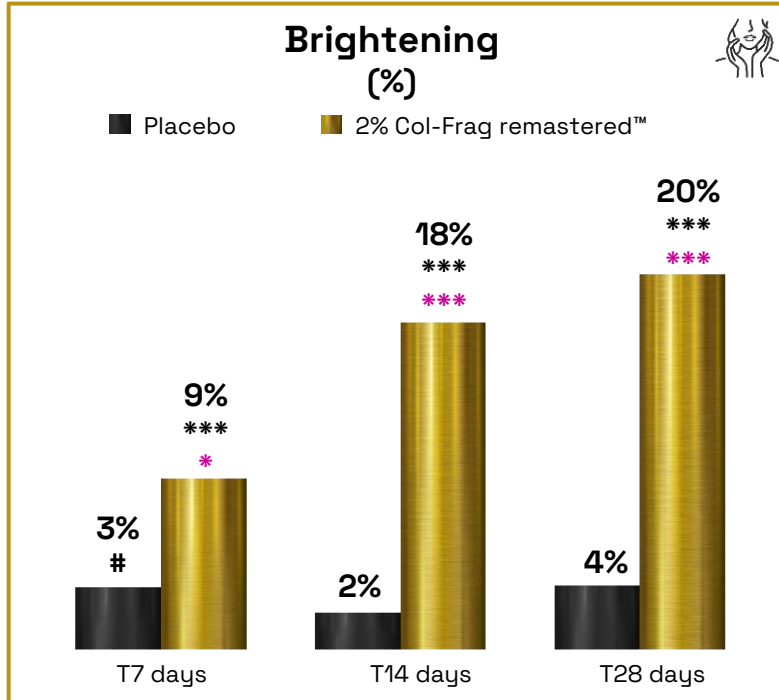
- ✓ 20 women (50-62 years old)
- ✓ Cream with 2% Col-Frag remastered™ vs placebo
- ✓ Twice a day for 28 days, half face
- ✓ PrimosCR high resolution large field
- ✓ ***p<0.001 vs T0
- ✓ ***p<0.01 vs placebo, *p<0.05 vs placebo

- ✓ 20 women (47-62 years old)
- ✓ Cream with 2% Ascorbyl Glucoside vs 1% Col-Frag remastered™ + 1% Ascorbyl Glucoside
- ✓ Twice a day for 28 days, half face
- ✓ PrimosCR high resolution large field
- ✓ ***p<0.001 vs T0
- ✓ ***p<0.01 vs placebo, **p<0.01 vs placebo

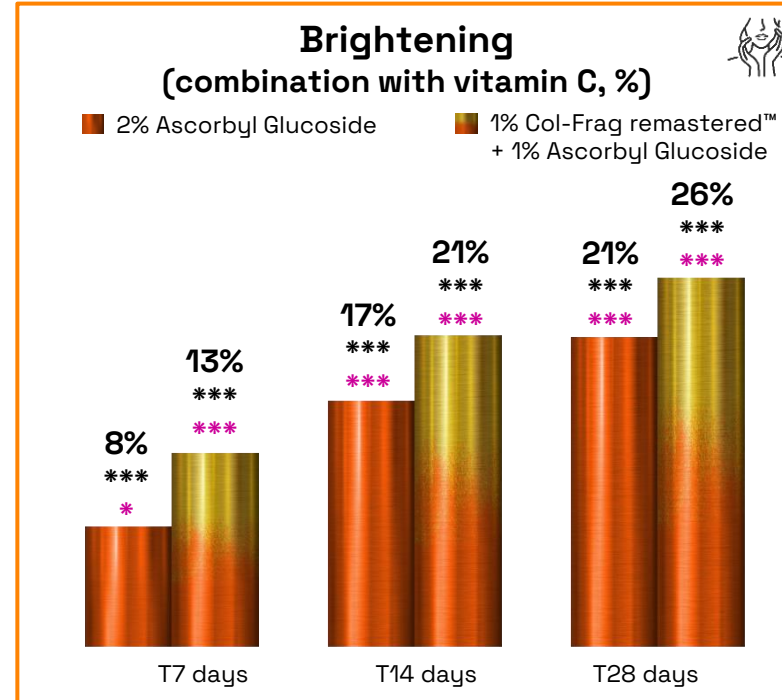
A new collagen era



+25% after 28 days in 85% volunteers



Up to:
 +26% in 7 days
 +47% in 28 days



Up to:
 +38% in 7 days
 +62% in 28 days

+26% after 28 days in 100% volunteers

- ✓ 20 women (50-62 years old)
- ✓ Cream with 2% Col-Frag remastered™ vs placebo
- ✓ Twice a day for 28 days, half face
- ✓ Spectrophotometer/Colorimeter
- ✓ ***p<0.001 vs T0; #p<0.1 vs T0
- ✓ ***p<0.01 vs placebo, *p<0.05 vs placebo

- ✓ 20 women (47-62 years old)
- ✓ Cream with 2% Ascorbyl Glucoside vs 1% Col-Frag remastered™ + 1% Ascorbyl Glucoside
- ✓ Twice a day for 28 days, half face
- ✓ Spectrophotometer/Colorimeter
- ✓ ***p<0.001 vs T0
- ✓ ***p<0.01 vs placebo, *p<0.05 vs placebo

A new collagen era

2% Col-Frag remastered™



Vol 6 (55 years old)

46.8% brightness



Vol 14 (55 years old)

41.4% brightness

A new collagen era

75%

“It looks like I have had
a facelift”

(using 1% Col-Frag remastered™
+ 1% Ascorbyl Glucoside)

85%

“It has improved my
skin sagginess”

(using 2% Col-Frag remastered™)

80%

“My skin looks
younger”

(using 1% Col-Frag remastered™
+ 1% Ascorbyl Glucoside)

85%

“It could become my
hero product”

(using 2% Col-Frag remastered™)

REMASTERED

COL-FRAG[™]
A NEW COLLAGEN ERA

Building new collagen

Plant-based human collagen

Biotechnological rejuvenating alternative to vitamin C

The new collagen era

Sustainable lifting

Illuminating face & Nature

Vegan suitable collagen

Technical information

- ✓ **Product name:** Col-Frag remastered™
- ✓ **Plant-based** biotechnological ingredient
- ✓ **Recommended dose:** 1-2%
- ✓ **INCI name of the active ingredient:** Collagen Amino Acids
- ✓ **99.999% Natural origin (ISO standard 16128)**
- ✓ **Vegan suitable**
- ✓ **Appearance:** Solution
- ✓ **Solubility:** Water soluble



IH-822/2.1/B94

REMASTERED

COL-FRAG™

A NEW COLLAGEN ERA