

SKINCEUTICALS

A.G.E. Advanced Eye



KEY TECHNOLOGY

A.G.E. Advanced Eye features a potent combination of anti-glycation, matrix integrity, and inclusive optical effect blend ingredients.

- 4.25% Wild Fruit Flavonoids (Blueberry 4%, Pomegranate 0.25%)
- 7.15% Proxylane
- 3.0% Matrixyl
- 0.5% Caffeine
- 0.2% Glycyrrhetic Acid
- 0.8% Inclusive Optical Effect Blend
 - 0.5% Pearlescent Pigments & 0.3% Boron Nitride

STUDY SUMMARY

SAFETY CLINICAL STUDIES		Approved Safety Claims
Use test under ophthalmological control	Passed	
HRIPT	Passed	
China tolerance use test	Passed	
MECHANISM OF ACTION STUDIES		
Flavonoid <i>ex vivo</i>	7 days	Inhibited UVA-induced AGEs in skin explants
Flavonoid <i>in tubo</i>	4 weeks	Inhibited AGEs fluorescence of collagen at 1 and 4 weeks.
Flavonoid <i>in tubo</i>	4 weeks	Inhibited AGEs fluorescence of bovine serum albumin and ribose at 1 and 4 weeks
CLINICAL STUDIES		
Flavonoid cream clinical (US)	8 weeks	Improved over 10 periocular skin attributes.
Flavonoid cream clinical (China)	8 weeks	Improved over 10 markers periocular skin attributes and achieved high satisfaction ratings.
Skin hydration/TEWL study	24 hours	Improved skin hydration at 15 minutes, 2 hours, 8 hours, and 24 hours.

MECHANISM OF ACTION STUDIES

BACKGROUND

Glycation is a complex, multi-phase process in which sugars bind to proteins, forming advanced glycation end-products (AGEs). This process significantly impacts long-lived proteins like collagen, an important component of the skin's structural integrity. As AGEs accumulate, collagen fibers become brittle, compromising their reparative ability and leading to a decline in overall tissue integrity. This accumulation, largely dependent on protein turnover rates, is exacerbated by chronological aging, making collagen particularly susceptible to glycation-induced damage.¹

The detrimental effects of AGE formation extend beyond structural alterations. Increased AGE levels are linked to functional changes in enzymatic activity, heightened vulnerability to oxidative stress, and chronic inflammation.¹ Furthermore, AGE formation triggers an autocatalytic cycle, accelerating the production of additional AGEs and further contributing to the deterioration of the extracellular matrix (ECM) and dermal-epidermal function.² These effects are most noticeable in periorcular skin, manifesting visibly as wrinkles (crow's feet), crepiness, and under-eye laxity.¹

With growing interest in utilizing botanical extracts to combat glycation-induced skin aging, the objectives of the Mechanism of Action studies were to (1) determine the inhibitory effects of blueberry and pomegranate extracts on ribose-induced glycation in a bovine serum albumin (BSA) solution, (2) evaluate the combined and individual efficacies of blueberry and pomegranate extracts on collagen glycation in an in vitro model, and (3) explore the topical benefits of these fruit extracts on AGE formation in a UV-induced ex vivo human skin model, respectively.

STUDY 1. IN TUBO BSA GLYCATION INHIBITION BY FRUIT EXTRACTS

OBJECTIVES

To evaluate AGEs inhibition efficacy of blueberry and pomegranate fruit extracts alone and in combination on (BSA+Ribose)-induced glycation, using an in tubo model.

STUDY DESIGN

A BSA solution (5mg/mL), with or without 100mM ribose, was incubated at 37°C for 1 and 4 weeks. Blueberry (4%), pomegranate (0.25%), or a combination of both extracts were added to the ribose-treated samples in triplicate. A.G.E. formation was assessed by fluorescence intensity (λ_{ex} 370nm / λ_{em} 440nm) after each incubation period.

RESULTS

After 1 and 4 weeks of incubation with ribose, 4% blueberry extract significantly inhibited A.G.E. formation in BSA by 77% ($p < 0.05$) and 70% ($p < 0.05$), respectively. The combination of 4% blueberry and 0.25% pomegranate extracts yielded even greater inhibition at both time points: 82% ($p < 0.05$) at week 1 and 72% ($p < 0.05$) at week 4. However, 0.25% pomegranate extract alone did not demonstrate significant inhibition (-33%, $p > 0.05$ at week 1; -8%, $p > 0.05$ at week 4).

