Sol-Gel
Advanced Topical Therapy

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Our Dermatology Company

- Primed to become a global dedicated dermatological company by developing a combination of branded and generic topical drug products
- Expecting results during 2019 from pivotal trials of two branded pipeline candidates, based on a proprietary topical microencapsulation delivery system
- Seven established collaborations with two strategic partners on generic candidates already resulted in one approval and one tentative approval by the FDA. First generic product reached the market in February 2019
- Proven track record combined with broad dermatological knowhow

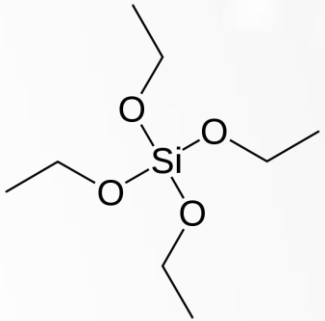
The Sol-Gel Process

- A sol is a stable dispersion of colloidal particles or polymers in a solvent. The particles may be amorphous or crystalline

- A gel consists of a three dimensional continuous network, which encloses a liquid phase, In a colloidal gel, the network is built from agglomeration of colloidal particles

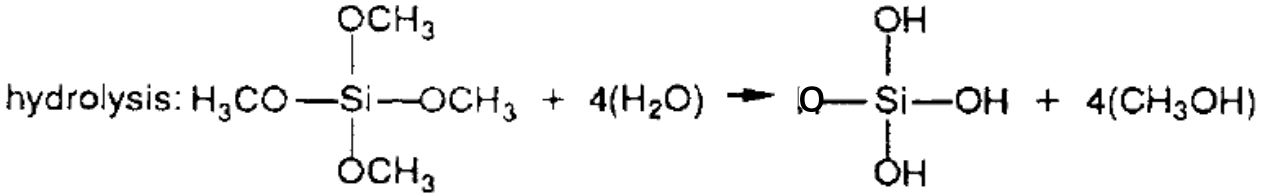
Sol-Gel Precursors

- The sol gel precursors are a metal or metalloid element with various ligands such as metal alkoxides that undergo hydrolysis in aqueous solutions. The most widely used metal alkoxides are alkoxysilanes, such as tetramethoxysilane (TMOS) and tetraethoxysilane (TEOS)



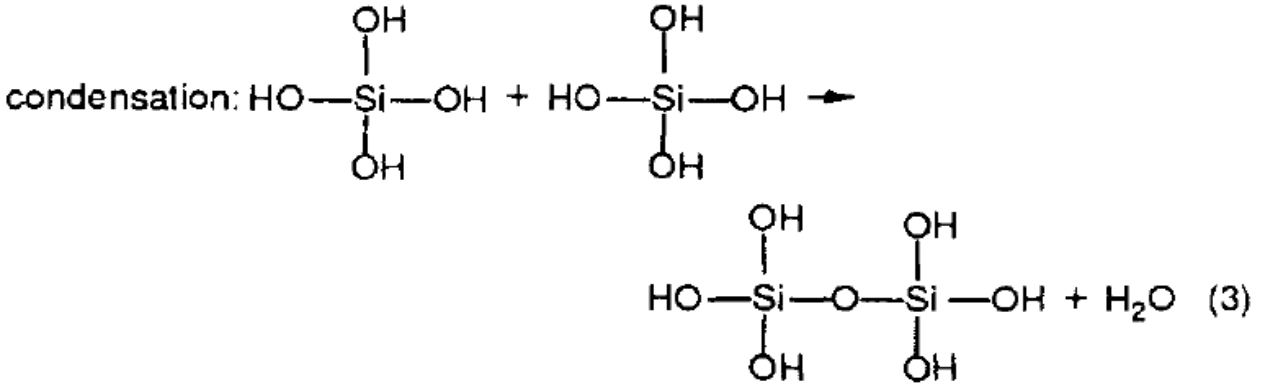
- The most common non-organic silica precursor is sodium silicate

Stages in The Process



$$TMOS + 4(H_2O) \rightarrow Si(OH)_4 + 4(CH_3OH) \quad (2)$$

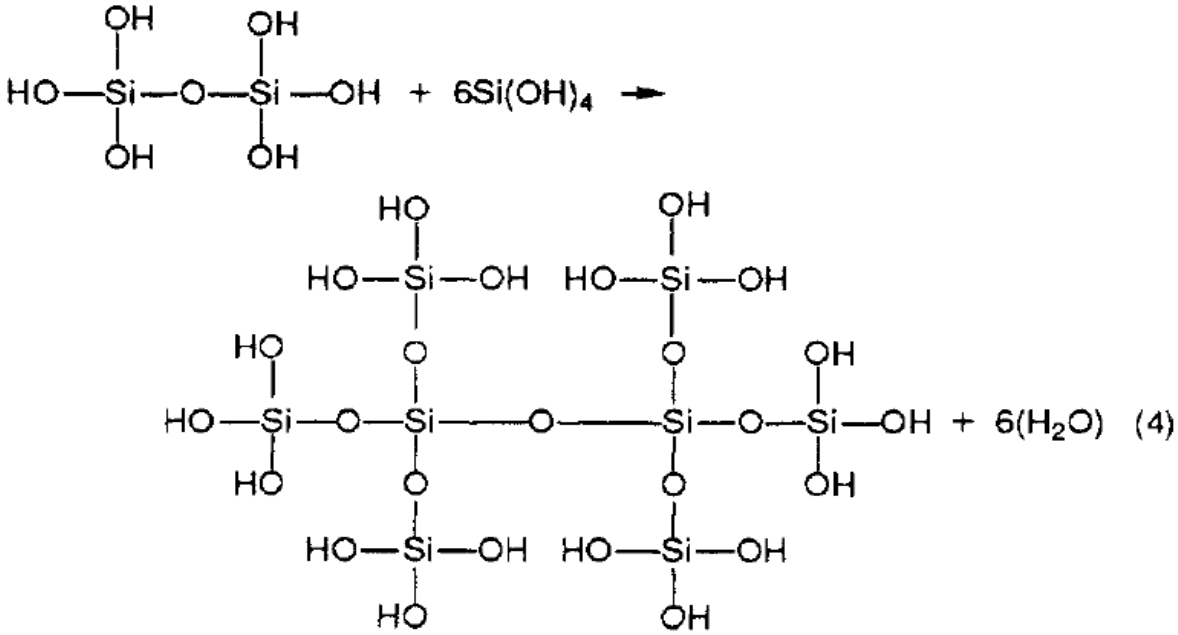
The hydrated silica tetrahedra interact in a condensation reaction (eq 3), forming ≡Si—O—Si≡ bonds.



