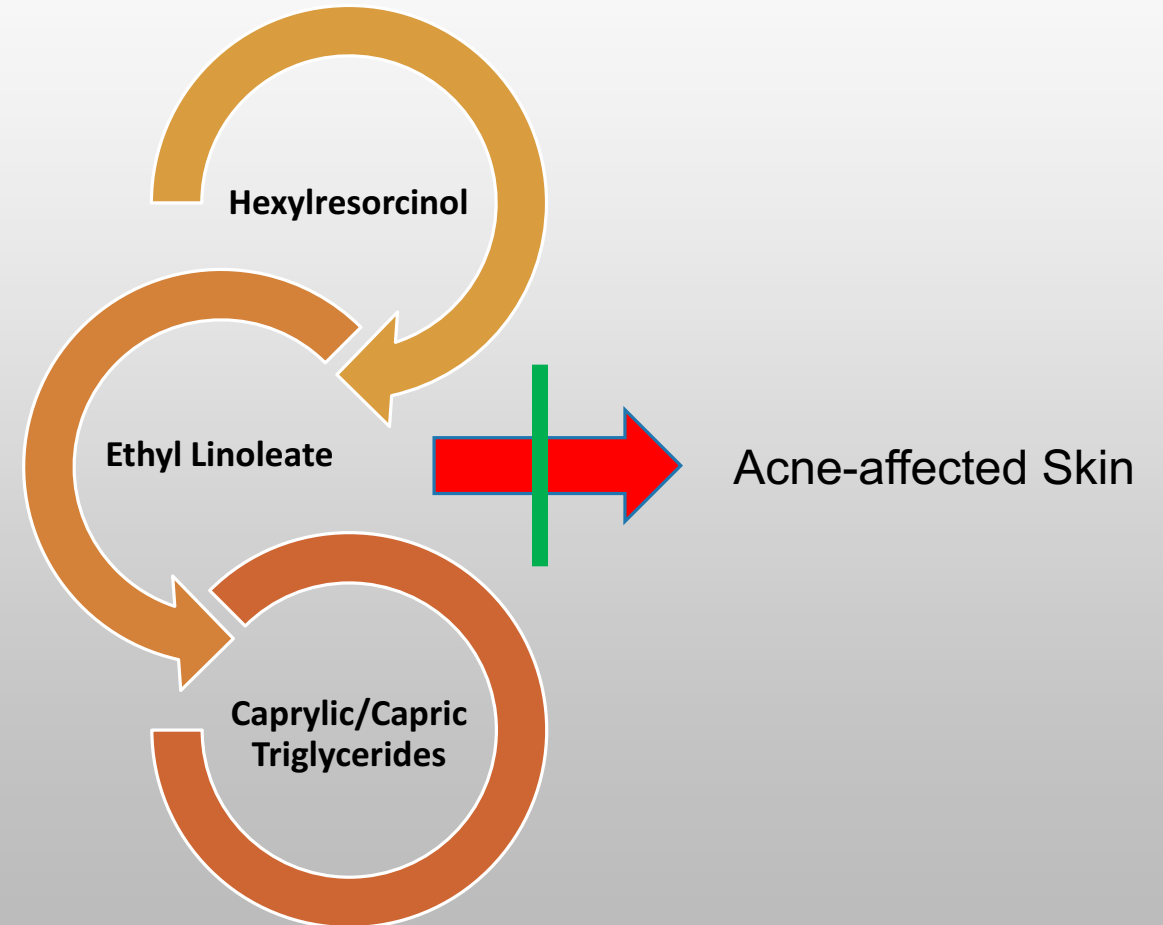


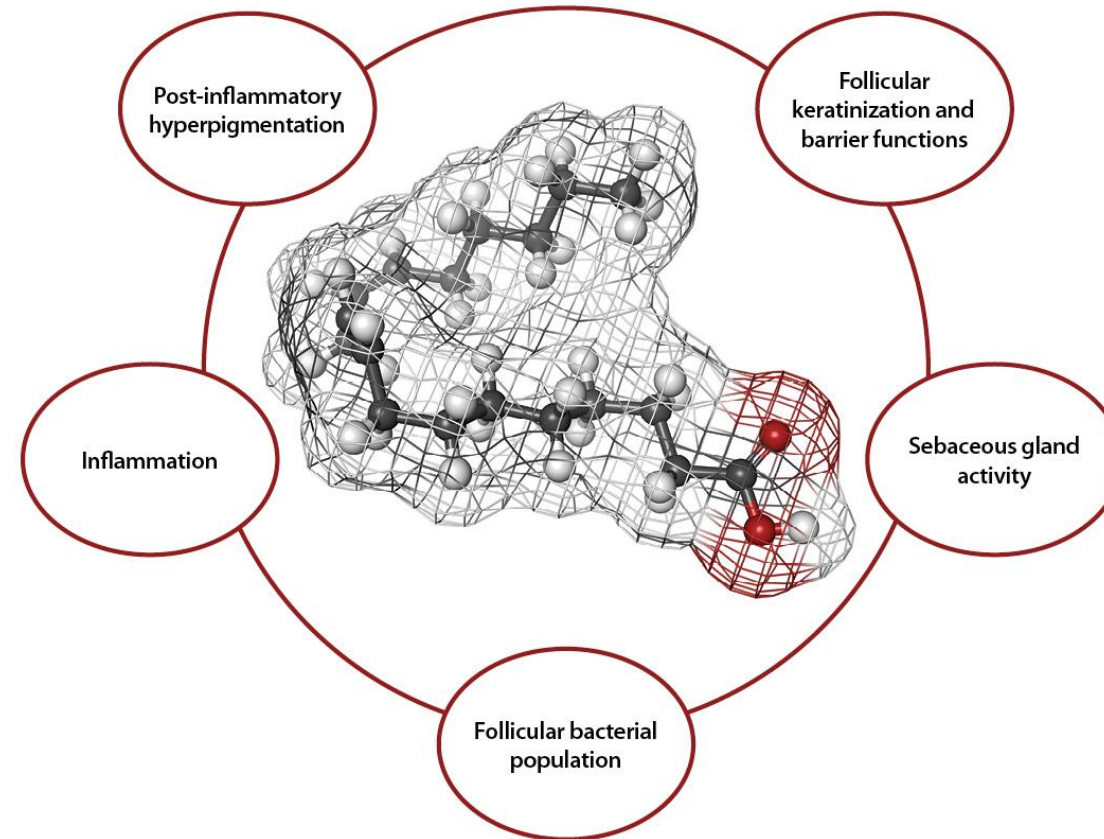
Synactin® AC:
Providing 5-in-1 Solutions for Mitigating Acne-affected Skin

Product Information

Trade Name	Synactin® AC
INCI name	Caprylic/Capric triglycerides and Ethyl Linoleate and Hexylresorcinol
CAS number	6531-09-1; 544-35-4; 136-77-6
ELINCS	265-724-3; 208-868-4; 205-257-4
Appearance	Yellow to yellowish brown liquid
