



BEL-EVEN®

*Future-proof your skin from
the effects of daily stress*

Master Presentation
04.2022

Today's 24/7 stressful lifestyle affects us physically and mentally, impacting our overall wellbeing



Across the globe, consumers increasingly perceive stress as health issue...



74% of UK adults declared “to be so stressed that they were unable to cope” at least once during the last year. Percentage raises to **81%** for women, **93%** for 18-24 y.o.*



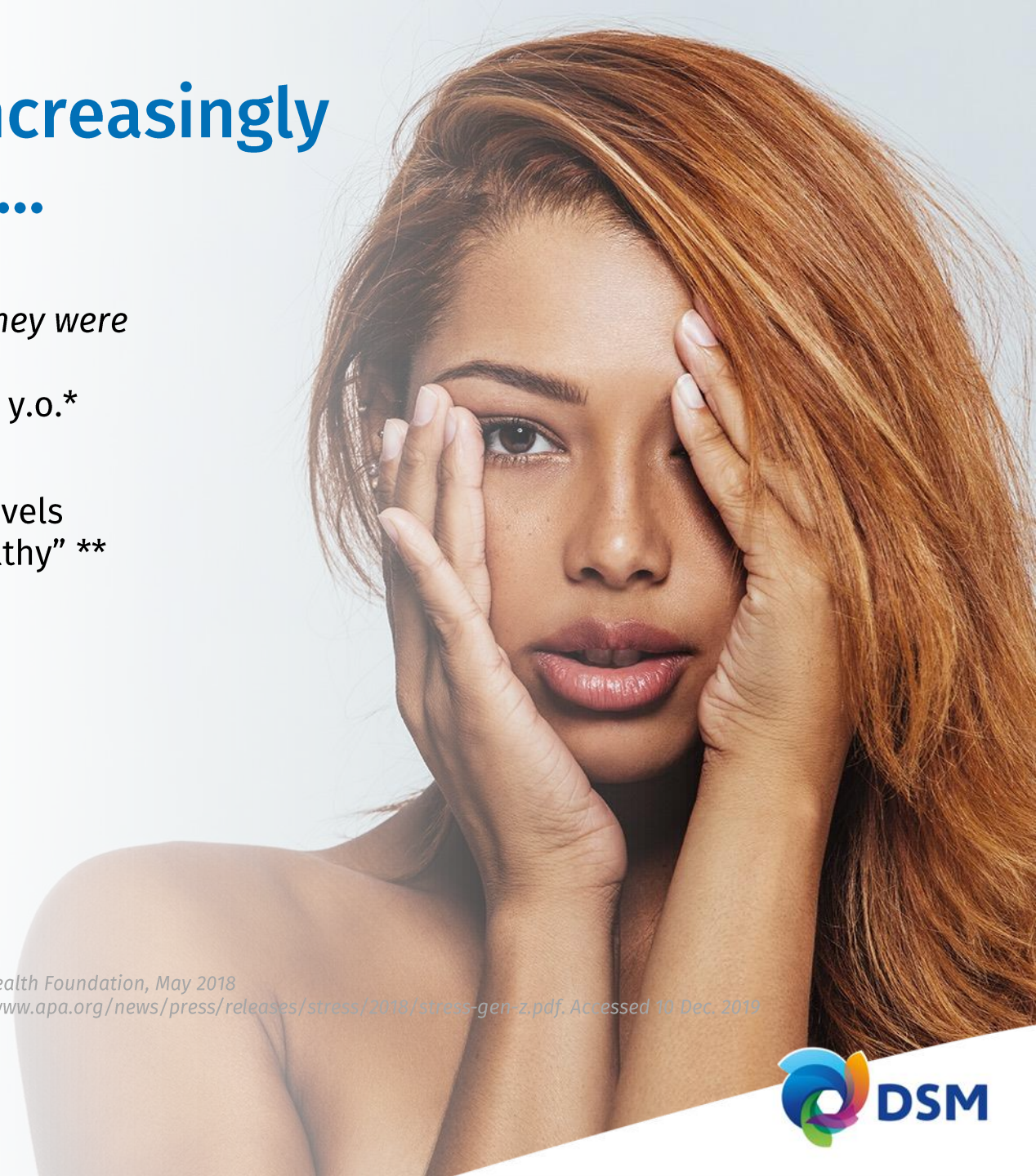
In US, Gen Z and Millennials’ self-reported stress levels were **+40% higher** than the ones perceived as “healthy” **



84% of Brazilian consumers actively seek ways to reduce stress ***



2017 Health and Nutrition Survey Report shows that **~40%** of the Japanese population fails to sleep more than 6 hours per night ****



*Source: from Mintel, reference to a study into the impact of stress, commissioned in UK by the Mental Health Foundation, May 2018

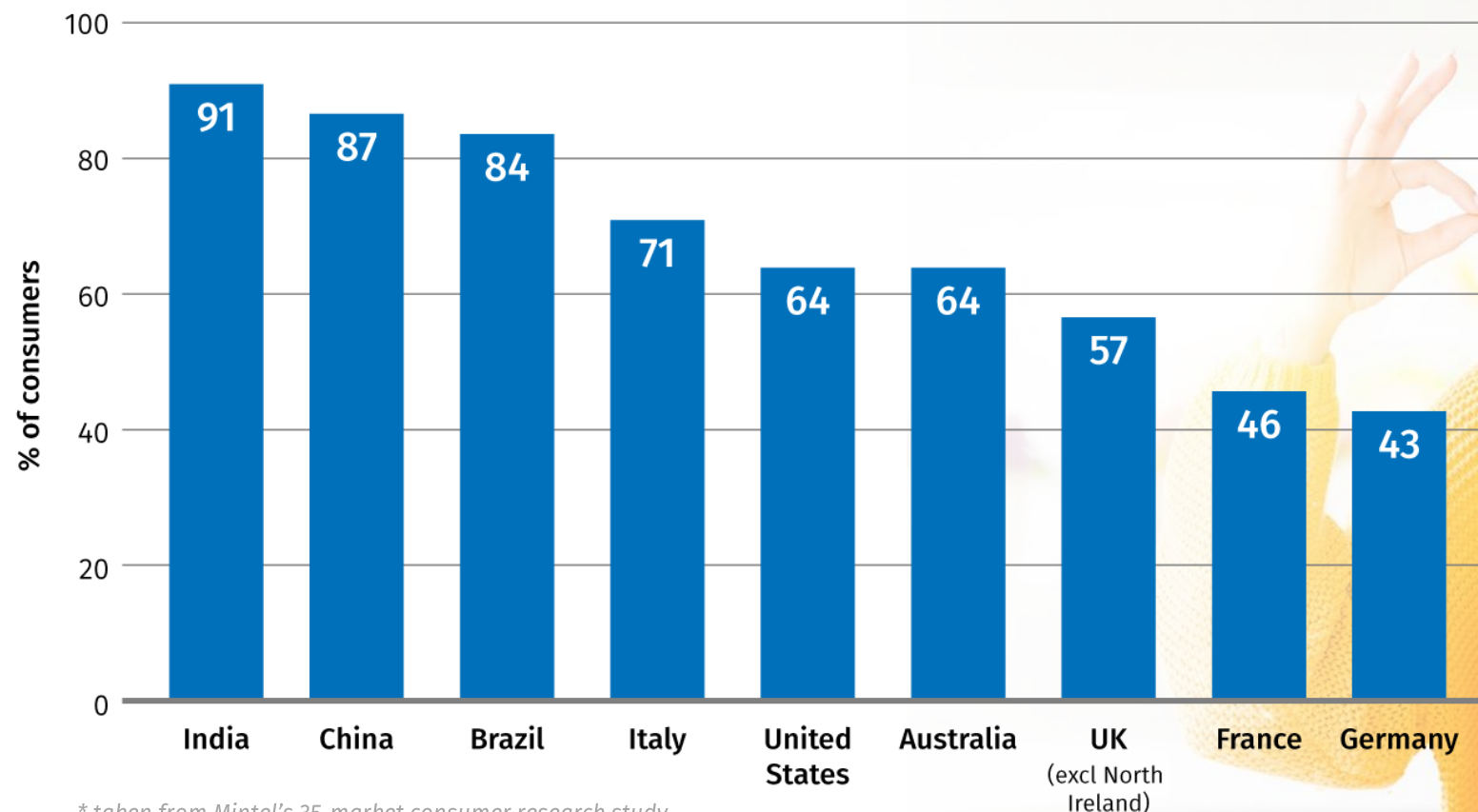
**Source: American Psychology Association. Stress in America, Generation Z. APA, October 2018. <https://www.apa.org/news/press/releases/stress/2018/stress-gen-z.pdf>. Accessed 10 Dec. 2019

