Lifitegrast Clinical Development Program: Key Findings From 3 Randomized Controlled Trials in Adult Subjects With Dry Eye Disease

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- Walter O. Whitley has been, within the last 3 years, a consultant for a company (Shire) with a business interest in the subject matter of this presentation, and has received speaker fees and served on advisory boards for Shire
- Edward J. Holland has been, within the last 3 years, a consultant for a company (Shire/SARcode) with a business interest in the subject matter of this presentation
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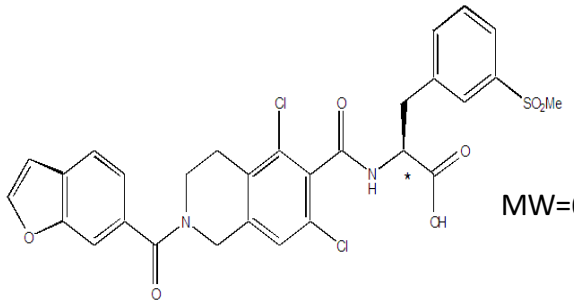
Lifitegrast

- Lifitegrast is a small molecule integrin antagonist that interferes with binding of ICAM-1 to the integrin LFA-1 on the T cell surface, inhibiting T cell recruitment and activation associated with dry eye disease (DED)



MW=615.5

- Lifitegrast ophthalmic solution 5.0% has been investigated in 3 (1 phase 2 and 2 phase 3) randomized controlled trials for treatment of DED[1–3]
- In this presentation, we discuss the clinical development of lifitegrast and the pattern of efficacy findings across these 3 studies, including findings of previously unreported post hoc analyses

ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1, MW, molecular weight (g/mol).

1. Semba CP, et al. *Am J Ophthalmol.* 2012;153(6):1050-60. 2. Sheppard JD, et al. *Ophthalmology*. 2014;121(2):475–83.
3. Tauber J, et al. *Ophthalmology*. 2015 Sep 10. [Epub ahead of print]

Study Designs

	Study 1	Study 2	Study 3
Study type	Phase 2	Phase 3 (OPUS-1)	Phase 3 (OPUS-2)
Clinicaltrials.gov	NCT00926185	NCT01421498	NCT01743729
Sample size (available for efficacy analysis)	Lifitegrast 5.0%, n=54; placebo, n=55*	Lifitegrast 5.0%, n=293; placebo, n=294	Lifitegrast 5.0%, n=358; placebo, n=360
(Co)primary sign	ICSS (0–4 scale)	ICSS (0–4 scale)	ICSS (0–4 scale)
Coprimary symptom	None	Visual-related function subscale	EDS (VAS; 0–100 scale; 0=no discomfort)
Duration	84 days	84 days	84 days
Key inclusion criteria	• Adults with DED • Corneal staining score ≥2 (pre CAE) • STT ≥1 and ≤10 mm • Change in ICSS ≥+1 (post CAE minus pre CAE)	• Adults with DED • Corneal staining score ≥2 (pre CAE) • STT ≥1 and ≤10 mm • Change in ICSS ≥+1 (post CAE minus pre CAE)	• Adults with DED • Corneal staining score ≥2 • STT ≥1 and ≤10 mm • ICSS ≥0.5 • EDS ≥40 • Artificial tear use in past 30 days
CAE	Yes	Yes	No

CAE, controlled adverse environment; EDS (VAS), eye dryness score (visual analogue scale); ICSS, inferior corneal staining score; STT, Schirmer Tear Test (without anesthesia). *Study 1 also included groups receiving lifitegrast ophthalmic solution 0.1% and 1.0%. Study 1 n's shown for key efficacy analysis, change from baseline to day 84 in ICSS.