Miscibility	A wide-range of hydrophobic emollient esters & solubilizers
Suggested use level	2 to 4%
Storage	Store in original container at 10 to 30 °C; Avoid exposure to light & heat
Skin tolerance	HRIPT at 10% in corn oil – Non-primary irritant & Non-primary sensitizer
Regulatory	Globally approved



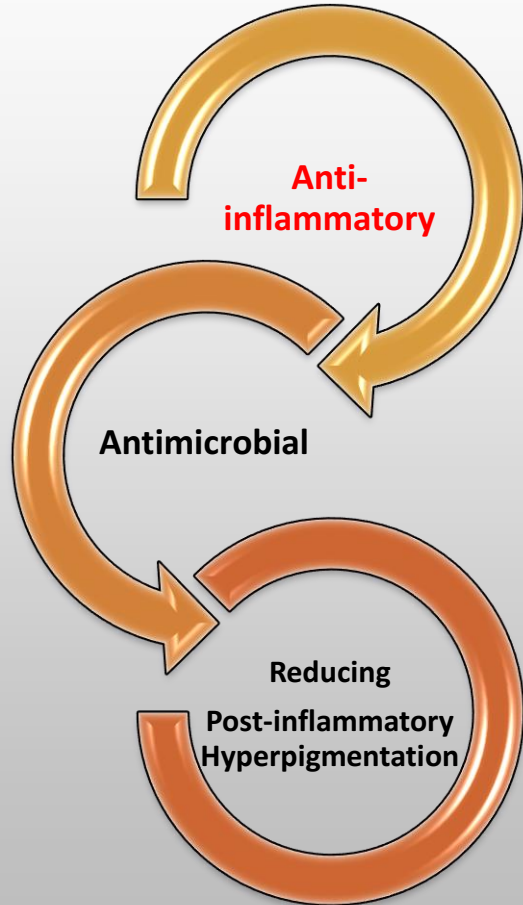
Key Strategic Targets for Mitigating Acne-affected Skin



Why Select Hexylresorcinol (Synovea® HR)?

