ACTIVE BEAUTY

PrimalHyal™ UltraReverse

The intracellular Hyaluronic Acid for skin longevity

Well-ageing / Prevention

Givaudan

Human by nature

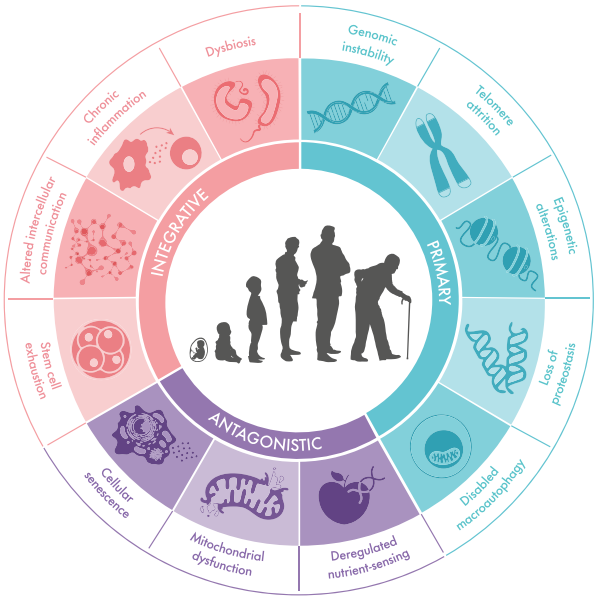
Focus on the product

Skin health & longevity – the future of Beauty?

Longevity has become a paramount trend in the Beauty industry. This shift reflects a deeper consumer interest in prevention, and the holistic concept of skin health, looking for more care and preservation of their skin's vitality over the long-term. In the meantime, they are getting more and more educated about the science of skin. They are now familiar with advanced concepts such as epigenetics, or the biological clock of the skin, helped by plenty of Beauty brands integrating deep scientific insights into their communication.

One of those critical scientific concepts getting more and more traction is about the 12 hallmarks of ageing, as highlighted by a collaborative research group over the past decade[1-2], with five primary hallmarks identified as the root causes of all skin damages: instability at the genome level, shortening of the telomeres, changes in the epigenetic control, loss of the proteostasis, and diminished autophagy.

By understanding these hallmarks, Active Beauty scientists can develop new and more effective strategies to decelerate skin ageing and preserve skin health for as long as possible.



PrimalHyal™ UltraReverse – the smallest and most sustainable Hyaluronic Acid ever made

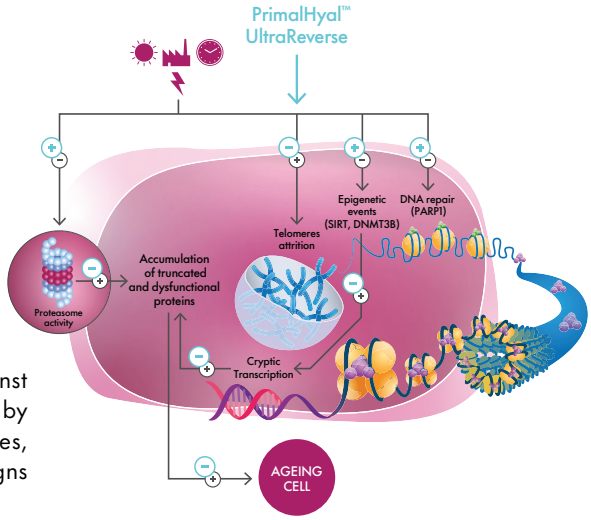
Based on their knowledge on Hyaluronic Acid biological properties, Active Beauty researchers decided to explore extremely low molecular weights HA, to unlock new biological benefits, never observed before. To do so, they leveraged on the learnings of the development of PrimalHyal™ 50 Life, the first HA obtained through a revolutionary precision fermentation process, with a demonstrated reduction of its environmental footprint by 10 fold, as demonstrated by a thorough Life Cycle Analysis.

By doing so, Active Beauty experts were able to craft PrimalHyal™ UltraReverse, the smallest HA ever made, with a molecular weight lower than 3 kDa (a combination of just a few monomers), and with an even lower impact on the environment[3].