***Source: Mintel's 35-market survey, December 2019. Base: 1,000 adults aged 16-55 in Brazil

**** Source: Japanese Beauty 2020 Consumer Trends

...and actively look for solutions to reduce it

Selected Countries: consumers actively seeking ways to reduce stress, jul 2019



* taken from Mintel's 35-market consumer research study

Base: India, China, US, Australia: 1,000 internet users aged 18+ in each country; Brazil, Italy, UK, France, Germany: 1,000 internet users aged 16+ in each country

Source: Dynata/Mintel; KuRunData/Mintel; Lightspeed/Mintel

COVID-19 context triggers anxiety

Consumers are concerned of protecting and maintaining their mental health, whatever will happen next

Raising of new concerns, beyond just the exposure to the virus.
From a recent Chinese digital consumers survey*:



declare to be moderately/extremely worried about future impact on lifestyle



say their financial status is worse-off



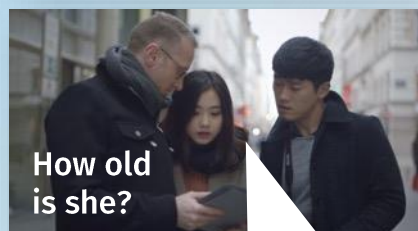
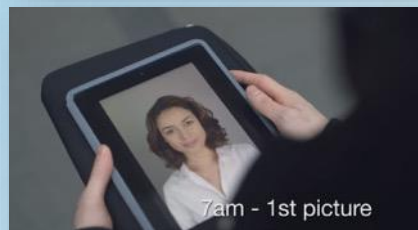
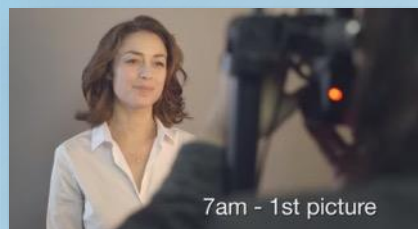
are most concerned about stress at work or their employment

Interest and use of products with mood boosting or stress reduction qualities is expected to increase further, due to the psychological toll from the pandemic

*Base: China: 1,200 internet users aged 18-59, 25 Mar-1 Apr 2020. Source: KuRunData/Mintel; Mintel's Global COVID-19 Tracker

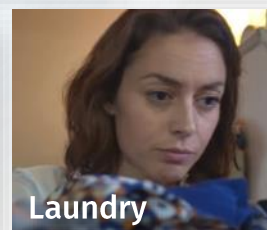
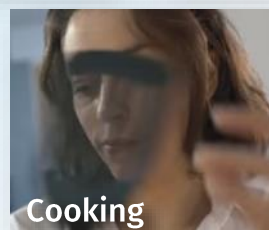
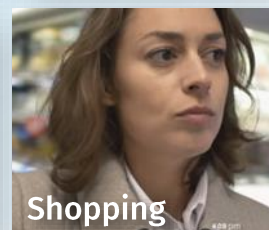
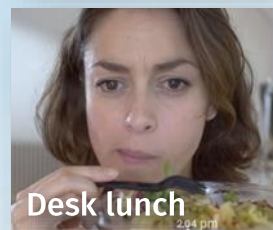
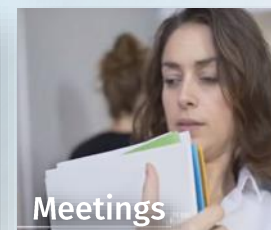
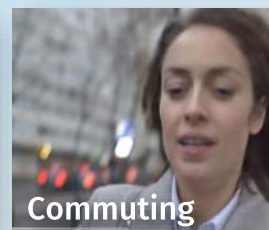
Sustained stress can also affect skin appearance

IN THE MORNING

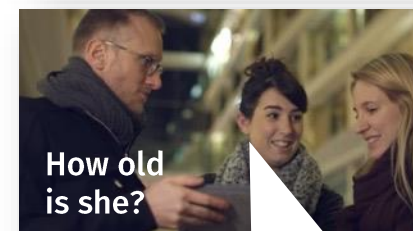
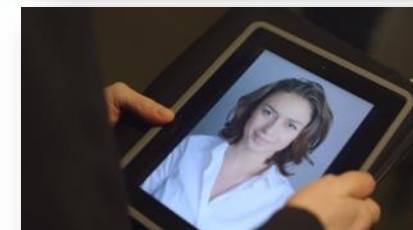


From 27 to 32 y.o.

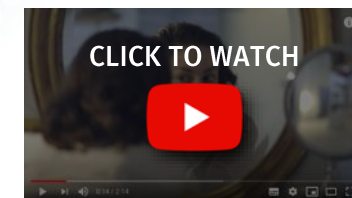
DAILY ROUTINE



IN THE EVENING



From 35 to 40 y.o.

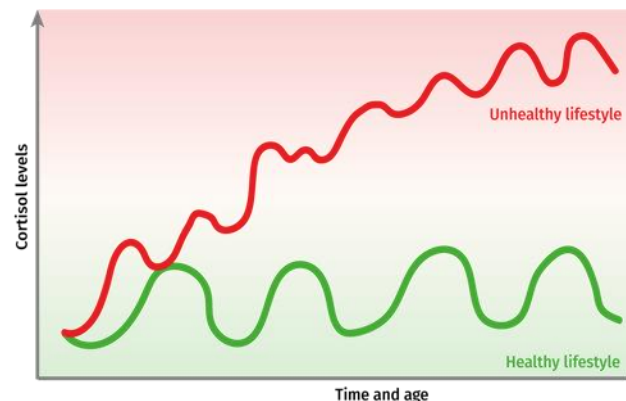
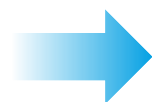
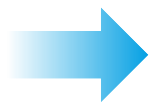


“into a woman’s skin”
video experiment

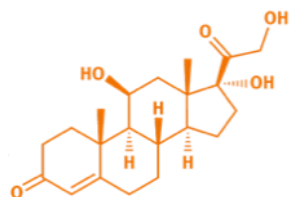
WATCH OUT!
Perceived
+10 yrs
in just 1 day

Source: Garnier experiment «into a woman's skin» <https://www.youtube.com/watch?v=zga0SUuzw-M>

How can chronic stress trigger skin aging?



To cope with stress, human body produces **Cortisol**, the so called “**stress hormone**”