¹ Zheng W, et al. *Nutrients*. Nov 1 2022;14(21):4588.

² Roig-Rosello E, et al. *Aging Cell*. Apr 2024;23(4):e14096.

Figures. BSA Glycation Via Fluorescence at 1 and 4 Weeks

Figure 1. BSA Glycation at 1 Week

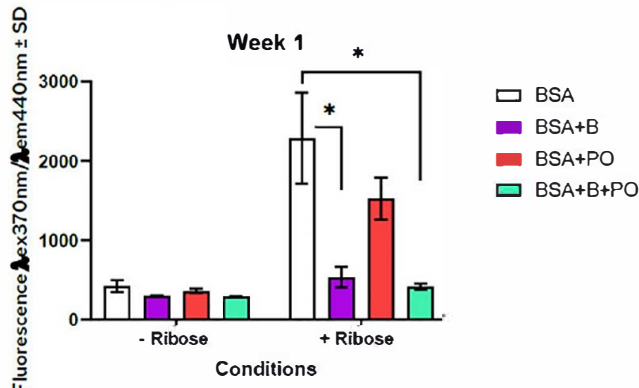
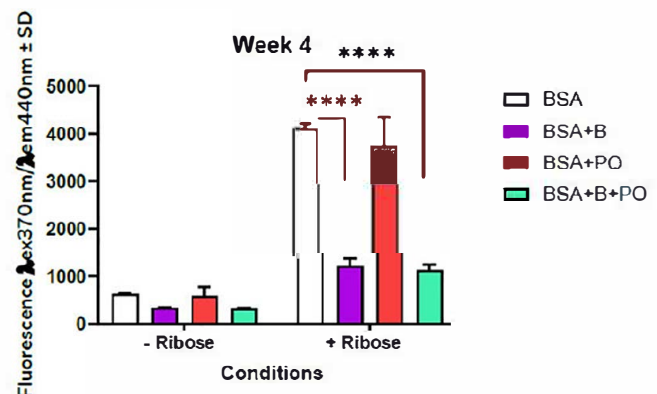


Figure 2. BSA Glycation at 4 Weeks



* $p < 0.05$; **** $p < 0.0001$; B = Blueberry extract; BSA = Bovine serum albumin; PO = Pomegranate

CONCLUSION

Taken altogether, 4% blueberry extract and the combination of 4% blueberry and 0.25% pomegranate fruit extracts significantly inhibited BSA glycation in tubo.

STUDY 2. IN TUBO COLLAGEN GLYCATION INHIBITION BY BLUEBERRY AND POMEGRANATE FRUIT EXTRACTS

OBJECTIVES

To evaluate AGEs inhibition efficacy of blueberry and pomegranate fruit extracts alone and in combination on (Collagen+Ribose)-induced glycation, using an in tubo model.