Source : The Sol Gel Process, L.L. Hench and J.K. west, Chem. Rev. 1990, 90, 33-72

Stages in The Process

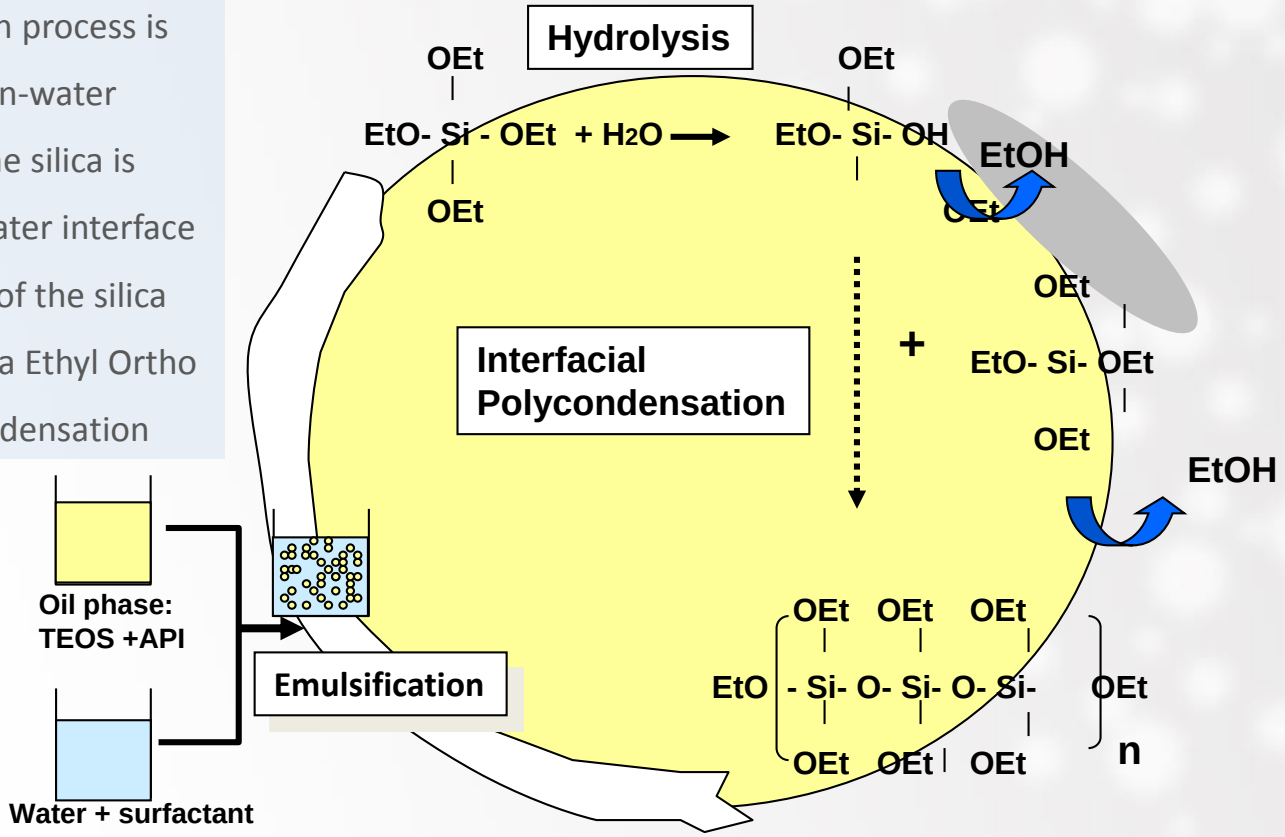
Linkage of additional ≡Si—OH tetrahedra occurs as a polycondensation reaction (eq 4) and eventually results in a SiO_2 network. The H_2O and alcohol expelled from the reaction remains in the pores of the network.



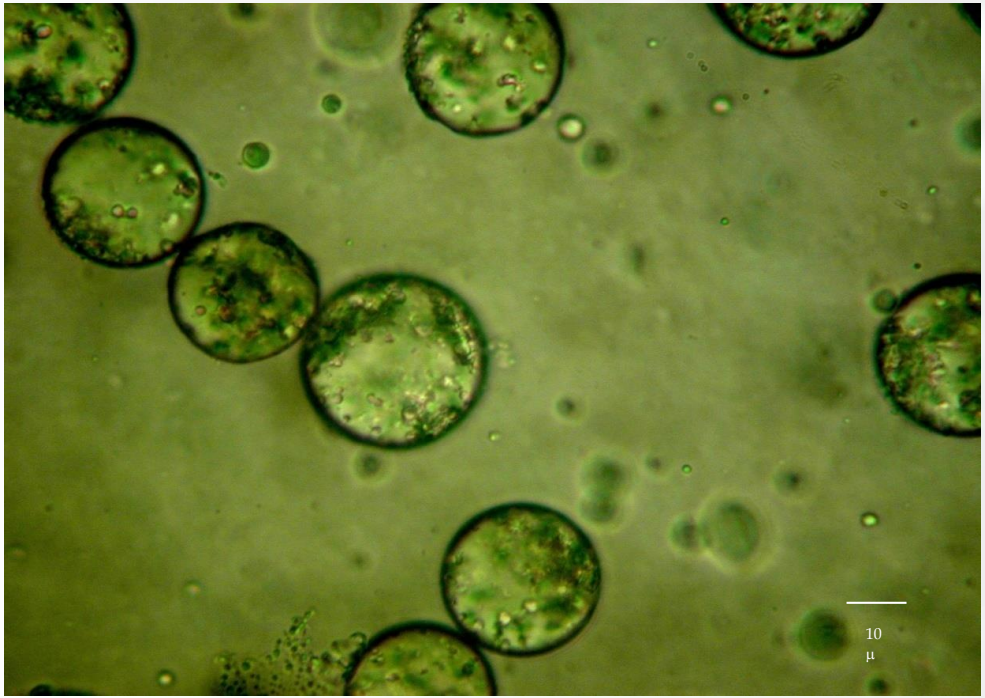
Source : The Sol Gel Process, L.L. Hench and J.K. west, Chem. Rev. 1990, 90, 33-72