Cortisol

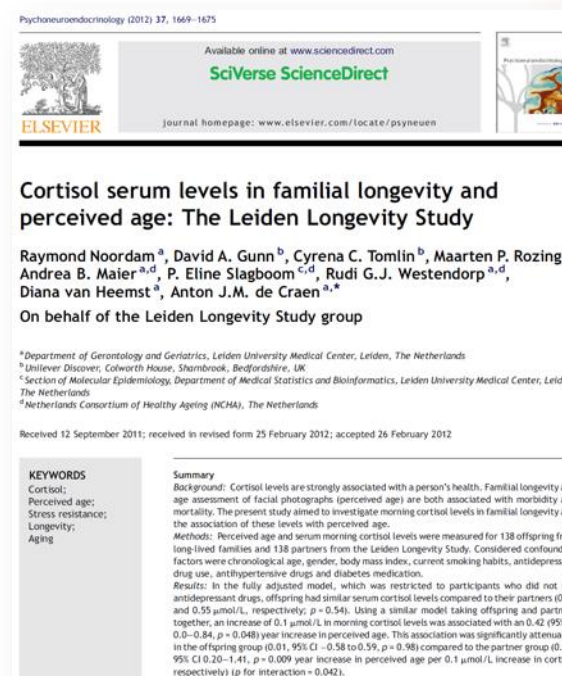
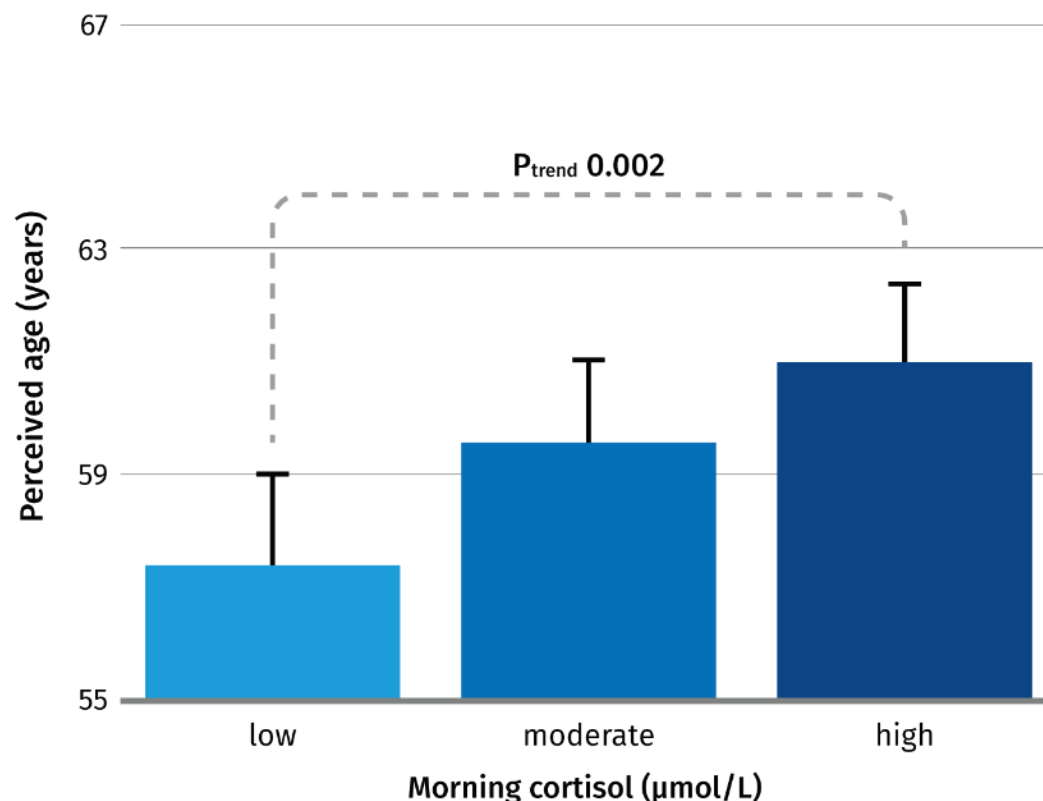
To **focus on stress-response** & **prevent inflammation** to spread, Cortisol temporary diverts resources from skin normal functioning, **slowing down important skin processes**

such as:
fibroblast growth,
Collagen and Elastin production,
epidermal cells turnover

Small amounts of Cortisol are good to manage stress, but **chronic stress results in permanently high and unhealthy levels of Cortisol** with negative impact on skin's health & appearance.

Persistent production of Cortisol **jeopardizes skin vitality**, resulting in premature signs of ageing: **cells can't rebuild Elastin & Collagen**, with consequent **wrinkles' appearance** and **loss of elasticity**, while compromised epidermal cells' turnover drives to **dull tone** and **tired look**.

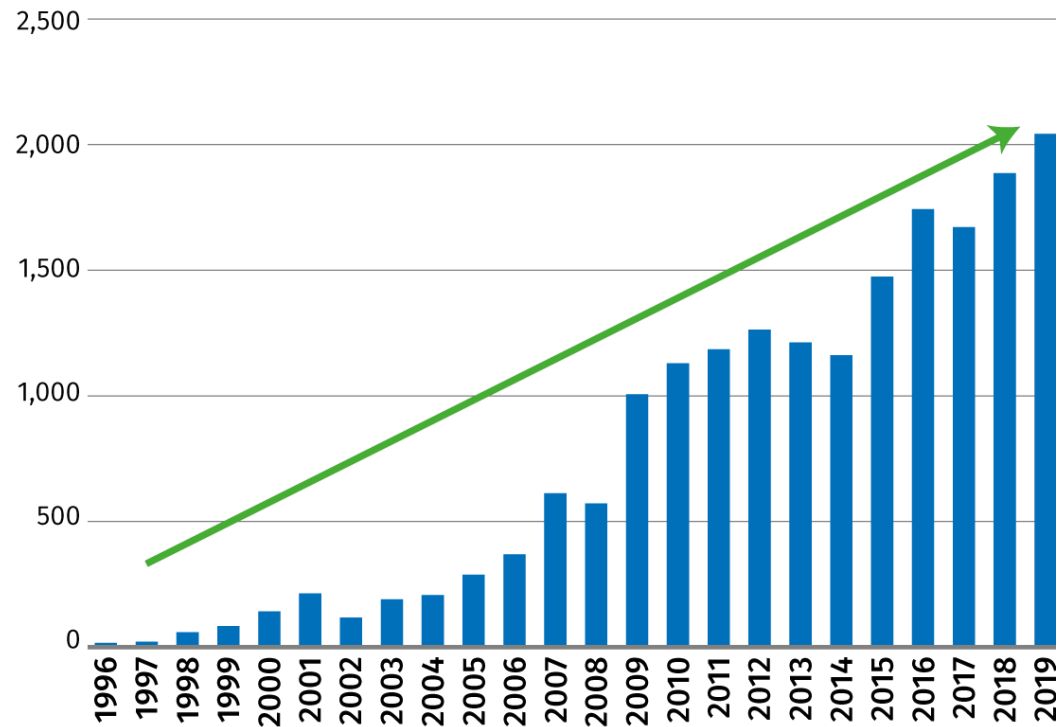
Higher Cortisol level is associated with higher perceived age



Sources: Noordam, R., Gunn, D. A., Tomlin, C. C., Rozing, M. P., Maier, A. B., Slagboom, P. E., ... de Craen, A. J. M. (2012). Cortisol serum levels in familial longevity and perceived age: The Leiden Longevity Study. *Psychoneuroendocrinology*, 37(10), 1669–1675. <https://doi.org/10.1016/j.psyneuen.2012.02.013>

Increasing demand for beauty products solving stress-related signs of aging

Facial innovations with “stress” related claims



Source: Mintel GNDP and DSM Trend Landscaping

**Mindful
Beauty**

Consumers increasingly link stress, diet, hydration, and UV exposure to skin health

66%

of UK women feel that lifestyle, including stress, has the biggest impact on the skin

Ultimately “stress” offers a new angle to the anti-aging story



Clé de Peau Beauté Key Radiance Care

Fights the damaging effects of stress on skin. Awakens and restores, balances and revives, moisturises and resists and activates skin's intuitive ability to repair and defend.

De-stresses skin

Lancôme Anti-Stress Glow Liquid Moisturizer

Hydrates, visibly de-stresses skin and supports the skin's moisture barrier for an instant glow that lasts all day, leaving skin softer, smoother, and revitalized.



Babor Stress rescue super serum

Fights signs of stress-induced ageing. Helps skin quickly recover from stress and reduce redness, strengthening the skin barrier, for beaming, resilient, youthful and stress-free skin

Promotes the regeneration of the stressed skin barrier

Babor Hemp Rebel De-Stress Ampoules

Helps the skin feel relaxed, recovered, fresh, and velvety soft. Hemp seed oil, to promote the regeneration of the stressed skin barrier.



