



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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**WITHDRAWAL ASSESSMENT REPORT
FOR**

**Retisert 590 microgram Intravitreal Implant
(Fluocinolone acetonide)**

EMEA/H/C/787

Day 120 Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Retisert 590 microgram Intravitreal Implant, an orphan medicinal product in the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye, was not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections, precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies: quality, quality in relation to safety, efficacy and safety.

EXECUTIVE SUMMARY

Problem statement

Uveitis is defined as inflammation of one or all parts of the uveal tract. The term ‘uveitis affecting the posterior segment’ in this application has been used to include non-infectious intraocular inflammation including posterior uveitis, intermediate uveitis and pan uveitis.

Anterior uveitis

Anterior uveitis comprises inflammation, primarily affecting the anterior segment, and includes iritis, iridocyclitis, and anterior cyclitis. It is the most common form of intraocular inflammation. Uveitic syndromes associated with primarily anterior segment involvement include HLA-B27 syndromes, herpes simplex and herpes zoster disease, Fuchs heterochromic iridocyclitis, and many arthritic syndromes. Secondary iatrogenic disease often is seen postoperatively, particularly following complications of surgery, trauma, scleral or seton implants, corneal transplants, capsular disruption, or fixed haptic and iris fixated intraocular lens implantation.

Intermediate uveitis

Middle uveitis, cyclitis, intermediate uveitis, pars planitis, peripheral uveitis, or chronic cyclitis often indicates a more severe form of ocular inflammation than isolated anterior disease. The inflammation consists of vitreous cells associated with a variable degree of macular oedema and swelling of the optic disc without focal choroidal or retinal pathology. Intermediate uveitis or cyclitis may be idiopathic in origin or may be associated with major granulomatous diseases (e.g., tuberculosis, sarcoidosis, Lyme disease).

Posterior uveitis

Posterior uveitis is inflammation of the choroid and the retina and includes retinochoroiditis, retinitis, and neuroretinitis. Choroiditis may occur with any of the granulomatous uveitides (e.g., tuberculosis, sarcoidosis, Lyme disease, lues), histoplasmosis, or more unusual syndromes, such as birdshot or serpiginous chorioretinitis. Papillitis may occur with toxoplasmosis, viral retinitis, lymphoma, or sarcoidosis.

Panuveitis

The term panuveitis is reserved for those situations in which there is no predominant site of inflammation, but inflammation is observed in the anterior chamber, vitreous, and retina and/or choroid (i.e., retinitis, choroiditis, retinal vasculitis).

Non-infectious uveitis affecting the posterior segment of the eye is a sight-threatening disease and a cause for blindness worldwide. Local, intraocular and systemic administration of corticosteroids and systemic therapy with non-steroidal immunosuppressive and cytotoxic agents are currently used as the standard of care for treating non-infectious uveitis affecting the posterior segment. There are a substantial number of patients for whom the currently available treatments are sub-optimal as they have limited efficacy in certain cases, or produce unacceptable side effects and this represents an unmet clinical need.

About the product

Retisert which is an intravitreal implant designed for prolonged release of fluocinolone in the implanted eye.

The indication sought in this application was for: 'the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye'.

The implant is intended to be surgically implanted through a pars plana insertion into the vitreous humour in the posterior segment of the eye. The applicant stated that consistent therapeutic levels of fluocinolone acetonide are delivered over a target period of 1,000 days.

The drug substance release rate is specified as 600 nanograms per day, decreasing over the first month to a steady state between 300 – 400 nanograms per day.

Fluocinolone acetonide is a known active substance, a synthetic corticosteroid, with anti-inflammatory activity.

The development programme/Compliance with CHMP Guidance/Scientific Advice

Retisert Intravitreal Implant was developed by Bausch & Lomb in partnership with Control Delivery Systems, Inc., Watertown, MA, US. The development and design of Retisert was based on the experience with Vitrasert™; an intravitreal prolonged release implant containing ganciclovir approved by the centralised procedure (EU/1/97/034/001) in 1997.

This application has been submitted as a complete application under article 8.3 (i) of Directive 2001/83/EC, as amended.