Addressing most of the primary hallmarks of ageing for the perfect well-ageing experience

By its unique ability to penetrate into skin cells, and act as deep as the cell's nucleus environment, at the DNA level, PrimalHyal™ UltraReverse is targeting most of the primary hallmarks of ageing, tackling ageing at its root, and bringing several benefits in terms of skin health and longevity:

- Hallmark #1 – Epigenetic alterations: restoring DNA methylation processes and Sirtuins activity, limiting cryptic transcription.
- Hallmark #2 – Genomic instability: boosting DNA repair mechanisms via the stimulation of PARP1.
- Hallmark #3 – Telomere attrition: reactivating telomerase expression and activity.
- Hallmark #4 – Loss of proteostasis: increasing the proteasome activity.



By doing so, PrimalHyal™ UltraReverse protects the skin, not only against chronological ageing, but also against the exposome. This is translated by a rejuvenated skin, with a significant improvement of the facial features, a reduction of the apparent age, and a correction of several ageing signs (wrinkles, sleep wrinkles, skin's firmness)...

PrimalHyal™ UltraReverse is a radical advance in the field of skin health, longevity and vitality, now available for all Beauty brands and consumers all over the world!

[1] Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, Guido Kroemer - The Hallmarks of Aging, Cell, Volume 153, Issue 6, 2013, Pages 1194-1217; [2] Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, Guido Kroemer - Hallmarks of aging: An expanding universe, Cell, Volume 186, Issue 2, 2023, Pages 243-278; [3] Life Cycle Analysis finalisation on-going (2025)

Biological activity

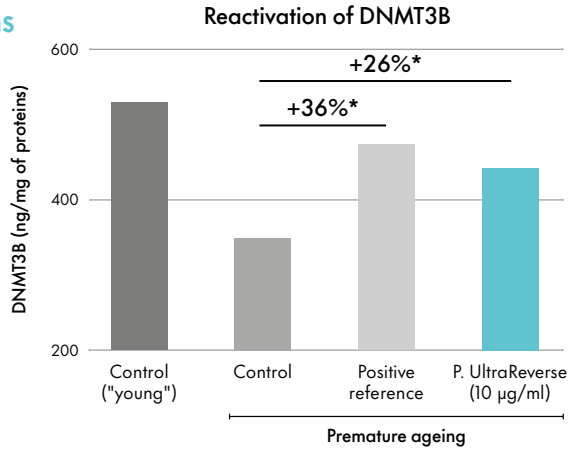
Action on Primary hallmark #1 – Epigenetic alterations

1. Restoring DNA methylation (*in vitro*)

Normal human epidermal keratinocytes (NHEKs) prematurely aged by replicative senescence were treated for 3 days with PrimalHyal™ UltraReverse (10 µg/ml) or with a positive reference (IL-6 at 50 ng/ml). Untreated NHEKs condition was used as young control reference.

At the end of the incubation period, nuclear proteins were extracted and the DNA-methyltransferase 3B (DNMT3B) was quantified using an ELISA kit.

Results: PrimalHyal™ UltraReverse significantly **upregulates the expression of DNMT3B, restoring the DNA methylation**.



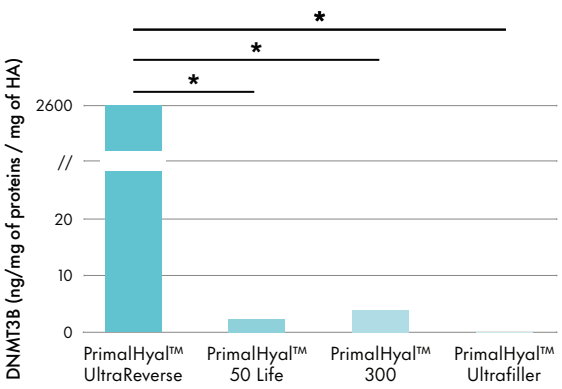
Student's t-test: *p<0.05

2. Uniqueness of PrimalHyal™ UltraReverse (*in vitro*)

NHEKs prematurely aged by replicative senescence were treated for 3 days with PrimalHyal™ UltraReverse, PrimalHyal™50 Life, PrimalHyal™ 300 or PrimalHyal™ Ultrafiller.

