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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PARTICIPANTS

Thomas Albini, MD, moderator
• Associate Professor of Clinical Ophthalmology at the Bascom Palmer Eye Institute in Miami, FL
• President of the Vit Buckle Society

Quan Nguyen, MD, MSc
• Professor of Ophthalmology at the Byers Eye Institute, Stanford University School of Medicine
• Secretary General for the Executive Committee of the International Ocular Inflammation Society

Sunil Srivastava, MD
• Physician at the Cleveland Clinic, Department of Ophthalmology
• Physician at the MetroHealth Hospital, Department of Ophthalmology

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%).

Please see full Prescribing Information on pages 8-10.
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 flucinolone 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. The primary outcome was prespecified to be visual acuity at 2 years. The MUST study also evaluated several secondary outcomes pertinent to ocular health. 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. Objective: To compare RETISERT versus systemic therapy in the treatment of long-term vision and other outcomes in patients with uveitis. Primary outcome: Change from baseline in best-corrected visual acuity in uveitic eyes. Secondary outcomes: Visual field sensitivity, uveitis activity, macular edema, quality of life.

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

**Key 2- and 7-Year Efficacy Outcomes**

<table>
<thead>
<tr>
<th>BASELINE</th>
<th>2 YEARS</th>
<th>2-YEAR OUTCOME</th>
<th>7 YEARS</th>
<th>7-YEAR OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RETISERT</td>
<td>SYSTEMIC THERAPY</td>
<td>RETISERT</td>
<td>SYSTEMIC THERAPY</td>
</tr>
<tr>
<td>Mean visual acuity¹</td>
<td>61.7 letters</td>
<td>65.0 letters</td>
<td>67.7 letters</td>
<td>68.1 letters</td>
</tr>
<tr>
<td>Percentage of patients with uveitis activity¹</td>
<td>80.3%</td>
<td>78.0%</td>
<td>13.7%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Percentage of patients with macular edema¹</td>
<td>36.3%</td>
<td>34.7%</td>
<td>18.9%</td>
<td>26.6%</td>
</tr>
<tr>
<td>Percentage of patients with a visual field mean deviation of &lt;10 dB¹</td>
<td>25.5%</td>
<td>21.4%</td>
<td>27.6%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

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

Please see Important Safety Information on page 1, and full Prescribing Information for RETISERT on pages 8-10.
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

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.
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

### 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

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.

### 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

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—Thomas Albini, MD
received neither systemic therapy nor RETISERT.

**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.

Please see Important Safety Information on page 1, and full Prescribing Information for RETISERT on pages 8-10.
“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. 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.

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.

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.


Please see Important Safety Information on page 1, and full Prescribing Information for RETISERT on pages 8-10.
Visit the RETISERT Collections page online at Eyetube.net/collections/retisert
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
Retisert®
(flucinolone acetonide intravitreal implant) 0.59 mg
STERILE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RETISERT safely and effectively. See full prescribing information for RETISERT.

RETISERT (flucinolone acetonide intravitreal implant) 0.59 mg for intravitreal use
Initial U.S. Approval: 1963

INDICATIONS AND USAGE
RETISERT is a corticosteroid indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. (1)

Dosage and Administration
• RETISERT is surgically implanted into the posterior segment of the affected eye through a pars plana incision. (2.1)
• RETISERT is designed to release flucinolone acetonide at a nominal initial rate of 0.6 mcg/day, decreasing over the first month to a steady state between 0.3-0.4 mcg/day over approximately 30 months. (2.1)
• Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure. (2.2)

Dosage Forms and Strengths
• 0.59 mg flucinolone acetonide intravitreal implant. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*
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To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2019
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.

5.3 Increase in Intraocular Pressure
Prolonged use of corticosteroids may result in elevated IOP and/or glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Patients must be monitored for elevated IOP.

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 [see Adverse Reactions (6.1)].

