Advances in the Management of Noninfectious Uveitis

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Background

Uveitis is 5th leading cause of vision loss in developed countries[1]

- Macular edema (ME) is the leading cause of vision impairment and vision loss in uveitis[2]
- ME is common
  - 40% to 60% of intermediate, pan-, and posterior uveitis[3]
  - 20% anterior[3]

Therapeutic options for ME

- Local periocular and intravitreal corticosteroids
- Systemic corticosteroids and steroid-sparing medications

1. Karim et al; Clin Ophthalmol. 2013;7:1109
2. Dick AD; *Br J Ophthalmol*. 1994;78:1
3. Lardenoye CWTA et al. *Ophthalmology*. 2006;113(8):1446

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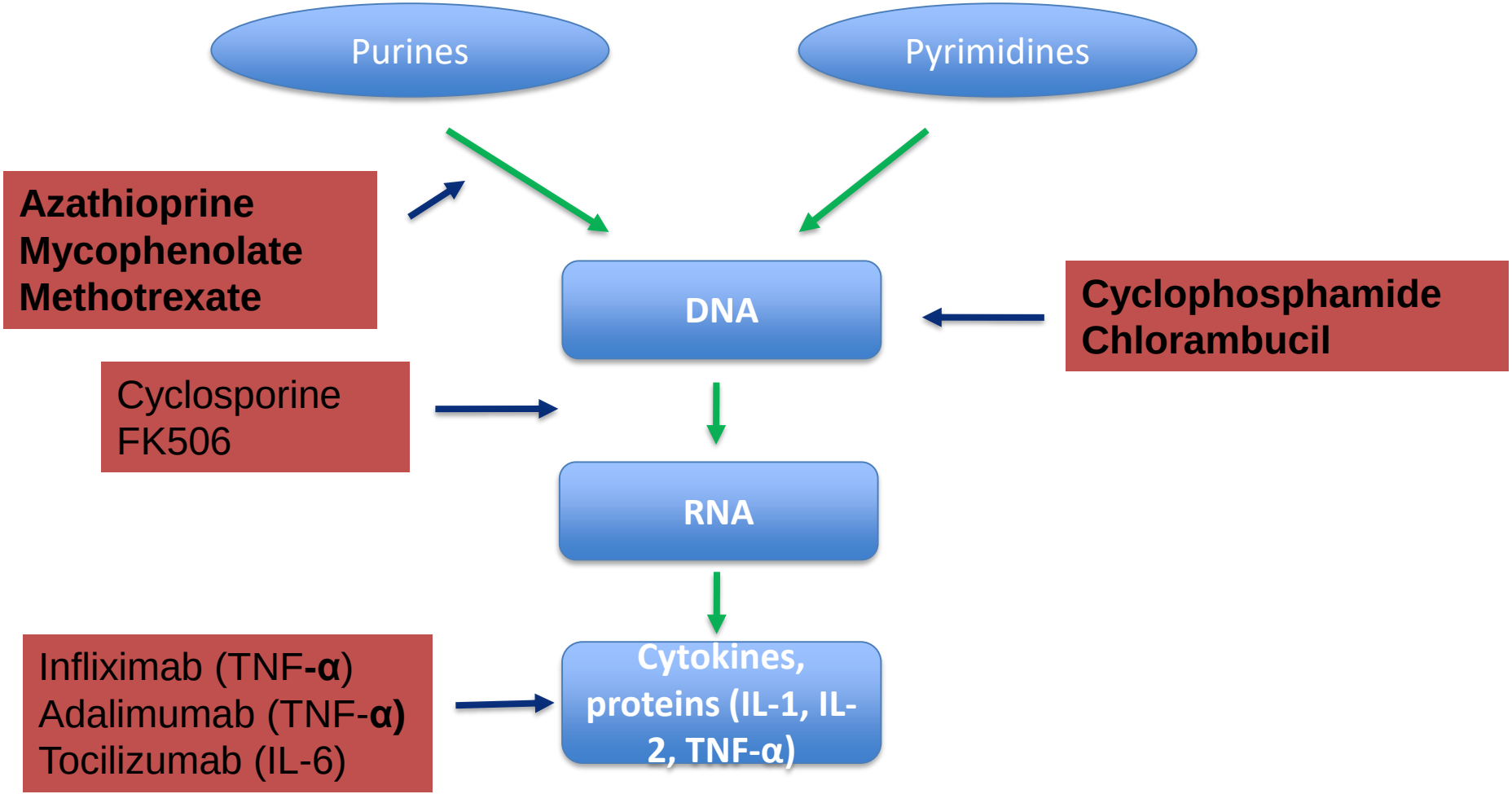

Purines
Pyrimidines
Azathioprine
Mycophenolate
Methotrexate
DNA
Cyclophosphamide
Chlorambucil
Cyclosporine
FK506
RNA
Infliximab (TNF-α)
Adalimumab (TNF-α)
Tocilizumab (IL-6)
Cytokines, proteins (IL-1, IL-2, TNF-α)

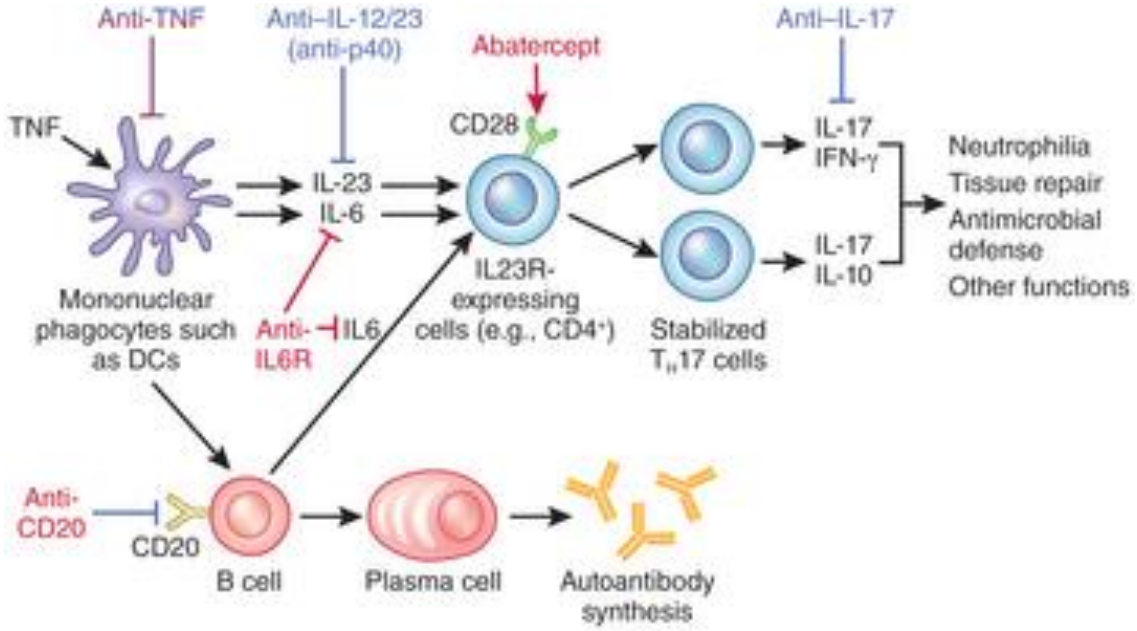
What is a "Biologic"?

"Wide range of products…vaccines, blood, and blood components.. gene therapy, tissues, and recombinant therapeutic proteins.. *Biologics* are isolated from a variety of natural sources – human, animal or microorganism – and may be produced by biotechnology methods"

www.fda.gov

	Biologics	Conventional Drugs
Manufacturing process	Manufactured in a living system	Chemical synthesis
Chemical structure	Complex, sometimes difficult to characterize	Well-defined structure

Biologic Therapies



Anti-TNF
Infliximab (Remicade)
Adalimumab (Humira)
Certolizumab (Cimzia)
Etanercept (Enbrel)

Anti-IL-6
Tocilizumab (Actemra)

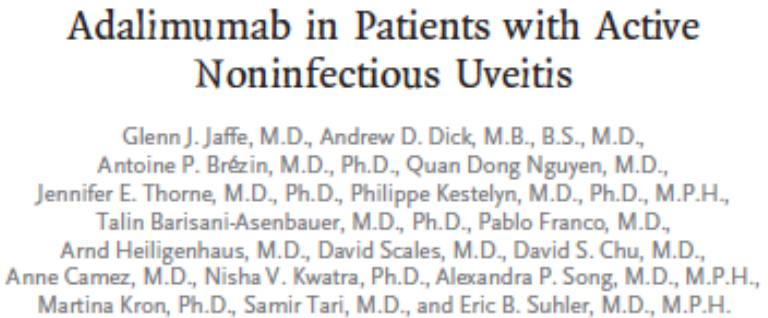
CTLA4-IgG1 fusion protein (Co-stimulation inhibitor)
Abatacept (Orencia)

Cho, Feldman *Nature Medicine* 2015

Adalimumab (Humira) for active uveitis

Multinational phase 3 trial for **active** intermediate, posterior or panuveitis

- 1:1 Randomization
  - Adalimumab (80 mg loading, 40 mg q 2 weeks) vs. placebo
- Patients received oral prednisone burst, followed by tapering over 15 weeks
- **Primary Efficacy Endpoint: Time to treatment failure after 6 weeks**
- Treatment Failure: Multi-component outcome based on new inflammatory lesions, BCVA, AC cell, and vitreous haze