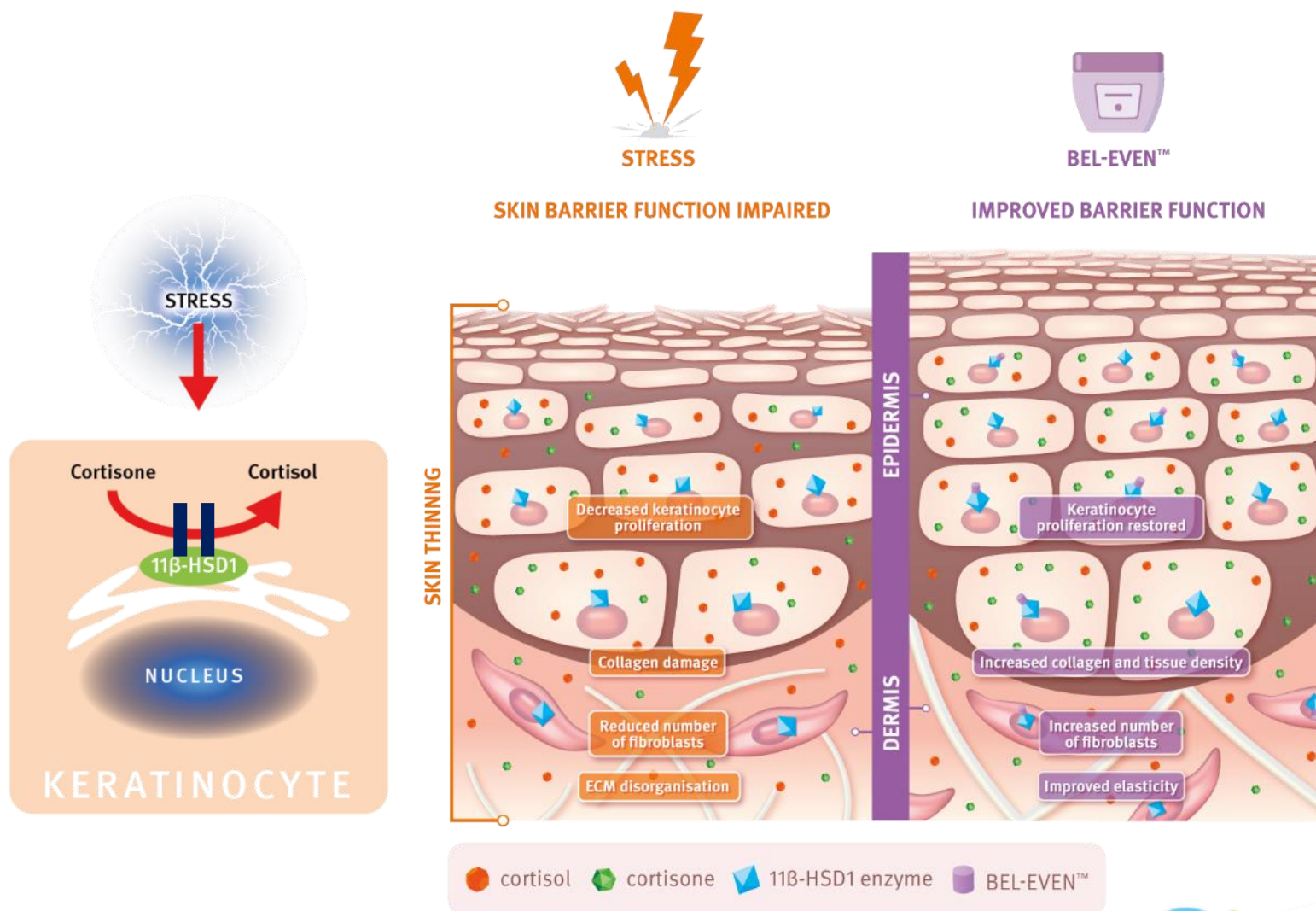
Introducing BEL-EVEN®!

DSM's perfect proposition for this market framework



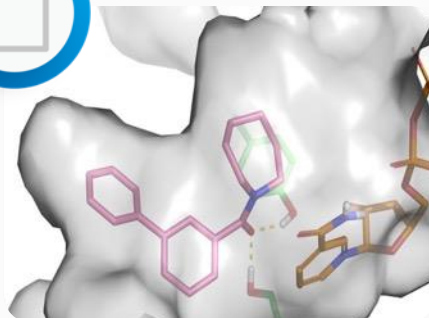
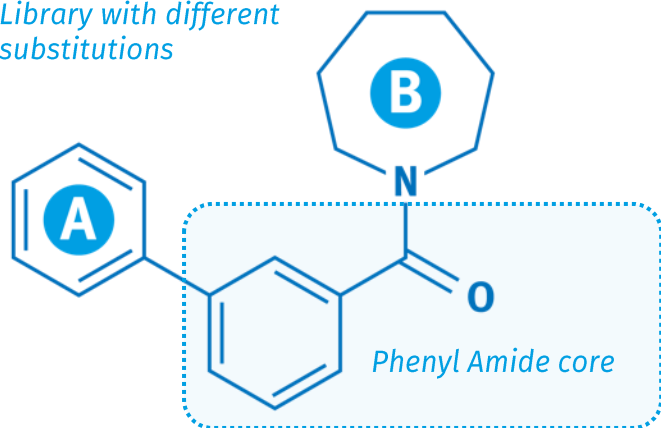
A unique mode of action that helps protect Collagen

- In human skin, Cortisol is generated from Cortisone by the Enzyme 11 β -HSD1
- BEL-EVEN® selectively inhibits the Enzyme 11 β -HSD1, rebalancing Cortisol levels in skin
- As a result, skin barrier (TEWL) is improved, Collagen is protected which leads to improved skin elasticity and density.



RATIONAL DESIGN: The key to reproducible effects

Library with different substitutions



INCI:

Biphenyl Azepanyl Methanone.

IUPAC name: Azepan-1-yl-[1,1'-biphenyl-3-yl]-methanone

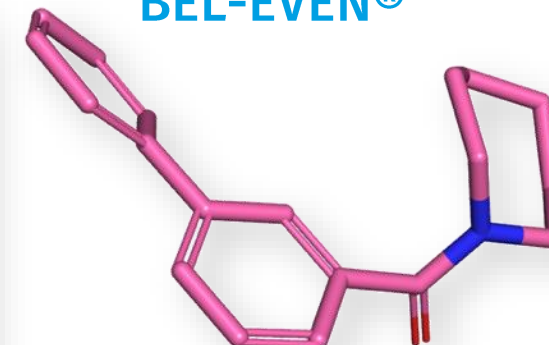
Synonyms:

N-(3-Phenylbenzoyl)-azepane

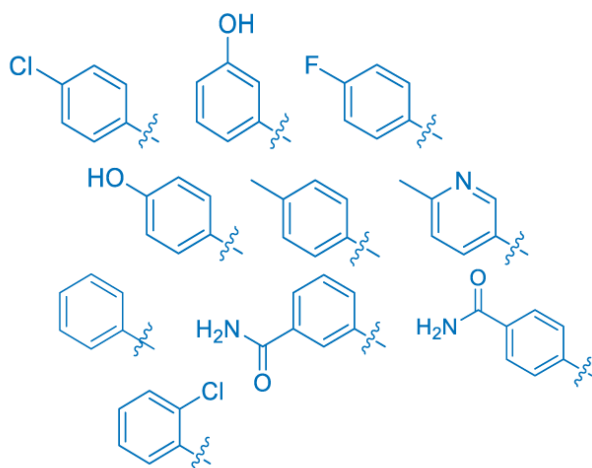
CAS: 1910069-14-5

IC50: 23 nM

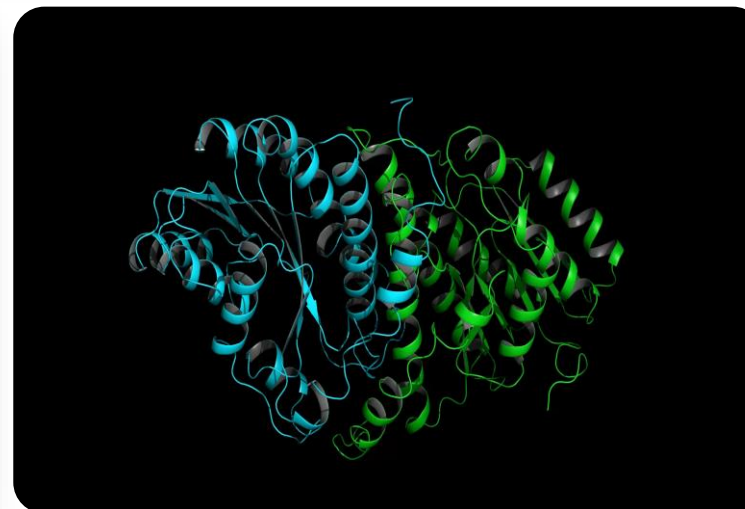
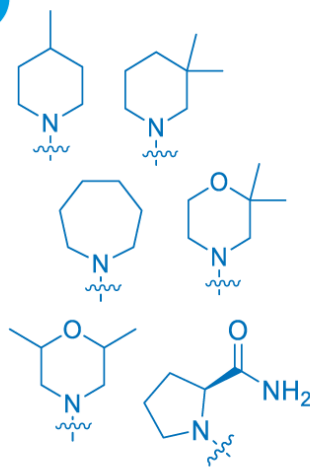
BEL-EVEN®