At the end of the incubation period, nuclear proteins were extracted and DNMT3B was quantified using an ELISA kit. Its expression is plotted relative to mg of HA.

Results: PrimalHyal™ UltraReverse **stimulates the expression of DNMT3B** significantly **more than any other grade of HA.**



Mann Whitney test: *p<0.05

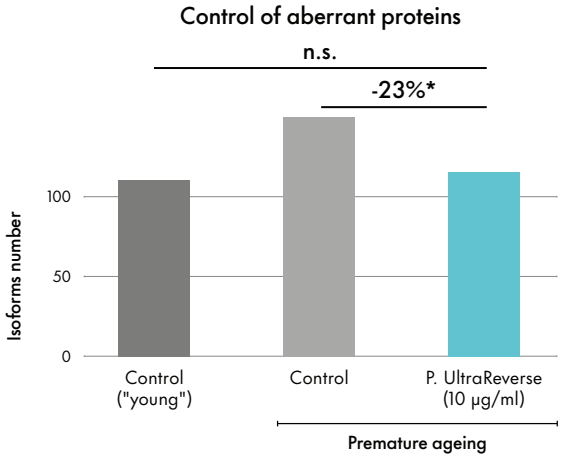
3. Preventing cryptic transcription (*in vitro*)

Cryptic transcription is an abnormal process occurring in ageing cells, where malfunctioning proteins are produced following errors in DNA transcription, ending up with a significantly higher number of transcript isoforms.

To quantify this phenomenon, NHEKs prematurely aged by replicative senescence were treated for 3 days with PrimalHyal™ UltraReverse (10 µg/ml). Untreated NHEKs were used as young control reference.

At the end of the incubation period, RNA was extracted and transcripts isoforms were analysed using precision nuclear run on sequencing (PRO seq).

Results: Premature ageing induced an increase of **aberrant transcripts, significantly reduced by PrimalHyal™ UltraReverse.**



Student's t-test: *p<0.05; n.s. not significant

4. Boosting a star longevity marker - SIRT1 (*in vitro*)

In two sets of experiments, NHEKs from an aged donor (67) were treated either with Primalhyal™ Ultrareverse (5 µg/ml or 10 µg/ml) or a positive reference (10 µM Rosiglitazone) for 24 hours.

At the end of incubation period, cellular lysates were collected and Sirtuin 1 expression and total sirtuins (1 to 7) activity were quantified by using respectively an ELISA kit or an enzymatic activity measurement kit.

Results: PrimalHyal™ UltraReverse significantly **boosts SIRT1 expression, and the activity of the whole sirtuins family,**, with a dose effect.

	Sirtuin 1 expression (ng/mg prot)	Sirtuins activity (ng/min/mg prot)
Positive reference	+149%*	+28%*
PrimalHyal™ UltraReverse (5 µg/ml)	+25%#	+9%*
PrimalHyal™ UltraReverse (10 µg/ml)	+136%*	+19%*

Mann Whitney test: *p<0.05; #p<0.1

Biological activity

Action on Primary hallmark #2 – Genomic instability

Boosting DNA repair mechanisms (*in vitro*)

Normal human epidermal keratinocytes (NHEKs) from an aged donor (67) were treated either with Primalhyal™ Ultrareverse (5 µg/ml or 10 µg/ml) or a positive reference (10 µM Rosiglitazone) for 24 hours.

At the end of the incubation period, nuclear proteins were extracted. PARP1 expression was then quantified using an ELISA kit, while PARP1 activity was quantified using an enzymatic activity measurement kit.

Results: PrimalHyal™ UltraReverse significantly **upregulates the expression and activity of PARP1,** and its activity, **reinforcing DNA repair mechanisms**.