Baseline Characteristics

	Study 1		Study 2		Study 3	
	LIF*	PBO	LIF	PBO	LIF	PBO
Mean (SD) age, y	62.3 (12.22)	60.4 (12.93)	60.2 (12.21)	61.1 (11.77)	58.7 (13.93)	58.9 (14.26)
Female, %	81.0	77.6	78.2	73.6	79.6	73.6
Mean (SD) baseline ICSS	1.77 (0.515)	1.65 (0.513)	1.84 (0.597)	1.81 (0.599)	2.39 (0.763)	2.40 (0.722)
Mean (SD) baseline EDS	51.58 (24.688)	51.81 (23.552)	40.18 (28.645)	41.62 (29.690)	69.68 (16.954)	69.22 (16.761)

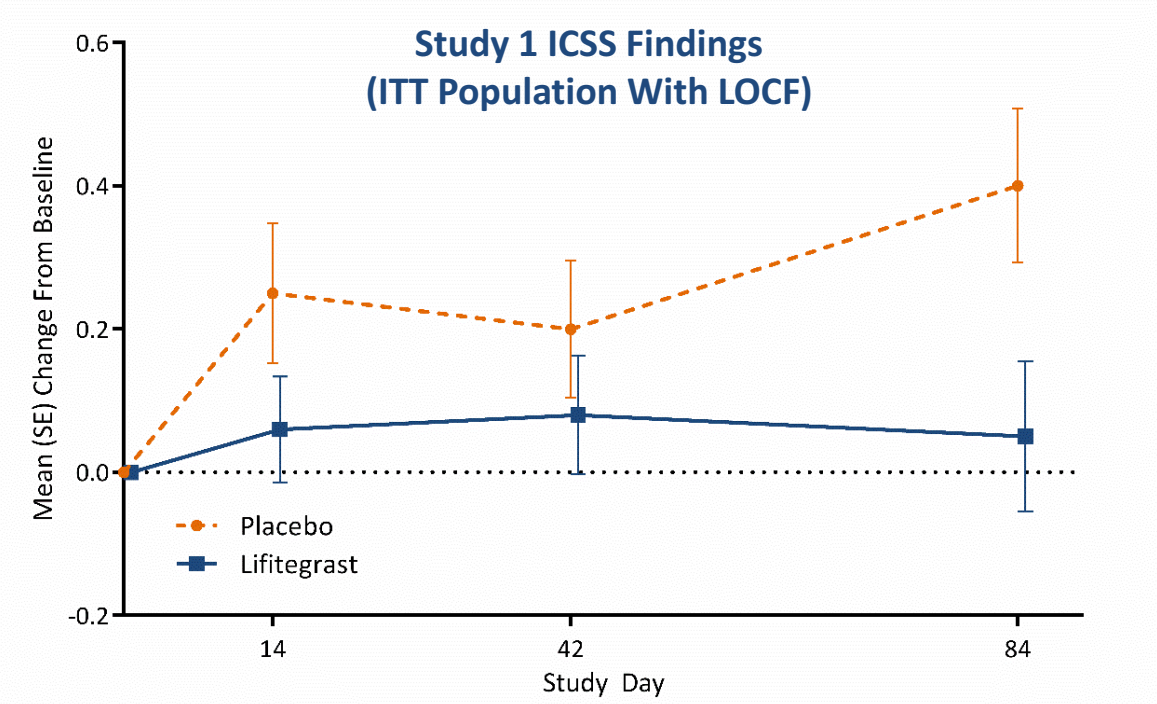
Mild to moderate baseline symptomatology

Moderate to severe baseline symptomatology

LIF, lifitegrast; PBO, placebo. *Group receiving 5.0% formulation of lifitegrast.

Study 1 Findings

- Primary endpoint, ICSS *at day 84*, was not met
- Prespecified sign endpoint, *change from baseline to day 84* in ICSS: treatment effect, 0.35; 95% CI, 0.05–0.65; *P*=0.0209



- On a prespecified secondary endpoint, change from baseline to day 84 on visual-related function subscale of a symptom scale, the lifitegrast group had greater improvement than the placebo group (*P*=0.0394)

ITT, intent to treat; LOCF, last observation carried forward.