□ Anti-inflammatory

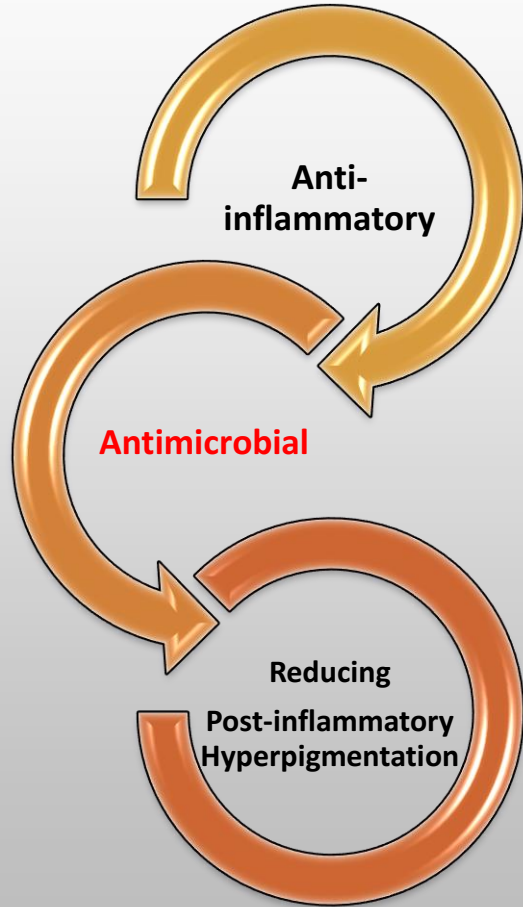
- *P. acne* causes inflammatory acne that is characterized by massive neutrophilic infiltration
- IL-8 plays an important role in the pathophysiology of acne
- NF-κB activation is involved in the IL-8 production in monocyclic cells stimulated by *P. acne* (Chen et al., J Dermatol Sci, 29(2);97-103, 2002)
- Inhibits transcription regulatory activity of NFκB (Yang et al., Food Chemistry 160, 338-345 (2014)); Far superior than the known inhibitors curcumin and resveratrol .
 - Used NFκB reporter kit; Designed for monitoring the activity of the NFκB signaling pathway in the cultured cells (Murine myoblast C2C12 cells; Transfected with an NFκB luciferase reporter gene)



Inhibition of Transcription Regulatory Activity of NFκB				
Product / μg/ml	25	12.5	6.25	3.125
Synactin® AC	100	0	0	0
Synovea® HR	X	X	94	11
Resveratrol	85	34	8	0
Curcumin	58	34	18	3

X = Cytotoxic; 0 = No activity

Why Select Hexylresorcinol (Synovea® HR)?



Antimicrobial

- *P. acne* constitutes a major part of the skin microbiome and contributes to human health
- It has also been implicated as a pathogenic factor in acne
- Broad antimicrobial activity is desired for acne treatments
 - Acne-affected skin has much higher levels of Staphylococcus & Candida (Noshijima et al., J Dermatol, 5:318-323, 2000)
 - Hexylresorcinol has broad-spectrum anti-microbial activity (Chaudhuri, Cosmeceuticals and Actives, 3rd Edition, Chapter 7, 73-83, 2015)

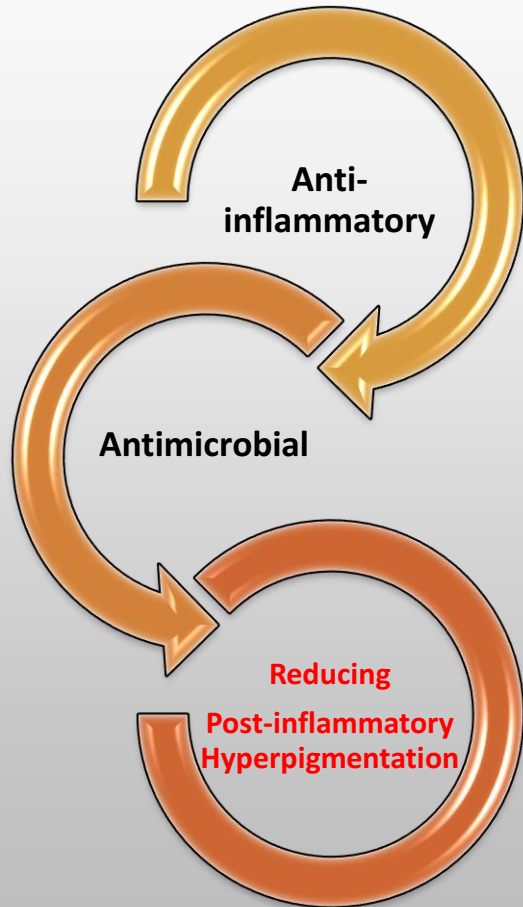
Microorganisms	MIC in µg/ml
<i>P. acne</i>	37.5
<i>S. aureus</i>	2.2
<i>S. epidermidis</i>	2.2
<i>Candida albicans</i>	1.7
<i>Streptococcus</i>	0.7
<i>Aspergillus</i>	0.1

Synactin® AC is an Effective Anti-acne Blend	
Product	<i>P. acne</i> in MIC in µg/ml
Synactin® AC	37.5
Synovea HR	37.5
Ethyl Linoleate	> 100

Why Select Hexylresorcinol (Synovea® HR)?