	PARP1 expression (ng/mg prot)	PARP1 activity (ng/min/mg prot)
Positive reference	+140%*	+59%*
PrimalHyal™ UltraReverse (5 µg/ml)	**+22%***	**+28%#**
PrimalHyal™ UltraReverse (10 µg/ml)	**+57%***	**+52%***

Mann Whitney test: *p<0.05; #p<0.1

Action on Primary hallmark #3 – Telomere attrition

Restoring the telomeres' protection (*in vitro*)

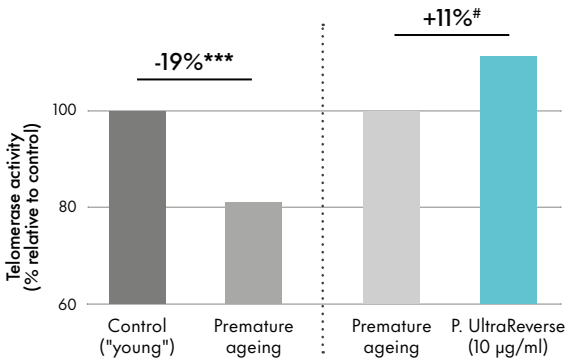
First, normal human epidermal keratinocytes (NHEKs) were treated for 24 hours with PrimalHyal™ UltraReverse (10 µg/ml).

At the end of the incubation period, cellular lysates were collected and telomerase expression was quantified in the nuclear extract.

In a second experiment, NHEKs were prematurely aged (replicative senescence) and treated with PrimalHyal™ UltraReverse (10 µg/ml) for 24 hours.

Untreated non senescent NEHKs were used as young control condition. RNA was extracted and qPCR was performed on cDNA targeting the telomerase gene.*

Restoration of telomerase activity



Student's t-test: ***p<0.001; *p<0.05; #p<0.1

Results: PrimalHyal™ UltraReverse significantly **stimulates the expression of telomerase** (+39%*, not shown) and its activity under senescent conditions, **reinforcing the telomeres' protection**.

Action on Primary hallmark #4 – Loss of proteostasis

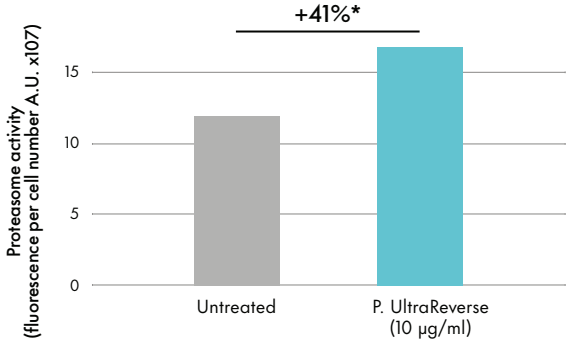
Enhancing the activity of the proteasome (*in vitro*)

Human primary keratinocytes were treated for 6 hours with PrimalHyal™ UltraReverse (10 µg/ml) then the substrate LLVY-R110 was added and incubated for 1 hour.

The cleavage of LLVY-R110 by the proteasome generates a fluorescent compound (Ex 490nm / Em 525nm) detected by a microplate reader. Fluorescence was normalised by the cell number and used to determine the proteasome activity.

Results: PrimalHyal™ UltraReverse significantly **stimulates the proteasome activity, reinforcing mechanisms of proteins recycling**.