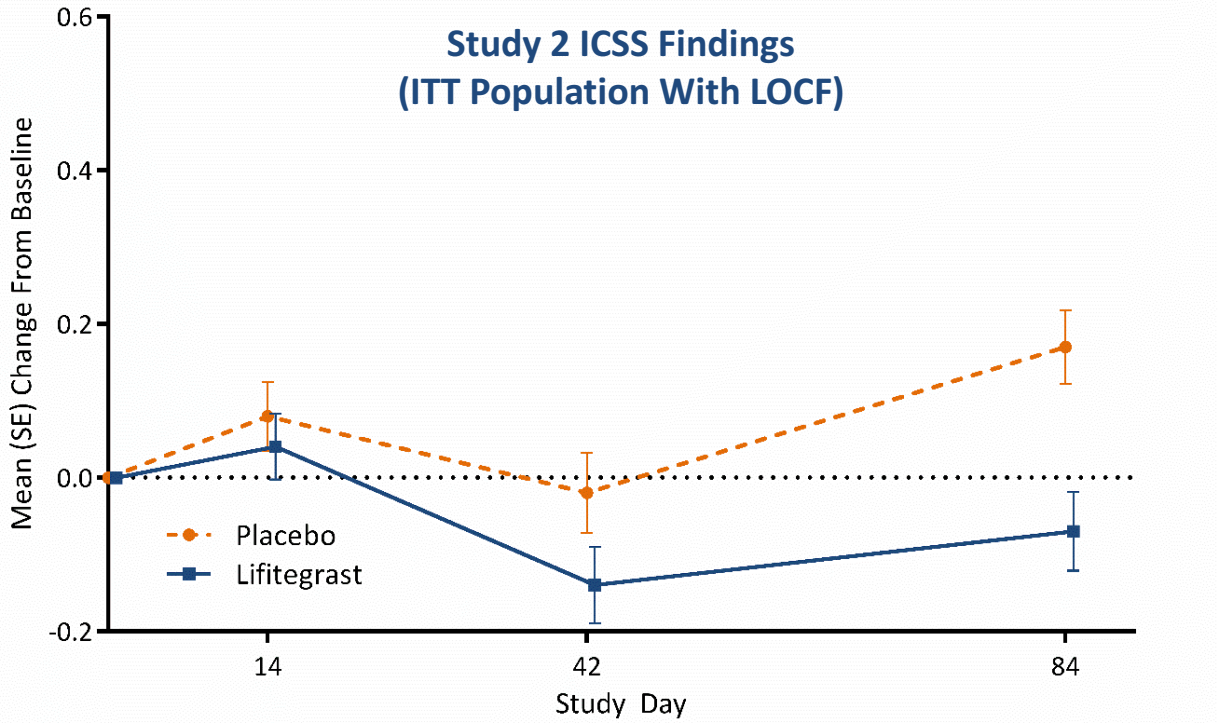
Learnings From Study 1

SIGN Change from Baseline to Day 84 in ICSS (Subjects With Mild to Moderate Symptoms)
Study 1: treatment effect, 0.35; 95% CI, 0.05–0.65; *P*=0.0209

- Dose response relationship for signs and symptoms, with greatest efficacy for 5.0% solution (vs 0.1% and 1.0%)
  - 5.0% solution chosen for further evaluation
- In Study 1, subjects with mild-to moderate symptomatology, lifitegrast improved ICSS versus placebo
  - Change from baseline to day 84 in ICSS chosen as coprimary sign endpoint for Study 2
- Lifitegrast improved visual-related function subscale versus placebo
  - Change from baseline to day 84 on visual-related function subscale chosen as coprimary symptom endpoint for Study 2