❑ Reducing Post-inflammatory Hyperpigmentation (PIH)

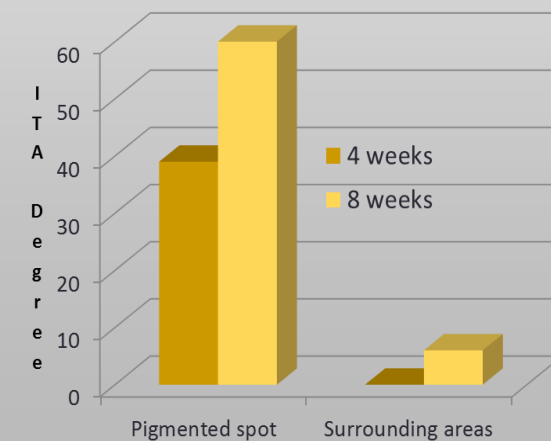
- PIH results from the over production of melanin
 - Rise in melanocyte activity is due to inflammatory mediators and ROS (Davis et al., J Clin Aesthet Dermatol, 3(7):20-31, 2010)
 - HR is an excellent NFκB inhibitor
 - HR stimulates endogenous antioxidant defense – glutathione, glutathione peroxidase & reductase (Chaudhuri, Cosmeceuticals & Active Cosmetics, 3rd Edition, Chapter 7, 73-83, 2015)
- HR is effective in reducing hyper-pigmented spots without affecting surrounding areas



PROTOCOL

- ❑ Human volunteers –18; Caucasian (10), Asian(7) and Hispanics (1)
- ❑ Study duration - 8 weeks
- ❑ Test sites – Hand
- ❑ Test substances – 1% Synovea® HR lotion
- ❑ Application frequency – Twice a day entire hand
- ❑ Methods used for performance evaluation –
 - Comparative ITA⁰ before & after treatment;
 - Expert & Panelists grading (scale 0 to 4) – (i) Skin tone, (ii) Reduction in hyperpigmentation spots & (iii) Roughness & dryness
 - Photography

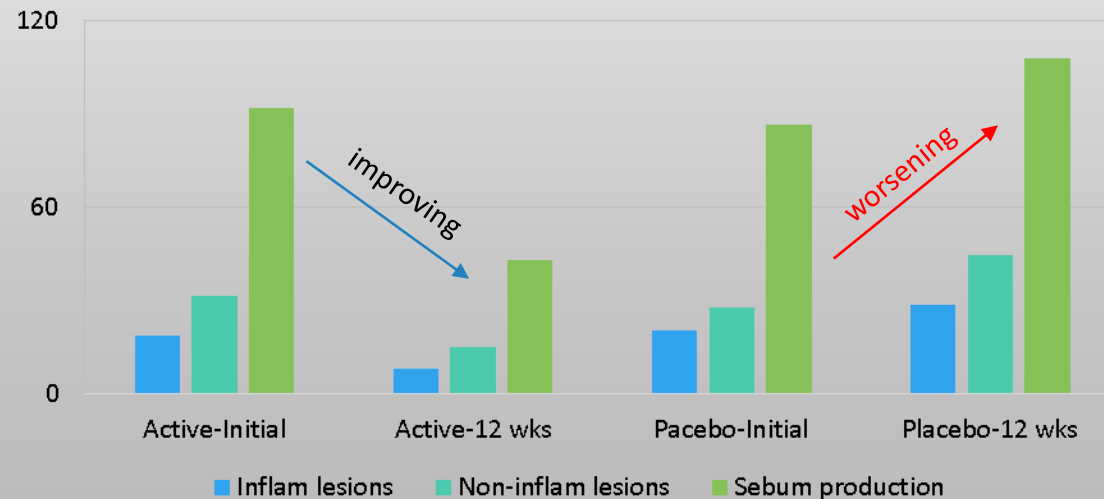
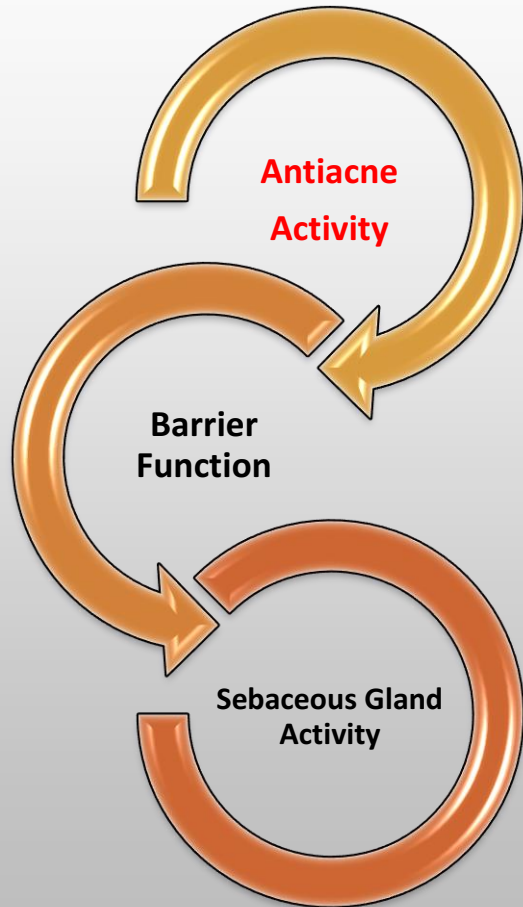
% Improvement in ITA⁰ after treatment