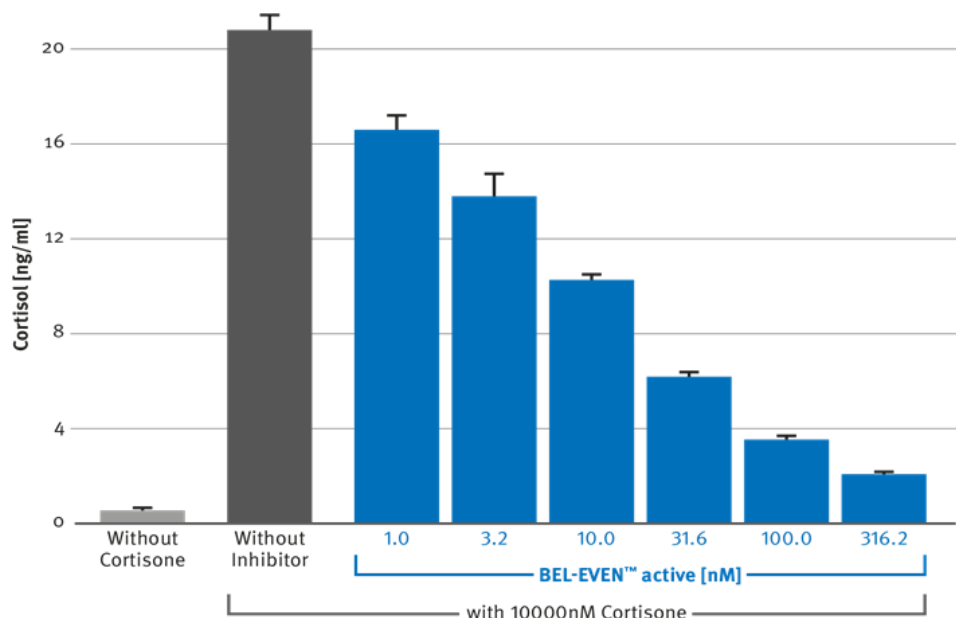
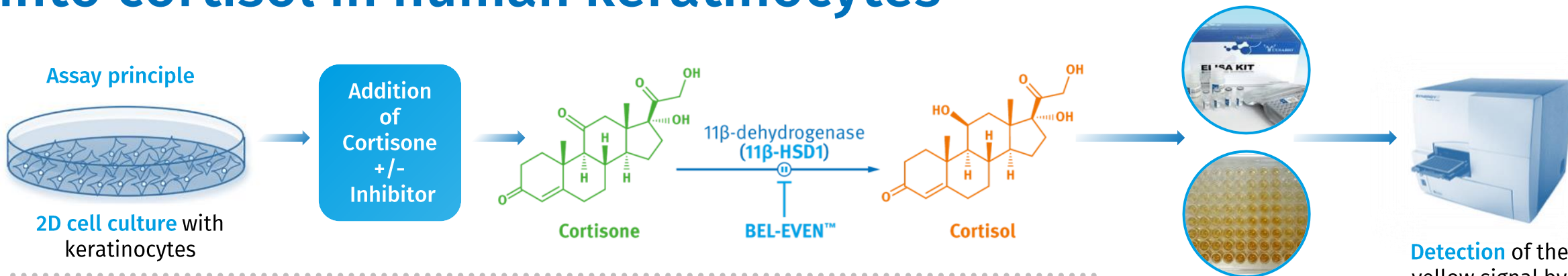
A



B



BEL-EVEN[®] inhibits conversion of cortisone into cortisol in human keratinocytes



IN VITRO PROOF

In vitro shows dose-dependent Cortisol inhibition.

Conversion of Cortisone into Cortisol was inhibited by the lead candidate

BEL-EVEN[®] is produced in a sustainable way

- ✓ Concise, patented two-step synthesis
- ✓ Catalytic reaction in pure water with very low catalyst loading
- ✓ No intermediate purification between the two steps
- ✓ Only one, non-toxic, organic solvent is used
- ✓ 1,3-propanediol as solvent obtained by corn fermentation



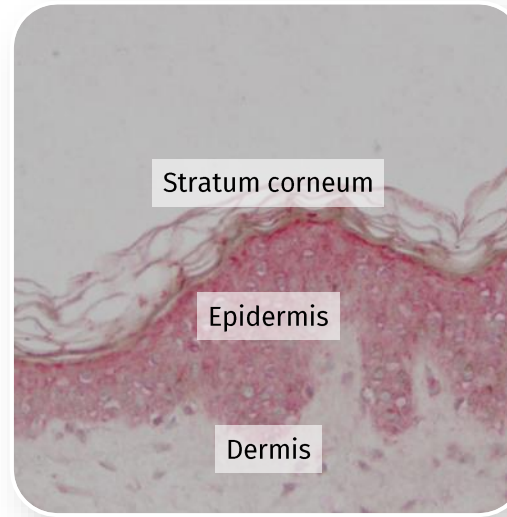
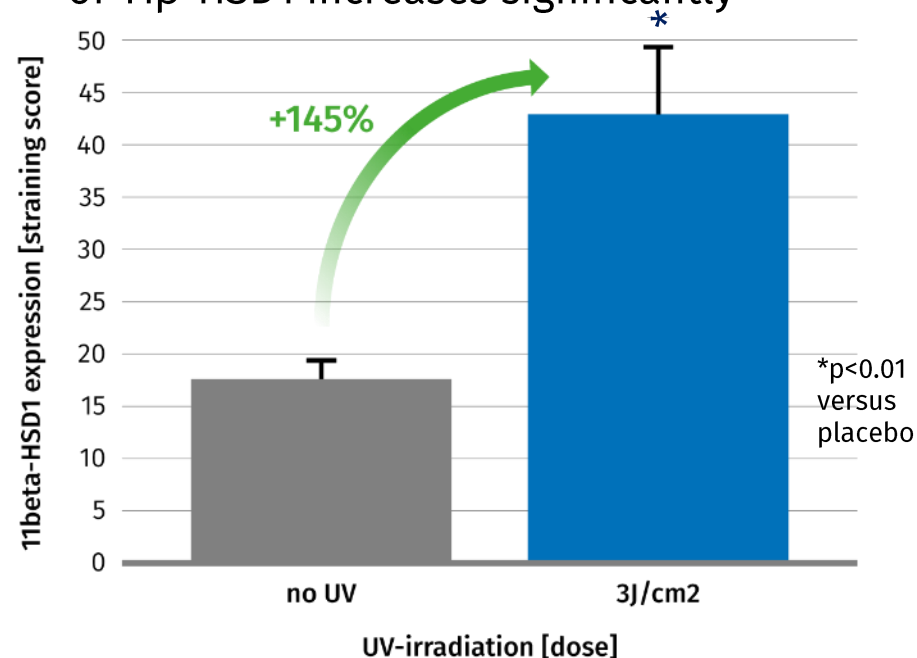
The efficacy
of BEL-EVEN[®]
has been proven
ex vivo and *in vivo*
with
amazing results!