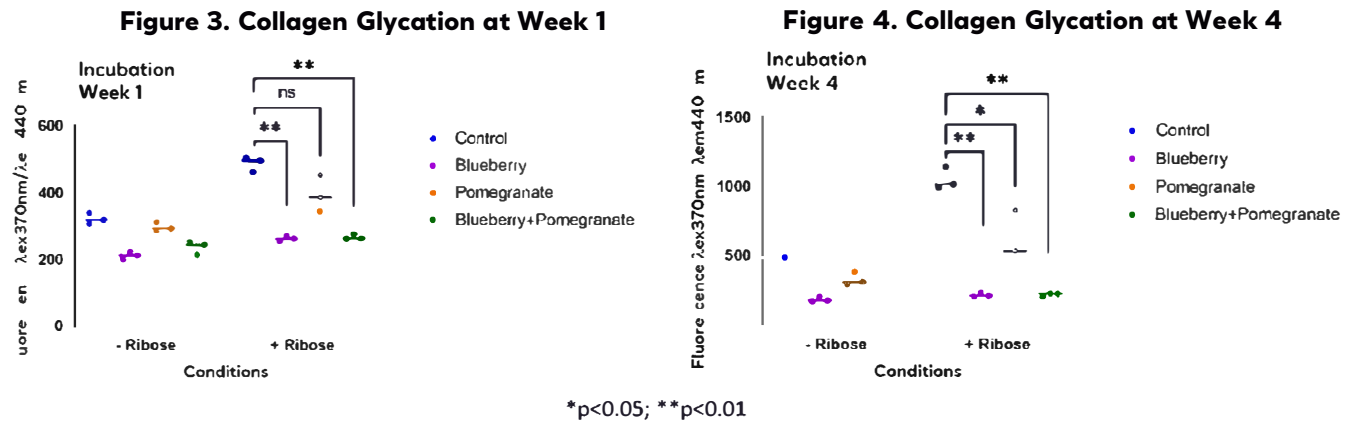
STUDY DESIGN

Collagen, with or without 100mM D-ribose, was incubated at 37°C for 1 and 4 weeks. Blueberry (4%), pomegranate (0.25%), or a combination of both extracts were added to the ribose-treated collagen samples in triplicate. AGE formation was then assessed by fluorescence intensity (ex 370nm / em 440nm) after each incubation period.

RESULTS

In the presence of ribose, both 4% blueberry extract and the combination of blueberry and pomegranate extracts significantly reduced AGE fluorescence in collagen at both Week 1 and Week 4. Blueberry alone demonstrated reductions of 46% ($p < 0.05$) at Week 1 and 80% ($p < 0.05$) at Week 4, while the combination yielded similar results (45%, $p < 0.05$ at Week 1; 80%, $p < 0.05$ at Week 4). Pomegranate (0.25%) alone only achieved significant inhibition at week 4 (44%, $p < 0.05$).

Figures. Collagen Glycation Measures at Weeks 1 and 4



CONCLUSION

Taken altogether, 4% blueberry extract, 0.25% pomegranate fruit extract, and the combination of both fruit extracts significantly inhibited collagen glycation in tubo.

STUDY 3. EX VIVO UV-INDUCED GLYCATION INHIBITION IN SKIN BY BLUEBERRY AND POMEGRANATE FRUIT EXTRACTS

OBJECTIVES

To evaluate AGEs inhibition efficacy of blueberry and pomegranate fruit extracts through a 7-day UV-induced glycation model in ex vivo human skin.

STUDY DESIGN

Human skin from abdominal plastic surgery was used with 12 replicates for each treatment. Every day for 6 days, the explants were irradiated with 8x the biological effective dose (BED) of UVA and treated topically with the appropriate test samples or control. Skin samples were then harvested for immunostaining analysis for AGEs at Day 7.

RESULTS

When applied topically to ex vivo skin, the combination of 4% blueberry and 2% pomegranate fruit extracts significantly reduced UVA-induced AGEs by 38% (p<0.05), compared to the untreated UVA control at Day 7. Moreover, topical application of 2% pomegranate fruit extract alone significantly reduced UVA-induced AGEs by 41% (p<0.05), while 4% blueberry extract alone did not exhibit any significant activity, compared to the untreated UVA control at Day 7.

Figure 5. UVA-induced AGEs inhibition efficacy by topical fruit extracts on ex vivo skin