Study 2 Findings: Signs

- Met coprimary sign endpoint, change from baseline to day 84 in ICSS

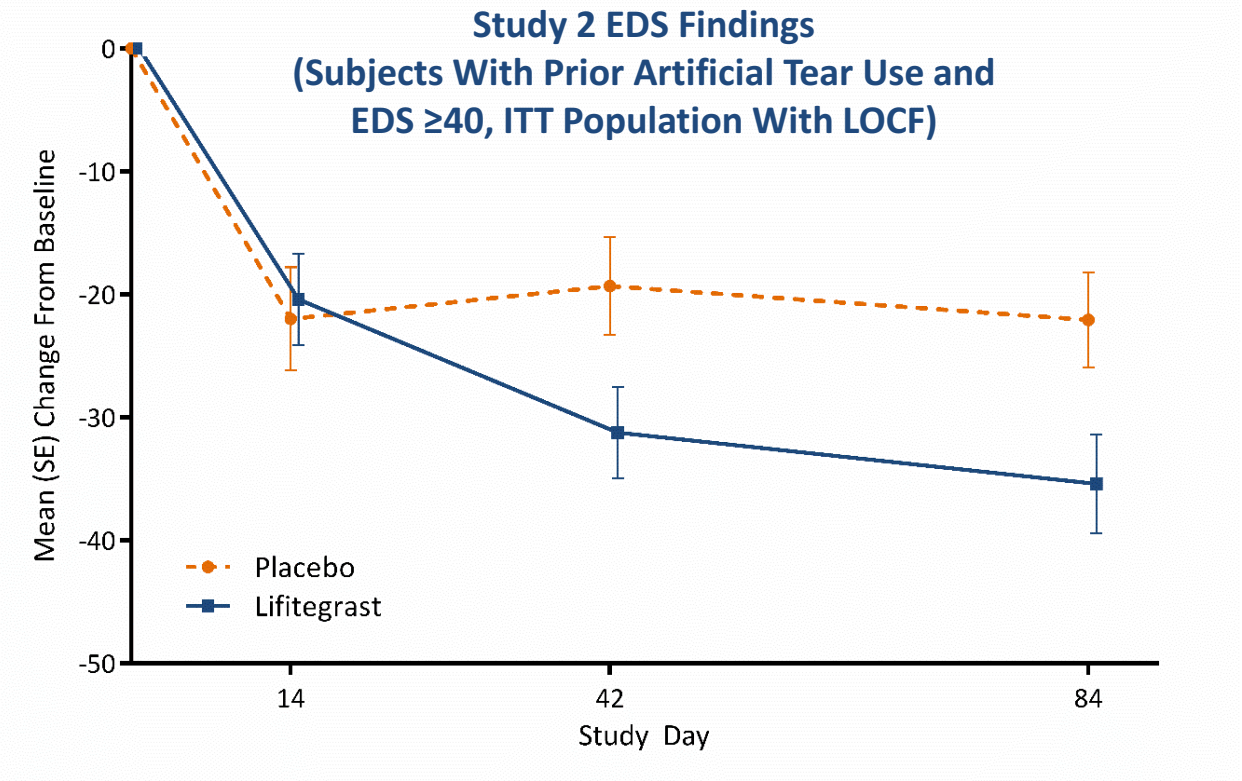


- Effect for ICSS was even stronger among less symptomatic subjects

Change From Baseline to Day 84 in ICSS	Full Study 2 Population (LIF, n=293; PBO, n=294)	Baseline EDS <40 (Post Hoc) (LIF, n=137; PBO, n=147)
Treatment effect (95% CI)	0.24 (0.10–0.38)	0.41 (0.21–0.60)
***P* value**	0.0007	<0.0001

Study 2 Findings: Symptoms

- Coprimary symptom endpoint (change from baseline to day 84 on visual-related function subscale of a symptom scale) was not met
- In post hoc analysis of subjects with prior artificial tear use and baseline EDS ≥40, lifitegrast improved EDS versus placebo (treatment effect, 13.34; 95% CI, 2.35–24.33; nominal *P*=0.0178; lifitegrast, n=63; placebo, n=67)