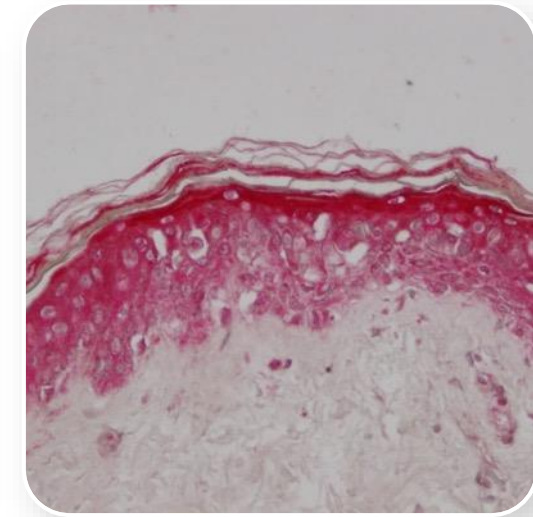
11 β -HSD1 expression increases under stress of UV Irradiation

Our ex-vivo skin studies confirm that:

- 11 β -HSD1 is expressed in the skin epidermis and dermis
- Upon UV irradiation (3J/cm²) expression of 11 β -HSD1 increases significantly



Non-irradiated skin



UV-irradiated skin

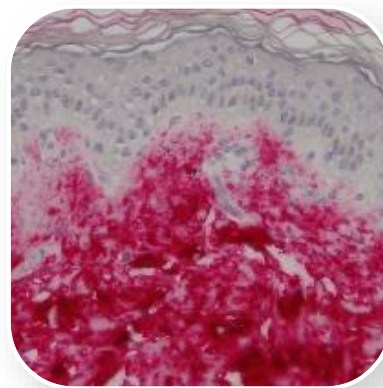
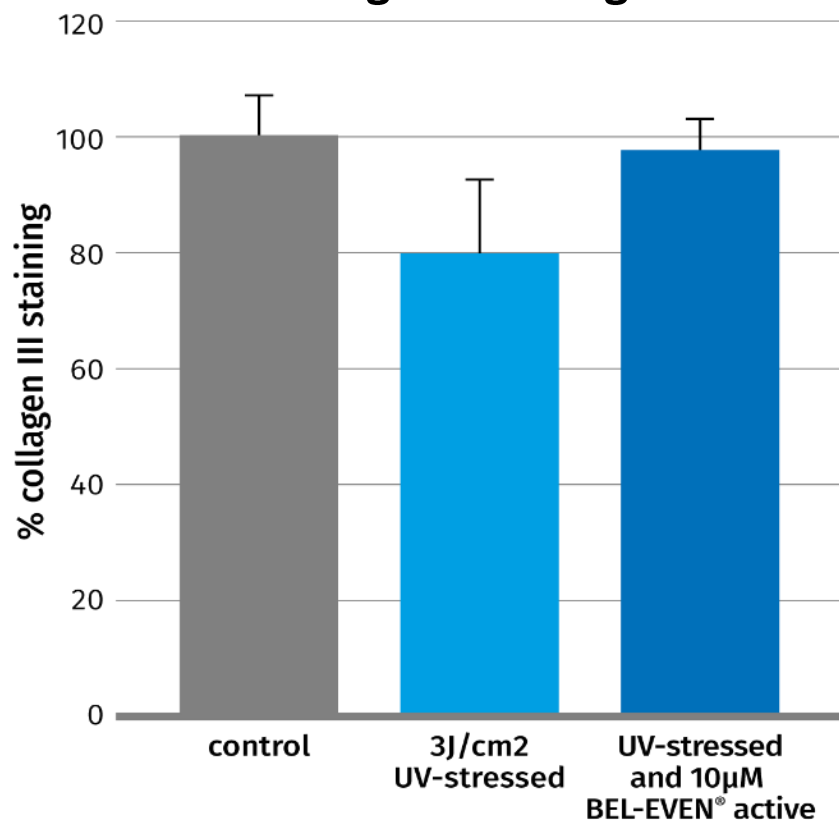
11 β -HSD1 protein expression (red staining).
There is a clear and visible increase in red staining intensity in the UV-irradiated tissues compared to non-irradiated skin

Human abdominal skin, 43 years old female donor

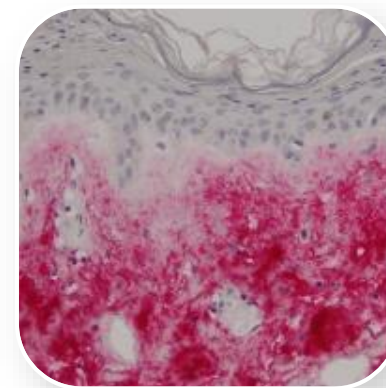
BEL-EVEN® prevents from UV-induced Collagen degradation

SCIENTIFIC
VALIDATION
ex vivo

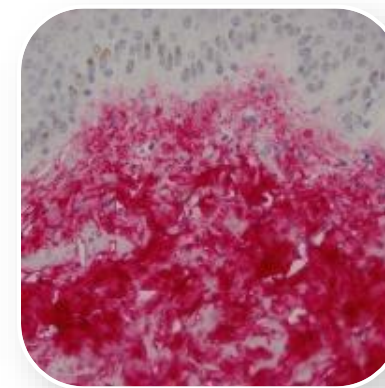
By inhibiting the enzyme 11 β -HSD1,
BEL-EVEN® prevents from UV-induced
Collagen III damage



Non-irradiated
skin



Vehicle,
3 J/cm2 UV

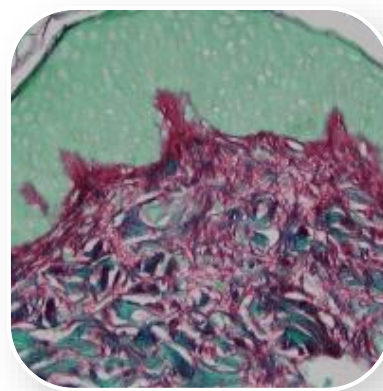
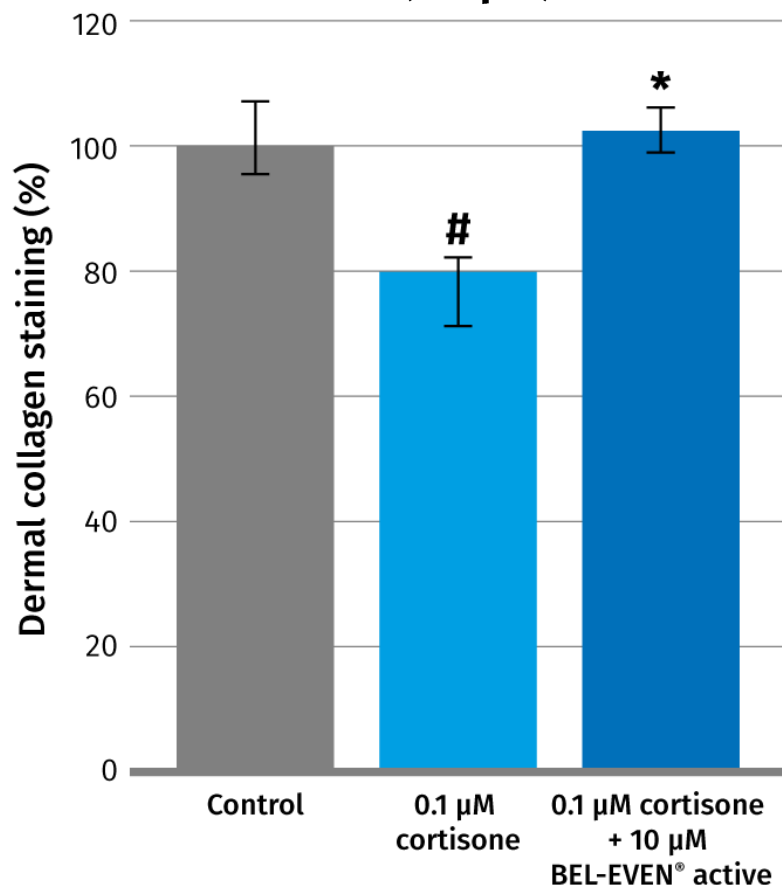


BEL-EVEN®,
3 J/cm2 UV
Increased Collagen
III levels using
BEL-EVEN®

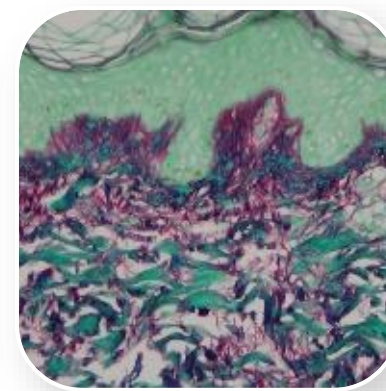
BEL-EVEN® prevents from Cortisol induced Collagen degradation

