A Randomized, Prospective Controlled, Phase II Study of a Topical Anti-TNFα Agent with Biomarkers in the Treatment of Ocular Discomfort in Severe Dry Eye Disease

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On behalf of the OCS-02/LME636 DED PoC Phase 2 trial investigators

Commercial Relationships Disclosure: Eric Donnenfeld, M.D.

I am a consultant for:

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TNFα is involved in dry eye disease

Inflammatory infiltrates in conjunctiva and increased tear TNFα levels

Inflammation in DED tissue

- CD4 T cell infiltrates in conjunctiva of DED patients[1]

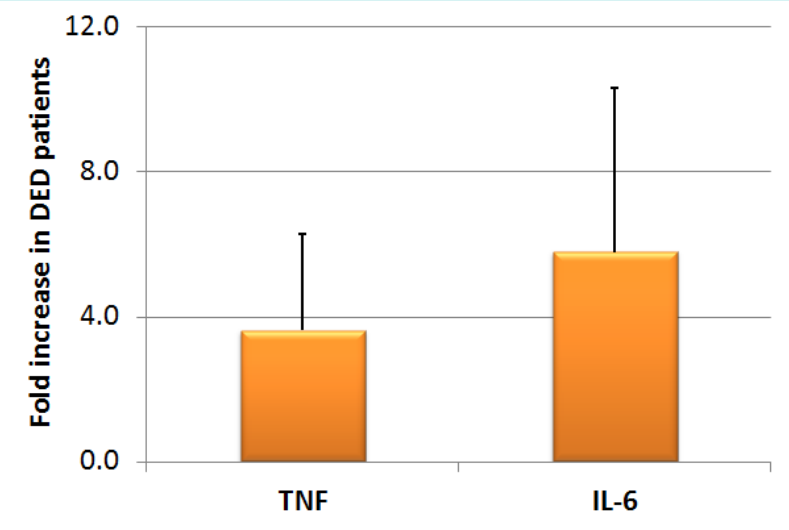
TNFα is involved

- Increased TNFα and IL-6 concentrations in tears and conjunctiva of DED patients[2]
- TNF antagonists are efficacious in animal models of DED[3]

Need for local delivery

- Systemic treatment of Sjögren patients with TNFα antagonists was not efficacious[4] (may be due to insufficient drug levels on ocular surface)

Anti-CD4 staining of conjunctiva[1]