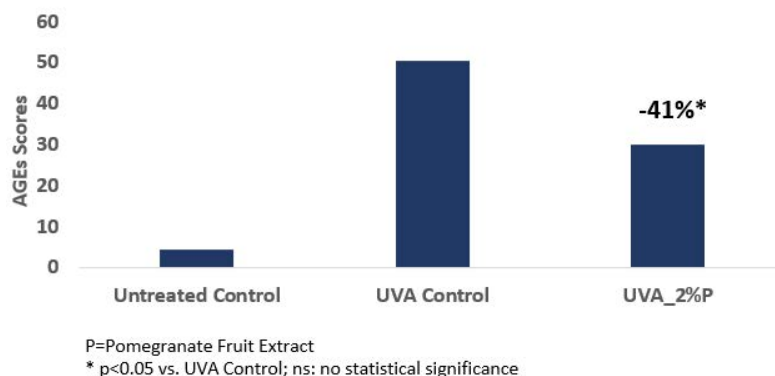
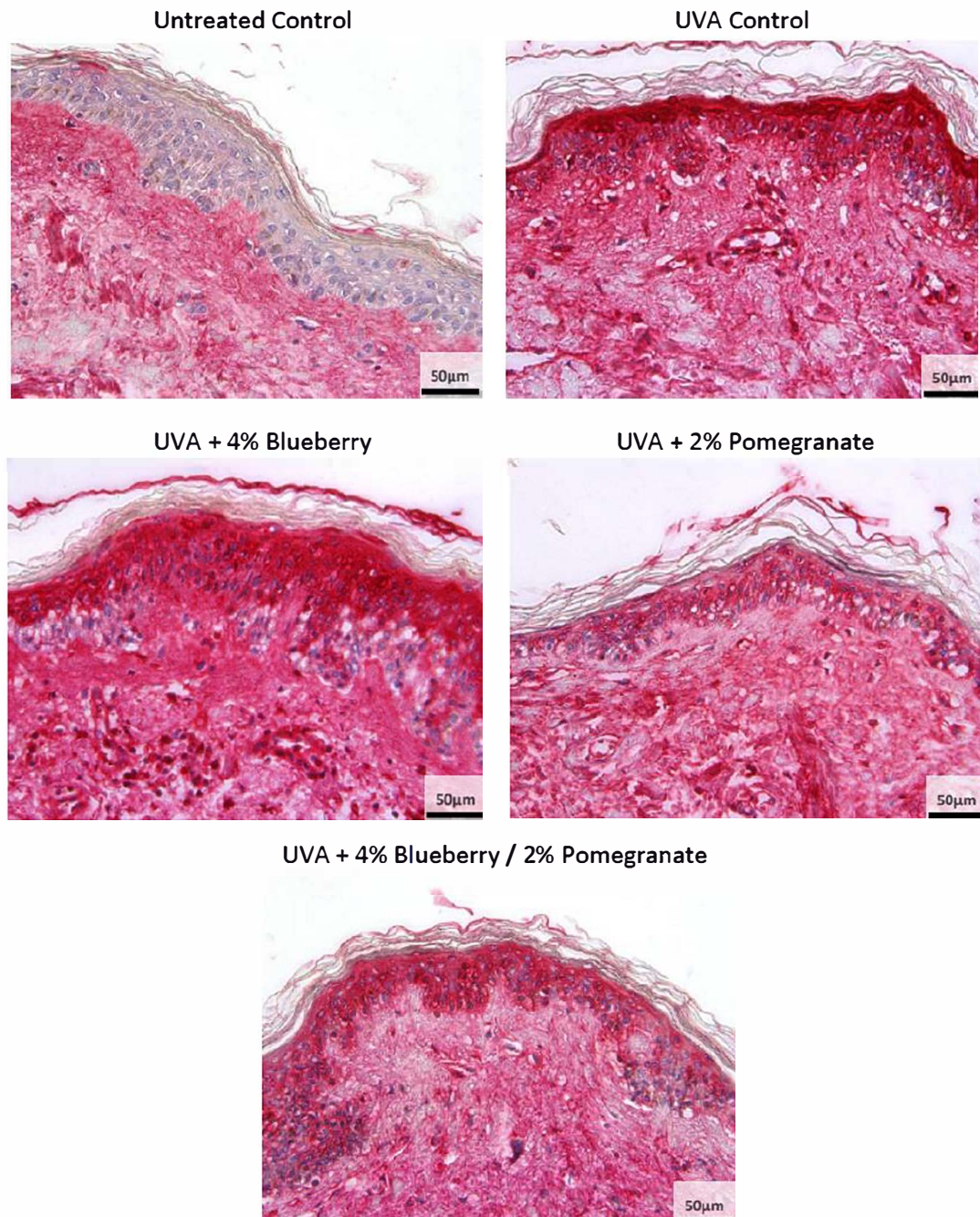


Figure 6. Representative images of skin samples immunostained for AGEs evaluation



CONCLUSION

For the first time, a combination of 4% blueberry and 2% pomegranate fruit extracts has been shown to inhibit UVA-induced glycation and exert anti-AGEs activity in ex vivo human skin, when applied topically.