SCIENTIFIC
VALIDATION
ex vivo

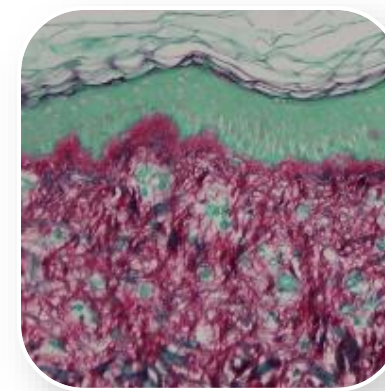
BEL-EVEN® inhibits the transformation of added Cortisone (0.1 μ m) to Cortisol



Vehicle



Vehicle,
0.1 μ m Cortisone



**BEL-EVEN®,
0.1 μ m Cortisone**

More Collagen
(red color) and
Improved skin
density with
BEL-EVEN®

Human abdominal skin, 45 years old female donor

p < 0.01 vs untreated and * p < 0.01 vs cortisone alone

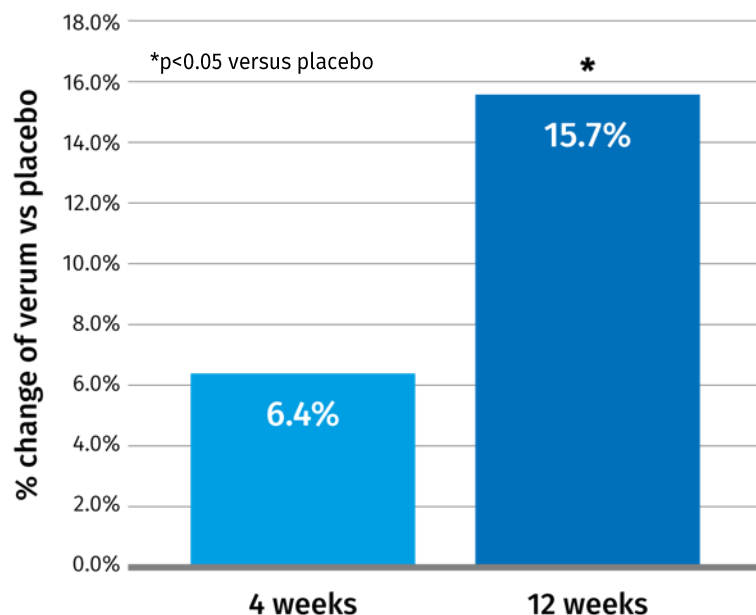
In vivo study design

- **3 months study,**
Oct-Dec in Switzerland
- Two groups of **30 female**
Volunteers **45-65 y.o.**
Blinded and **placebo** controlled
- **1 %** use level (20ppm)

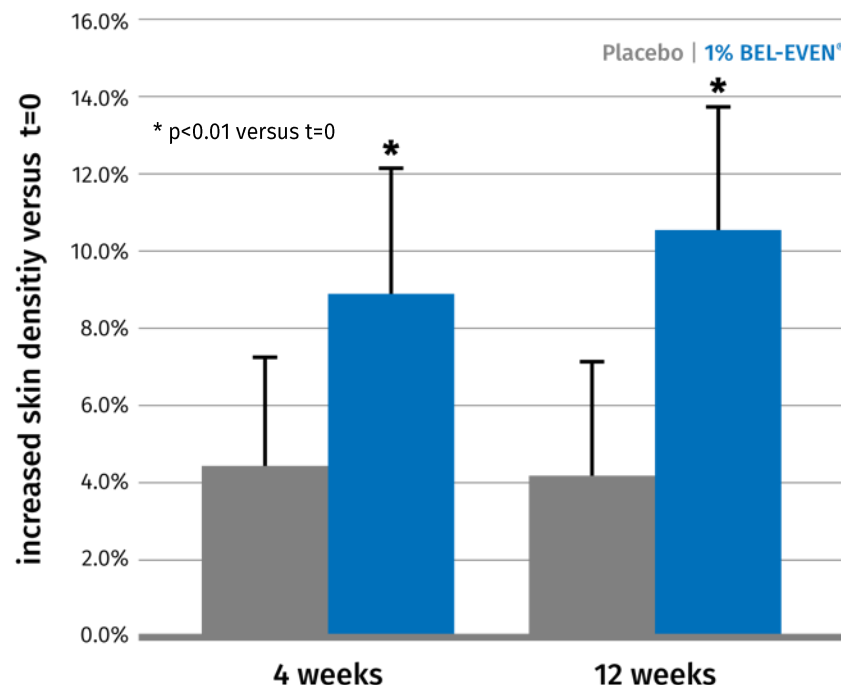


BEL-EVEN® improves skin elasticity and density

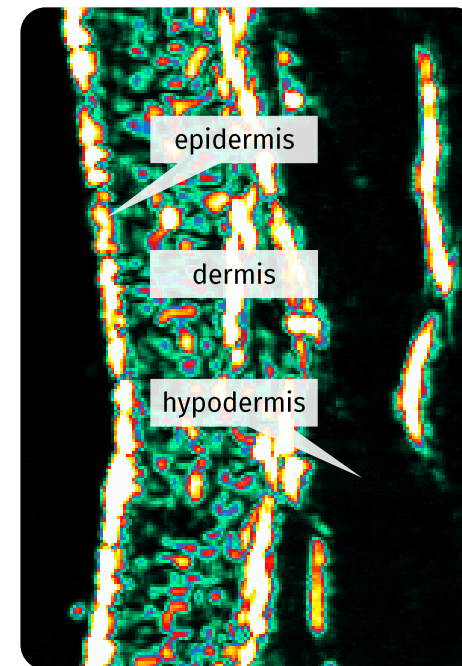
Outperformance of 1% BEL-EVEN® vs placebo



After 12 weeks with **BEL-EVEN®** facial **skin elasticity** significantly improves by **+15.7%** relatively to placebo