The applicant has previously obtained scientific advice concerning the clinical development of the product, from the EMEA, and also the UK, France, Ireland and Germany, in the period 2000 to 2003.

The applicant received Scientific Advice from the CHMP on 15 November 2001 and 26 June 2003. The Scientific Advice pertained to the clinical aspects of the dossier.

There is no paediatric development programme.

General comments on compliance with GMP, GLP, GCP.

Satisfactory copies of EU GMP manufacturers' licences have been provided for the sites of manufacture, assembly, sterilisation, QC testing and batch release. No GMP inspections were required.

The GLP status of the literature references is not known. Pivotal pharmacokinetic, toxicology and biocompatibility studies were reported to have been performed in compliance with GLP.

The applicant claims that all clinical trials for Retisert have been performed in accordance to Good Clinical Practice (GCP). The CHMP requested a GCP inspection of the pivotal BLP 415-002 study.

Type of application and other comments on the submitted dossier

▪ *Legal basis*

This was a centralised application for Retisert, which is an intravitreal implant designed for prolonged release of fluocinolone in the implanted eye. The application was submitted under article 8(3) of Directive 2001/83/EC as amended.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug Substance

The EDMF procedure has been used to submit data for fluocinolone acetonide drug substance.

In general, the dossier is compliant with Ph Eur requirements. However, a major deficiency has been identified, mainly relating to the Restricted Part of the EDMF, concerning the manufacture of the drug substance.

Other points have been raised, with the main concerns relating to the control of impurities.

The EDMF does not fully comply with the EU Guideline Active Substance Master File Procedures because information about the known polymorphic character of the drug substance is absent. However, the applicant has provided additional data, including comprehensive data on polymorphism.

The drug substance is also micronised.

The applicant has provided satisfactory data to support the absence of control of polymorphism in the Drug Substance Specification.

Finished Product

The dosage form is presented as Intravitreal implant. This is not a Standard term of the European Pharmacopoeia as such, however can be obtained combination of standard terms. No single existing Standard Term is appropriate to describe the product and the presented is acceptable. EDQM should be notified.

The development package is comprehensive, but a major concern has been raised because lower release rate implants were not fully studied. This supports the medical assessor's concern that the optimal dose has not been established.

During clinical trials, and stability testing, delamination of the implant, where it splits into two, was observed in early batches. Steps were undertaken to address this but these are not considered reassuring given stability data that show the adhesive bond between the two parts of the implant weakening on storage. A major concern has been raised on this issue.

Satisfactory data are provided to support the release rate statements.

The release rate is controlled by a semi-permeable membrane, concerns have been raised over the development of the membrane and its reproducible manufacture and control.

Compatibility of the excipients with the active substance needs to be addressed

The method of manufacture consists of a number of separate preparation steps, before final assembly, giving rise to concerns with the prolonged storage periods for the components of the implant.

The method of terminal sterilisation is by gamma irradiation, for which satisfactory validation has been provided.

Process validation data for this non-stand method of manufacture are missing and should be provided. Three new impurities have been found due to the terminal gamma sterilisation of the product. These are adequately addressed.

The control of excipients is generally satisfactory.

Points have been raised relating to the Finished Product Specification, where limits could be tightened.

Apart from concerns relating to the adhesive bonding of the product, the stability data generally support the proposed shelf life and storage conditions of 36 months, store below 25°C; store in original container. Do not freeze.

However, some methodological data is missing and should be provided, together with updated stability data.

Non clinical aspects

Pharmacology

The anti-inflammatory properties of corticosteroids are well known. The applicant reasoned that clinical experience with corticosteroids in the treatment of ocular inflammation and particularly uveitis, support the proposed indication. Nonclinical literature data were provided in support of the argument that intraocular corticosteroids are effective anti-inflammatory agents and there are some experimental data relating to sustained release intravitreal implants for the delivery of corticosteroids in experimentally induced uveitis.

As systemic exposure to fluocinolone acetonide (FA) resulting from the use of the proposed product is reported to be negligible, no secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction studies were performed. The applicant reports that in the clinic, fluocinolone acetonide has not been detected in plasma from a random selection of patients treated with a 0.59mg or 2.1mg implant.