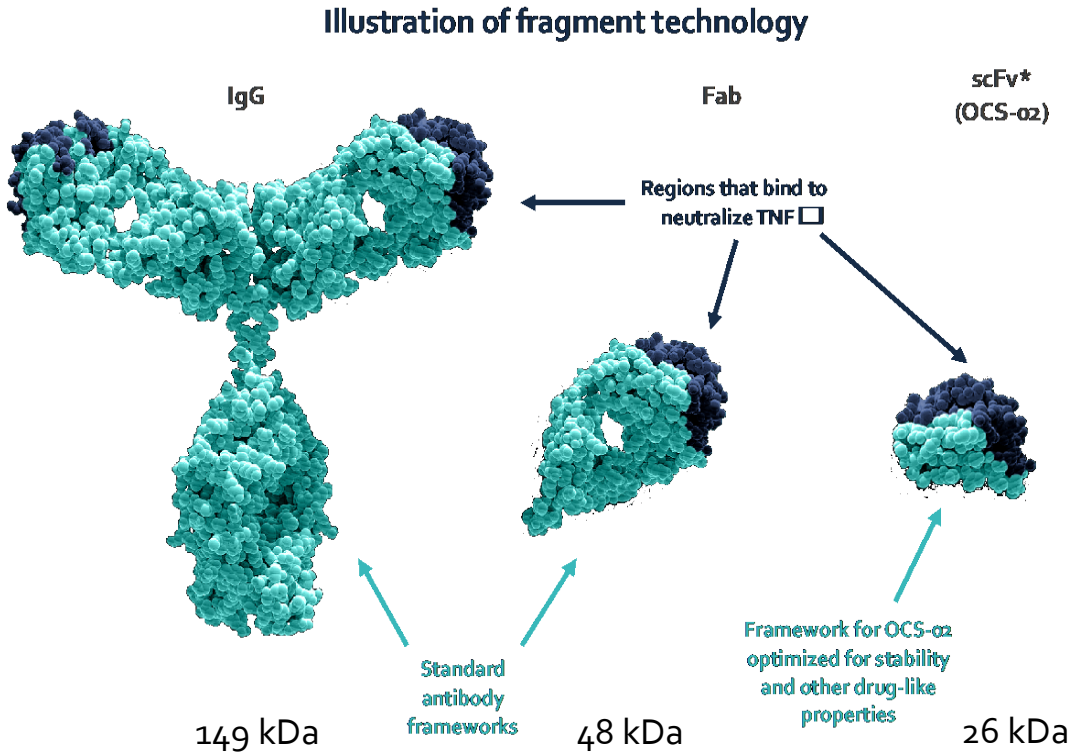


[1]Stern 2002, Pflugfelder 1999, Jones 1998; [2]Lee 2013, Massingale 2009, Boehm 2009, Lam 2009, Li 2008, Yoon 2007; [3]Ji 2013, Li 2012, Trousdale 2005; [4]Sankar 2004, Mariette 2004, Zandbelt 2004

OCS-02* anti-inflammatory MoA aligns with DED mechanism of disease

Developed as an eye drop to to block TNFα

- **OCS-02 is a first-in-class humanized antibody fragment (scFv) that inhibits the inflammatory cytokine TNFα**
- **It is formulated as an eye drop.** It penetrates the conjunctiva and anterior chamber
- **OCS-02 binds to human TNFα with very high affinity**
- It binds soluble as well as transmembrane TNFα
- In DED, the anti-inflammatory effect of TNFα inhibition has the potential to persistently relieve ocular discomfort, with good tolerability and a rapid onset of action