Learnings From Study 2

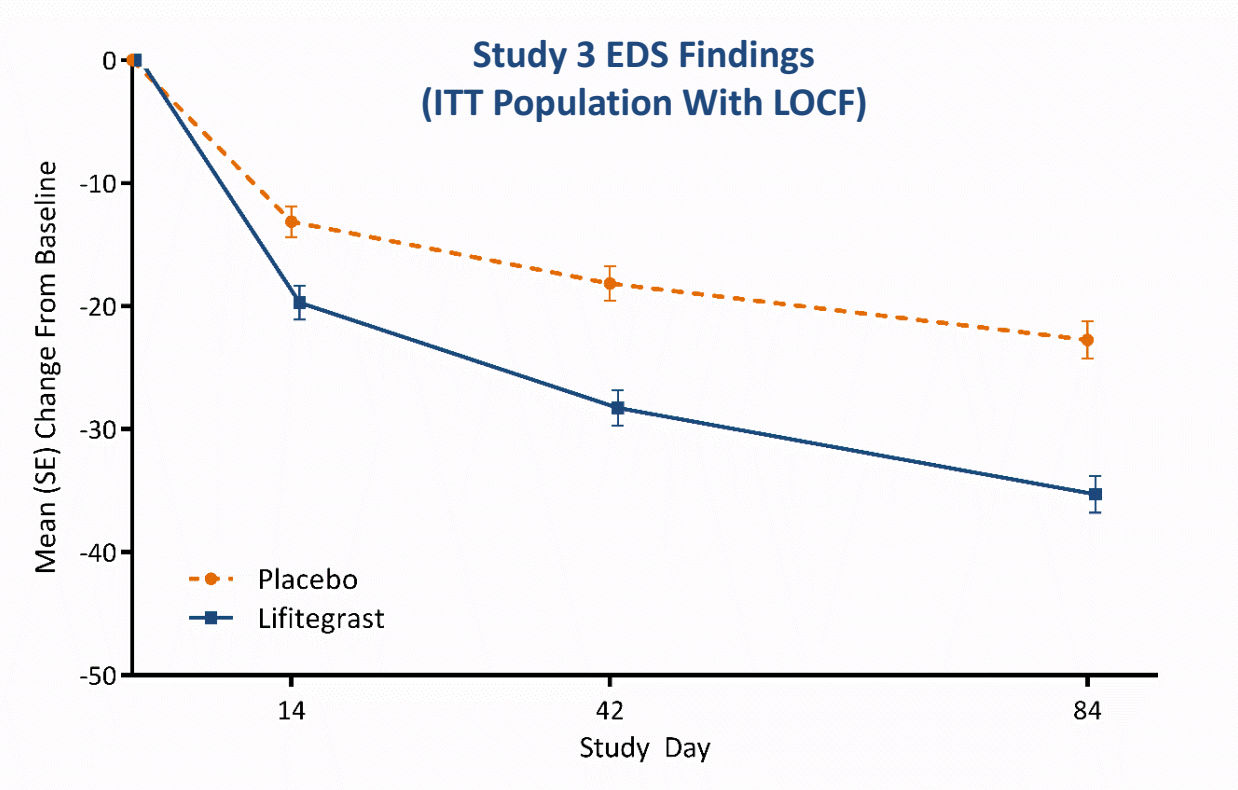
SIGN Change from Baseline to Day 84 in ICSS (Subjects With Mild to Moderate Symptoms)	SYMPTOM Change from Baseline to Day 84 in EDS (Subjects With Moderate to Severe Symptoms)
Study 1: treatment effect, 0.35; 95% CI, 0.05–0.65; *P*=0.0209	**Study 2 (post hoc*): treatment effect, 13.34; 95% CI, 2.35–24.33; nominal *P*=0.0178**
Study 2: treatment effect, 0.24; 95% CI, 0.10–0.38; *P*=0.0007	

- Coprimary sign endpoint met significance, validating Study 1
  - Effect on signs was more pronounced in less symptomatic subjects
- Effect on symptoms was more pronounced in subjects with moderate to severe baseline symptomatology
- Populations enrolled in Studies 1 and 2 were mildly to moderately symptomatic
- Based on findings of Studies 1 and 2, all subjects enrolled in Study 3 had prior artificial tear use and baseline EDS ≥40, and thus were moderately to severely symptomatic

*Subjects with prior artificial tear use and baseline EDS ≥40.

