THE MULTICENTER UVEITIS STEROID TREATMENT (MUST) TRIAL: A Closer Look at the 7-Year Findings

This supplement captures content from a roundtable discussion held in August 2017 at the American Society of Retina Specialists (ASRS) meeting in Boston, MA.

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The participants are paid consultants for Bausch + Lomb.

Indication

RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is a corticosteroid indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Important Safety Information

- Surgical placement of RETISERT (fluocinolone acetonide intravitreal implant) 0.59 mg is contraindicated in active viral, bacterial, mycobacterial or fungal infections of the eye.
- Based on clinical trials with RETISERT, during the 3-year post-implantation period, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.
- As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place RETISERT into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.
- Following implantation of RETISERT, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately one to four weeks post-operatively.
- Use of corticosteroids may result in elevated IOP and/or glaucoma. Based on clinical trials with RETISERT, within 3 years post-implantation, approximately 77% of patients will require IOP lowering medications to control intraocular pressure and 37% of patients will require filtering procedures to control intraocular pressure.
- Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of RETISERT. Physicians should periodically monitor the integrity of the implant by visual inspection.
- Ocular administration of corticosteroids has been associated with delayed wound healing and perforation of the globe where there is thinning of the sclera.
- The most frequently reported ocular adverse events in clinical trials with RETISERT occurring in 50-90% of patients included: cataract, increased intraocular pressure, procedural complications and eye pain. The most common non-ocular event reported was headache (>33%).

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Retisert®
(fluocinolone acetonide intravitreal implant) 0.59 mg

INTRODUCTION

Controlling inflammation in uveitis helps to preserve anatomy and visual function, and patients typically do better when inflammation is controlled. That, of course, can come at a cost—there are potential side effects from all treatments. Thus, we must try to initiate with the lowest appropriate aggressive therapy that is sufficient to control inflammation and try to be very sensitive in our recognition of failure to control inflammation. In very difficult cases of chronic noninfectious posterior uveitis, an intravitreal fluocinolone acetonide implant (RETISERT) is an option to help control inflammation.

The 2017 publication of the 7-year data for the Multicenter Uveitis Steroid Treatment (MUST) study in *JAMA: The Journal of the American Medical Association* represents one of the largest and longest-duration studies in uveitis. The MUST study randomized patients to either receive real-world systemic therapy with steroids and steroid-sparing agents, or to receive RETISERT.[1] The primary outcome was prespecified to be visual acuity at 2 years.[1] The MUST study also evaluated several secondary outcomes pertinent to ocular health.[1] In this supplement, my colleagues and I will review the design of the MUST study, examine the 7-year outcomes, and discuss some of the issues with interpretation of that data and what it means for our patients.

–Thomas Albini, MD

The MUST trial study design

The MUST trial was designed as a 2-year randomized clinical trial, followed by a nonprespecified longitudinal follow-up of the trial cohort.[1]

Objective: To compare RETISERT versus systemic therapy in the treatment of long-term vision and other outcomes in patients with uveitis[1]

Primary outcome: Change from baseline in best-corrected visual acuity in uveitic eyes[1]

Secondary outcomes: Visual field sensitivity, uveitis activity, macular edema, quality of life[1]

The key efficacy outcomes at years 2 and 7 are summarized in Table 1 below.

Key 2- and 7-Year Efficacy Outcomes

BASELINE			2 YEARS		2-YEAR OUTCOME	7 YEARS		7-YEAR OUTCOME
	RETISERT	SYSTEMIC THERAPY	RETISERT	SYSTEMIC THERAPY	DIFFERENCE IN OUTCOMES	RETISERT	SYSTEMIC THERAPY	DIFFERENCE IN OUTCOMES
Mean visual acuity[1]	**61.7** letters	**65.0** letters	**67.7** letters	**68.1** letters	**Favored RETISERT by 2.84 letters**	**55.8** letters	**66.2** letters	Favored systemic therapy by 7.12 letters
Percentage of patients with **uveitis activity**[1]	**80.3%**	**78.0%**	**13.7%**	**33.7%**	**Favored RETISERT by 22.4%**	**18.7%**	**13.8%**	Favored systemic therapy by 2.5%
Percentage of patients with **macular edema**[1]	**36.3%**	**34.7%**	**18.9%**	**26.6%**	**Favored RETISERT by 9.2%**	**15.2%**	**7.3%**	Favored systemic therapy by 6.4%
Percentage of patients with a **visual field mean deviation** of <-10 dB[1]	**25.5%**	**21.4%**	**27.6%**	**22.4%**	Favored systemic therapy by 1.1%	**40.2%**	**29.1%**	Favored systemic therapy by 7.0%