Stimulation of proteasome activity



Mann Whitney test: *p<0.05

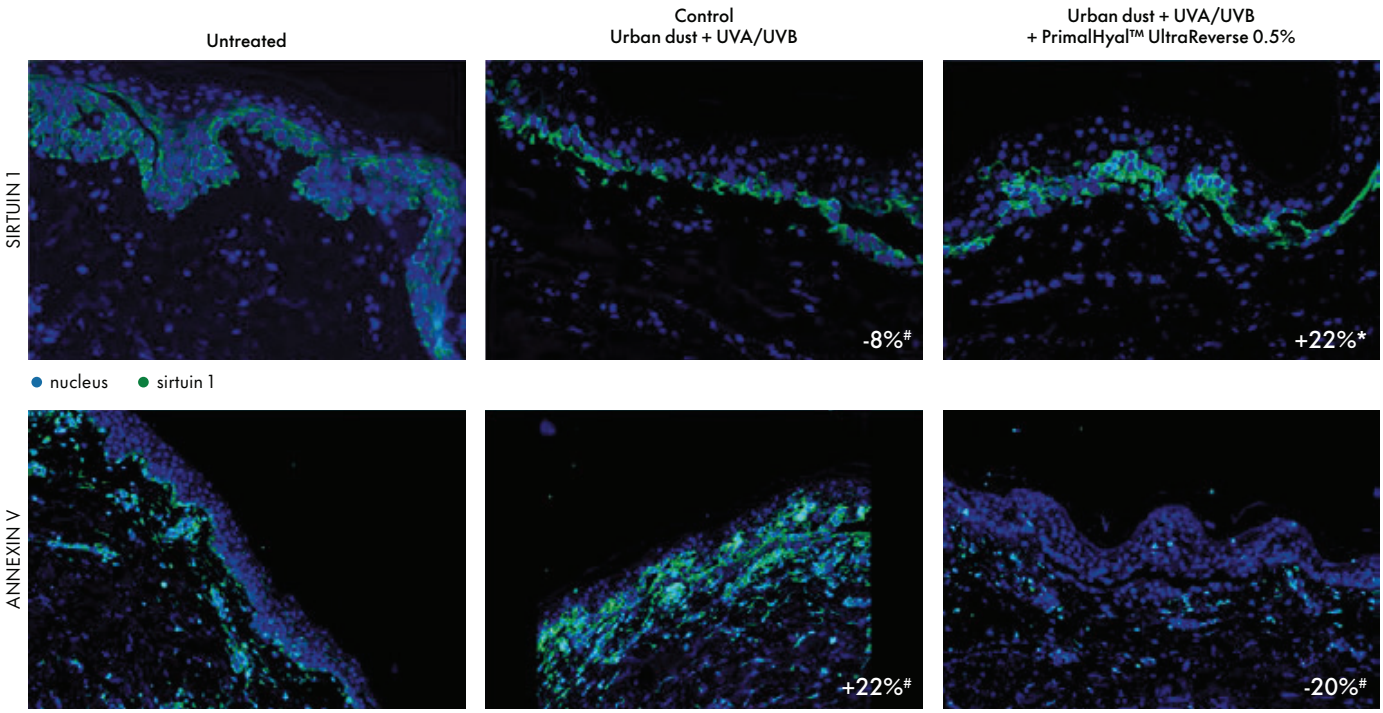
Biological activity

Demonstration of skin longevity benefits under photo-pollution conditions

Regulation of a key longevity biomarker & reduction of apoptosis (*ex vivo*)

Skin explants of a mature donor (53 years old) were put in survival for 5 days. A photo-pollution stress (4.5 J UVA + 0.15 J UVB + 200 µg/mL urban dust) was applied at D1, D2 and D3 during daytime, while PrimalHyal™ UltraReverse (0.5%) was applied overnight, after each stress period.

After the culture, skin explants were fixed and immunoassays followed by quantification were performed to assess the levels of two biomarkers linked to skin longevity: Sirtuin 1 and Annexin V, a typical marker of cellular apoptosis.



Mann Whitney test: *p<0.05, #p<0.1

Results: After the photo-pollution stress, the expression of SIRT1 is significantly reduced, while the expression of Annexin V is significantly increased, demonstrating the deleterious impact of the exposome on the skin.

The use of PrimalHyal™ UltraReverse at 0.5% enables to significantly **restore the expression of SIRT1** and significantly **decrease the production of Annexin V**, demonstrating its efficacy in maintaining skin health and longevity under photo-pollution conditions.