CLINICAL STUDIES

STUDY 1. USA CLINICAL STUDY (23-02859, FINAL REPORT)

OBJECTIVES

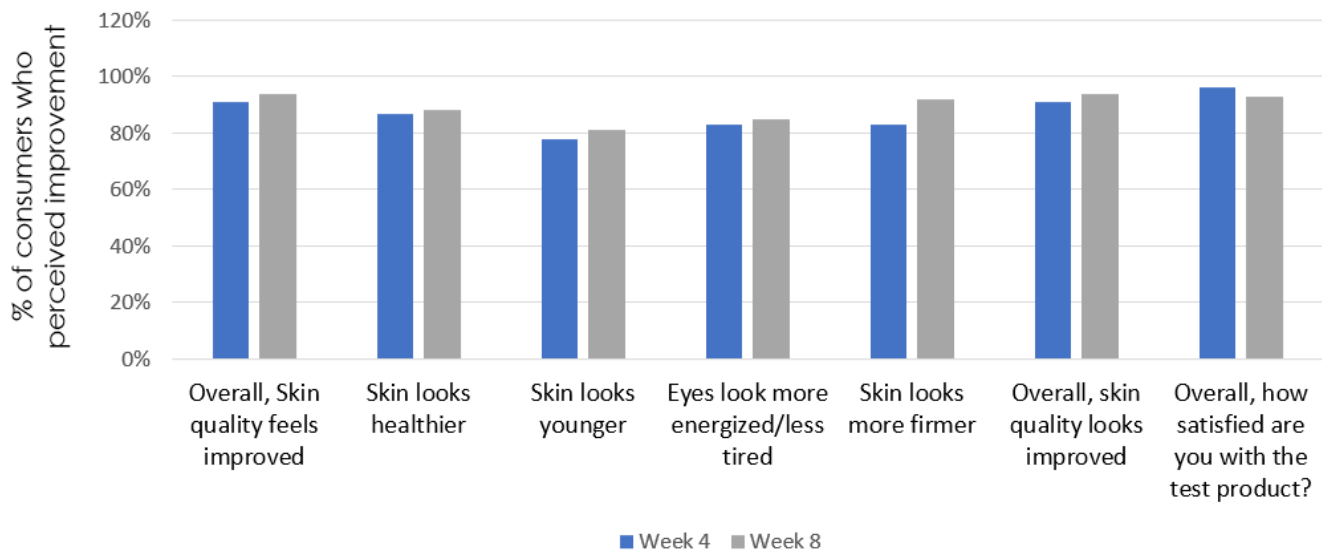
To assess the efficacy and skin tolerance of SkinCeuticals A.G.E. Advanced Eye after 8 weeks of product use.

STUDY DESIGN

- Total number of subjects: n=89
- Inclusion criteria: Females aged 35-65; willing to adhere to study conditions
- Twice daily application: Wash face per usual routine and pat dry. Apply A.G.E. Advanced Eye under the eyes, following the orbital bone and around the brow area in the morning and evening
- Duration of study: 8 weeks (56 days)
- Clinical evaluation: Clinical grading of efficacy parameters, VISIA-CR imaging, Antera 3D imaging, ultrasound measurements, self-assessment questionnaire, tolerability evaluation
- Time points: Baseline, 15 Minutes Post-application, Week 4, Week 8