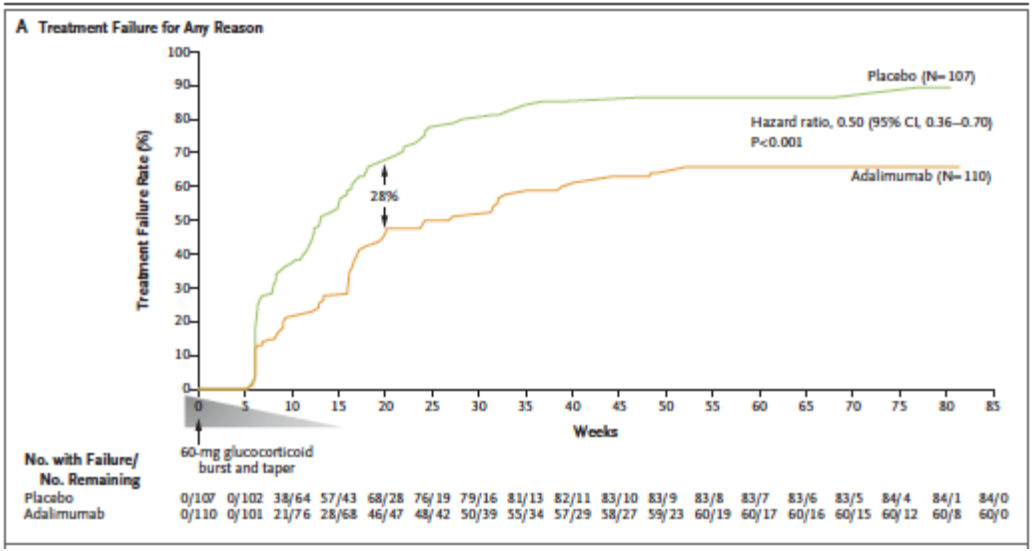
Adalimumab in Patients with Active Noninfectious Uveitis

Glenn J. Jaffe, M.D., Andrew D. Dick, M.B., B.S., M.D., Antoine P. Brézin, M.D., Ph.D., Quan Dong Nguyen, M.D., Jennifer E. Thorne, M.D., Ph.D., Philippe Kestelyn, M.D., Ph.D., M.P.H., Talin Barisani-Asenbauer, M.D., Ph.D., Pablo Franco, M.D., Arnd Heiligenhaus, M.D., David Scales, M.D., David S. Chu, M.D., Anne Camez, M.D., Nisha V. Kwatra, Ph.D., Alexandra P. Song, M.D., M.P.H., Martina Kron, Ph.D., Samir Tari, M.D., and Eric B. Suhler, M.D., M.P.H.

Jaffe et al *NEJM 2016*

Adalimumab (Humira) for active uveitis

Treatment failure for any reason



Time to treatment failure was 24 weeks in the adalimumab group vs. 13 weeks in the placebo group

Adalimumab group less likely than placebo to have treatment failure (Hazard ratio 0.50, 95% CI 0.36 to 0.70, P< 0.001)

Jaffe et al *NEJM 2016*

Adalimumab (Humira) for inactive uveitis

Multinational phase 3 trial for inactive intermediate, posterior or panuveitis in patients on prednisone 10 – 35 mg/day

- 1:1 Randomization
  - Adalimumab (80 mg loading, 40 mg q 2 weeks) vs. placebo
- Mandatory prednisone taper at week 2
- **Primary Efficacy Endpoint: Time to treatment failure**
- Treatment Failure: Multi-component outcome based on new inflammatory lesions, BCVA, AC cell, and vitreous haze

Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial

Quan Dong Nguyen, Pauline T Merrill, Glenn J Jaffe, Andrew D Dick, Shree Kumar Kurup, John Sheppard, Ariel Schlaen, Carlos Pavesio, Luca Cimino, Joachim Van Calster, Anne A Camez, Nisha V Kwatra, Alexandra P Song, Martina Kron, Samir Tari, Antoine P Brézin

Nguyen et al *Lancet 2016*

Adalimumab (Humira) for inactive uveitis

Treatment failure for any reason

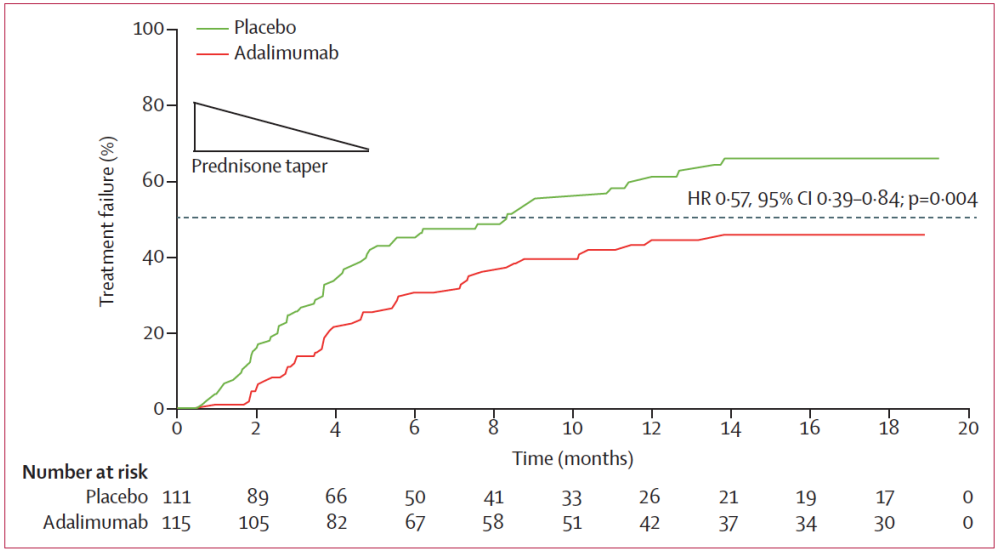


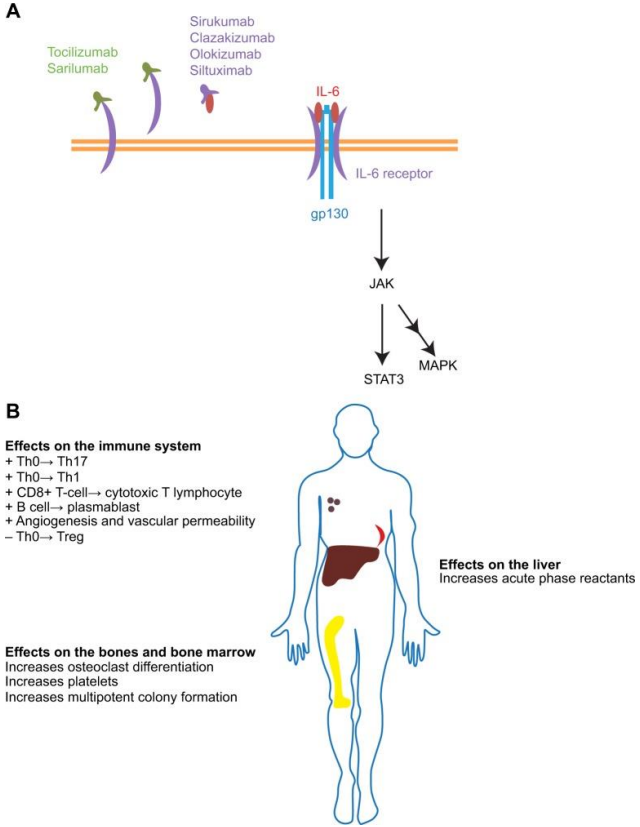
***Figure 2*: Kaplan–Meier plot of treatment failure for any reason**
HR=hazard ratio.

Time to treatment failure was 18 months in the adalimumab group vs. 8.3 months in the placebo group

Hazard ratio 0.57, 95% CI 0.39-0.84, P=0.004

Nguyen et al *Lancet 2016*

Interleukin-6 inhibition



Pleitropic cytokine implicated in many immune-mediated disorders including uveitis

Uveitis syndromes where IL-6 implicated include Behcet's disease, VKH and sarcoidosis

Cellular basis: Differentiation of T-cells into TH1 and TH17 cells

Signaling basis: IL-6/IL-6R binding → gp130 signal transduction → JAK/STAT pathways → IL-6 responsive genes (CRP, fibrinogen, VEGF)

Tocilizumab (Actemra) for refractory uveitis

Birdshot retinochoroidopathy (Calvo Rio et al)

- Two patients who had failed multiple agents (corticosteroid, TNF-alpha inhibition)
- Visual acuity and OCT improved in all four eyes
- Corticosteroid-sparing effect also observed

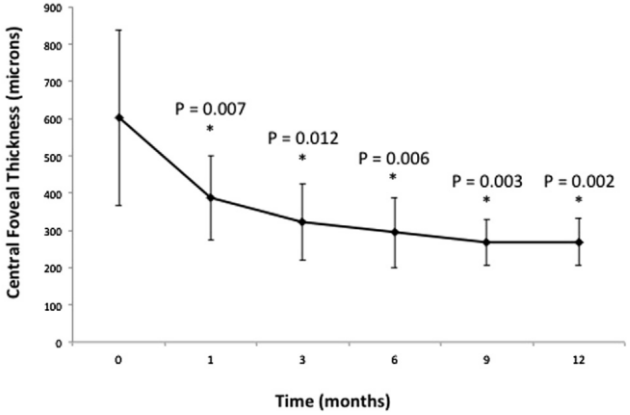
Uveitic macular edema (Deuter et al)

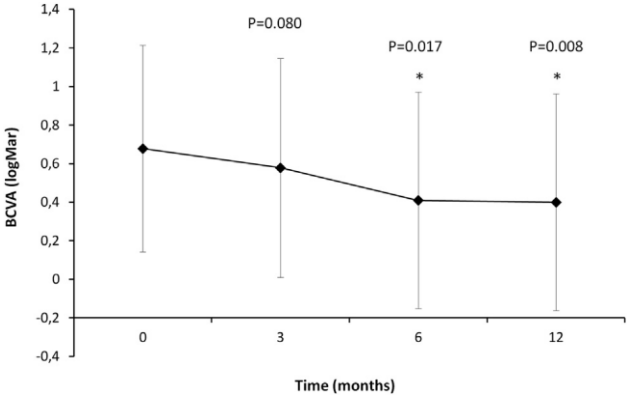
- Eight eyes of 5 patients treated previously with corticosteroid, at least one immunosuppressive drug, and a biologic
- At 3 months, >/= 25% reduction in macular edema achieved in 6 eyes (75%)
- Complete resolution of macular edema in 5 of eight eyes (62.5%)
- Tocilizumab was well-tolerated with no side effects

Calvo-Rio et al *Ocular Immunol and Inflammation*
Deuter et al *Ocular Immunol and Inflammation*