Why Select Ethyl Linoleate (Synovea® EL)?

□ Anti-acne Activity

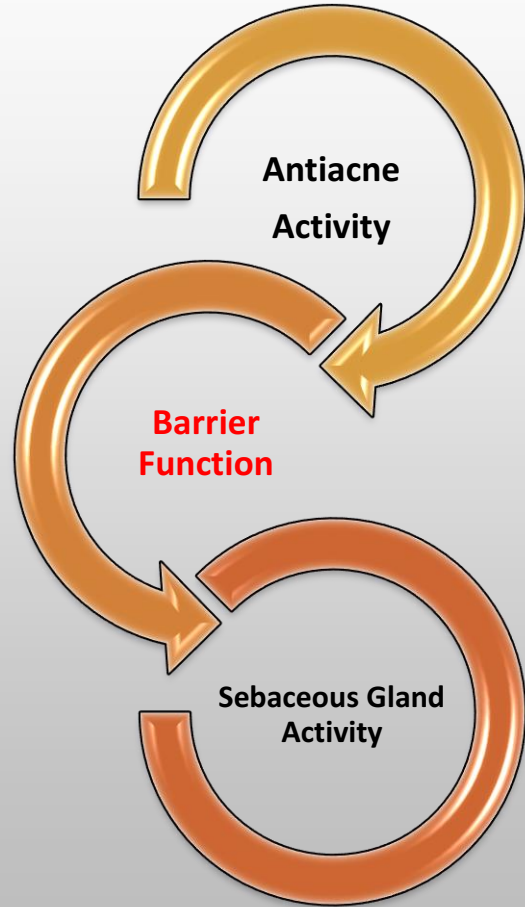
- Linoleic acid (LA) is an essential fatty acid needed for skin nourishment; EL is a stable version of LA
- Low level of LA is found in acne subjects (Ottaviani et al., Mediators of Inflammation, Article ID 858176, 2010)
- EL has been clinically proven to have anti-acne property (Charakida et al., Brit J Dermatol, 157(3):569-574, 2007)
 - Parameters – Inflammatory & Non-inflammatory lesions & sebum production; Photography
 - 12 weeks treatment: Significant improvement in reducing acne severity (from 4 to 2) whereas placebo worsens (from 4 to 5)



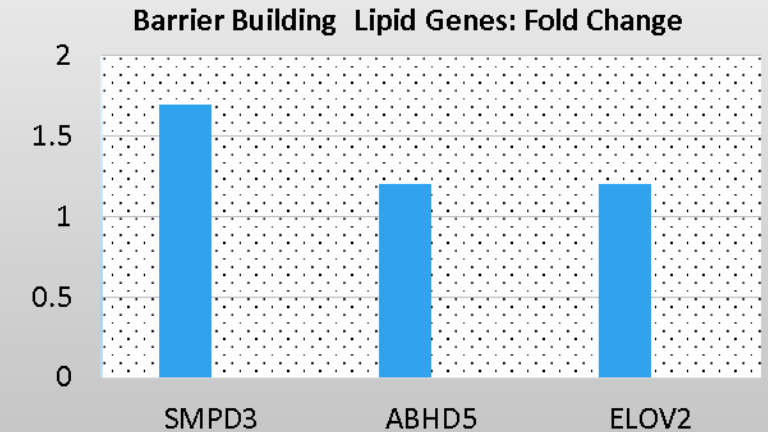
Why Select Ethyl Linoleate (Synovea® EL)?