5.4 Separation of Implant Components
In vitro stability studies show that the strength of the adhesive bond between the silicone cup reservoir and the suture tab is reduced with prolonged hydration, indicating a potential for the separation of these components. The suture tab composition is a silicone elastomer reinforced with a polyester mesh. Physicians should periodically monitor the integrity of the implant by visual inspection.

5.5 Other Corticosteroid Induced Adverse Reactions
RETISERT should be used with caution in patients with a history of a viral, bacterial, mycobacterial or fungal infection of the cornea and conjunctiva including epithelial herpetic simplex keratitis (dendritic keratitis), vaccinia, and varicella. Use of corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections (bacterial, fungal, and viral), in acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term application of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used.

Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation should not be carried out, in order to limit the potential for bilateral post-operative infection.

Ocular administration of corticosteroids has also been associated with delayed wound healing and perforation of the globe where there is thinning of the sclera.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience - Ocular Events
The available safety data includes exposure to RETISERT in patients with chronic non-infectious uveitis affecting the posterior segment in two multicenter controlled clinical trials. Patients were randomized to dosage regimens of 0.59 mg or 2.1 mg implants.

The most frequently reported ocular adverse events were cataract, increased intraocular pressure, procedural complication, and eye pain. These events occurred in approximately 50 - 90% of patients. Cataract includes aggravated cataract, and posterior capsular opacification. Procedural complications include post-op complication, post-op wound complication, post-op wound site erythema, and wound dehiscence.

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. IOP lowering medications to lower intraocular pressure were required in approximately 77% of patients; filtering surgeries were required to control intraocular pressure in 37% of patients. Ocular adverse events occurring in approximately 10 - 40% of patients in decreasing order of incidence were ocular/conjunctival hyperemia, reduced visual acuity, glaucoma, conjunctival hemorrhage, blurred vision, abnormal sensation in the eye, eye irritation, maculopathy, vitreous floats, hypopyon, pruritus, ptosis, increased tearing, vitreous hemorrhage, dry eye, eyelid edema, macular edema and visual disturbance.

Ocular adverse events occurring in approximately 5 - 9% of patients in decreasing order of incidence were eye discharge, photophobia, blepharitis, corneal edema, iris adhesions, choroidal detachment, diplopia, eye swelling, retinal detachment, photopsia, retinal hemorrhage and hyphema.

6.2 Clinical Trials Experience - Non-Ocular Events
The most frequently reported non-ocular adverse event was headache (33%). Other non-ocular adverse events occurring in approximately 5-20% of patients in decreasing order of incidence were nasopharyngitis, arthralgia, sinusitis, dizziness, pyrexia, upper respiratory tract infection, influenza, vomiting, nausea, cough, back pain, limb pain, and rash.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
No adequate animal reproduction studies have been conducted with fluocinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Fluocinolone acetonide when administered subcutaneously at a dose of 0.13 mg/kg/day (approximately 10,000 times the daily clinical dose of RETISERT), during days 6 to 18 of pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week. When administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 mcg/kg/day (approximately 4,000 times the clinical dose of RETISERT), fluocinolone acetonide caused abortions and malformations in a few surviving fetuses.

There are no adequate and well-controlled studies in pregnant women. RETISERT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when RETISERT is implanted in a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
RETISERT® (fluocinolone acetonide intravitreal implant) 0.59 mg is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 mcg/day, decreasing over the first month to a steady state between 0.3-0.4 mcg/day over approximately 30 months. The drug substance is the synthetic corticosteroid fluocinolone acetonide, represented by the following structural formula:

\[
\text{C}_{24} \text{H}_{28} \text{F}_4 \text{O}, \text{ Mol. Wt. 452.50}
\]

Chemical Name: Pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy-16,17-[(1-methyl-ethylidene)bis(oxy)](6x,11y,16x)-

Fluocinolone acetonide is a white crystalline powder, insoluble in water, and soluble in methanol. It has a melting point of 265-266°C. Each RETISERT consists of a tablet containing 0.59 mg of the active ingredient, Fluocinolone Acetonide, USP, and the following inactives: magnesium stearate, microcrystalline cellulose, and polyvinyl alcohol.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortin. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂. Corticosteroids are capable of producing a rise in intraocular pressure.