Long-term effects of tocilizumab for macular edema due to uveitis

- Eleven eyes of 7 patients
- Mean duration of ME was > 14.2 years; Mean F/U 15.2 months
- Diagnoses: Birdshot (3), JIA (3), Idiopathic panuveitis (1)
- Mean central foveal thickness improved from 550 um to 274 um at 12-months (P=0.002)
- Mean logMAR BCVA improved from 0.67 to 0.4 at 12-months (P=0.008)





Mesquida et al *Ophthalmol 2014*

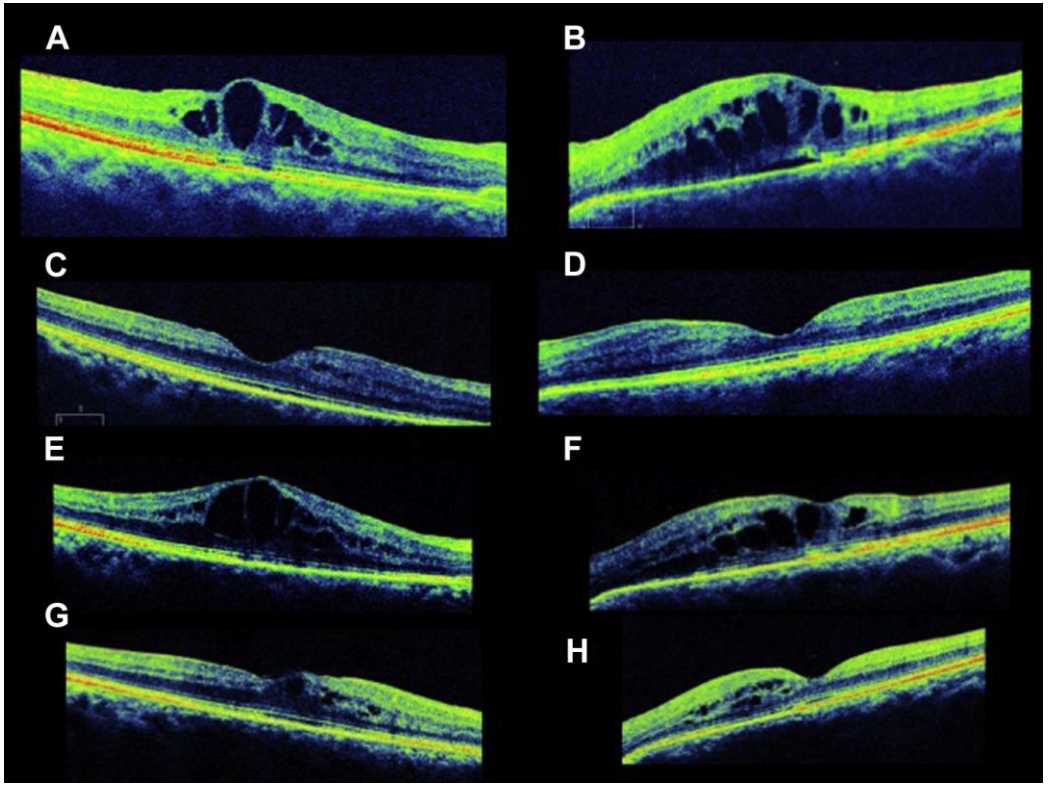
Long-term effects of tocilizumab for macular edema due to uveitis

Baseline

12 months

Medication withdrawal

Medication restarted



Mesquida et al *Ophthalmol 2014*

Rituximab for refractory scleritis and uveitis

Prospective, dose-ranging, randomized, double-masked Phase I/II clinical trial

Patients randomized to 500 mg (n=5) or 1000 mg (n=7) arms of rituximab at study day 1 and day 15

Primary outcome

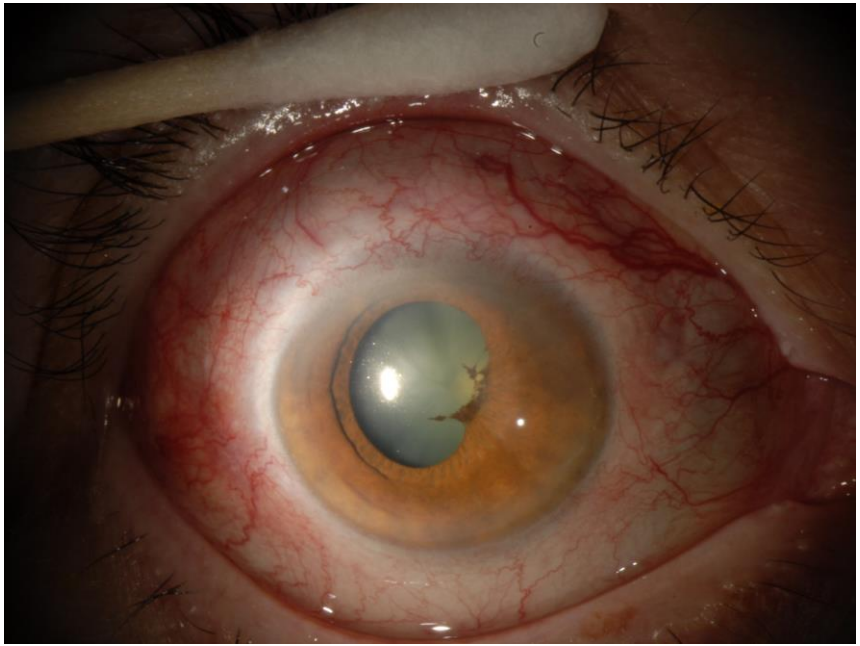
1. Reduction of inflammation by scleritis grading scale
2. Reduction of corticosteroid by ≥ 50%

Nine patients met SGS endpoint; 4 patients reduced corticosteroid by ≥ 50%

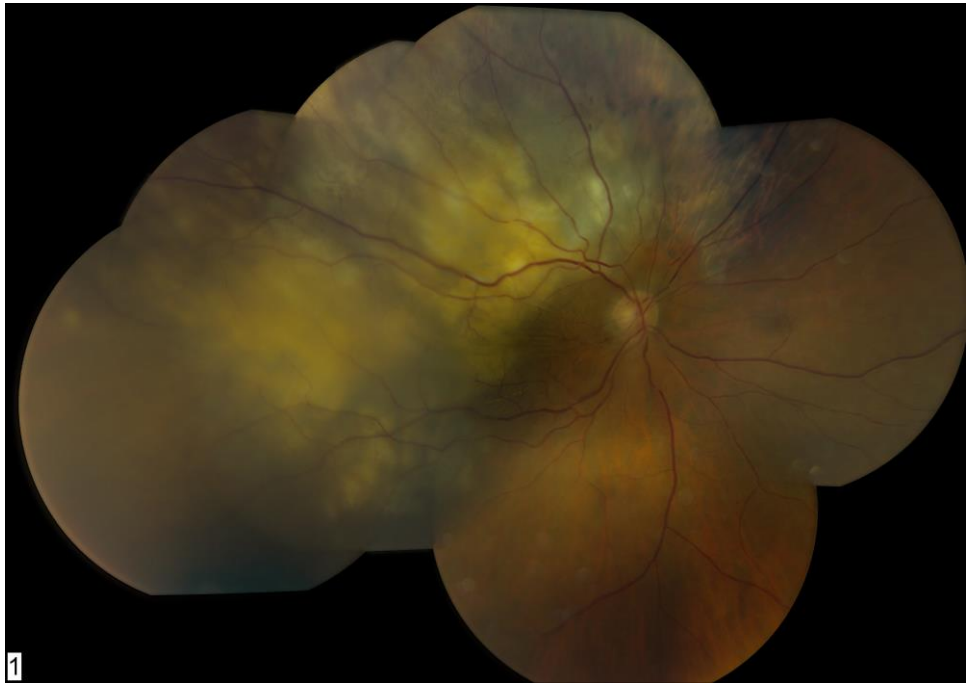
Suhler et al *Ophthalmology 2014*

Rituximab for refractory scleritis and uveitis

- 64 year-old female patient with rheumatoid arthritis & chronic inflammatory demyelinating polyneuropathy
- Bilateral, diffuse anterior and posterior scleritis with panuveitis
- Refractory/recurrent disease despite methotrexate, cyclophosphamide, adalimumab, oral prednisone



Rituximab for refractory scleritis and uveitis



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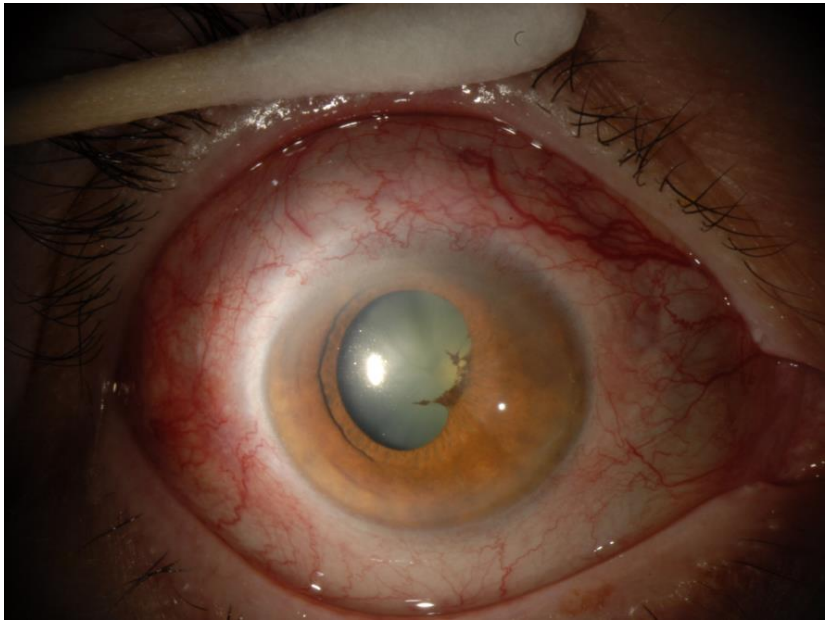