Table 1. Key 2- and 7-Year Efficacy Outcomes

Please see Important Safety Information on page 1, and full Prescribing Information for RETISERT here.

Clinical perspectives regarding the study design

Thomas Albini, MD: The study was designed as a 2-year study. The primary outcome was prespecified to be assessed at 2 years, and the data that were collected subsequently were observational.[1] All of the analysis here is intent-to-treat, so, if a subject was randomized to RETISERT, they remained in the RETISERT group even if the clinician ultimately decided that the subject needed systemic therapy for any reason, and vice versa.[1]

Sunil Srivastava, MD: We are not looking at a "true" 7-year dataset, because these patients were not treated identically at the end of the study versus at the beginning of the study. There are limitations to the study design, but they are important to discuss because it is great to see long-term data on patients. I always say that you take these things with a grain of salt.

Quan Nguyen, MD, MSc: RETISERT had been FDA-approved and was in use at the time the MUST trial was designed. This study was certainly done with the idea in mind that local therapy may not be as effective as systemic therapy. Some of my colleagues wanted to test whether using local therapy was sufficient for treatment of uveitis, especially in cases of uveitis that occurred secondary to a systemic underlying disease.

Sunil Srivastava, MD: What I liked about the study was that it was an active study—it included patients who had active disease and were randomized to systemic versus local treatment. However, the MUST trial did not analyze the data in a manner I would have analyzed it. Once someone received a RETISERT implant in their eye, it did not matter that they had received systemic therapy at the beginning of the study. In my practice, I had patients enrolled in the study who were assigned to systemic therapy, flipped to RETISERT, and did great. There were also some RETISERT patients who flipped to systemic therapy, which is fine, but we should analyze the patients who flipped and see how they did. This gets lost in this analysis.

Thomas Albini, MD: It would be nice to see that as a secondary analysis.

Challenges with long-term follow-up in a 7 year study

Thomas Albini, MD: The baseline characteristics of the patients who made it through versus those who did not make it through the 7 years of this observational study are fairly well balanced.[1] It is very interesting that 30% of the patients did not complete the study. These are pretty good outcomes for a 7-year study, as it is very hard to follow people as they move around the country and so forth. However, one factor to keep in mind when looking at the 7-year data is that it only represents 70% of the initial population.[1]

"We are not looking at a 'true' 7-year dataset, because these patients were not treated identically at the end of the study versus at the beginning of the study."

–Sunil Srivastava, MD

Sunil Srivastava, MD: There are so many issues with long-term follow-up, which cannot be controlled for. A 30% loss over 7 years is pretty good. If I were to monitor a set of my uveitis patients from 7 years ago and look carefully at how many returned, I doubt it is 70%. It is probably, at best, 30% or 40%.

Quan Nguyen, MD, MSc: In my experience, the most common reason for a patient not to return for follow-up has been relocation to another city by either the physician or the patient. When the physician is no longer there, the patient does not feel like they need to return, especially if they feel they are doing well. A strategy that can be used to ensure patients return for follow-up visits is providing an explanation and warning to the patient. Sometimes patients do not realize they have a problem, or they forget that they have an implant in their eye.

A closer look at the treatment utilization patterns between the RETISERT and systemic therapy groups over 7 years

Sunil Srivastava, MD: Crossovers occurred fairly frequently.[1] There were patients who were assigned to the systemic therapy group and received RETISERT at a later time, but who were still counted as receiving systemic therapy.[1] I was enrolling patients at the time this trial was conducted, and we would always tell patients, "If you're not responding with one treatment, we can always flip you to the other treatment." This was used as a recruitment tool, but that switch is never fully discussed in the MUST study publication.