The encapsulation process using Sol-Gel technology

Sol Gel encapsulation process is performed in an oil-in-water emulsion in which the silica is formed at the oil/ water interface following hydrolysis of the silica precursor TEOS (Tetra Ethyl Ortho Silicate) and polycondensation

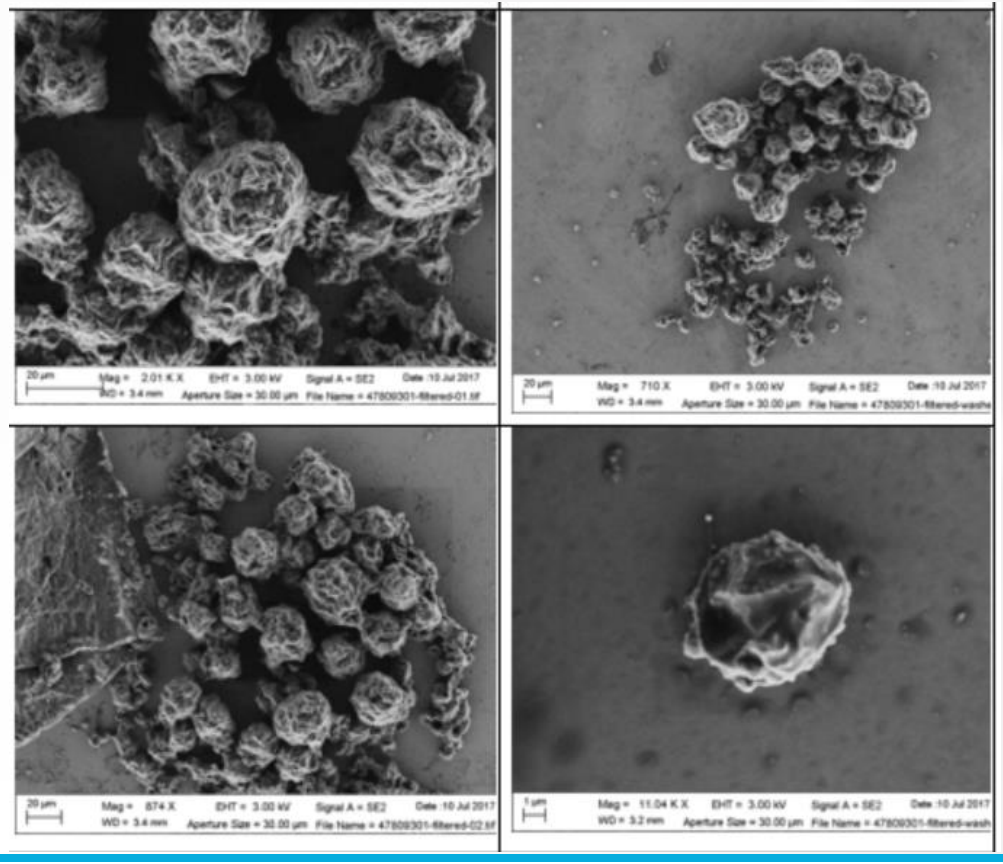


Encapsulated tretinoin

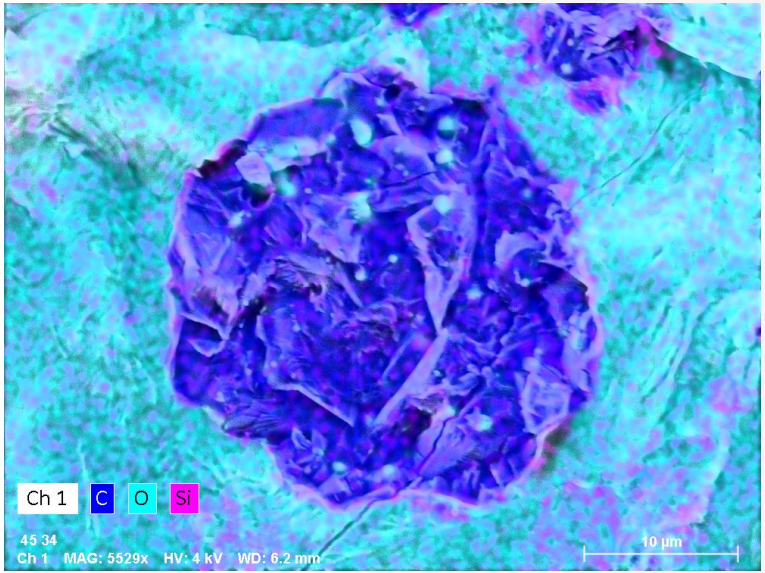


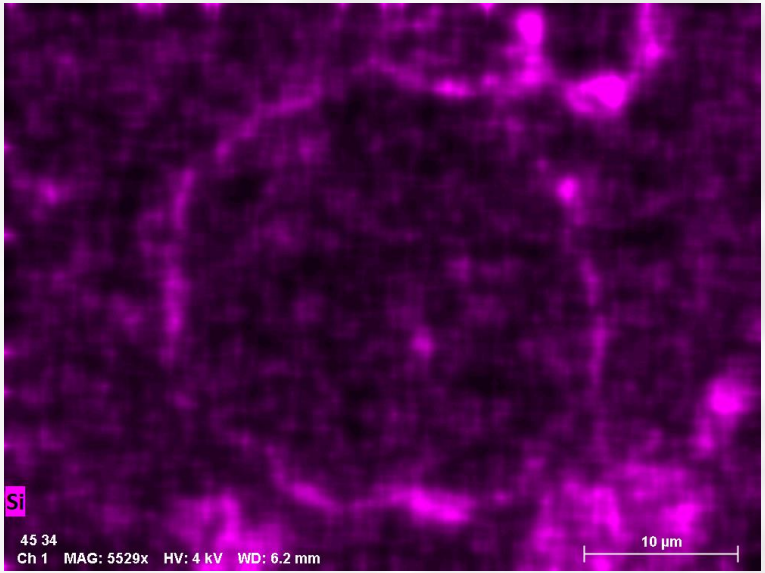
Light microscope pictures of the microcapsules

SEM pictures of encapsulated tretinoin



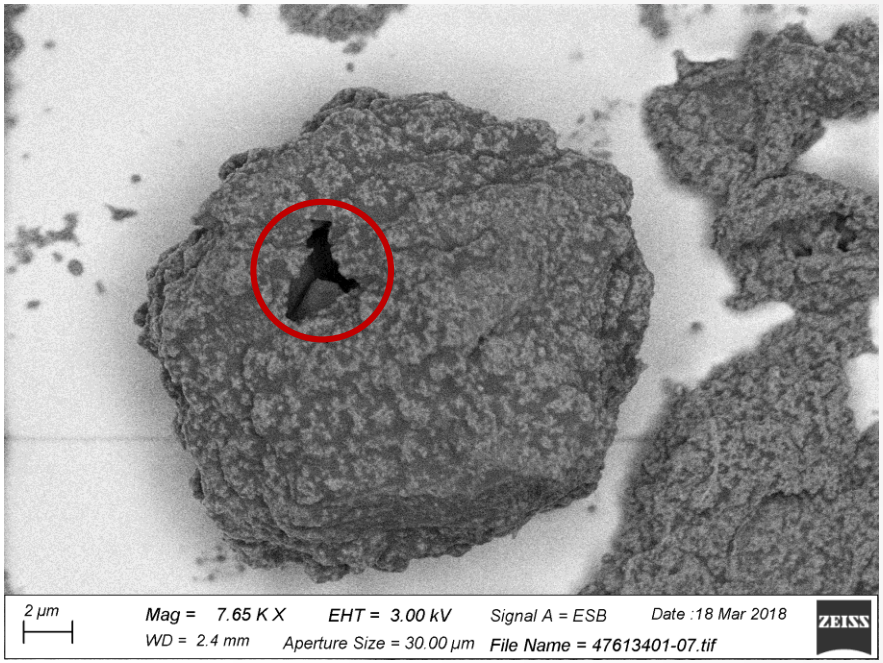
Cryo-SEM pictures of encapsulated tretinoin: EDS analysis



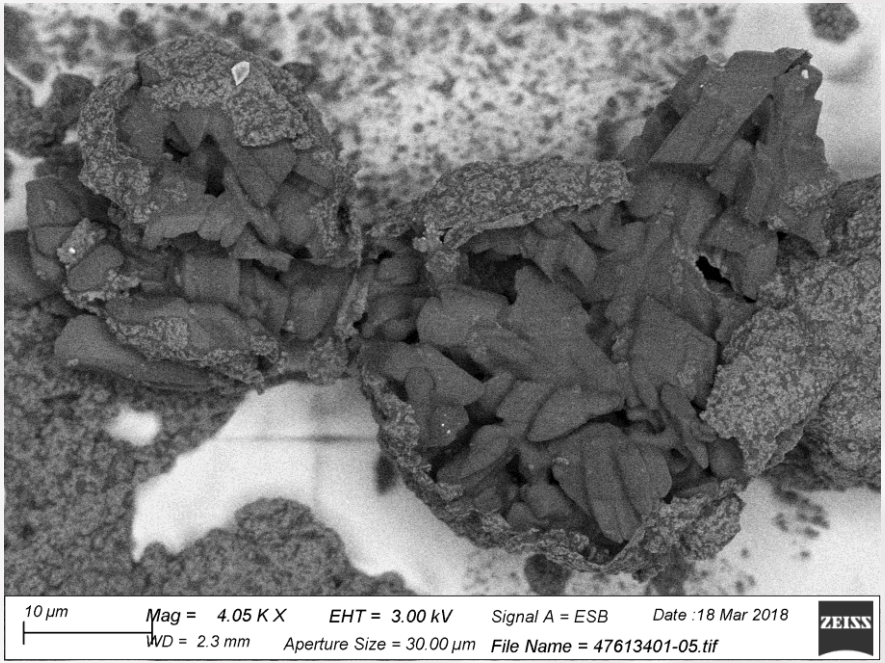


SEM pictures of encapsulated tretinoin

Encapsulated tretinoin microcapsule



Encapsulated tretinoin crystals inside broken microcapsule



Common Indications Requiring Better Therapies

Acne Vulgaris

- A disease of the pilosebaceous unit, involving abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation and inflammation
- Benzoyl peroxide (BPO) and tretinoin are mainstay therapies
- Tretinoin is the most widely used Rx topical retinoid, but is rapidly decomposed by BPO and causes irritation
- BPO/tretinoin combination does not currently exist on the market
- ~$2.7 billion sales in the U.S. in 2018 of several promoted topical brands and many generics, of which fixed-dose combination drugs account for ~$0.9 billion
- Dermatologists often prefer branded topical drugs even though cheaper generics and OTC alternatives exist