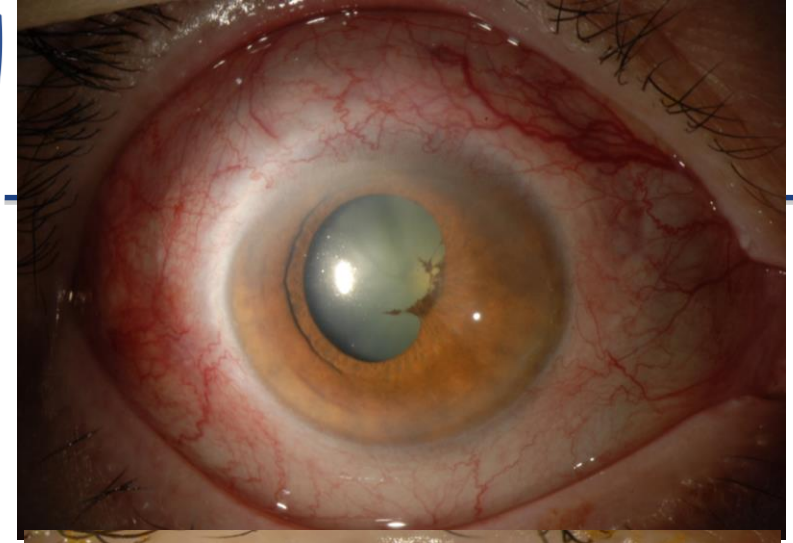

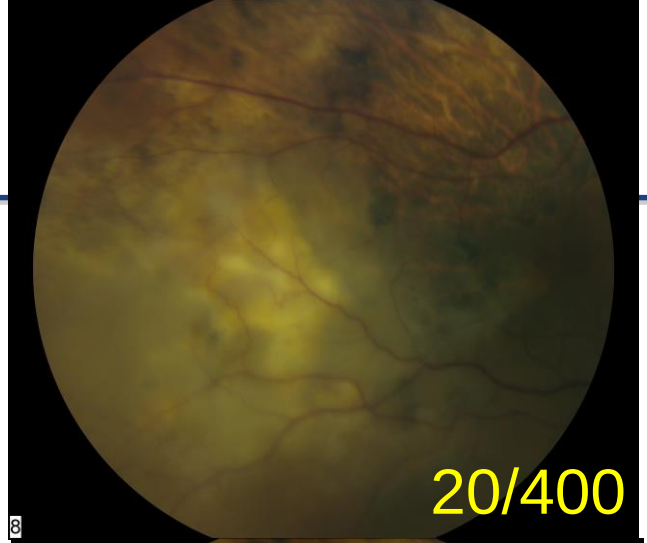
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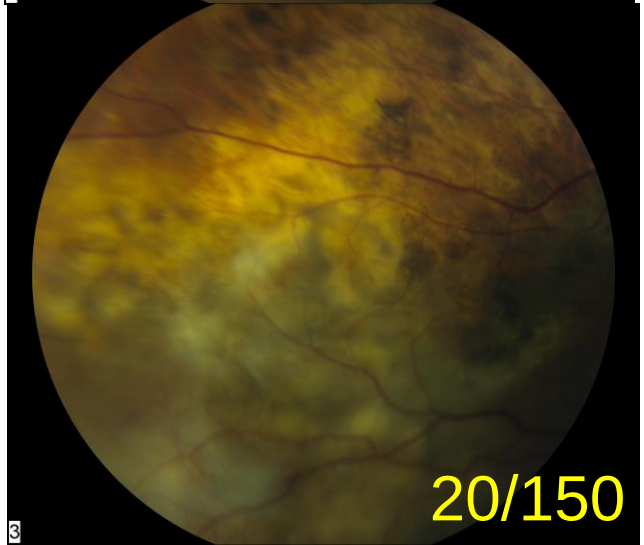
s/p Rituximab and IV solumedrol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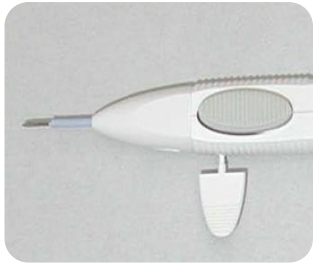
Local Corticosteroid and Immunotherapeutic Options

Dexamethasone
0.7 mg (Ozurdex)



Intravitreal injection

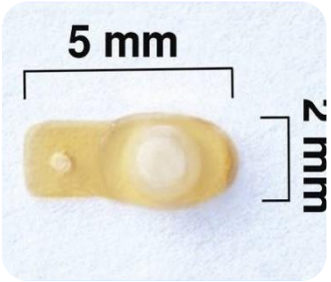
22-gauge

Duration: 4-6 months

HURON Trial

Lowder et al. *Arch Ophthalmol 2011*

Fluocinolone acetonide
0.59 mg (Retisert)



Surgical intravitreal implant

3.5 mm wound

Duration: 30 months

Multicenter Uveitis Steroid Treatment (MUST) Trial

Kempen, Jabs et al. *Am J Ophthalmol 2010*
Kempen, Jabs, et al *Ophthalmology 2011*

Triamcinolone acetonide
4 mg (Triescence; Kenalog)

Intravitreal; Periocular

25- or 27-gauge

Duration: 4-6 months

**POINT Trial Ongoing

Sen et al. *Ophthalmology 2014*
Leder, Thorne et al. *AJO 2011*

Novel Local Therapies

Fluocinolone acetonide implant

Jaffe et al. *Ophthalmology* 2016

Sirolimus (mTOR Inhibition)

Nguyen et al. *Ophthalmology* 2016 (SAKURA)

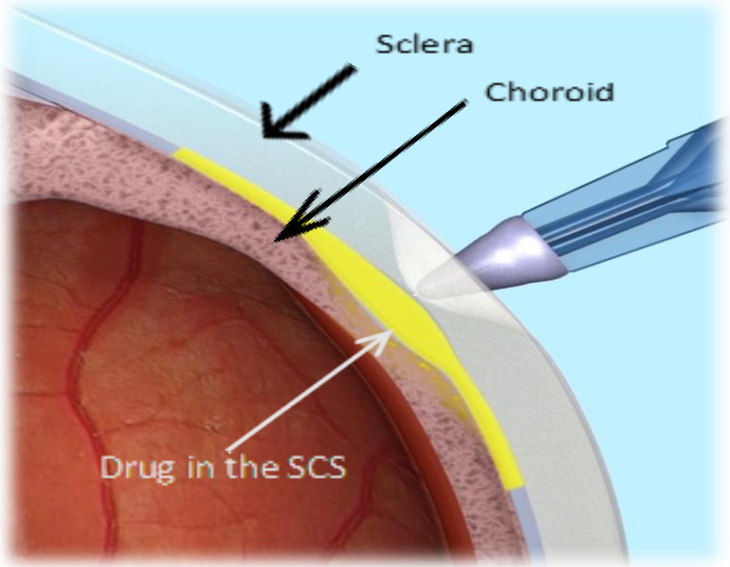
Ibrahim, Nguyen et al. *TVST* 2015 (SAVE)

Suprachoroidal triamcinolone acetonide

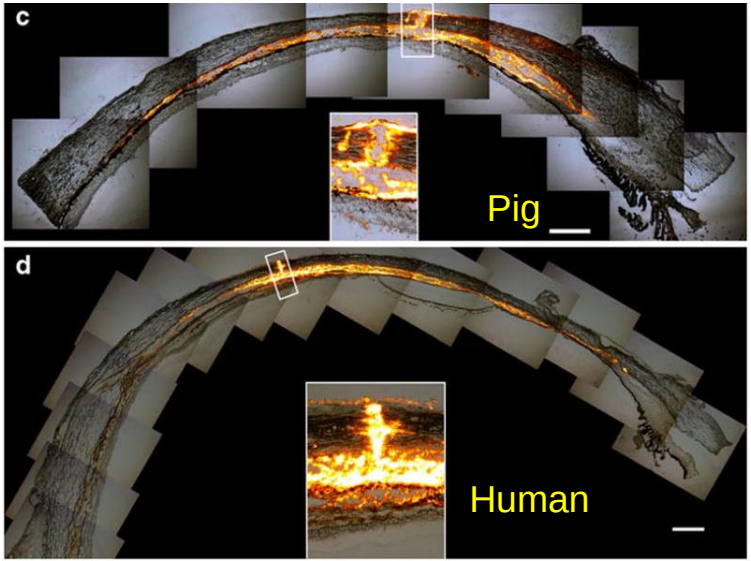
Goldstein et al. *TVST* 2016

Suprachoroidal Injection for Posterior Segment Disease

- **Novel technique for suprachoroidal injection**
  - 30G needle approx. 1000 micron in length
  - Proprietary microinjector syringe
- **Potential benefits**
  - Efficacy advantages due to higher bioavailability
  - Longer duration
  - Fewer side effects

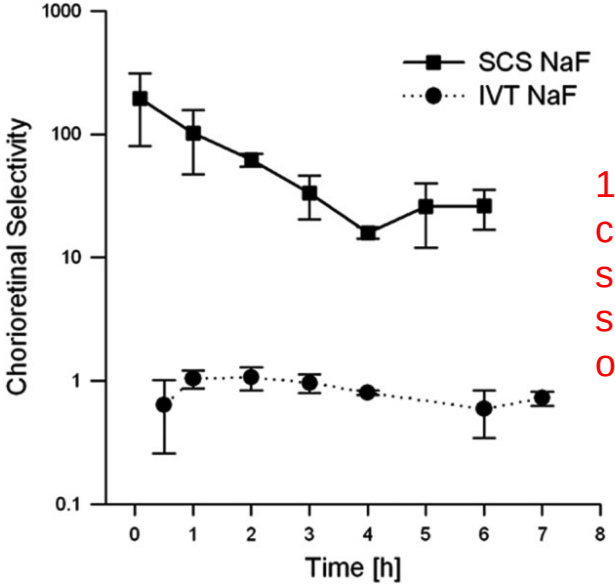


Suprachoroidal Drug Delivery: Laboratory Investigation



Rhodamine-tagged nanoparticles

Patel S., Lin, A, Edelhauser, H.F., Prausnitz, M.R.
Pharm Research 2011



10-fold greater chorioretinal selectivity with suprachoroidal over IVT

Chorioretinal Selectivity =
Concentration of NaF at choroid/retina interface versus lens/vitreous

Patel S. et al *IOVS 2012*

Suprachoroidal Corticosteroid Administration for Noninfectious Uveitis: Phase I/II Study