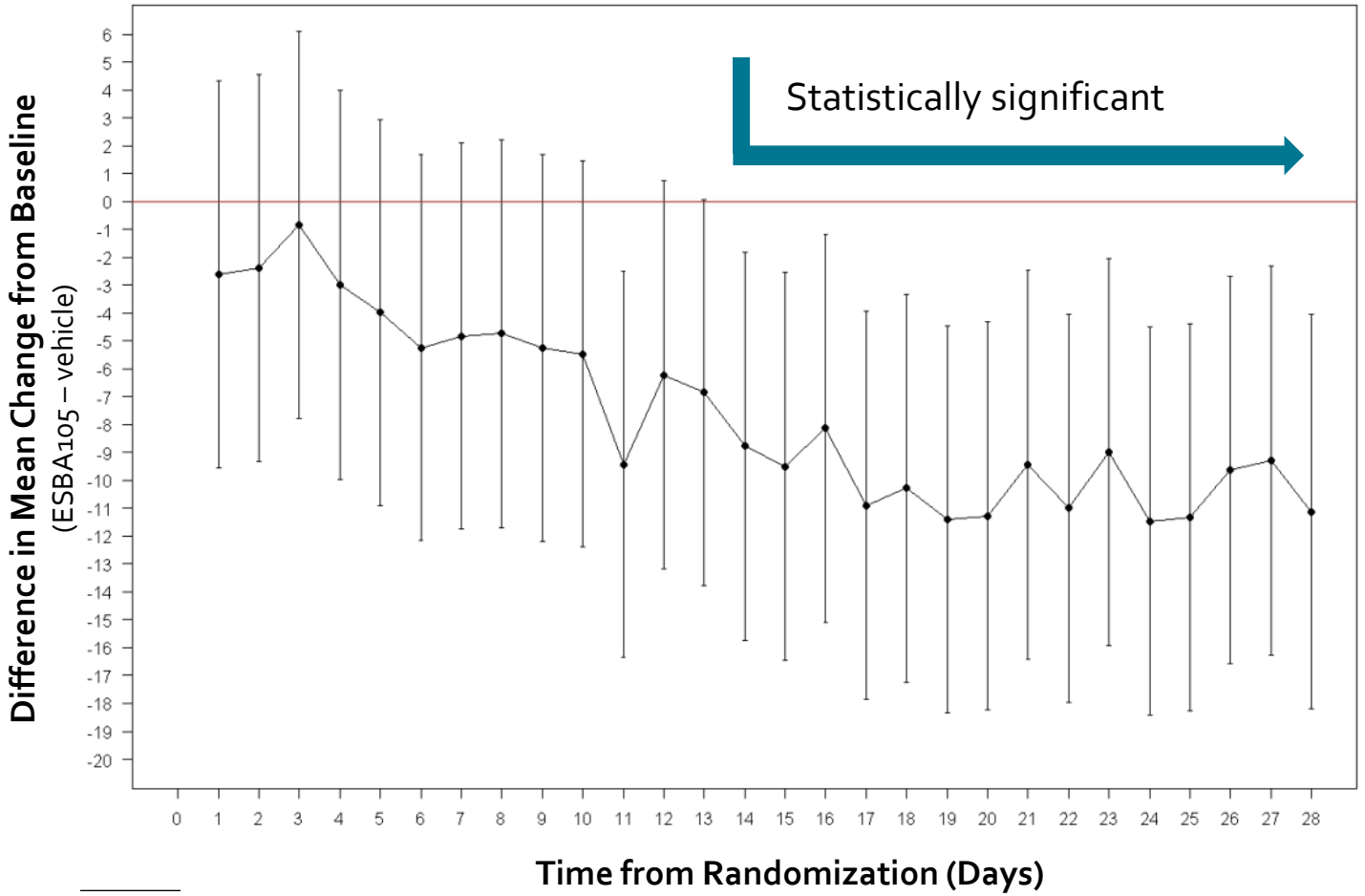


*OCS-02 was formelly known as LME636

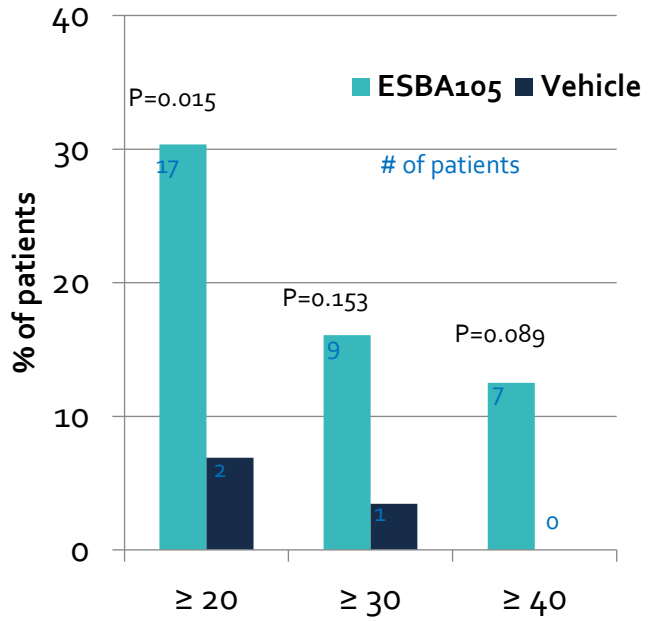
1st generation anti-TNFα scFv: ESBA105 improved ocular discomfort in DED

Positive mean change from baseline and responder analysis (post-hoc)

A) Mean change from baseline



B) Responder analysis



	ESBA105	Vehicle
N	56	29

Four PoC clinical trials have been conducted with the precursor ESBA105: healthy volunteers, PK, AAU and DED

Potencies of TNFα inhibitors

OCS-02 has greater potency than adalimumab and infliximab*

TNFα inhibitor	IC_{50} (ng/mL)	IC_{50} (pM)	Relative potency to OCS-02 (IC_{50} of OCS-02 (pM)/IC_{50} of inhibitor (pM))
OCS-02	1.2	44 ± 4	1.0
ESBA105	12.9	492 ± 41	0.09
Etanercept	1.8	12 ± 1	3.69
Certolizumab pegol	2.1	42 ± 3	1.06
Adalimumab	9.2	61 ± 4	0.73
Infliximab	15	100 ± 5	0.44
Golimumab	3.2	21 ± 2	2.11

- *as measured by molar concentration
- Potencies of TNFα inhibitors in inhibiting TNFα-induced apoptosis in L929 cells
- ESBA105 is a predecessor to OCS-02 that binds primate and human TNFα. OCS-02 binds to human TNFα but not to TNFα from any of the other species