Papulopustular Rosacea

- A chronic, inflammatory skin condition affecting nearly 5 million people in the US
- ~$0.4 billion sales of topical products in the U.S. in 2018 : Soolantra®, Finacea® and generic metronidazole
- Poor patient adherence to current drugs

Sources: IQVIA (IMS); T. Pigeon, Practical Dermatology, July 2010

Our Branded Drug Product Candidates

TWIN

acne vulgaris

- **A cream containing a fixed-dose combination of encapsulated tretinoin and encapsulated benzoyl peroxide**
- Major challenges were the instability of tretinoin in the presence of benzoyl peroxide and irritation
- Encapsulation allows stabilization and is also expected to contribute to patient compliance
- Opportunity exists for shift from prescribing tretinoin and existing combinations to prescribing TWIN
- We estimate peak annual sales of $350M - $400M(†).

Epsolay®

papulopustular rosacea

- **A cream containing encapsulated benzoyl peroxide, 5%**
- Encapsulation was designed to reduce irritation caused by benzoyl peroxide
- Potential to be the 1st FDA-approved single-active benzoyl peroxide prescription drug product
- We estimate peak annual sales of $75M - $100M(†)

(†) Our estimation takes into consideration current payers' requirements and tier 3 limitations

BPO/tretinoin - Stability Challenge

- A major challenge in the development of BPO/tretinoin combination is to make it stable. Scientific literature reports stability of approved tretinoin products Retin-A Micro® and Atralin® as limited to 7 hours and no stability of tretinoin gel when combined with BPO. As a result, no fixed-dose combination of BPO/tretinoin is available on the market
- Another challenge is the tolerability of such combination

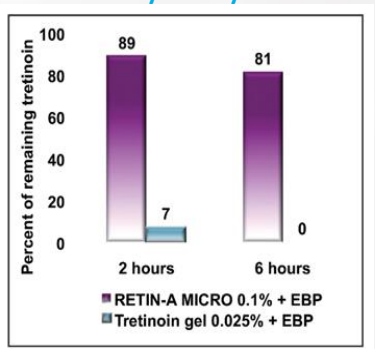
Limited stability of tretinoin in the presence of BPO (various works)

Table 3: BP/Clindamycin Tube Gel + Tretinoin Microsphere Gel 0.1%: 24-Hour Stability Data

Time Point	Percent Theoretical		
	Tretinoin	Benzoyl Peroxide	Clindamycin
0 hr	96%	99%	101%
1 hr	95%	100%	102%
2 hr	92%	100%	105%
4 hr	87%	104%	104%
6 hr	84%	105%	103%
24 hr	56%	102%	106%

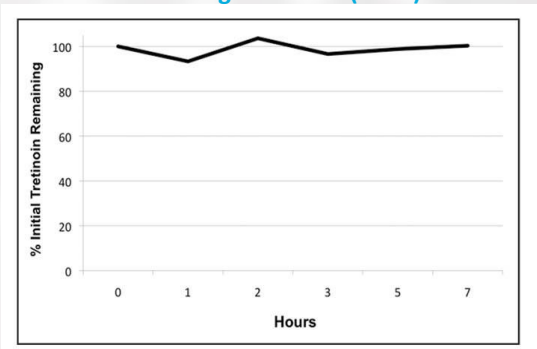
Source: Del Rosso, Cosmetic Dermatol., 2006

Stability in presence of erythromycin-BPO



Source: Kircik, JCAD Online, 2011

Percentage of initial tretinoin in Atralin® remaining over time (7hrs.)



Source: Del Rosso, JCAD Online, 2010

TWIN Drug Candidate

- A fixed-dose combination of encapsulated benzoyl peroxide and encapsulated tretinoin that has the potential to be a highly effective treatment for acne vulgaris

- Encapsulation allows the stabilization of tretinoin in the presence of benzoyl peroxide and to reduce irritation

TWIN Phase II Trial Design

Design	▪ 726 subjects, aged 9 or older were enrolled at 36 sites in the U.S. ▪ Randomized 1:1:1:1:1:1:1 to receive once daily treatment with TWIN High, TWIN Low, encapsulated tretinoin (“E-ATRA”) high monad, E-ATRA low monad, encapsulated BPO (“E-BPO”) monad, and vehicle ▪ Clinical evaluations performed at weeks 2, 4, 8, and 12 ▪ Study Medical Monitor – Dr. Guy Webster
Main inclusion criteria	▪ Facial acne with >25 and <100 non-inflammatory lesions and >20 and <50 inflammatory lesions ▪ Score of 3 or 4 (“moderate” or “severe”) on a 5-point Investigator Global Assessment (“IGA”) scale ranging from 0 (“clear”) to 4 (“severe”) ▪ Two or fewer cysts or nodules
Co-primary efficacy endpoints	▪ Proportion of subjects with an assessment of “clear” or “almost clear” with at least a 2-grade improvement in IGA at week 12 based on the ITT population ▪ Mean absolute change from baseline in inflammatory and non-inflammatory lesion counts at week 12 based on the ITT population
Efficacy analysis	▪ Statistical superiority in efficacy as compared to the vehicle ▪ Numerical superiority in efficacy of TWIN as compared to encapsulated BPO and encapsulated tretinoin monads
Cutaneous adverse events	▪ Investigator assessment was used for rating of hyper- and hypo-pigmentation, erythema and scaling on a scale ranging from 0 (“none”) to 3 (“severe”) ▪ Patient reported outcome questionnaire was used for assessment of local tolerability rating itching, burning, and stinging on a scale ranging from 0 (“none”) to 3 (“severe”)
Safety assessment	▪ Electrocardiogram (12-lead ECG) was done at baseline, week 2 and week 12 or early termination ▪ Clinical chemistry, hematology and urinalysis were evaluated at baseline, week 8 and week 12 or early termination
Related and emerged adverse events (“AEs”)	▪ Related, probably related or possibly related AEs leading to study discontinuation ▪ Related, probably related or possibly related AEs, which are worsening of a condition present upon entry or noted as medical history