Study Design

- Single suprachoroidal injection of triamcinolone acetonide (TA) 4 mg/0.1 mL) following topical anesthetic
- Safety, tolerability, and preliminary efficacy evaluated
- 26-week follow-up

Participants (Anatomic Classification)

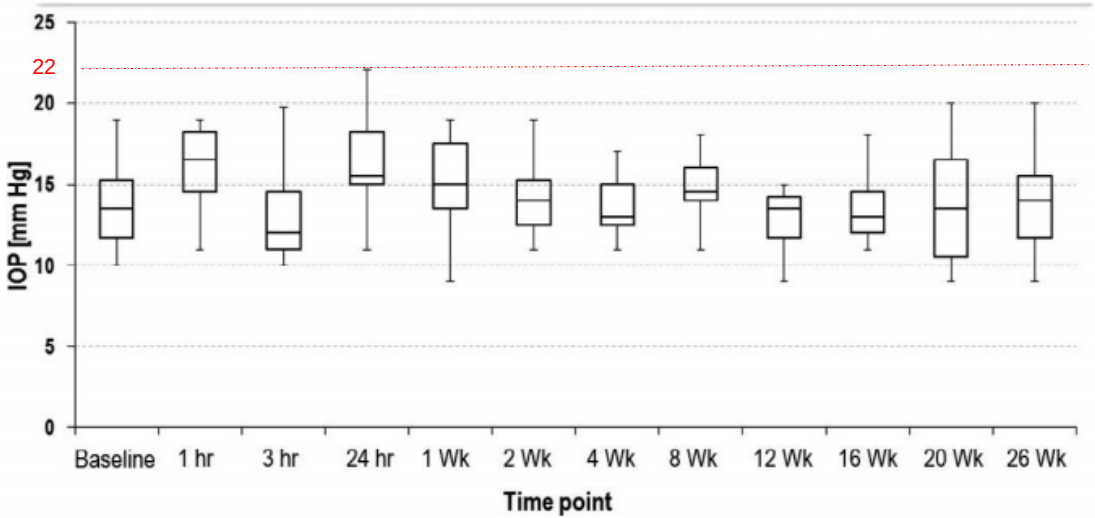
- Anterior/Intermediate (3, 33%)
- Intermediate (1, 11%)
- Panuveitis (5, 56%)

Goldstein et al; *TVST* Dec 2016

Suprachoroidal Corticosteroid Administration for Noninfectious Uveitis: Safety and Tolerability

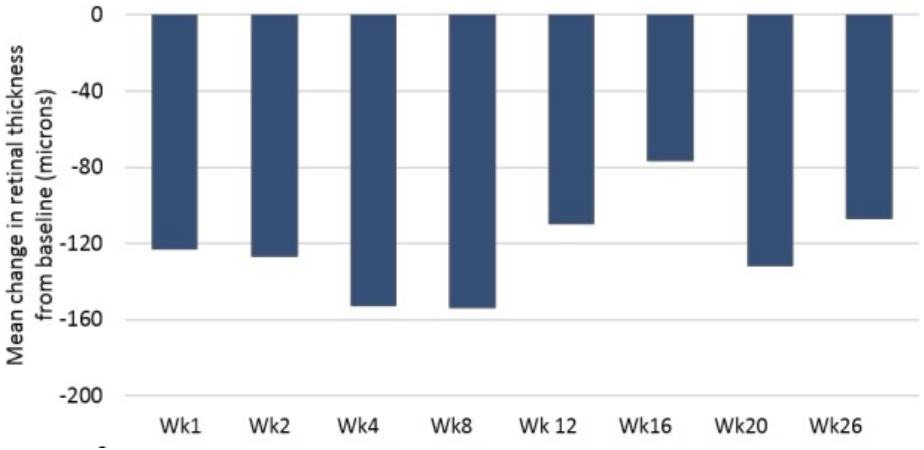
Table 2. Ocular Adverse Events

Adverse Event (MedDRA Preferred Term)	Incidence, $N = 11$, n (%)	No. of Events
Eye pain	5 (45)	6
Cystoid ME[a]	3 (27)	4
Visual acuity reduced	2 (18)	2
Vision blurred[b]	1 (9)	2
Cataract[b]	1 (9)	1
Cataract operation[b]	1 (9)	1
Eye irritation	1 (9)	1
Eyelid margin crusting	1 (9)	1
Punctate keratitis	1 (9)	1
Retinal ischemia	1 (9)	1
Retinal neovascularization	1 (9)	1
Uveitis	1 (9)	1



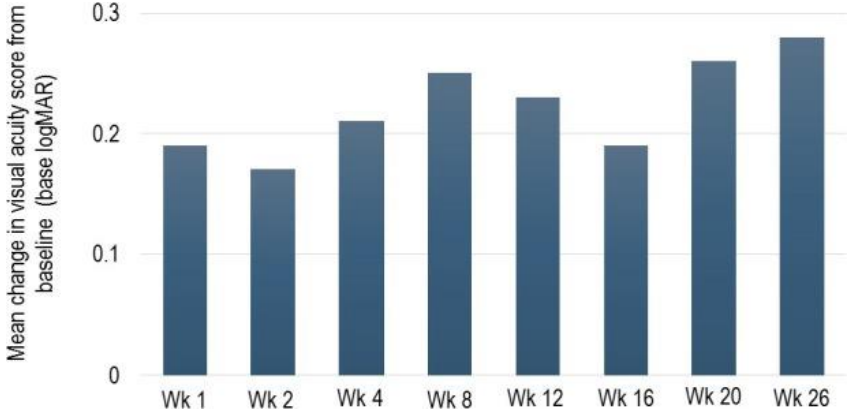
Goldstein et al; *TVST* Dec 2016

Suprachoroidal Corticosteroid Administration for Noninfectious Uveitis: Efficacy



Central retinal thickness reduction

- Mean reduction in CRT 154 um by week 8
- 20% reduction in baseline CRT in 4/7 patients

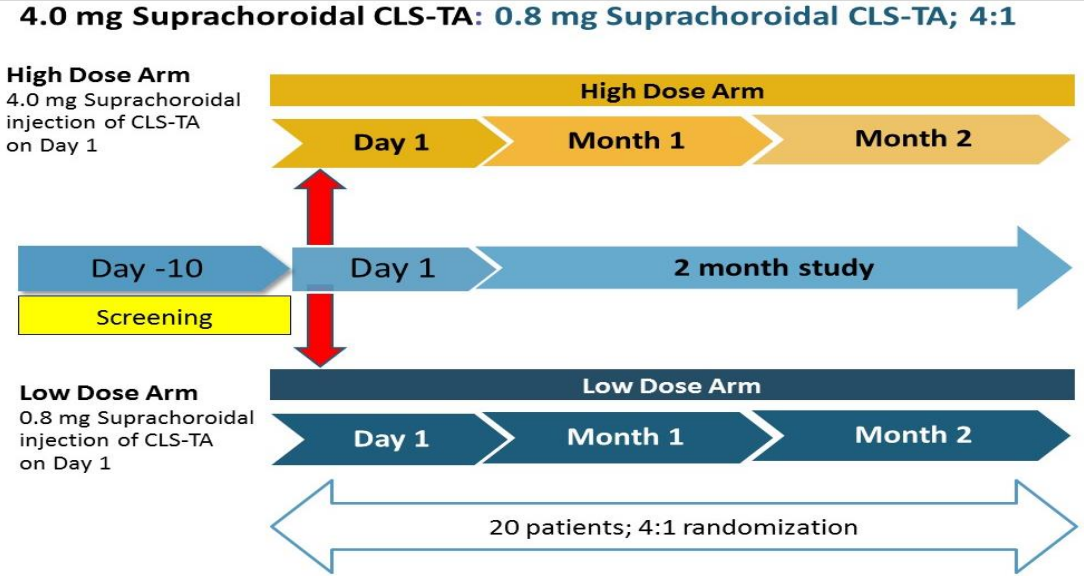


Visual acuity improvement

- Mean logMAR VA improvement ranged from 0.17 to 0.28 (i.e. 8 to 14 letters)

Goldstein et al; *TVST* Dec 2016

Phase 2 DOGWOOD Study Design



- The study was a randomized, masked, controlled, multi-center study in subjects with uveitis
- Macular edema ≥310 µm in the central subfield (CSF) using a Heidelberg Spectralis
- ETDRS BCVA score of ≥ 20 letters read (20/400 Snellen approximate) in each eye
- Study was powered only for the 4.0 mg dose; only these data will be presented

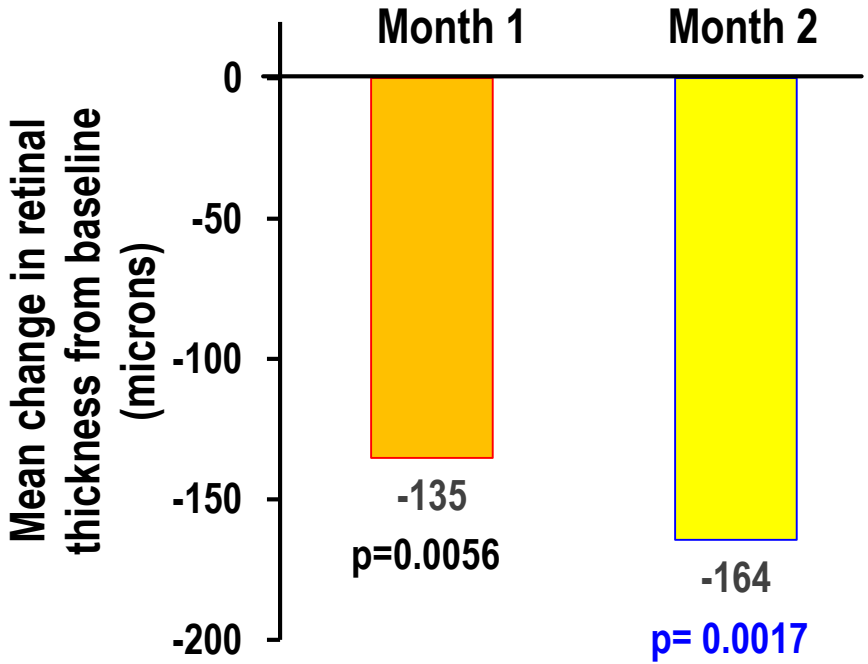
Diagnosis Overview / Uveitis Distribution