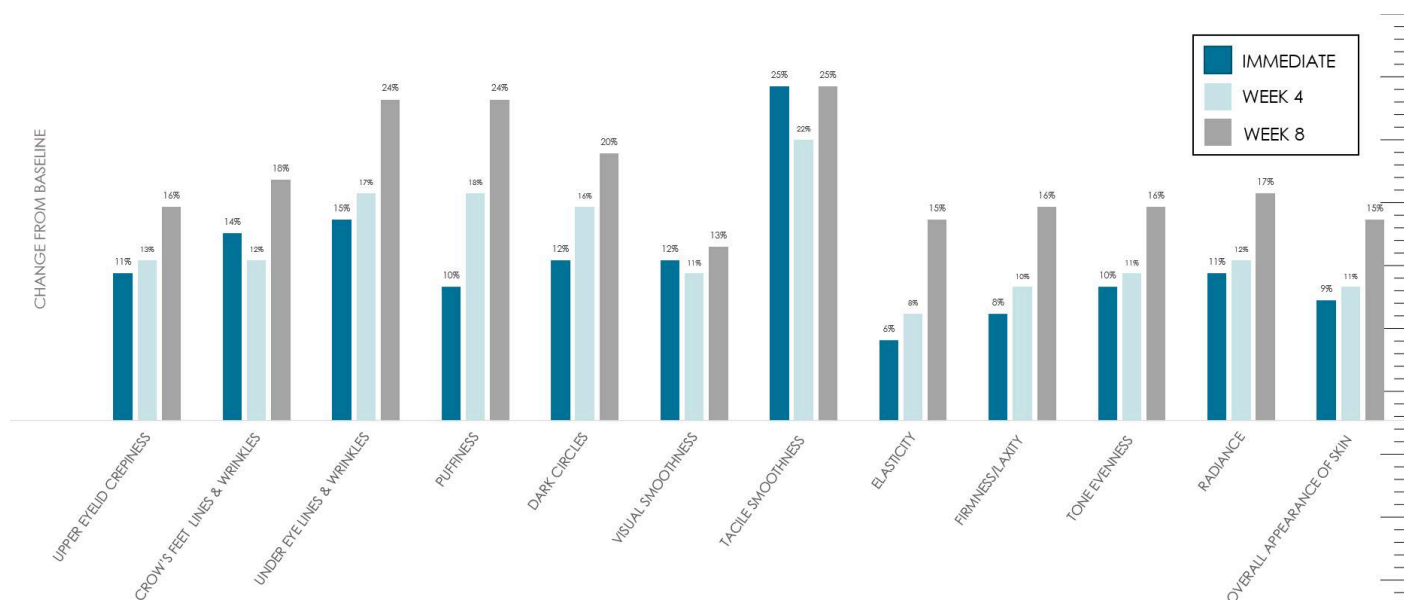
RESULTS

Figure 8. A.G.E. Consumer Self-Report Results



Majority of consumers favored the aesthetic aspects of A.G.E. Advanced Eye and perceived skin improvement in areas around the eyes after product usage, with growing satisfaction over time.

Figure 9. Changes to Skin Attributes at 4 and 8 Weeks



CONCLUSION

A.G.E. Advanced Eye demonstrated a statistically significant improvement in more than 10 markers of skin quality through 8 weeks post-application.

STUDY 2. CHINA CLINICAL STUDY (23-11798, TOPLINE)

OBJECTIVES

To determine the efficacy of SkinCeuticals A.G.E. Advanced Eye on anti-aging after 8-week application and evaluate safety for skin tolerance after product use.

STUDY DESIGN

Total number of subjects: n=65

Study Duration: 8 weeks (Evaluations at Baseline, Immediately Post, 4 Weeks, 8 Weeks)

Application: Apply to areas under the eyes following the orbital bone and around the brow 2X daily in the morning and night before moisturizer. Follow with provided SPF in the morning.

Inclusion criteria:

- Asian females aged 37-60
- All skin types (at least 10% each) – normal, oily, dry, & combination
- Self-perceived sensitive skin: n=33 (50.8%)
 - Self-perceived sensitive eyes: n=27 (41.5%)
 - Contact lens wearer: n=12 (18.5%)
- Basic eye cream users and willing to use A.G.E. Advanced Eye in replacement
- Basic eye makeup users
- Current basic moisturizer users with 30 days of safe usage, continued use on the face required
- No usage of any anti-aging eye products for the past 30 days prior to the study
- Willing to maintain baseline visit 1 condition of eyebrows and eyelashes during the study
- No facial treatments in the past 6 months and willing to withhold for duration of study
- Self-perceived: Rough, crepey skin, lack of firmness, red-looking skin on the eye area, and upper eyelid drooping.

RESULTS

Figure 10. Ultrasound Measurements of Skin Density and Thickness

Assessment	Time point	Fla. 794030 57				
		n	Mean (±SD)	Mean change from baseline (±SD)	Mean % change from baseline ^a	p-value ^b
Thickness of Dermis	Baseline	65	1062.92 (±155.74)			
	Week 8	65	1209.82 (±193.41)	146.91 (±163.56)	13.82%	<0.0001
Density of Dermis	Baseline	65	5.47 (±1.47)			
	Week 8	65	8.18 (±2.01)	2.71 (±2.15)	49.51%	<0.0001
Thickness of Epidermis	Baseline	65	90.58 (±8.47)			
	Week 8	65	49.63 (±39.68)	-40.95 (±40.77)	-45.21%	<0.0001
Density of Epidermis	Baseline	65	36.45 (±8.47)			
	Week 8	65	26.43 (±7.71)	-10.02 (±9.91)	-27.48%	<0.0001
Thickness of Total	Baseline	65	1153.50 (±156.72)			
	Week 8	65	1259.45 (±186.75)	105.95 (±158.60)	9.19%	<0.0001
Density of Total	Baseline	65	8.05 (±2.12)			
	Week 8	65	8.89 (±2.20)	0.85 (±2.72)	10.52%	0.0147