12.3 Pharmacokinetics
In a subset of patients who received the intravitreal implant, and had blood samples taken at various times (weeks 1, 4 and 34) after implantation, plasma levels of fluocinolone acetonide were below the limit of detection (0.2 ng/mL) at all times. Aqueous and vitreous humor samples were assayed for fluocinolone acetonide in a further subset of patients. While detectable concentrations of fluocinolone acetonide were seen throughout the observation interval (up to 34 months), the concentrations were highly variable, ranging from below the limit of detection (0.2 ng/mL) to 589 ng/mL.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed on RETISERT to evaluate the carcinogenic potential or the effect on fertility of fluocinolone acetonide.
Fluocinolone acetonide was not genotoxic in vitro in the Ames test, the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.

**CLINICAL STUDIES**

In two randomized, double-masked, multicenter controlled clinical trials, 224 patients with chronic (a one year or greater history) non-infectious uveitis affecting the posterior segment of one or both eyes were randomized to receive a 0.59 mg RETISERT. The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the study eye in the 34 week pre-implantation period compared to the rate of recurrence in the 34 week post-implantation period. Uveitis recurrence rates at 1, 2, and 3 year post-implantation were also compared to the 34 week pre-implantation period.

Detailed results are shown in Table 1 below:

### Table 1: Uveitis Recurrence Rates

<table>
<thead>
<tr>
<th>TIME POINT</th>
<th>STUDY 1</th>
<th>STUDY 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=108</td>
<td>N=116</td>
</tr>
<tr>
<td>Uveitis Recurrence Rates1,2</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>34 Weeks Pre-implantation</td>
<td>58 (53.7)</td>
<td>46 (39.7)</td>
</tr>
<tr>
<td>34 Weeks Post-implantation</td>
<td>2 (1.8)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>1 Year Post-implantation</td>
<td>4 (3.7)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>2 Years Post-implantation</td>
<td>11 (10.2)</td>
<td>16 (13.8)</td>
</tr>
<tr>
<td>3 Years Post-implantation</td>
<td>22 (20.4)</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td>3 Years Post-implantation</td>
<td>33 (30.6)</td>
<td>28 (24.1)</td>
</tr>
</tbody>
</table>

1 Recurrence of uveitis for all post-implantation time points was compared to the 34 weeks pre-implantation time point.
2 p-value <0.01 from McNemar’s \( \chi^2 \) test.
3 Results presented include imputed recurrences. Recurrences were imputed when a subject was not seen within 10 weeks of their final scheduled visit.

**HOW SUPPLIED/STORAGE AND HANDLING**

The implant consists of a tablet encased in a silicone elastomer cup containing a release orifice and a polyvinyl alcohol membrane positioned between the tablet and the orifice. The silicone elastomer cup assembly is attached to a silicone elastomer suture tab with silicone adhesive. Each RETISERT is approximately 3 mm x 2 mm x 5 mm.

Each implant is stored in a clear polycarbonate case within a foil pouch within a Tyvek peelable overwrap. Each packaged implant is provided in a carton which includes the package insert.

NDC 24208-416-01 0.59 mg 1 count

Storage: Store in the original container at 15°-25°C (59°-77°F). Protect from freezing.

**PATIENT COUNSELING INFORMATION**

Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of RETISERT.

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, temporary decreased visual acuity, 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.

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 [see Adverse Reactions (6.1)].

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.

Manufactured for:
Bausch & Lomb Incorporated
Bridgewater, NJ 08807 USA

Manufactured by:
Bausch Health Ireland Limited
d/b/a Bausch & Lomb Ireland
Waterford, Ireland

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