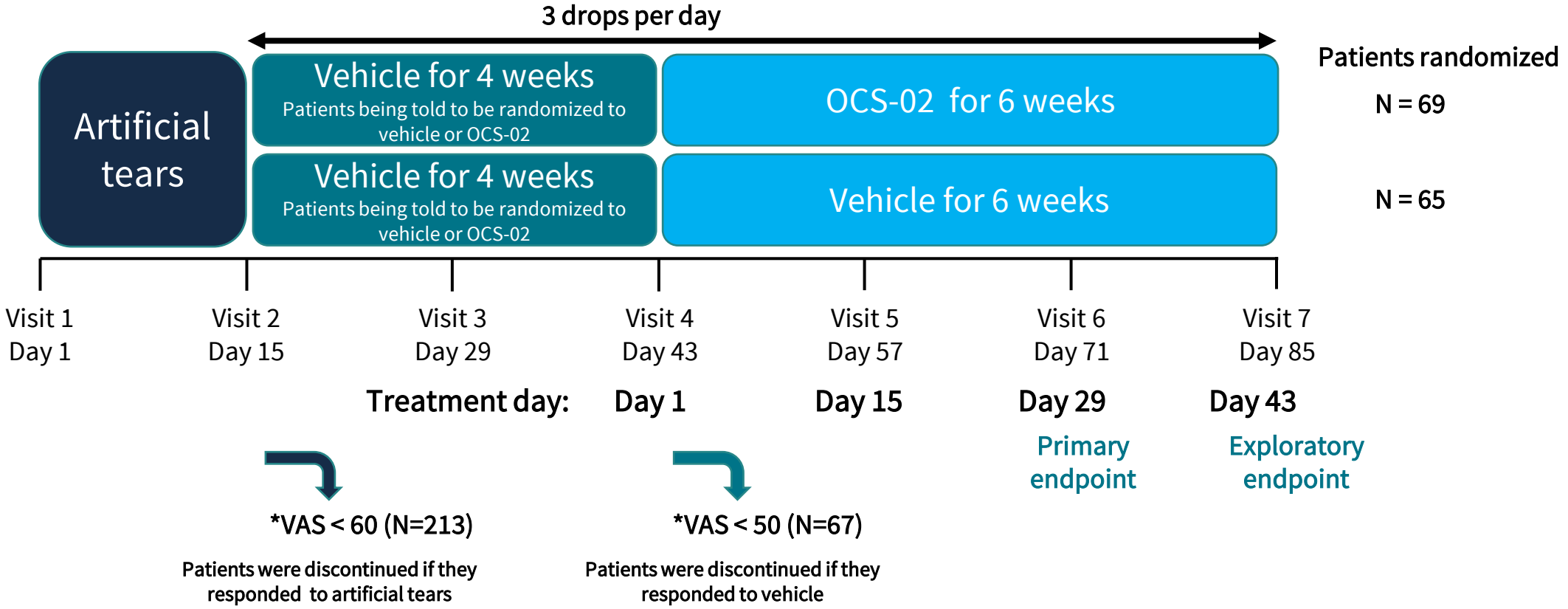
OCS-02 PoC Phase 2 trial in dry eye disease

Study design focused on reducing the variability of treatment results

Primary endpoint: global ocular discomfort score at Day 29 (composite of frequency and severity)

Secondary endpoint: percentage of patients with improvement in global ocular discomfort score >20