Thomas Albini, MD: It is very important to highlight that the intent of the MUST trial was for patients to receive at least one RETISERT implant for the entire 7 years.[1] The real crux of the problem is reimplantation. In the RETISERT arm, a large proportion of patients received their RETISERT implant in the first 6 months of the study.[1] Once the RETISERT implants became 3 years old, a majority of the patients who received RETISERT were not reimplanted (Figure 1, page 4).[1] Approximately half of them wound up on systemic therapy, and about half of them wound up on nothing.[1] In my opinion, these patients were undertreated from Year 3.5 onward.

Sunil Srivastava, MD: In the RETISERT group, 84% of subjects received at least one implant (Figure 2, page 4), and 24% of subjects received at least 2 implants.[1] For a 7-year study, I would expect that the percentage of subjects who received greater than 2 implants should be closer to 84%. It should be comparable to the treatment patterns that are seen with the systemic therapy group, where 77% of patients were receiving either oral corticosteroids, immunosuppressants, or biologic agents at Year 7.[1]

Sunil Srivastava, MD: I also think that, once you get past 2.5 or 3 years, it is very, very difficult to understand what happens because the treatment of these patients is not being mandated.

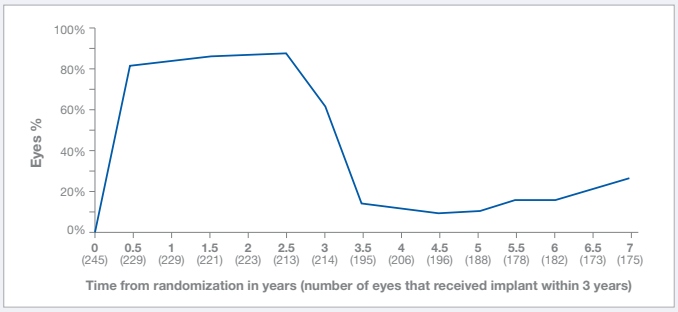

Figure 1. RETISERT utilization over time in the RETISERT treatment group[1]

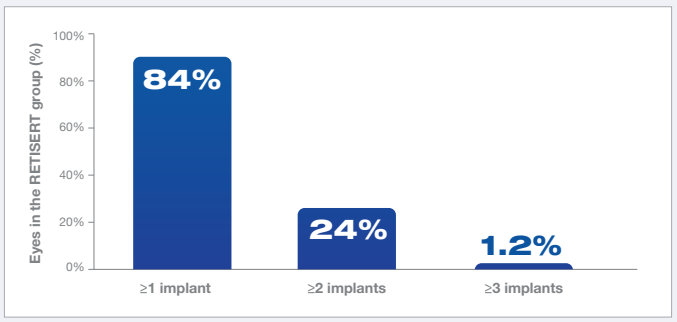

Figure 2. The number of RETISERT implants received by uveitic eyes in the RETISERT treatment group[1]

Thomas Albini, MD: An interesting question to discuss is why did patients who were randomized and finished the 2-year study not receive a second RETISERT? In the article, they say that a large portion of the patients were not reimplanted, and they make reference to surgical complications.[1]

Quan Nguyen, MD, MSc: In my experience, if a patient chooses to have a localized treatment, they may end up having a complication that prevents them from receiving the implant again.

Sunil Srivastava, MD: My understanding is that the complication rate associated with reimplantation is similar to the first implantation.[2] It could be that patients and doctors were lulled into thinking that they were done after one implant. If we examine the treatment pattern for RETISERT, we can see that there are patients who have no RETISERT coverage and are not active.[1] These patients are not being treated until they flare the next time. With the systemic therapy group treatment pattern, the proportion of patients receiving therapy is consistent all the way across the study period.[1]

The importance of reimplantation

Thomas Albini, MD: I have always told patients, especially those with a persistent disease that requires chronic immunosuppression, we have to reimplant because RETISERT only lasts approximately 2.5 years.[3] This makes sense from the way we treat systemic disease, but I agree that many people fail to do it. Patients naturally want to avoid surgery, and if they are doing well, it is difficult to talk them into surgery.

Sunil Srivastava, MD: The lesson is making sure my patients know, even after 4 or 5 years of having a RETISERT implant, that we may need to go back and address it.