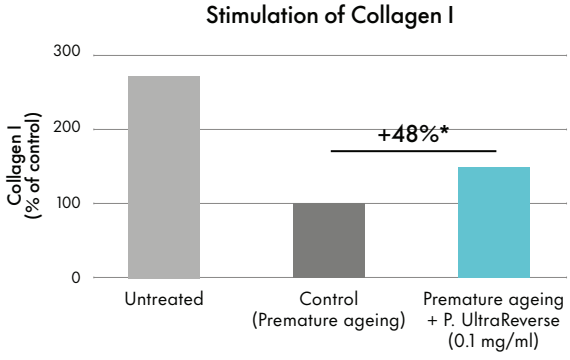
Benefits on collagen production

Restoring collagen I synthesis (*in vitro*)

Normal human dermal fibroblasts (NHDFs) were prematurely aged with H_2O_2 (500 µM) for 3 hours or not.

They were then treated with PrimalHyal™ UltraReverse (0.1 mg/ml) for 72 hours or kept untreated as a control. Immunostaining of pro-collagen I was then performed on fixed cells and quantification was done by fluorescent detection on post imagery processing.

Results: PrimalHyal™ UltraReverse significantly **stimulates the expression of collagen I, by +48%**.



Mann Whitney test: *p<0.05

Clinical efficacy

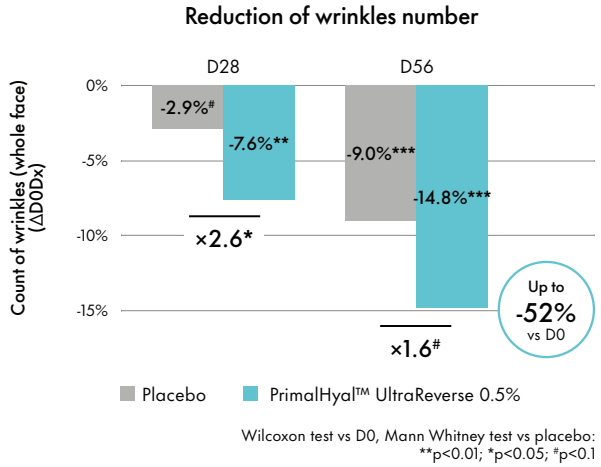
Anti-wrinkle efficacy, with a drastic reduction of sleep wrinkles (clinical study #1, France)

A double blind clinical evaluation was carried out on 40 volunteers (Caucasian women from 50 to 75 years old, 61 in average, with visible wrinkles and fine lines on the face), divided into 2 groups.

Volunteers applied a cream twice a day either containing PrimalHyal™ UltraReverse (0.5%) or the same exact formula without the active as a placebo, for 56 days.

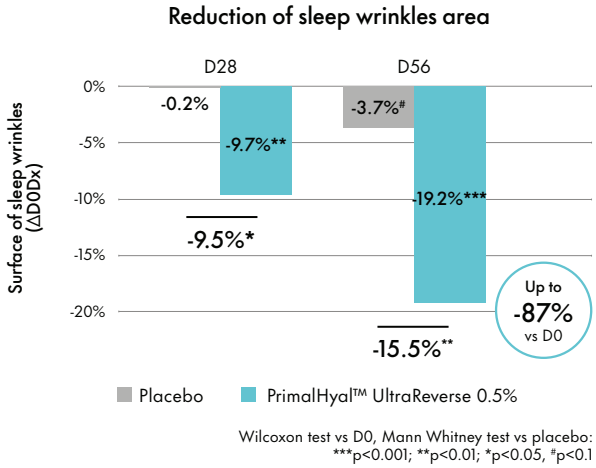
Efficacy was then evaluated using the Visia® CR2.3 technology at D28 and D56, by investigating the global wrinkles number (full face) or the winkled area on three specific zones representative of the sleep wrinkles, a newly discovered type of wrinkles, not only related to gravity, but also to compressive forces due to the position in which we sleep.[4]

1. Global reduction of the facial wrinkles



Wilcoxon test vs D0, Mann Whitney test vs placebo: **p<0.01; *p<0.05; #p<0.1

2. Reinforced efficacy on the sleep wrinkles



Wilcoxon test vs D0, Mann Whitney test vs placebo: ***p<0.001; **p<0.01; *p<0.05, #p<0.1

Results: PrimalHyal™ UltraReverse at 0.5% significantly **decreases the wrinkles count**, by -14.8% versus D0, and up to 2.6x more efficiently than the placebo.