TWIN Phase II Baseline Characteristics (ITT)

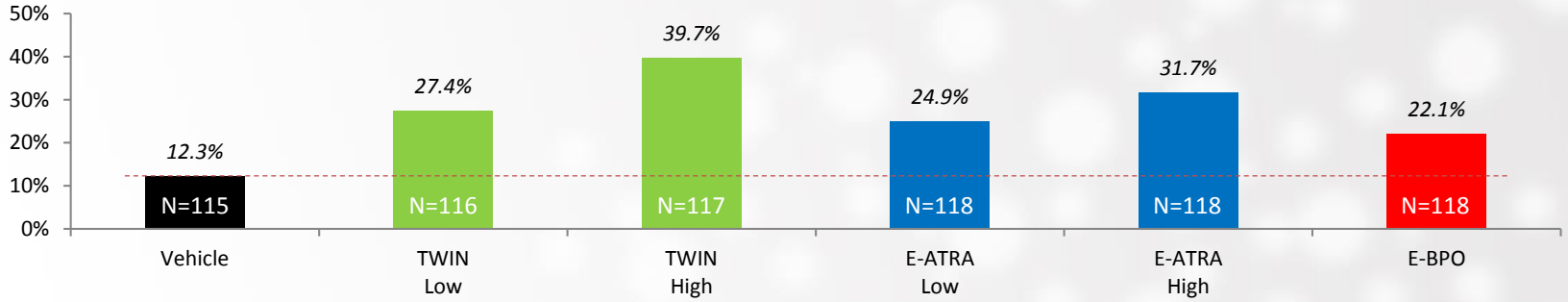
Summary of Subject Baseline Characteristics

	Vehicle Cream (N=115)		TWIN High (N=116)		TWIN Low (N=117)		E-ATRA High (N=118)		E-ATRA Low (N=118)		E-BPO (N=118)	
Inflammatory Lesion Count												
N	115		116		117		118		118		118	
Mean	28.6		26.7		27.8		26.2		26.7		27.9	
SD	8.31		6.84		8.13		5.74		5.64		7.09	
Median	26.0		25.0		26.0		25.0		25.0		26.0	
Min. to Max.	18 to 50		16 to 49		20 to 86		18 to 48		19 to 46		18 to 50	
Non-Inflammatory Lesion Count												
N	115		116		117		118		118		118	
Mean	42.5		42.9		43.3		42.3		41.6		42.6	
SD	16.80		16.95		17.28		16.57		16.41		17.04	
Median	37.0		38.0		37.0		36.0		35.0		36.5	
Min. to Max.	25 to 98		25 to 98		25 to 100		25 to 91		25 to 96		25 to 96	
Investigator's Global Assessment												
N	115		116		117		118		118		118	
0 – Clear	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
1 – Almost Clear	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
2 – Mild	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
3 – Moderate	102	(88.7%)	102	(87.9%)	104	(88.9%)	107	(90.7%)	102	(86.4%)	101	(85.6%)
4 – Severe	13	(11.3%)	14	(12.1%)	13	(11.1%)	11	(9.3%)	16	(13.6%)	17	(14.4%)

Positive TWIN Factorial Phase II Results (ITT)(†)

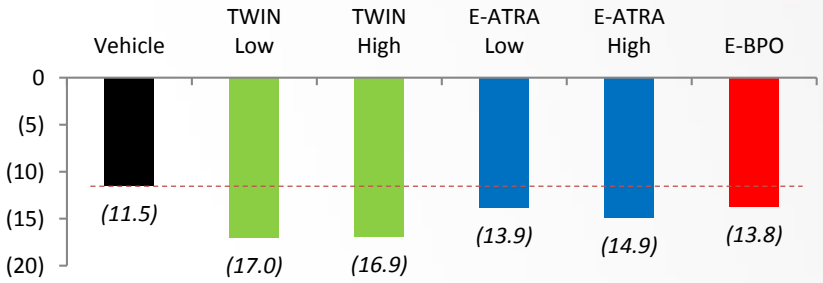
Success in Dichotomized IGA at Week 12

	Vehicle	TWIN Low	TWIN High	E-ATRA Low	E-ATRA High	E-BPO
P-value vs. vehicle		0.006	<0.001	0.015		0.001
	12.3%	27.4%	39.7%	24.9%	31.7%	22.1%
	N=115	N=116	N=117	N=118	N=118	N=118



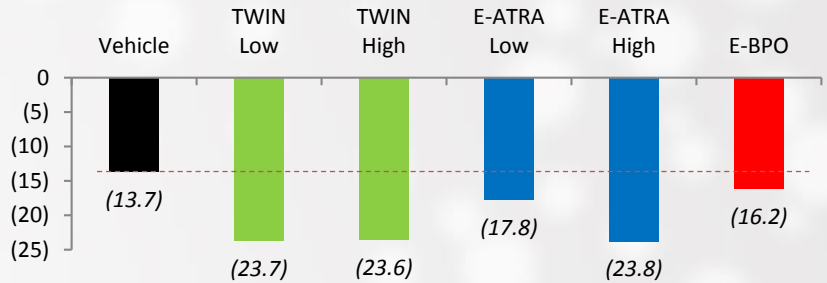
Inflammatory Lesion Mean Absolute Change from Baseline at Week 12

	Vehicle	TWIN Low	TWIN High	E-ATRA Low	E-ATRA High	E-BPO
	(11.5)	(17.0)	(16.9)	(13.9)	(14.9)	(13.8)
P-value vs. vehicle		<0.001	<0.001	0.060	0.003	