Quan Nguyen, MD, MSc: In my practice, we would consider placing an implant if we can clearly see that a patient's disease activity has returned. However, there are many factors to consider when assessing that type of patient because not all patients will "flare." If a patient is on systemic treatment, regardless of whether they have active disease, the drug is always there. The group that was randomized to RETISERT should always have the drug onboard as well, but that was not the case due to a low rate of reimplantation. If subjects did not demonstrate signs of disease, complain about their symptoms, or find some other way to demonstrate to the clinician that they have active disease, they would likely not be receiving a repeat implant.

Important factors to consider when evaluating efficacy outcomes of the MUST trial

Thomas Albini, MD: Best-corrected visual acuity was the primary efficacy outcome at 2 years. The patients in the RETISERT group had comparable vision to the systemic therapy group by Year 2, but their vision began to decrease from Years 4 through 7.[1] However, the vision of the patients in the systemic therapy group was maintained.[1] One could naively interpret these findings to say RETISERT does not work after 3 years. However, if one considers the fact that so few patients in the study received a second RETISERT implant, one would realize that the patients in the RETISERT group started to lose vision because they were undertreated—I think this is the best way to interpret this data.

Sunil Srivastava, MD: I would agree with that. By Year 2, both treatment groups had the same vision outcomes, but, at Year 4, the vision in the RETISERT group has started to decrease.[1] Again, in my opinion, no one in this group is receiving treatment in Years 4, 5, 6, and 7.

Quan Nguyen, MD, MSc: When uveitis is undertreated, patients will do poorly and their vision outcomes will be poor.

Thomas Albini, MD: What we are seeing in this primary outcome is a very small difference. And this difference speaks not to a complete lack of treatment, but rather to undertreatment. There were still some eyes receiving treatment. I would estimate that the difference is even more magnified among the eyes that did not receive any treatment—that received neither systemic therapy nor RETISERT.

"I have always told patients, especially those with a persistent disease that requires chronic immunosuppression, we have to reimplant because RETISERT only lasts approximately 2.5 years.[3]"

–Thomas Albini, MD

> ***"If one considers the fact that so few patients in the study received a second RETISERT implant, one would realize that the patients in the RETISERT group started to lose vision because they were undertreated."***
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Thomas Albini, MD: In the RETISERT arm, we see a very aggressive rise in the number of failures, if one defines failure as 20/200 or worse—severe vision loss.[1] Again, with this data, we notice a trend that is consistent with the majority of patients in the RETISERT arm are not receiving a reimplant after Year 3.5. As for the other secondary outcomes, I would expect the visual fields in the RETISERT arm to be worse because of the much higher rate of glaucoma in the RETISERT arm.[1]

Sunil Srivastava, MD: Absolutely, and glaucoma is a serious concern. However, if the glaucoma is treated aggressively, I would not expect it to worsen, unless patients are having vasculitic attacks or macular edema that is causing them to lose central vision, which may be happening in these patients.

Thomas Albini, MD: Uveitis activity is one of the key secondary endpoints, for many of us. In the first 4.5 years, RETISERT was better than systemic therapy in controlling uveitis.[1] This was statistically significant at every timepoint until Year 4.5.[1]

Sunil Srivastava, MD: If we examine the uveitis activity data at Year 3.5, the RETISERT group is under 10% and the systemic therapy group is still at about 30%.[1] Even though hardly anyone in the RETISERT group is being reimplanted, that difference holds up for another year and a half—so those patients are doing very well.

A similar trend is also observed with the macular edema results. At 6 months, fewer eyes had macular edema in the RETISERT group than in the systemic therapy group.[1] This pattern was reversed at Year 6, where the RETISERT group had more eyes with macular edema than the systemic group.[1] This trend is reflective of undertreatment in the RETISERT group and consistent with the data that RETISERT patients are losing vision at Year 6 and Year 7.

Thomas Albini, MD: It is important to remember that at Year 6, most patients in the RETISERT arm did not have an active RETISERT implant in place in the 3 years prior to that time point.[1] Thus, we cannot confidently conclude that RETISERT did not work at controlling macular edema out to Year 6. All we can conclude is that undertreatment, or insufficient treatment, resulted in increased macular edema.