	CLS-TA 4.0 mg (N=17)	CLS-TA 0.8 mg (N=5)	Total (N=22)
Classification of Uveitis n (%)			
Study Eye			
Anterior Uveitis	2 (11.8)	2 (40.0)	4 (18.2)
Intermediate Uveitis	5 (29.4)	2 (40.0)	7 (31.8)
Posterior Uveitis	1 (5.9)	0	1 (4.5)
Panuveitis	9 (52.9)	1 (20.0)	10 (45.5)

Diagnosis Overview / Uveitis Distribution

Diagnoses Associated with Noninfectious Uveitis – N (%)	CLS-TA 4.0mg (N=17)	CLS-TA 0.8mg (N=5)	Total (N=22)
Idiopathic	12 (70.6)	2 (40.0)	14 (63.6)
Sarcoidosis	3 (17.6)	1 (20.0)	4 (18.2)
Behcet's Syndrome	1 (5.9)	0	1 (4.5)
HLA-B27 Related	1 (5.9)	0	1 (4.5)
Birdshot Retinochoroidopathy	2 (11.8)	0	2 (9.1)
Pars Planitis	2 (11.8)	1 (20.0)	3 (13.6)
Other	0	1 (20.0)	1 (4.5)

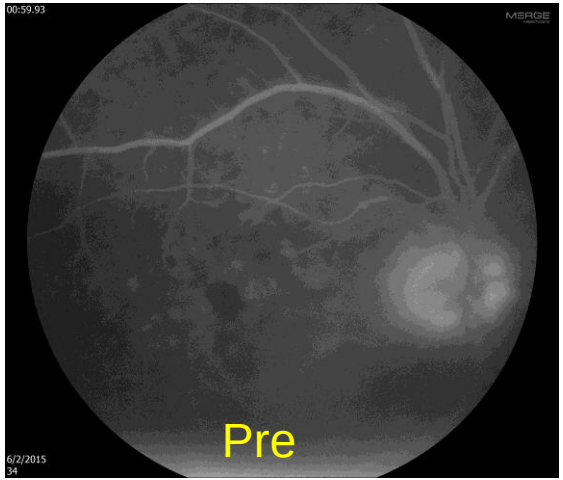
Reduction in Central Subfield Thickness (4 mg)

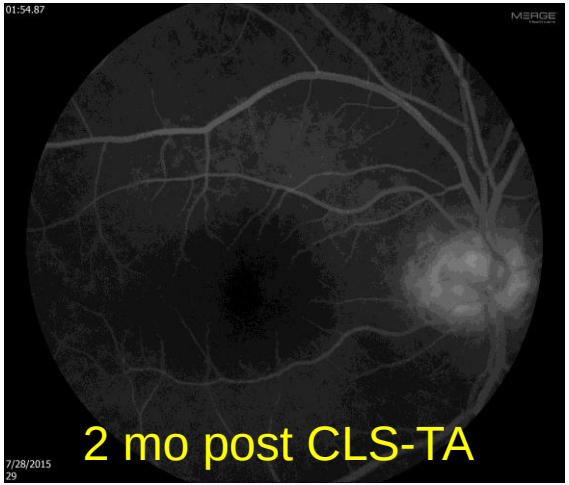


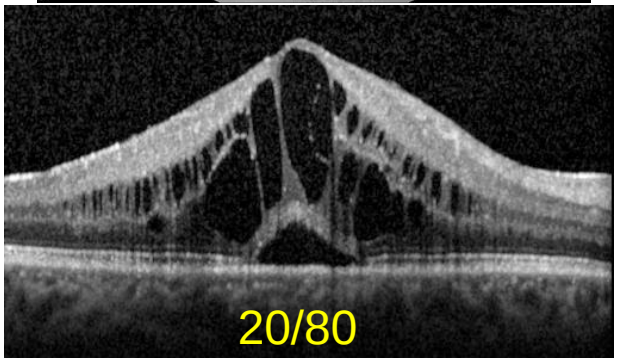
N=16
ITT population

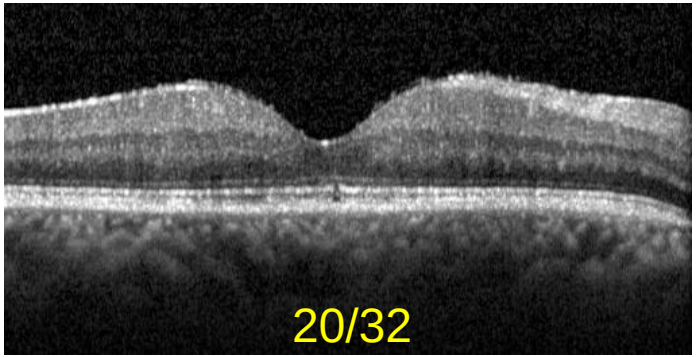
Mean baseline = 526 µm

Illustrative Patient

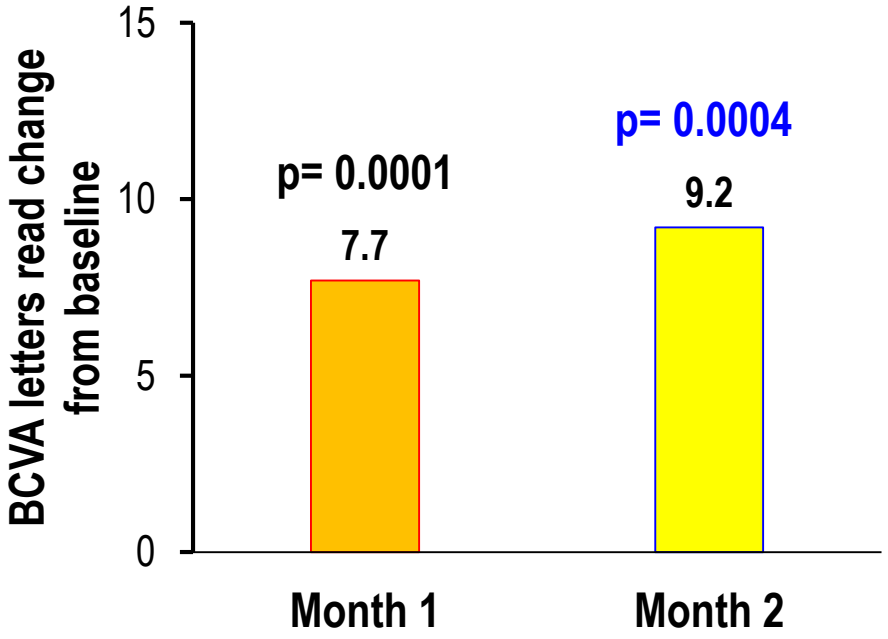








Visual Acuity Improvement: 4.0 mg Dose



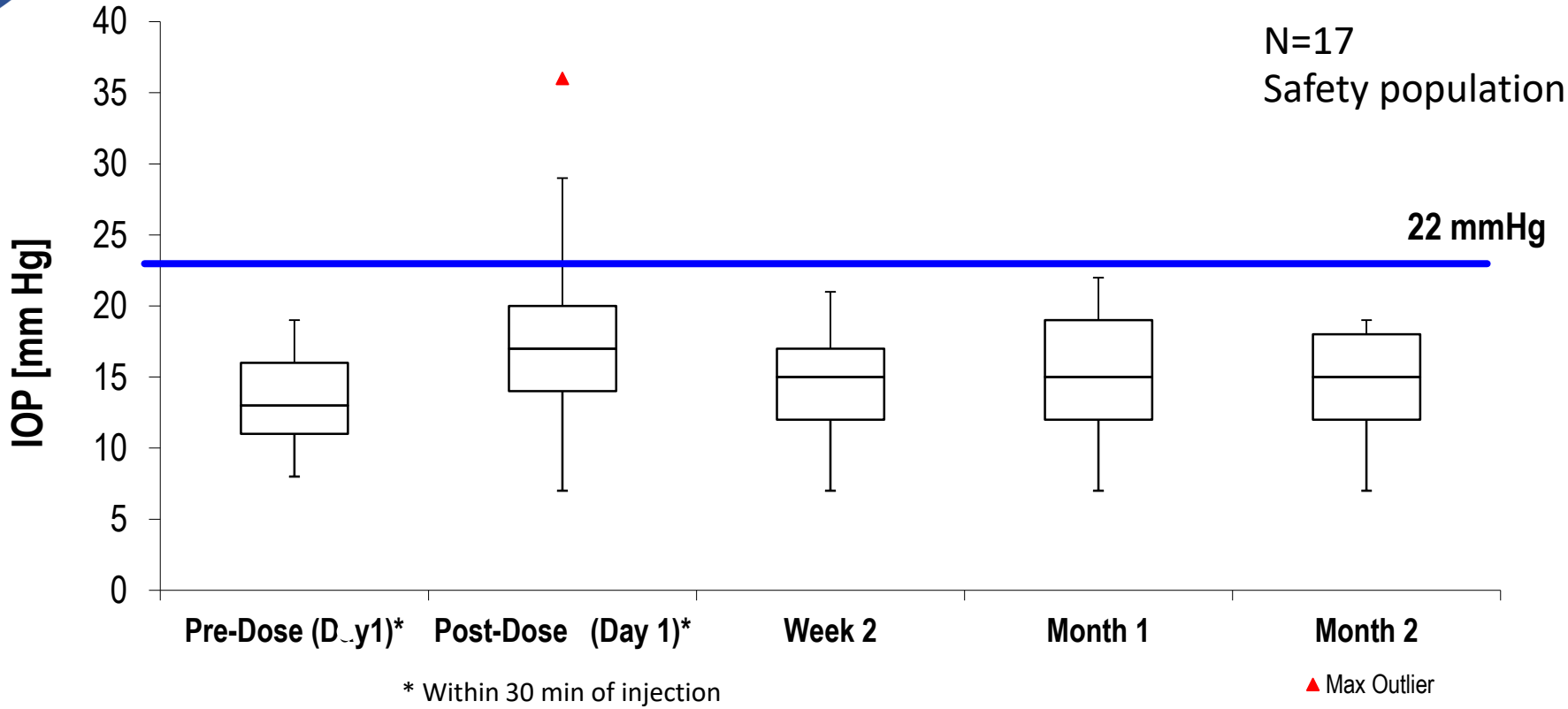
N=17
ITT population

Mean baseline = 60 letters

Ocular Adverse Events

Parameter	CLS-TA 4.0 mg N=17; n (%)
Total number of adverse events	**12**
Number of subjects with at least 1 AE	8 (47)
Eye Disorders	**6 (35)**
Conjunctival hemorrhage	1 (6)
Conjunctival edema	1 (6)
Dry Eye	1 (6)
Eye Pain	3 (18)
Ocular discomfort	1 (6)
Punctate keratitis	1 (6)
Uveitis	1 (6)
General disorders and admin. Site Conditions	**2 (12)**
Injection site pain	1 (6)
Papillitis	1 (6)
Intraocular pressure increased	1 (6)