Barrier Function Improvement

- A major pathogenic factor of acne is the disturbed keratinization due to decrease in LA in the sebum
- Alteration of skin surface lipids & linoleate deficiency results in dysfunctional lipid metabolism



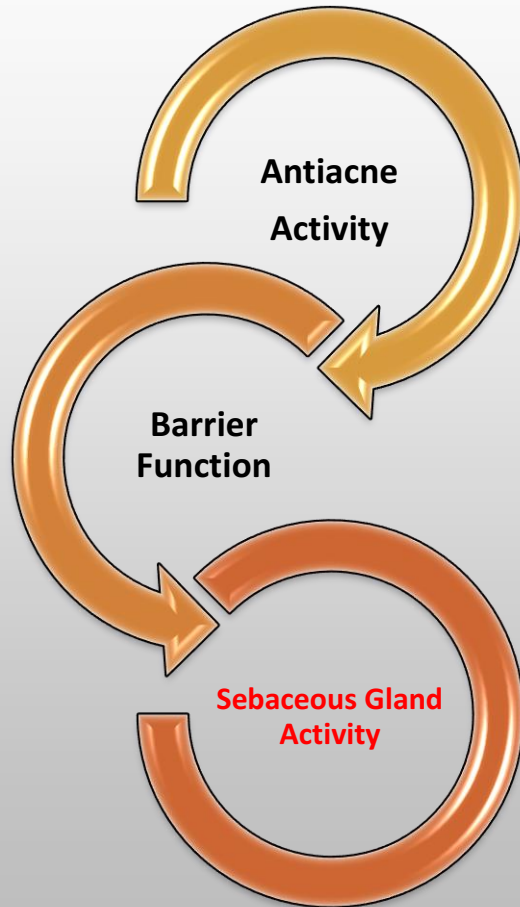
Gene	Full Name	Key Biological Functions
SMPD3	Sphingomyelin phosphodiesterase 3	Catalyzes hydrolysis of sphingomyelin to ceramide.
ABHD5	CGI-58 acid lipase	Generates diacylglycerides and FFAs from triacylglycerides (J Lipid Res, 49(4):697-714, 2008)
ELOVL2	Elongation of very long chain fatty acids	Found not only as constituents of cellular lipids such as sphingolipids and glycerophospholipids but also as precursors of lipid mediators (Biomol Ther (Seoul), 22(2): 83-92, 2014)



Protocol

- Used EpidermFT human full thickness skin substitute tissues from Mattek; 48 hrs. incubation
- Expression profile vs placebo with $p < 0.05$ taken into consideration

Why Select Ethyl Linoleate (Synovea® EL)?



□ Improvement in Sebaceous Gland Activity

- Normal function of sebum is to produce & secret sebum
- Sebum lubricates the skin to protect against friction and makes it more impervious to moisture
- Low level of LA is found in acne subjects (Ottaviani et al., Mediators of Inflammation, Article ID 858176, 2010)
- The biological function of sebocytes is regulated by several factors, linoleic acid one of the key lipids (Makrantonaski et al., Dermatoendocrinology, 3(1):41-49, 2011)
 - Lacking any one of the lipids makes sebaceous gland dysfunctional with increasing severity of acne