Quan Nguyen, MD, MSc: In my experience, macular edema will recur if you do not have a drug on board. Without a drug, there is nothing to control the macular edema.

Thomas Albini, MD: One important consideration when discussing visual acuity is that a large proportion of eyes entering the study had good vision. The median visual acuity in the better-seeing eye in the MUST study was 20/25 at the start of the study.[4] A lack of improvement is tempered by the fact that so many of these eyes were seeing reasonably well at the start. The secondary endpoint of inflammatory control is, in my opinion, somewhat more meaningful because most eyes were inflamed at the beginning, and we can observe how many of them showed resolution of inflammation as the study progressed. It is important to remember that the MUST trial was designed to be a 2-year study, and retrospective review of the patients was performed whenever data was available after year 2.[1] There was no protocol to define the treatment of patients after year 2. The fact that patients or third-party payers were paying for treatment after year 2 means the options for expensive imaging and treatment (like RETISERT) were limited.

An analysis of the adverse events of the MUST trial and strategies to manage ocular adverse events when treating uveitis patients with RETISERT

Thomas Albini, MD: The safety outcomes in the MUST study are straightforward. We know that systemic therapy outperforms RETISERT in terms of preventing ocular hypertension and glaucoma. By 7 years, 41.9% of RETISERT patients have had an IOP greater than 30 mm Hg at some point during the course of the study, compared to only 10.5% in the systemic therapy group.[1] That is quite impressive. It's important to inform patients and the physicians that IOP may increase, and it needs to be checked even if patients are feeling great.

When examining cataract surgery rates, there was a big difference between the study arms. In both groups, if a cataract was present, cataract surgery was almost universally performed.[1] Overall, cataract surgery occurred at a much higher rate in the RETISERT group than in the systemic therapy group.[1]

Quan Nguyen, MD, MSc: In the systemic therapy group, 72.3% of subjects had infections that required treatment.[1] If I compare this to what I see with the systemic therapy population in my own practice, that seems relatively high to me.

Thomas Albini, MD: The high rate of infections in the systemic therapy group seems like bias on the part of the treating clinician. If a patient is on immunosuppressive therapy, then the clinician is more likely to give the patient antibiotics. It does not necessarily mean that the actual rate of infection is higher. If you look at the rates of hospitalizations, they are the same in the RETISERT and systemic therapy groups. It is just the antibiotic use that is different—at least that is my interpretation.

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> ***"To manage ocular adverse events, it's extremely important that the patients are under inflammatory control when reimplanting RETISERT."***
>
> –Thomas Albini, MD

Thomas Albini, MD: It's extremely important that the patients are under inflammatory control when reimplanting RETISERT. The only criterion in the study was to eliminate the anterior chamber inflammation before implantation.[1] In my experience, I have had a couple cases that did not go as perfectly as I would have liked, when the patient shows up with active inflammation. There is a tendency to perform the reimplantation when the eyes have active inflammation, and physicians should be very aggressive about controlling inflammation when they are performing a reimplantation. An implant exchange or even introduction of a secondary implant, in my opinion, is more difficult and more likely to be proinflammatory than the introduction of the initial implant.

Sunil Srivastava, MD: In my practice, patients usually have active inflammation when they receive a second implant. I would usually give them an intravitreal corticosteroid injection, and then try to perform the reimplantation within a short period of time afterwards. I have taken care of a couple of patients where it is very clear the IOP is dropping, but the patient still has active inflammation, and I try to quiet their inflammation as much as possible. However, such an eye is probably less than ideal for reimplantation, and it will take more time to recover.

Quan Nguyen, MD, MSc: The MUST trial publication has not changed anything that I have done in my practice because we chose RETISERT for a reason, and those reasons have not changed. The outcomes are the same with RETISERT and systemic therapy, and I emphasize that uveitis is a very chronic disease. We need to emphasize to our patients that they need to come in for regular follow-up, regardless of the treatment they are on, because complications will occur if they are undertreated or not being monitored properly. We have dissected the MUST trial manuscript, and we have concluded that the presence of therapeutic agent was not equal in the 2 study groups, which likely explains why we do not see similar outcomes in the 2 study groups.