^a Blue indicates statistically significant improvement. Positive mean percent change values indicate an improvement.

^b Bold red indicates statistical significance p-value ≤ 0.05.

Figure 11. 3D Primos Measurements of Periorbital Skin

Assessment	Time point	Fla. 794030 57				
		n	Mean (±SD)	Mean change from baseline (±SD)	Mean % change from baseline ^a	p-value ^b
Crow's feet wrinkles						
Average depth	Baseline	65	52.56 (±11.06)			
	Week 8	65	55.51 (±13.28)	2.95 (±7.91)	5.61%	0.0038
Count	Baseline	65	370.33 (±87.81)			
	Week 8	65	246.89 (±59.32)	-123.44 (±38.18)	-33.33%	<0.0001
Volume	Baseline	65	6.05 (±1.23)			
	Week 8	65	5.79 (±1.49)	-0.26 (±0.86)	-4.36%	0.0165
Under eye wrinkles						
Average depth	Baseline	65	52.62 (±12.77)			
	Week 8	65	53.76 (±15.23)	1.14 (±8.04)	2.17%	0.3620
Count	Baseline	65	260.16 (±56.07)			
	Week 8	65	167.65 (±37.44)	-92.51 (±28.67)	-35.56%	<0.0001
Volume	Baseline	65	4.68 (±1.27)			
	Week 8	65	4.40 (±1.41)	-0.28 (±0.66)	-6.09%	<0.0001

^a Blue indicates statistically significant improvement.

^b Bold red indicates statistical significance p-value ≤ 0.05.

CONCLUSION

A.G.E. Advanced Eye demonstrated significant improvements in periorbital skin density and thickness alongside reductions in periorbital wrinkle count. The product demonstrated strong clinical efficacy and patient-reported outcomes.

STUDY 3. SKIN HYDRATION AND SKIN BARRIER STUDIES: FLA 794030 54 (22-17526, TOPLINE) & FLA 794030 57 (23-17140, TOPLINE)**OBJECTIVES**

To assess the efficacy and tolerance of SkinCeuticals A.G.E. Advanced Eye on skin hydration and skin barrier function.

STUDY DESIGN

Total number of subjects: n = 25 (22-17526); n = 30 (23-17140)

Comparison of A.G.E. Advanced Eye-treated skin versus untreated skin across various timepoints

Measurement timeline:

- Skin hydration (corneometer) – Baseline, 15 minute, 2 hour, 8 hour, 24 hour
- Skin barrier function maintenance (TEWL) – Baseline, 1 hour

RESULTS

Figure 12. Summary of hydration and TEWL maintenance results.

Claim	Assessment	15 minute	1 hour	2 hour	8 hour	24 hour
Improvement in skin hydration	Instrumental	X		X	X	X
Improvement in skin barrier function	Instrumental		X			

X indicates statistically significant improvement when compared to untreated site ($p \leq 0.05$)

When evaluating hydration over time for sites treated with A.G.E. Advanced Eye, there was a statistically significant improvement in skin hydration measurement at all time points – 15 minutes, 2 hours, 8 hours, and 24 hours post-application – when compared to baseline measurement. Similarly, compared to untreated sites, the treated sites demonstrated greater improvement in skin hydration at all time points. When evaluating barrier function over time for sites treated with A.G.E. Advanced Eye, there was a statistically significant improvement in skin barrier function measurement at 1 hour post-application when compared to baseline measurement, with greater improvement in skin barrier function (TEWL) at the 1 hour time point compared to untreated skin.

CONCLUSION

A.G.E. Advanced Eye improves skin hydration for up to 24 hours and skin barrier function for up to one hour when compared to untreated skin.