Non-Inflammatory Lesion Mean Absolute Change from Baseline at Week 12

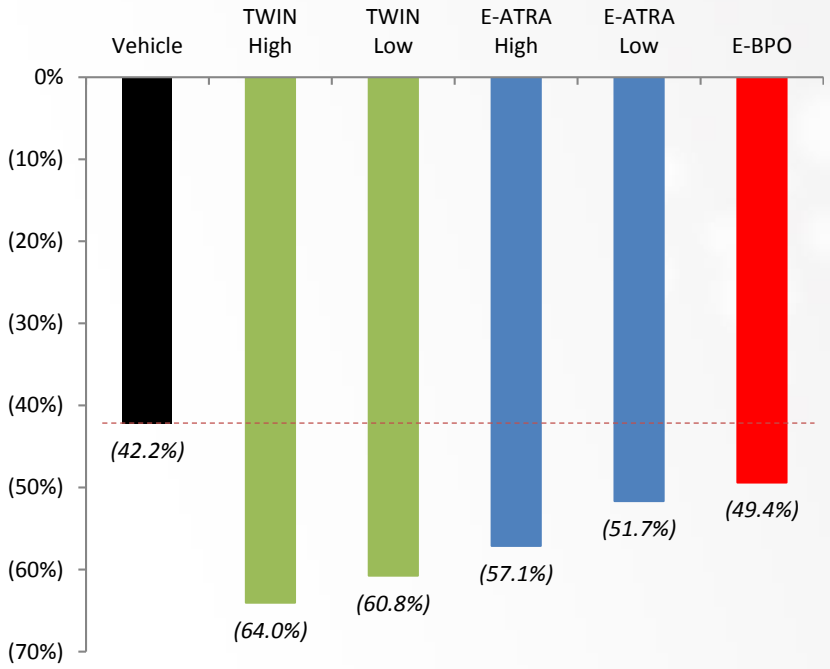
	Vehicle	TWIN Low	TWIN High	E-ATRA Low	E-ATRA High	E-BPO
	(13.7)	(23.7)	(23.6)	(17.8)	(23.8)	(16.2)
P-value vs. vehicle		<0.001	<0.001	0.002	<0.001	



(†) The above calculations were made using Markov Chain Monte Carlo multiple imputation method for handling missing data and without data from one center that discontinued the study. Analyses without imputation (with or without the discontinued center) were highly consistent with the above

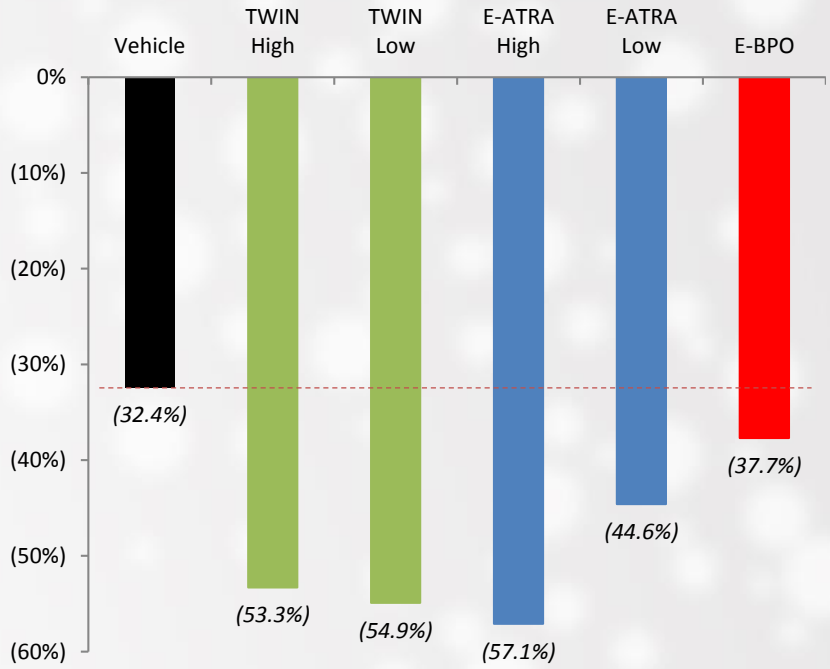
TWIN Phase II Trial Secondary Efficacy Results (ITT)(†)