Sunil Srivastava, MD: I am excited that this MUST trial paper was published, despite my concerns with it, because it demonstrates what happens to a large population of RETISERT patients after Year 3.5. We previously lacked a strong dataset. This publication has changed my practice. I think this study has placed a lot more emphasis in my mind on carefully observing my patients. In a population setting, we can say that these patients do poorly if they fail to receive reimplantation. It is now up to us, as clinicians, to ensure that this does not happen.

Thomas Albini, MD: This publication reinforces a lot of what I was doing, as Dr. Nguyen was saying. It has taught me that there are benefits and downsides to both RETISERT and systemic therapy treatment. In either case, we have to be aggressive about treatment and try not to tolerate recurrent chronic inflammation while treating our patients.

Key clinical takeaways of the MUST trial

Sunil Srivastava, MD: The clinical outcomes with RETISERT and systemic therapy are going to be very similar. However, when choosing a therapy, the side effect profile must be considered. As physicians, we have to work with our patients to decide the course of action. For me, RETISERT is an option to be utilized after systemic therapy. I usually start my younger patients on systemic therapy first, and wait to see how they tolerate the medicine.

> ***"This publication has changed my practice. I think this study has placed a lot more emphasis in my mind on carefully observing my patients."***
>
> –Sunil Srivastava, MD

References: 1. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA*. 2017;317(19):1993-2005. **2.** Taban M, Lowder CY, Kaiser PK. Outcome of fluocinolone acetonide implant (Retisert) reimplantation for chronic noninfectious posterior uveitis. *Retina*. 2008;28(9):1280-1288. **3.** RETISERT [prescribing information]. Bausch & Lomb Incorporated. **4.** Multicenter Uveitis Steroid Treatment Trial Research Group. The Multicenter Uveitis Steroid Treatment trial: rationale, design, and baseline characteristics. *Am J Ophthalmol*. 2010;149(4):550-561.e10.

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to watch experts discuss RETISERT and the 7-year MUST trial findings

Limitations of the MUST study design and its implementation

THOMAS ALBINI, MD identifies the limitations of the MUST trial study design and its implementation, and how these limitations affect study results and interpretation

Reimplantation with RETISERT may be needed after 2.5 years

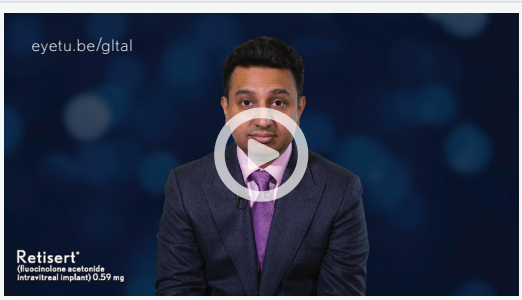
THOMAS ALBINI, MD discusses the factors that drive his decision to reimplant RETISERT

Goals to consider for RETISERT reimplantation

QUAN NGUYEN, MD, MSC discusses the importance of proper treatment protocol with RETISERT and continuing to follow up with patients

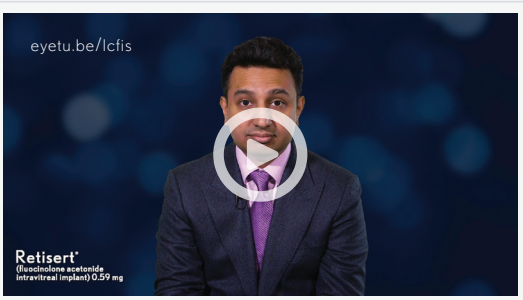
Best practices to follow up with RETISERT patients

QUAN NGUYEN, MD, MSC & SUNIL SRIVASTAVA, MD offer strategies for offices to continue to follow up with their RETISERT patients to ensure continued implant success



Key efficacy outcomes in the MUST Trial

SUNIL SRIVASTAVA, MD provides potential explanations of the differences in efficacy outcomes in the first 2-4 years of the study versus later timepoints



Help manage ocular adverse events when treating uveitis patients

SUNIL SRIVASTAVA, MD discusses ways to help manage adverse events with RETISERT treatment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