Pharmacokinetics

The applicant has provided data from a pilot 1 week study in rabbits, a pilot 1 year study in rabbits, a GLP compliant 1 year study in rabbits and a GLP compliant 1 year study in dogs.

In all of the applicant's studies, plasma fluocinolone acetonide (FA) levels were at or below the Limit of Quantification (LOQ) suggesting that systemic exposure arising from implantation of the device was low. In the GLP compliant 1 year study in rabbits, FA levels were also assessed in urine; levels were detected at 2 weeks and 12 months in 3 of 4 animals that received 2.1mg implants. Levels (232-357pg/ml) were only slightly above the LOQ. In animals implanted with 0.59mg devices FA levels in the urine were less than the LOQ. According to the applicant, it is reported that in the clinic, FA has not been detected in plasma from a random selection of patients treated with a 0.59mg or 2.1mg implant.

In all studies, ocular levels of FA were highly variable between animals implanted with the same strength of device (standard deviations were often >>50% of mean tissue levels). In addition, *in vivo* release rates were seen to vary very considerably over time.

The data suggest that the *in vivo* release rate is dramatically greater at early time points compared to at later time points, and even at 12 months after implantation the *in vivo* release rate is at least 1.5 times the target *in vitro* release rate. The applicant argued that the technical limitations of the extraction procedure and the inherent variability of the FA assay mean that a release rate calculation based on these rabbit explants does not provide a reliable estimate of the *in vivo* release rate. However, it was notable that the pattern of FA release suggested by analyses of the retrieved implants is similar for both the 0.59mg and the 2.1mg devices. From measured FA levels in ocular tissues and based on the available data on *in vivo* release, it appears that FA release rate from the implants is highly variable. The reason behind the observed *in vivo* variability in release rate, as well as the variability of the proposed product, and on the clinical significance of these findings has not been provided and the reason why the *in vivo* release data is considered to be nonrepresentative of the performance of the proposed product has also not been clarified.

In the pilot 1 week study in rabbits, measured FA levels in retrieved devices were significantly in excess of the label claim. This finding warranted further explanation.

In vitro experiments in which FA release from implants has been monitored in protein-free and protein-containing media have shown that *in vitro* drug release rates are increased by 20% in protein-containing media. The potential clinical significance of this finding has not been clarified.

The applicant had not performed any studies relating to the metabolism or excretion of FA. Furthermore, the applicant reported that there is no information on the metabolic pathways of FA available from the literature, and that there is no definitive review of ocular drug metabolising enzymes, although in general, the mechanisms for ocular metabolism do not appear to be appreciably different from those described for systemic metabolism. The applicant reported that drugs administered into the eye are cleared by passage into the blood stream via capillaries or through the ciliary body, and assumes that FA will be eliminated by these same routes.

The applicant has speculated on possible metabolites of FA based on known metabolic pathways for structurally similar corticosteroids (particularly triamcinolone acetonide, fluticasone propionate and flunisolide), and concluded that possible metabolites including the 6 β -hydroxy and C21 carboxylic acid metabolites, would be expected to have reduced affinity for steroid receptors. Esterification of FA would also be possible, which may trap the drug intracellularly, creating a local depot that could be reactivated via the action of esterases. There are reports of covalent binding between corticosteroids and lens proteins, and these findings have been associated with cataract formation. The possibility of such an effect occurring with FA cannot be ruled out.

The applicant concluded that the available literature suggests that the majority of the metabolism of FA would be likely to occur in the liver.

The absence of a comprehensive examination of the metabolism, distribution and excretion of FA, either in the eye or systemically, represents a serious failing. The lack of relevant studies (particularly radiotracer studies) was particularly concerning given the known ability of similar corticosteroids (e.g. dexamethasone) to covalently bind to lens proteins, an effect associated with cataract formation.

Toxicology

The applicant's toxicology studies have concentrated on the long-term local effects of Retisert implanted into the eye of the dog and rabbit. The applicant reports that these species were chosen because the anatomy of the eyes permits implantation of the complete Retisert implant, and that these species were considered to be well adapted to the detection of ocular adverse events from long-term corticoid therapy. However, it should be noted that the authors of the 1 year rabbit and dog studies report that neither animal reliably developed ocular hypertension in response to corticosteroid therapy.