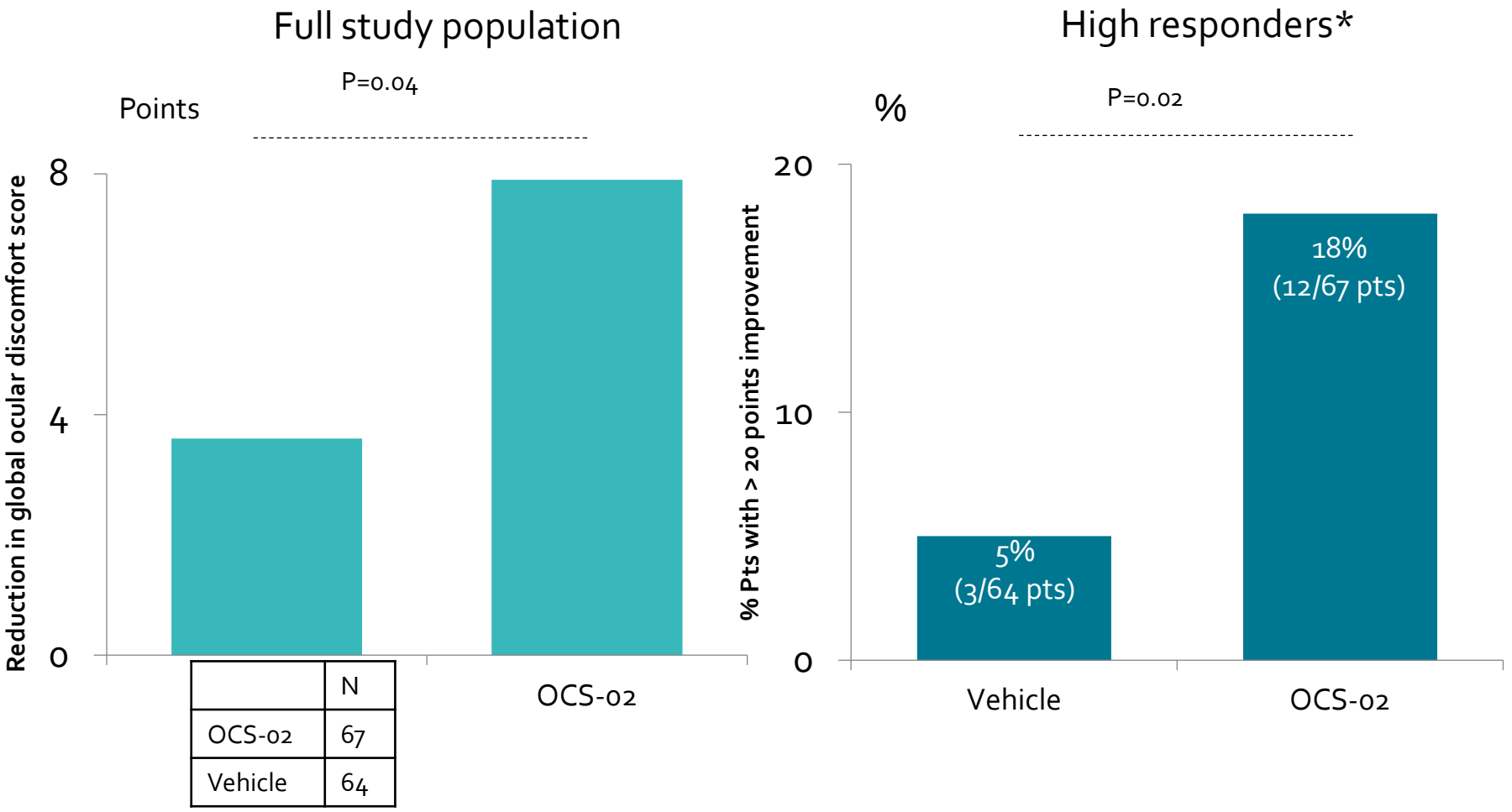
Exploratory Pharmacogenetic sub study



*VAS: visual analog scale

OCS-02 PoC Phase 2 efficacy results

Change from baseline in global ocular discomfort score was statistically significant



* High responders defined as the subjects who presented with > 20 points improvement on the global ocular discomfort score

Safety

No meaningful safety clinical findings

- The most common AEs in the OCS-02 group were dry eye and eye pruritus:
  - Each reported in 2 (2.9%) and 0 (0%) in the vehicle group
- Vehicle: 1 patient had an SAE (pneumonia)
- OCS-02: 1 patient discontinued treatment due to conjunctivitis
- Mean changes from baseline in IOP by treatment group were minimal
  - –0.3 mmHg for OCS-02 and +0.2 mmHg for Vehicle at treatment day 43 and similar in all study arms