Inflammatory Lesion Mean Percent Change from Baseline at Week 12



P-value vs. vehicle	*<0.001*	*<0.001*

Non-Inflammatory Lesion Mean Percent Change from Baseline at Week 12



P-value vs. vehicle	*<0.001*	*<0.001*

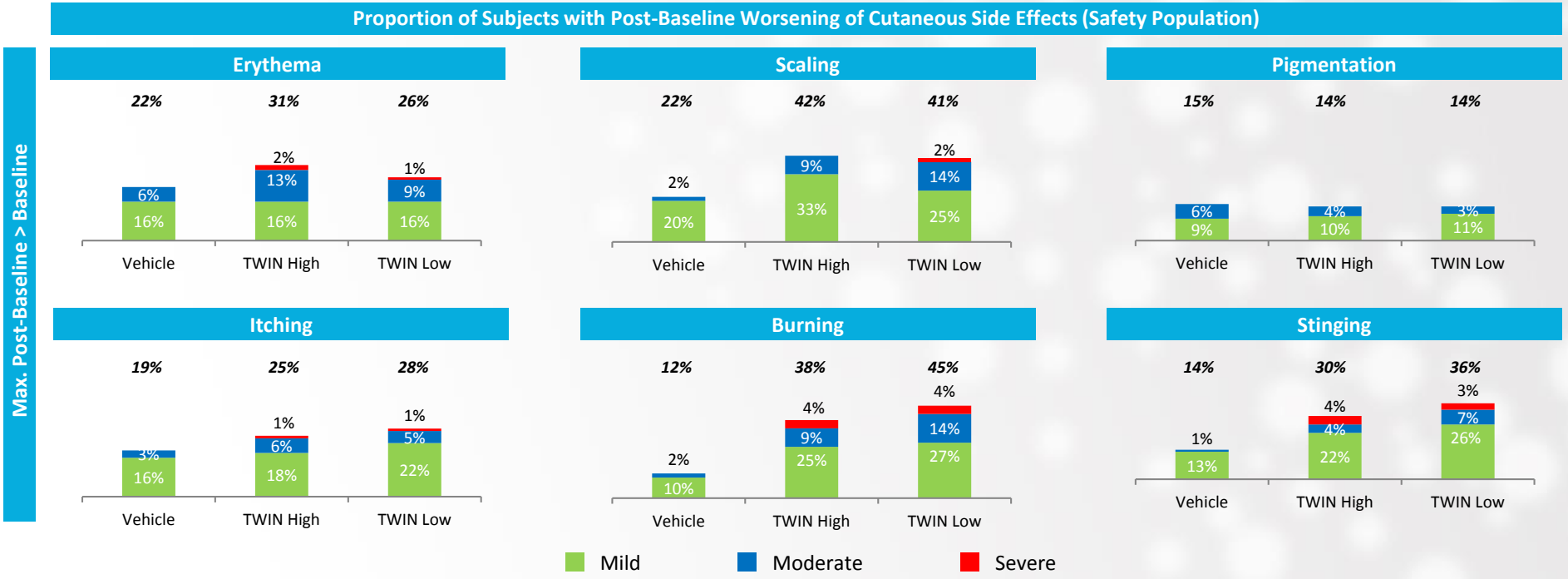
(†) The above calculations were made using Markov Chain Monte Carlo multiple imputation method for handling missing data and without data from one center that discontinued the study. Analyses without imputation (with or without the discontinued center) were highly consistent with the above

Efficacy Results of Recent Acne Trials(†)

Treatment Arm:									
Number of Patients	Severe	14		61	64	37	118	70	79
	Moderate	102		292	305	296	620	413	440
	Mild	0		0	0	0	0	0	0
Baseline # of Lesions	Inflamed	26.7		42.4	42.9	31.6	30.7	29.7	30.3
	Non-inflamed	42.9		59.1	62.8	50.5	49.7	42.4	42.3

(†) Sol-Gel did not conduct a head-to-head comparison trial or study. The results described above are for illustrative purposes only and should not be construed as conclusions to be drawn as if we conducted a head-to-head comparison trial or study

Phase II Cutaneous Tolerability of TWIN

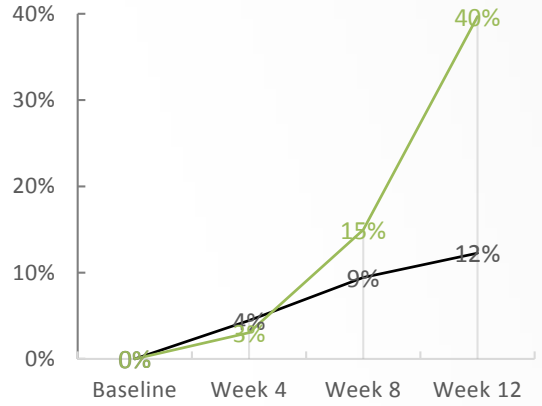


TWIN Co-Primary Efficacy Results Over Time (ITT)

The success in IGA at week 12, the decrease from baseline in inflammatory lesions at week 8 and12 and for non-inflammatory lesion count at weeks 4, 8 and 12, respectively, were statistically significantly greater than for vehicle

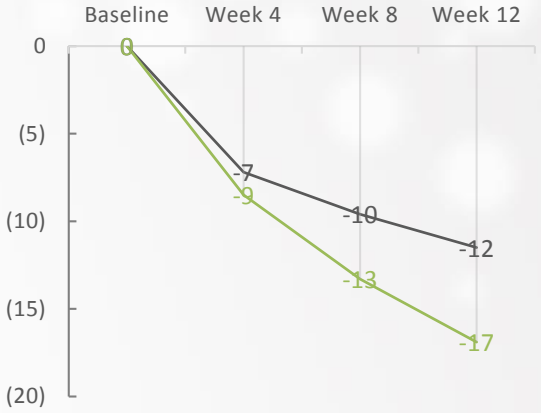
Success in IGA

P-value vs. vehicle *<0.001*



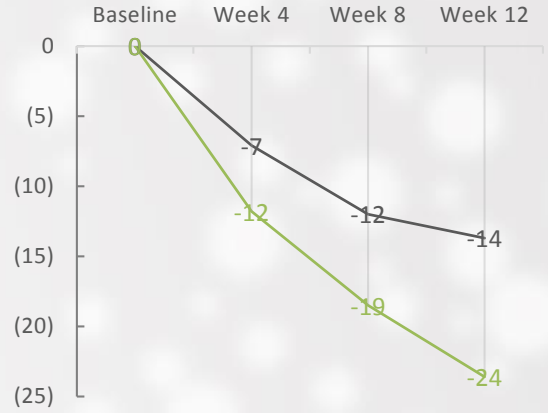
Change in Inflammatory Lesion Count

P-value vs. vehicle *0.001* *<0.001*



Change in Non-Inflammatory Lesion Count

P-value vs. vehicle *0.011* *<0.001* *<0.001*



Legend: Vehicle TWIN High

Highly-Powered Phase III Trials and Mitigated Risks

- Only TWIN and vehicle are required for the pivotal trials, as the requirements of the combination rule act were satisfied in our Phase II trial
- Each pivotal trial is planned to enroll 420 subjects in a 2:1 ratio, with a power of 99%
- No LTSS is required to support our future marketing application, as long as we demonstrate that the systemic exposure of our product is comparable to our reference-listed drug (RLD)
- No pediatric clinical studies are required to support our future marketing application
- Subject to favorable results from our Phase III clinical program, we plan to submit an NDA in 2020

NASDAQ: SLGL

www.sol-gel.com