Study 3 Findings

- Coprimary sign endpoint (ICSS) was not met
- On coprimary symptom endpoint, lifitegrast significantly improved EDS versus placebo (treatment effect, 12.61; 95% CI, 8.51–16.70; *P*<0.0001)



- All prespecified secondary symptom endpoints achieved statistical significance

Learnings From Study 3

SIGN Change from Baseline to Day 84 in ICSS (Subjects With Mild to Moderate Symptoms)	SYMPTOM Change from Baseline to Day 84 in EDS (Subjects With Moderate to Severe Symptoms)
Study 1: treatment effect, 0.35; 95% CI, 0.05–0.65; *P*=0.0209	**Study 2 (post hoc*): treatment effect, 13.34; 95% CI, 2.35–24.33; nominal *P*=0.0178**
Study 2: treatment effect, 0.24; 95% CI, 0.10–0.38; *P*=0.0007	**Study 3: treatment effect: 12.61; 95% CI, 8.51–16.70; *P*<0.0001**

- Coprimary symptom endpoint met significance, validating Study 2 findings in this population of moderately to severely symptomatic subjects (baseline EDS ≥40) with history of artificial tear use
- Coprimary sign endpoint failed to separate from placebo in this more symptomatic population, suggesting a discordant behavior between the 2 coprimary variables

*Subjects with prior artificial tear use and baseline EDS ≥40.

Summary

SIGN Change from Baseline to Day 84 in ICSS (Subjects With Mild to Moderate Symptoms)	SYMPTOM Change from Baseline to Day 84 in EDS (Subjects With Moderate to Severe Symptoms)
Study 1: treatment effect, 0.35; 95% CI, 0.05–0.65; *P*=0.0209	**Study 2 (post hoc*): treatment effect, 13.34; 95% CI, 2.35–24.33; nominal *P*=0.0178**
Study 2: treatment effect, 0.24; 95% CI, 0.10–0.38; *P*=0.0007	**Study 3: treatment effect: 12.61; 95% CI, 8.51–16.70; *P*<0.0001**

- In 2 studies, lifitegrast improved **signs** of DED in subjects with mild to moderate baseline symptomatology
- In 2 studies, lifitegrast improved **symptoms** of DED in subjects with moderate to severe baseline symptomatology
- Lifitegrast appeared to be well tolerated in these studies with no serious ocular treatment-emergent adverse events

*Subjects with prior artificial tear use and baseline EDS ≥40.

Observations

- As in previous DED research, outcomes for signs and symptoms of DED are poorly correlated in the lifitegrast clinical trials
- For EDS, there may be a “floor effect” (seen in Study 2) in which efficacy can be demonstrated only when baseline symptoms are sufficiently severe
- In contrast, subjects with high baseline ICSS grades may have underlying conditions not responsive to a short course of treatment, or there may be difficulties in grading ICSS
- Because of the paradoxical relationship between signs and symptoms of DED observed in the lifitegrast clinical trials, it may not be possible to achieve statistical success with coprimary (sign and symptom) endpoints in the same study

Conclusions

- In 3 randomized, double-masked, controlled trials, lifitegrast improved inferior corneal staining score in subjects with mild to moderate symptomatology and eye dryness score in subjects with moderate to severe symptomatology at baseline
- Lifitegrast merits consideration as a treatment for signs and symptoms of DED