Ocular TEAEs*

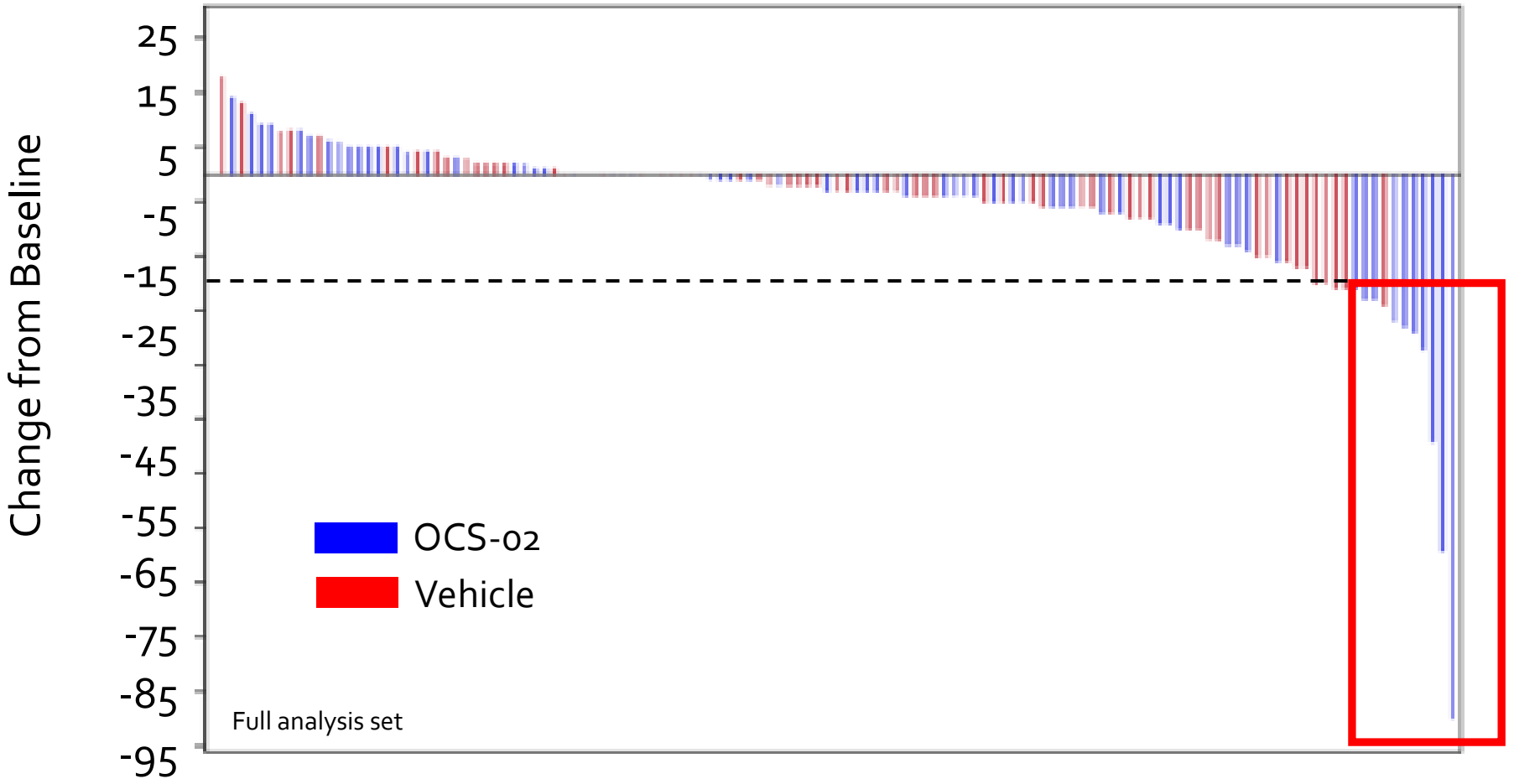
Severity (Any event)	OCS-02 n=69 (%)	Vehicle n=65 (%)
Mild	7 (10.1)	2 (3.1)
Moderate	2 (2.9)	0 (0.0)
Severe	0 (0.0)	0 (0.0)

Safety Analysis Set
*Treatmetn Emergent Adverse Events

CSR Tables 12.15, 14.87, 14.93, 14-101

OCS-02 PoC Phase 2 results in dry eye

Some patients responded dramatically to OCS-02



High responders: patients with > 20 points improvement on the Global Ocular Discomfort Score

A pre-planned pharmacogenetic sub study was used to elucidate the high response to treatment

- **It required a separate informed consent signed at the same time as the main informed consent for the primary study**

SNP screening for global ocular discomfort score

Patients with identified SNP did not show any effect on response to vehicle, regardless of genotype