Results: PrimalHyal™ UltraReverse at 0.5% significantly **decreases the sleep wrinkles area**, by -19.2% versus D0, and up to -87% for the best respondents in the panel.

3. Extrapolation of longevity benefits using an artificial intelligence generated avatar

A 3D avatar was generated using the clinical results, to illustrate the benefits of using PrimalHyal™ UltraReverse in the long term. Illustrative pictures are presented below to represent skin's evolution after 5 years time.

Day 0

Placebo PrimalHyal™ UltraReverse

Year 5

Placebo PrimalHyal™ UltraReverse

[4] Goesel Anson, Michael A.C. Kane, Val Lambros, Sleep Wrinkles: Facial Aging and Facial Distortion During Sleep, Aesthetic Surgery Journal, Volume 36, Issue 8, September 2016, Pages 931–940

Clinical efficacy

4. Perceivable reduction of the apparent age

An artificial intelligence algorithm, trained to evaluate the apparent age of volunteers based on image analysis, was used to determine the evolution of volunteers' facial features and the impact on their apparent age.

Illustrative pictures of a volunteer using PrimalHyal™ UltraReverse at 0.5%
Intense anti-wrinkle & rejuvenating activity (GP15, 56 years old)

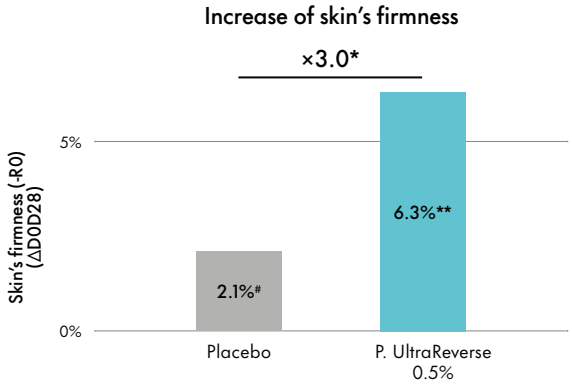
Results: : PrimalHyal™ UltraReverse at 0.5% is able to significantly **decrease the apparent age of volunteers, down to 6 years younger, and by 2.7 years in average after only 28 days!**

Boosting skin elasticity in polluted conditions, with a single daily application (clinical study #2, China)

A double blind clinical evaluation was carried out on 40 volunteers (Asian women from 43 to 60 years old, 53 in average, living in Guangzhou, China, outdoor workers with long-term exposure to pollution, with a slack skin and visible wrinkles, glabella wrinkles and fine lines on the face), divided into 2 groups.

Volunteers applied a cream once a day, in the evening, either containing PrimalHyal™ UltraReverse (0.5%) or the same exact formula without the active as a placebo, for 28 days.
Efficacy was then evaluated using the Cutometer® at D28, by quantifying the firmness parameter (R0).

Results: PrimalHyal™ UltraReverse at 0.5% significantly **improves the skin's firmness**, by 6.3% versus D0, 3.0x more efficiently than the placebo.



Wilcoxon test vs D0, Mann Whitney test vs placebo:
**p<0.01; *p<0.05; #p<0.1

Summary

Technical information

INCI:	Hydrolyzed Sodium Hyaluronate
Origin:	White biotechnology
Preservation:	None
Appearance:	White powder
Solubility:	Hydrosoluble
Dosage:	0.5%
Processing:	Add at the beginning or at the end of the formulation process (with water solubilisation), at a temperature below 80°C and a pH between 4 and 8, and under gentle stirring or high shear mixing.

Benefits

Claims:	Anti-ageing, well-ageing, longevity, keep the skin healthy, collagen booster, anti-wrinkle, skin texture improvement, skin elasticity, improve primary hallmarks of ageing.
Applications:	Facial care products, anti-ageing serums and creams, hyaluronic acid serums, night creams, anti-wrinkle serums, skin care for mature skin, skin perfector, fine lines erasers.

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Human by nature

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