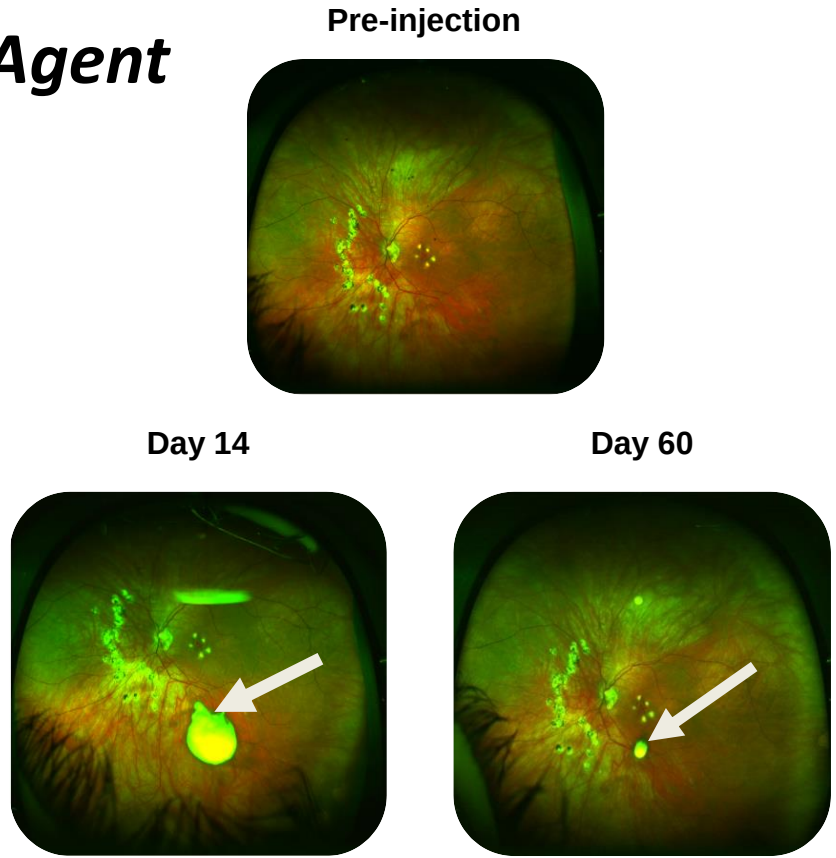
Intraocular pressure - 4.0 mg Dose



Intraocular Pressure Safety Set Listing 16.2.6-1.3 (1/18/16)

Intravitreal Sirolimus:
A Novel Immunoregulatory Agent

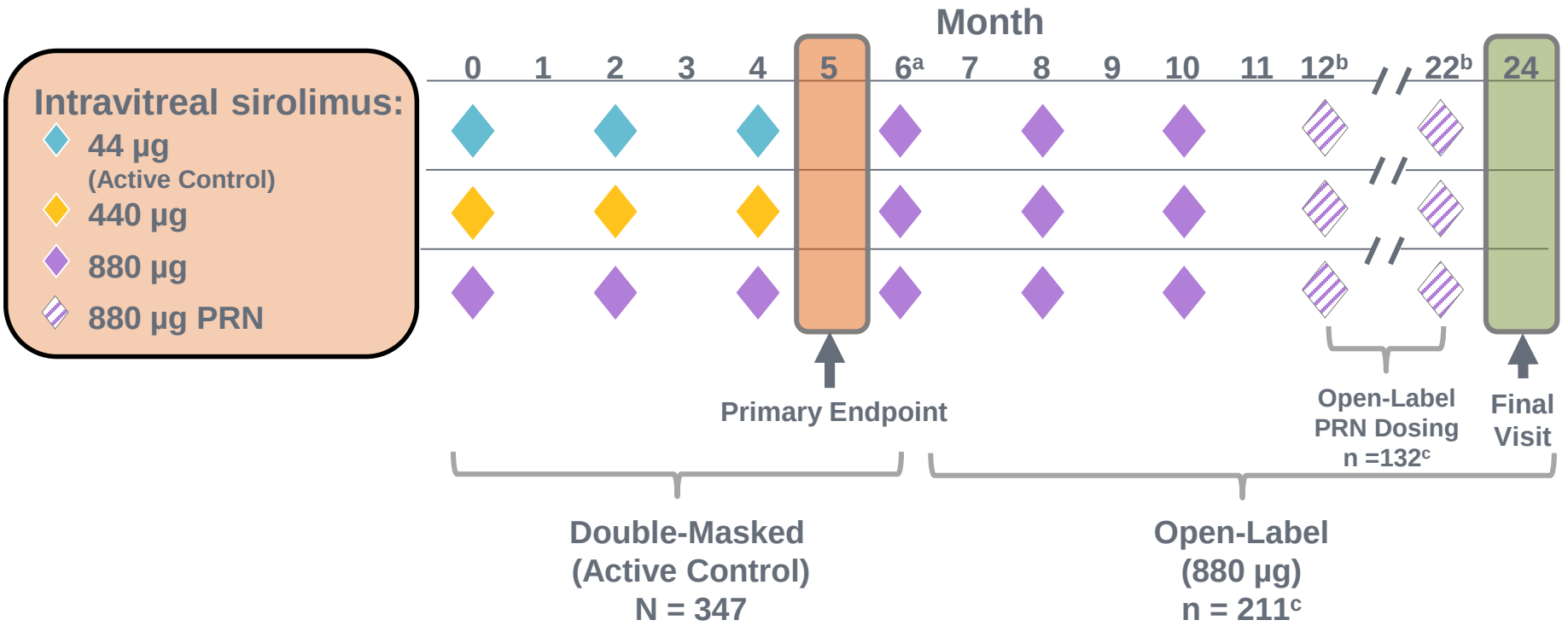
- Locally delivered mTOR inhibitor for non-infectious uveitis of the posterior segment (NIU-PS)
- Immunoregulates by interrupting the inflammatory cascade and promoting immune tolerance[1,2]
  - Inhibits T-cell activation, proliferation, and differentiation
  - Increases regulatory T lymphocytes (Tregs)
- Proprietary IVT formulation[3]
  - Forms depot in vitreous
  - Slow diffusion over 2 months
  - Minimal systemic exposure



Sirolimus Drug Deposition (Multifocal Choroiditis, Humans)

Images courtesy of Q. Nguyen.
IL, interleukin; IVT, intravitreal; mTOR, mammalian target of rapamycin.
1. Powell JD et al. *Annu Rev Immunol*. 2012;30:39-68; 2. Gonzalez J et al. *Blood Cells Mol Dis.* 2001;27:572-585;
3. Mudumba S et al. *J Ocular Pharmacol Ther*. 2012;28:507-514.

SAKURA Study 1 Design: 3 Active Arms



[a]Patients initially continued on their assigned group. Subsequent study amendments called for all patients to receive 880 µg starting at Month 6. [b]Subjects must meet retreatment criteria to receive injections. [c]Denotes subjects who received treatment during this period.
Study report date 10/2015.

SAKURA Key Inclusion/Exclusion Criteria

- Age ≥18 years
- Diagnosis of active NIU of the posterior segment (investigator determined)
  - If an anterior component is present, it must be less than the posterior component
- VH score >1+ (study eye) (modified SUN scale)
- BCVA: ≥19 ETDRS letters or 20/400 (study eye)
- Vision ≥20/200 (fellow eye)
- Uncontrolled glaucoma (IOP >21 mm Hg while on medical therapy)
- Active infectious uveitis
- Ocular or periocular infection
- Vision-compromising ocular diseases (including, but not limited to, PDR, NPDR, neovascular AMD, CVO)
- Lens opacities that prevent reliable posterior segment evaluation
- Previous vitrectomy
- Recent intraocular surgery

ETDRS, Early Treatment Diabetic Retinopathy Study; VH, vitreous haze; BCVA, best corrected visual acuity; IOP, intraocular pressure; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy;
AMD, age-related macular degeneration; CVO, central vein occlusion.