The nonclinical studies used 0.59mg, 2.1mg, 6mg and 15mg implants. The 0.59mg implants used in these nonclinical studies are similar although not identical to the implants intended for marketing. The 0.59mg device used in the nonclinical studies is considered to be representative of the final product.

The applicant performed three studies in rabbits: a 1 week feasibility study (non-GLP), a 1 year pilot study (non-GLP) and a pivotal 1 year study (GLP-compliant).

In the 1 week pilot study, increased cortisol and serum triglycerides were noted. While the applicant suggests that these may represent a stress response associated with the surgery, possible fluocinolone acetonide effects cannot be ruled out. The study report noted that the increase in serum triglycerides was beyond historical control ranges in the laboratory and was considered to represent an effect of insertion of the test article implants.

In the pilot 1 year study and in the pivotal 1 year study, notable findings related to the ERG results. In the pilot study a slight modification in b-wave amplitude was seen during the first 3 weeks and at

week 28, but returned to normal at study termination. In the pivotal study a significant reduction in the amplitude of the 'b' wave was seen in some treated groups. The amplitude changes were not supported by any change or trend in latencies, and the effect appeared maximal at the 6 month time point and did not have a clear dose response relationship. The clinical significance of these findings is uncertain. Overall, the applicant concludes that the rabbit studies showed no evidence of drug related ocular toxicity or systemic toxicity.

The applicant also provided two dog studies: a 1 month GLP compliant study and a 1 year GLP compliant study. In the 1 month study dogs received either 6mg implants or sham implants (i.e. only the suture tab). The most notable finding was inflammation following test and sham implantations. Retinal detachment was noted in 2 dogs and the applicant suggests that this may have been the result of a more posterior placement of the implant in these animals. The applicant concluded that there was no evidence of adverse effects on the retina or lens in response to the FA implant, and notes that the dog eye is prone to sterile inflammation following surgery.

In the 1 year dog study each test and sham operated animal received the implant (sham, 0.59mg, 2.1mg or 6mg) in the right eye only, the left eye serving as an untreated control. Sham operated animals received the suture tab only. Additionally, there was an untreated control group. As a result of post surgical complications a total of eleven animals were euthanized early. These animals experienced intraocular inflammation and became sightless (in the right eye) and/or suffered pain. The applicant considers that these post surgical complications were not related to ocular exposure to FA. However, none of the sham operated animals suffered post surgical complications so severe as to warrant early euthanasia. The possibility that FA, as a result of its suppressive effects on the immune system and its ability to impair wound healing may be responsible for the severe adverse effects seen in dogs needs further clarification.

The 1 year dog study also revealed cataracts, graded as minimal to moderate, in a number of test and sham-operated animals. The cataracts are reported to have started where the implant could be seen to be in contact with the lens posterior capsule. As no dose response effect was seen, the cataracts were attributed to mechanical contact between the implant and the lens. The study author reported that similar, small, non-progressive lenticular opacities where the implant contacts the lens had been reported in humans receiving a ganciclovir intravitreal implant. The study report noted that mechanical contact may have been exacerbated by the activity of the dogs. A further factor that may have been contributory could have been the migration of implants. The ophthalmic examination report noted that implant migration was recognised in several dogs but no further detail was provided.

A further ocular effect seen in this study was the occurrence of corneal opacities occupying a poorly defined area of up to two thirds of the central cornea. The opacities, which are reported not to have affected vision, developed 6-7 months after surgery and were only present in test animals (6 of 8 animals in the 0.59mg group, 7 of 8 animals in the 2.1mg group and 5 of 8 animals in the 6mg group). They were reported not to have been related to the degree of post-operative inflammation. Examination of corneas with special histochemical stains, scanning electron microscopic examination, and X-ray photoelectron spectroscopic examination failed to identify deposition of calcium, neutral lipids, cholesterol or cholesterol esters as the cause of the opacities. The applicant noted that it was possible that the opacities were removed during fixation. The applicant also reported that corneal opacities had not been seen in humans or rabbits following long-term exposure.