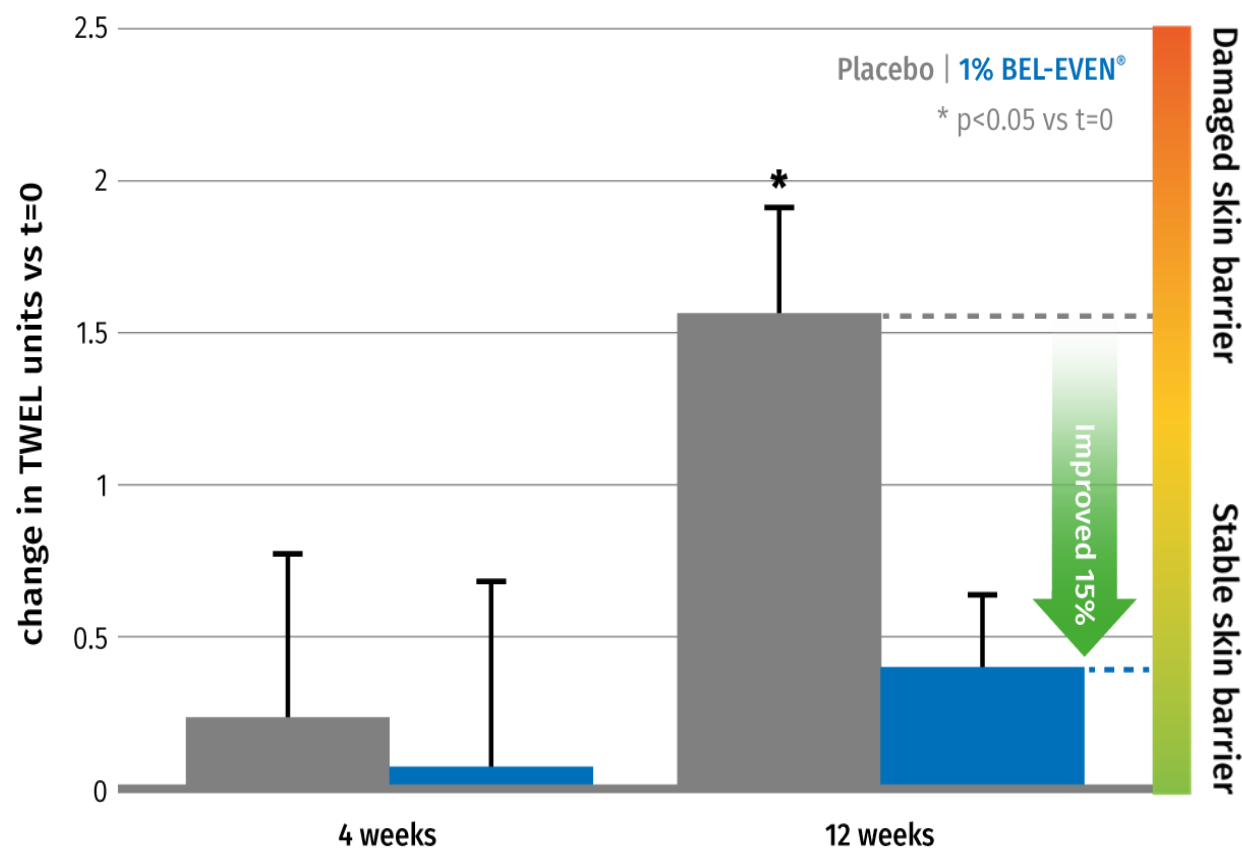


BEL-EVEN® helps increase **skin density** significantly after 4 & 12 weeks. A higher skin density is resulting from an increased protein (mostly collagen) content in the dermis



Example of
Dermascan image

BEL-EVEN® improves barrier function vs placebo as panelists move into the winter months



- In the placebo group, TEWL increase over time was driven by seasonal stress (study Oct-Dec in Switzerland): TEWL increase means skin barrier becomes weaker
- In the BEL-EVEN® group the TEWL stayed low vs Placebo and the skin barrier was stable
- With BEL-EVEN® skin was better protected against external stress factors, such as cold driving to dryness

Visual assessment on crow's feet wrinkles

Set-up:

- Standardized facial images
- Assessors could look at two pairs of images from two different individuals before and after treatment
- They did not know how the individuals were treated (placebo or **BEL-EVEN®**)
- They had to judge which individual showed better reduction of wrinkles over time

In total 2700 votes were given

(30x placebo treated compared to 30x BEL-EVEN® treated rated by 3 assessors)



Conclusion:

- **BEL-EVEN®** treated subjects were significantly better rated in terms of visual wrinkle development ($p < 0.001$)
- **BEL-EVEN®** revealed visual effects on the reduction of wrinkles

With BEL-EVEN® skin appears firmer and smoother

Wrinkles visible improvement

Click to watch the video: evolution T0-T3



Week 0



Week 4



Week 12

Amazing
result
of
BEL-EVEN®
application
on
Volunteer 24

Standardized controlled conditions



0 weeks



12 weeks

- The standard lighting allows to visualize in an optimal way the crow's feet wrinkles.
- A color registration is performed on the images to avoid the lighting variations between the acquisitions.

Volunteer 24

Alternative video



Volunteer 44

Powerful supported claims!



BEL-EVEN® rebalances the negative impact of daily stress on skin



BEL-EVEN® visibly relieves the premature signs of stress-induced skin ageing



BEL-EVEN® significantly improves skin elasticity and strengthens skin barrier functionality



With **BEL-EVEN®** skin is visibly firmer and smoother



BEL-EVEN® eases skin stress: it's like yoga for the skin!



“Skin:Yoga” concept

Inspiration for execution

Help your skin to unwind and rebalance,
regulating its stress levels for a youthful, healthy look.

BEL-EVEN® Stress-recovery pro-aging serum

supports skin cells’ natural repairing process,
helping reduce and prevent premature stress-induced signs of aging,
for a renewed skin vibrancy. **It’s like yoga for your skin!**

Skin is more resilient, firmer, youthful
& supple looking.

Ease your stress and bounce-back,
with **BEL-EVEN®**

Products are for experimental use only and are not for sale.
DSM is not responsible for final products claims



BEL-EVEN® Stress-recovery pro-aging serum

BEL-EVEN® visibly reduces signs of a stressful lifestyle, for fuller, more supple-looking skin with improved skin elasticity and greater barrier integrity



	Ingredient	INCI name	% w/w	Supplier
A	Water Dem.	Aqua	77.489	
	Zemea Propanediol	Propanediol	7.00	101015
	Adeka Nol GT-730	PEG-240/HDI Copolymer BIS-Decyltetraceth-20, Ether, Aqua, Butylene Glycol, Potassium Laurate, Tocopherol	4.00	101037
	Dekaben CP	Chlorphenesin	0.20	100665
B	Emulium Mellifera MB	Polyglyceryl-6 Distearate, Jojoba Esters, Polyglyceryl-3 Beeswax, Cetyl Alcohol	3.00	100413
	Xiameter PMX-200 50cs	Dimethicone	2.00	100404
	Myritol 318	Caprylic/Capric Triglyceride	2.00	100037
	Cetiol C5	Coco-Caprylate	2.00	100037
C	BEL-EVEN™	Propanediol, Biphenyl Azepanyl Methanone	1.00	100288
	Frag 49454695 Sail Away	Parfum	0.20	101007
	Euxyl PE 9010	Phenoxyethanol, Ethylhexylglycerin	1.00	100444
	FD&C Red n°40 - 1% Solution	CI 16035, Aqua	0.021	100080
D	Citric Acid 10% Solution	Citric Acid, Aqua	0.09	105032

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Procedure

- Heat Phase A to 75-80°C under stirring.
- Heat Phase B to 75-80°C under stirring.
- Add phase B to A and homogenize with high shear mix (2 min at 13500 rpm).
- Cool down to 40°C while stirring and add ingredients of phase C one by one.
- Adjust the pH with phase D.

This serum helps to rebalance skin from the visible effects on daily stress. Its “memory form” texture instantly engages the senses by quickly recovering when pressed, for a true “anti-stress” effect.

BEL-EVEN® Formulation Guidelines

Solubility:

- BEL-EVEN® is miscible in water
- BEL-EVEN® is well soluble in alcohol, glycols and glycerin

Use level

- For skin care preparations, the addition of a concentration up to 1 % BEL-EVEN® is recommended

Incorporation

- BEL-EVEN® is easy to use
- BEL-EVEN® can be incorporated into the aqueous phase of a cosmetic formulation
- BEL-EVEN® can be processed either cold or warm ($\leq 85^{\circ}\text{C}$). The incorporation at the end of the production at $T < 40^{\circ}\text{C}$ is still recommended to avoid unnecessary heating of the active

Compatibilities

- In general, BEL-EVEN® shows very good compatibility with all groups of raw materials like emulsifier systems, emollients and waxes, preservatives, hydrocolloids, sunscreens, detergents and other commonly used substances
- Recommended pH of the final formulation: 3.5 – 7.5, it can be adjusted with commonly used neutralizing agents
- Compatible with up to 50% ethanol (max. concentration tested)



Let DSM ease your stress!



DISCLAIMER

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UV Sensitivity Test

- Inflammation is an important immunological response to protect the body against harmful stimuli. It signals the body about tissue damage and starts the tissue repair process. However, prolonged inflammation has harmful effects to the tissue and it is important to carefully regulate this process.
- Cortisol plays an important role in the regulation of inflammation in the body. It fights against inflammation reducing the amount of proinflammatory cytokines and helps stop the inflammatory process once it has served its purpose.
- As 11 β -HSD1 inhibitors reduce cortisol levels at the local level, it was important to rule out that they interfere with the inflammation process.
- A UV-B challenge study was performed to see if the BEL-EVEN® treatment induces a different response than placebo or no treatment.
- UV-B challenge test is commonly used to measure SPF response. In this type of studies subjects are typically exposed to varying amounts of UV radiation and the redness of the skin is measured with the aim of determining the minimum dose that causes Erythema (a typical sign of inflammation).
- A study was performed where volunteers were exposed to different doses of UV irradiation and the redness of the skin was assessed.
- The test showed that there were no difference in the response toward UV irradiation between BEL-EVEN®, placebo and no treatment.
- No influence on UV-sensitivity could be detected after 7 days of treatment with BEL-EVEN®

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