Treatment	Genotype	LS Mean change	SE	(90% CI)	Nominal p-value
OCS-02	CC (n=4)	-29.48	6.52	(-40.34, -18.61)	<0.0001
	CT (n=25)	-0.09	3.52	(-6.01, 5.83)	
	TT (n=14)	-3.90	3.51	(-9.79, 1.99)	
Vehicle	CC (n=8)	-1.08	3.74	(-7.32, 5.15)	0.9863
	CT (n=19)	-4.05	2.82	(-8.77, 0.67)	
	TT (n=16)	-4.03	2.80	(-8.71, 0.65)	

Patients treated with OCS-02 or vehicle for 29 day. Per protocol analysis set

- The polymorphism variant identified is determined by the single change from the reference nucleotide T to C.
- The prevalence of CC (each C alllele inherited from a parent) is 19.9% and 12.7% in Caucasian and African, respectively, as reported in 1000 human genome database.
  - In this study, the prevalence of CC was 11.5% (11/96) and 12.7% (2/19) in Caucasian and African, respectively

SNP: Single Nucleotide Polymorphism (gene sequence variant in a particular position) as compared to the reference genome
SNP Genotype: the combination of nucleotide variants from each parent

Genetic Biomarker is associated with soluble TNFR1

sTNFR1 is associated with other human inflammatory/ autoimmune diseases and may help modulate TNFα activity in DED

- *rs1800693* causes exon-6 skipping* and results in soluble TNFR1 (sTNFR1) and increased TNFα responses
- Soluble TNFR1 (sTNFR1) is constitutively released by TNFα -converting enzyme, and its level increases in the course of various human inflammatory/autoimmune diseases
  - Tear sTNFR1 increased in **Sjögren syndrome and GVHD**
  - Intraocular sTNFR1 increased in **uveitis**
- In contrast, periodic syndrome (an autoinflammatory disorder) is caused by autosomal-dominant mutations in the TNFR1 gene that prevents production of sTNFR1
- Mechanistic studies: sTNFR1 may act as physiological attenuator of TNFα activity or may function as a buffer system to enhance the effect of TNFα or may increase signaling to TNFα through intracellular localization

Source: Gregory et al. Nature. 2012; Housley et al. Sci Transl Med. 2015; *Sakimoto et al. IOVS. 2014*; *Sugita et al. IOVS. 2007*; *McDermott et al. Cell. 1999; Van et al. PNAS. 1992; Aderka et al. J. Exp. Med. 1992*

* part of the gene sequence is spliced out by mRNA and consequently the protein generated is different than the original

Conclusions

Positive PoC Phase 2 in DED and a potential genetic biomarker for OCS-02 response identified

- **Primary endpoint: OCS-02 showed a statistically significant change from baseline in global ocular discomfort score**
- In addition, there was a dramatic response to treatment in a subset of patients
- **Among the 8 SNPs tested, in the pre specificed pharmacogenetics sub study, one SNP in the TNFR1 gene showed significant effect on the response to OCS-02**
    - Genotype effect on symptomatic improvement existed in the patients who were treated with OCS-02 only but not in those who were treated with vehicle
    - **Patients with CC genotype tended to have larger improvement than those with CT or TT genotypes.**
- Biological mechanism underlying the pharmacogenetic finding is being further explored

OCS-02, a novel topical anti-TNFα has demonstrated statistically significant effect in symptoms of DED. The the role of a genetic variant in the response to treatment will be further evaluated

Thank you

OCS-02 DED PoC Phase 2 Trial Principal Investigators, Study Team and Participants

- Marc Abrams
- James Branch
- William Christie
- Charles Crane
- Jung Dao
- Michael Endl
- Asra Firozvi
- Robert Foerster
- Ronald Frenkel
- Gary Jerkins
- Edward Koo
- Norman Liu
- Jodi Luchs
- Joseph Martel
- Eugene McLaurin
- Edward Meier
- Andrew Moyes
- Matthew Paul
- James Peace
- Allison Rand
- Steven Rauchman
- Kenneth Sall
- Michael Sheety
- Philip Shettle
- Blake Simmons
- Stephen Smith
- Stacy Smith
- Matthew Swanic
- Navin Tekwani
- Michael Tran
- David Wirta