Synactin® AC: Pilot Anti-acne Study Protocol

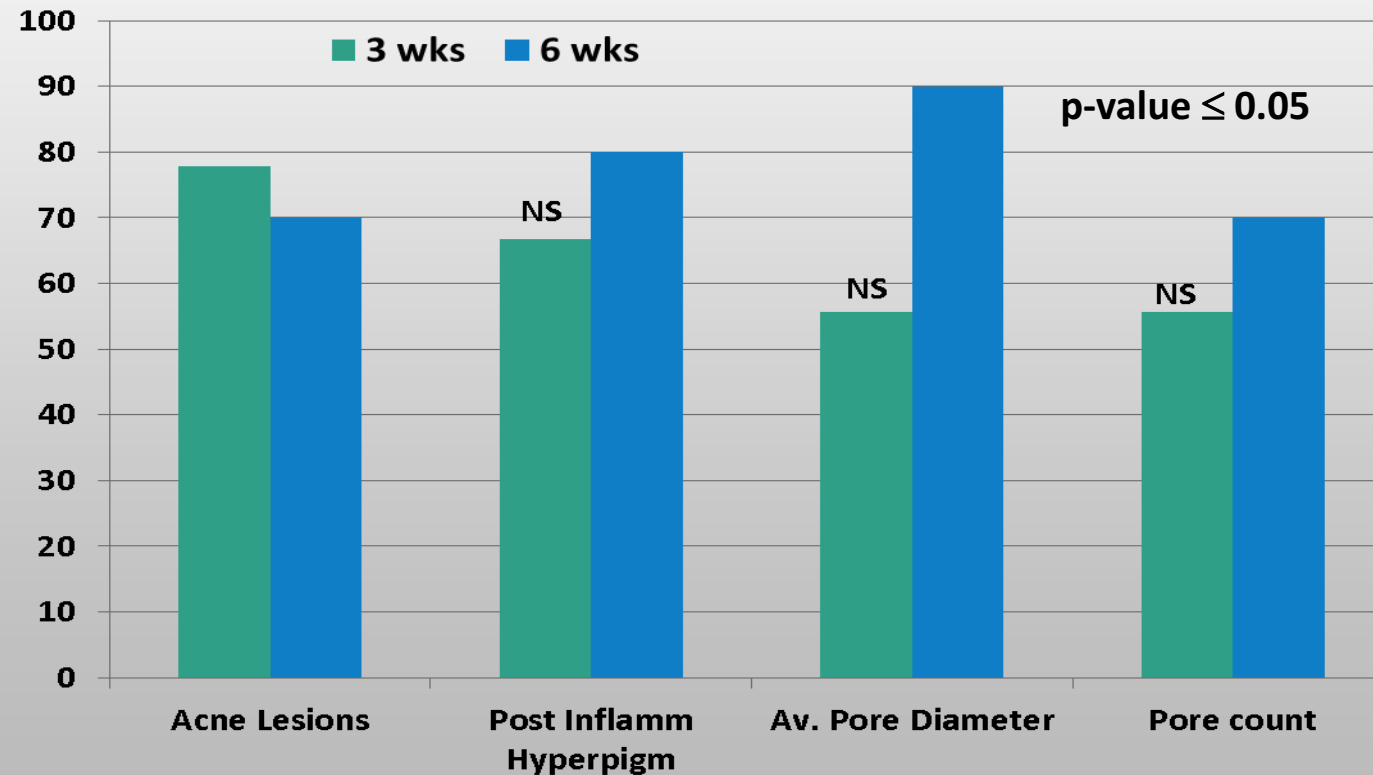
Protocol

- Subjects (10): Mild acne as graded by trained expert
 - ≥ 5 and ≤ 20 total lesions (inflammatory and non-inflammatory lesions); ≥ 3 inflammatory lesions
 - Age: 21.30 ± 4.54
 - Fitzpatrick skin Type: Skin type II (2), III (6) & IV (2)
 - Race: White (9); Hispanics (1)
 - Gender: Male (5); Female (5)
- Duration of the study: 6 weeks; March 27 to April 25, 2014
- Frequency of application: Twice a day
- Product: Synactin® AC (3% lotion)
- Assessment of Efficacy - Methodology
 - Tolerance evaluation – Objective (Dryness; Erythema & Edema) & Subjective (Stinging; Tingling; Itching & Burning)
 - Well tolerated; 50% of subjects showing reduction in erythema ($p < 0.015$)
 - Photography - Clarity 2D Ti image analysis – Acne lesions; Post-inflammatory hyper-pigmentation; Pores
 - Subjective questionnaire – Comparison to baseline

Synactin® AC: Pilot Anti-acne Study Results

Photography - Clarity 2D Ti Image Analysis

% of Subjects Showing Improvement from Baseline



Synactin® AC: Pilot Anti-acne Study Results

Subjective Questionnaire

% of Subjects Responded Favorably



Reduced the appearance of:

1. Total acne lesions
2. Inflammatory acne lesions (Whiteheads)
3. Non-inflammatory acne lesions (Blackheads)
4. Post inflammatory hyperpigmentation

Improved the appearance of:

5. Overall texture / appearance of skin

CONCLUSION

Acne Control Lotion with Synactin® AC showed:

- Improvement in skin condition in subjects with mild acne
- Showed reduction in erythema, lesion counts, PIH and improvement in pores
- Found to be well tolerated by the study panel