SAKURA: Primary Endpoint

- VH = 0 response rate at Month 5 (study eye)[a]

- SAKURA used a modified SUN Scale that included a VH of 1.5+[b]

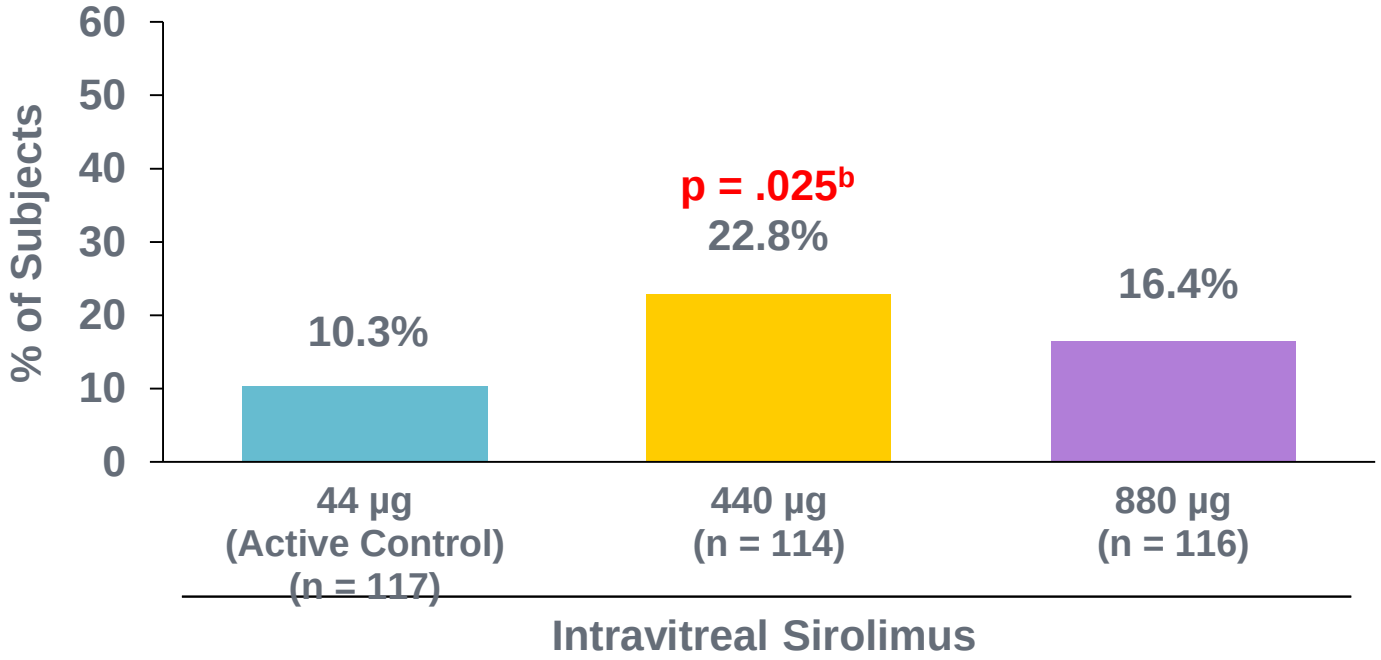
[a]Intent-to-treat population with last observation carried forward (LOCF). Subjects rescued before Month 5 are treated as non-responders.
[b]Defined as optic nerve head and posterior retina view obstruction >1+ but <2+.

SAKURA: Key Secondary Endpoints

- VH = 0 or 0.5+ response rate at Month 5 (study eye)[a]
- VH = 0 or ≥2-unit improvement response rate at Month 5 (study eye)[a]
- Corticosteroid tapering success rate: the overall prednisone-equivalent dose tapered to ≤5 mg/d at Month 5[b]

[a]Intent-to-treat population with last observation carried forward. Subjects rescued before Month 5 are treated as non-responders.
[b]For the intent-to-taper population; ie, subjects who were taking systemic corticosteroid(s) at Day 1 (Baseline) with the overall prednisone-equivalent dose >5 mg/d.

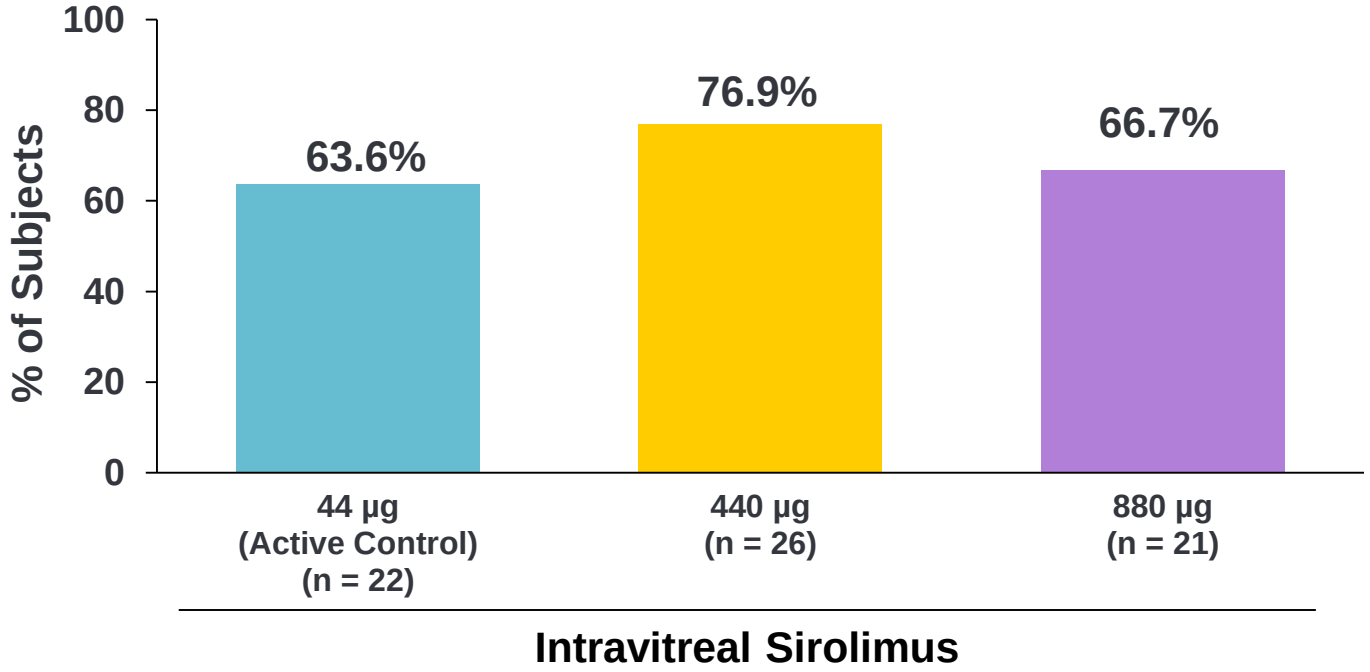
Primary Endpoint: Proportion of Subjects With VH = 0 at Month 5[a]



[a]Results are for the study eye.

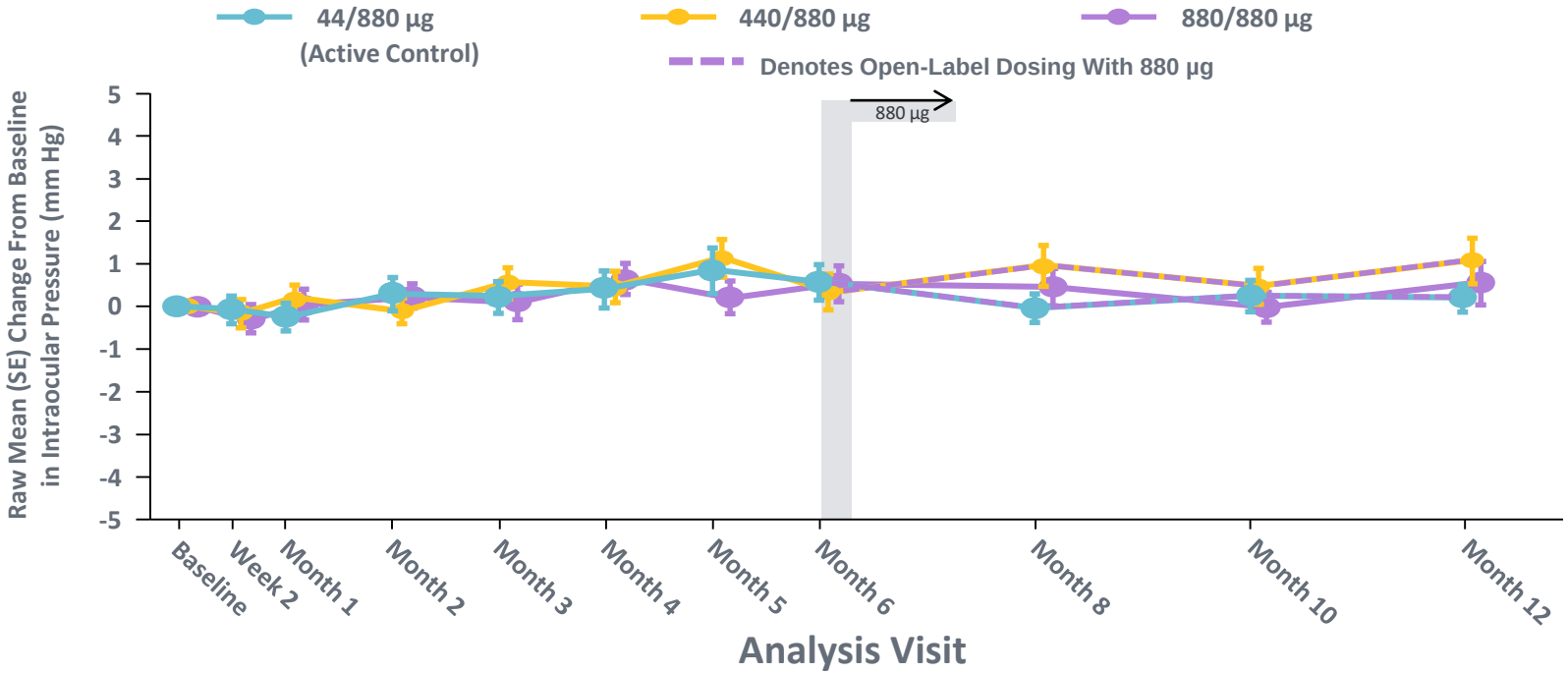
[a]Adjusted for multiplicity. p-value is for comparison between the 440-µg dose and the 44-µg (active control) dose of intravitreal sirolimus.

Tapering Successes: Proportion of Subjects With the Overall Prednisone-Equivalent Dose Tapered to ≤5 mg/d at Month 5 (Intent-to-Taper Population)



Subjects randomized through March 31, 2013. Study report date October 2015.

Intraocular Pressure: Raw Mean (SE) Change From Baseline by Analysis Visit[a]



[a]Results are for the study eye.

Fluocinolone acetonide injectable (FAi)

- Jaffe et al treated 11 eyes of 11 patients
- VA improved from 0.56 logMAR to 0.25 logMAR and 0.17 logMAR VA at 12 and 24 months
- Average # of recurrences in 12-months pre-implant = 1.54 → No recurrences post implant

Jaffe et al *Ophthalmol 2016*

Summary

- Increasing numbers of biologics (e.g. monoclonal antibodies, soluble protein receptors) used in the treatment of uveitis
- Local therapeutics involve changes in drug delivery strategy (suprachoroidal) and different mechanism of action compared to corticosteroids