Clinical Study-Panelist 09TAD, Right

BASELINE



AFTER 6 WEEKS



Clinical Study- Panelist 01AMR, Left

BASELINE

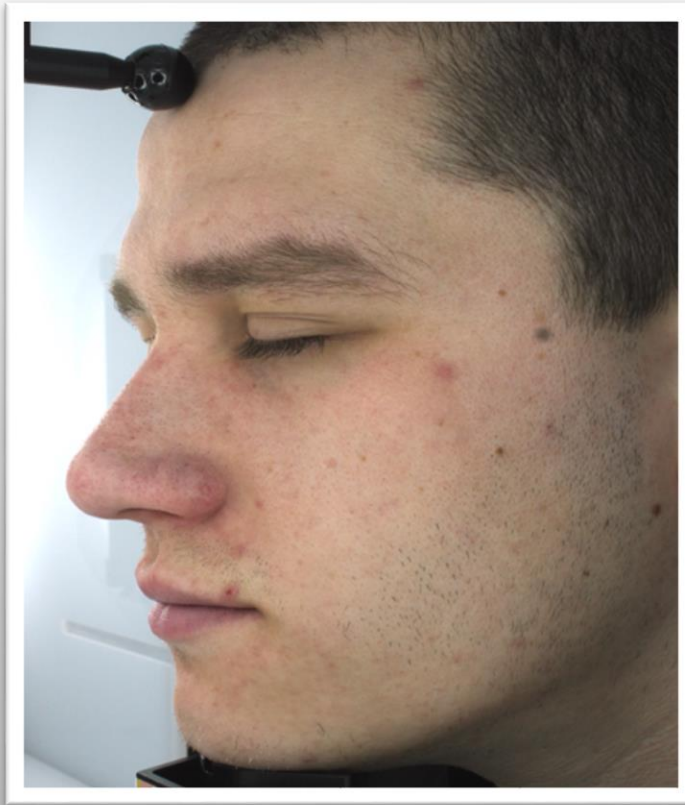


AFTER 6 WEEKS



Clinical Study- Panelist 03MB, Left

BASELINE



AFTER 6 WEEKS

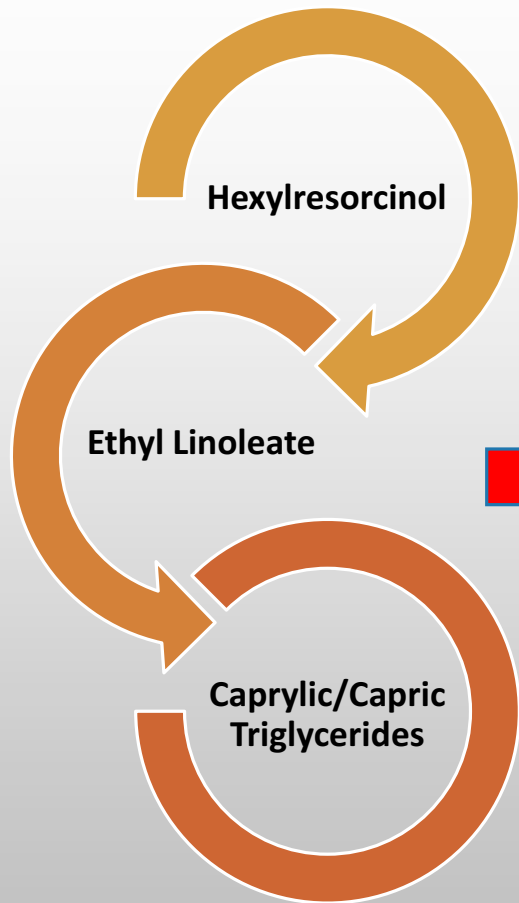


Formulation Guidelines

- ❑ Add Synactin® AC to the oil phase directly or after making the lotion while cooling at ~40 °C
- ❑ For preparation of serum or transparent gel, use non-ionic solubilizers having high HLB values. Use PEG-40 hydrogenated castor oil, Laureth 23, Polysorbate 20 or 80
- ❑ Addition of a chelant (~0.1%) resolves the coloration problem, if any, due to the presence of iron or copper; Propyl gallate (~0.15 to 0.2%) can be used to stabilize formulation color, if needed
- ❑ The finished product must be acidic, preferably having pH below 6.5
- ❑ Formulations containing Synactin®AC may cause drop in viscosity. Acidic (such as, Xanthan gum) or neutral thickeners (such as, Cellulosics) are good for maintaining desired viscosity
- ❑ The finished product should be protected from prolonged exposure to heat and light

Suggested co-actives for improving anti-acne benefit

Co-actives	Rational/Skin Benefits	Use Level
Salicylic Acid	Helps unclog the pores to resolve & prevent lesions (http://www.webmd.com/skin-problems-and-treatments/acne/understanding-acne-treatment)	2%
Sytenol® A (INCI: Bakuchiol)	Required for inhibiting formation of squalene peroxide which promotes acne, roughening of skin, & wrinkling (Chiba et al., Exper Dermatol, 8:471-479, 1999); Sytenol® A is an excellent peroxidation inhibitor (IC ₅₀ = 0.61; IC ₁₀₀ = 1.46 µg/ml) (Chaudhuri & Ou, 130:64-75, 2015) & a very effective anti-acne agent (Chaudhuri & Marchio, C&T, 126:502-510, 2011)	0.25%
Niacinamide	Provides potent anti-inflammatory activity without reducing bacterial resistance (Shalita et al, Int J Dermatol, 34(6):434-437, 1995); Multiple skin benefits	2%



Providing 5-in-1 Solutions for Mitigating Acne-affected Skin

Synactin® AC:

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Thank You