Non-ocular findings in the 1 year dog study were limited to slight organ weight and histopathological changes in adrenals, liver and thymus. While these findings could be the result of systemic FA exposure, the applicant considered that they were more likely to have been secondary to topical/systemic corticosteroid therapy used to combat post surgery inflammation in a number of dogs. There does appear to have been a correlation between the occurrence of adrenal findings and topical/systemic corticosteroid therapy, and the incidence of liver findings was sufficiently low to possibly be a background effect. While incidence of thymus findings did not show a neat dose response it was notable that the incidence was far greater in the 2.1mg and 6mg implant groups than in the control animals (no relevant histology findings were seen in the 0.59mg group). Some support for the applicant's argument that these effects were not drug related comes from the finding that, with one

exception, all FA plasma levels at 6 and 12 months were below the LOQ. The exception was a female in the 2.1mg group, in which a plasma FA level of 0.105ng/ml was found at 12 months.

Interspecies comparisons of plasma FA levels were not possible as levels tended to be less than the LOQ. There are insufficient data to enable interspecies comparison of ocular exposure.

The genotoxic potential of FA was evaluated in a standard battery of *in vitro* and *in vivo* studies. No evidence of genotoxicity was seen.

No carcinogenicity studies had been performed. The applicant justified this by arguing that no evidence of preneoplastic or hyperplastic lesions were observed in long term (1 year) toxicity studies in dogs and rabbits, and genotoxicity testing suggested that FA is without mutagenic potential. Furthermore animal and human pharmacokinetic data showed negligible systemic absorption following use of the intravitreal implant. While it is accepted that the risk of carcinogenic effects arising from systemic exposure is low, the possibility of carcinogenic effects in the eyes remains unknown. The technical feasibility of undertaking carcinogenicity studies in a standard rodent species should have been explored.

No reproductive and development toxicity studies were performed by the applicant. The applicant argued that this is acceptable as systemic exposure following Retisert implantation had been shown to be low/negligible and the degree of traumatic surgical interference required to implant Retisert would make most forms of reproduction testing impracticable. Literature data indicate that, in rats and rabbits, repeated subcutaneous doses of 50µg/kg FA caused abortions, skull malformations in both species and cleft palate in the rat. The applicant reported that based on body surface area, the dose used in these studies was at least 800 (rat) and 600 (rabbit) fold higher than the dose likely to result from the use of the 0.59mg Retisert implant. However, these figures did not represent safety margins as the literature studies referred to FA used at a single dose and did not establish NOAELs. Additionally, as *in vivo* data suggested that FA release rates are very significantly accelerated in the initial period following device implantation, the possibility of systemic and embryo/fetal exposure occurring during this period may be greatly increased. While it is accepted that performing standard reproductive toxicology studies in rats is likely to be impracticable, performing embryo-fetal development studies in rabbits could have been more manageable. The absence of embryo-fetal development studies in rabbits, particularly in the light of the increased potential for embryo/fetal exposure arising as a result of the significantly increased FA release rates seen in the initial period following device implantation should have been justified.

No specific immunotoxicity studies had been performed. Corticosteroids are known to cause immunosuppression. The applicant reported the result of a study from the literature in which FA inhibited mouse fetal thymus organ cultures, with an EC₅₀ as low as 5x10⁻¹¹M. Additionally, thymic atrophy was seen in the applicant's 1 year study in dogs. The applicant concluded that the potential risk of immunosuppression could not be ruled out.

Proposed drug substance limits for some impurities require qualification as they exceed the ICH qualification threshold. It is considered that, if the impurities are poorly cleared from the vitreous, their concentrations in the vitreous body could reach pharmacologically/toxicologically significant levels. While a number of studies have been performed with implant strengths of greater than 0.59mg, the actual *in vivo* release rates of these implants are not known, which makes it difficult to confidently rely on these data for the qualification of the impurity limits. Additionally, given that in all batches used for nonclinical and clinical testing, levels of relevant impurities were below the proposed limits, existing nonclinical data could not be considered to have qualified the proposed limits. Proposed limits should be reduced or additional qualification data should have been provided.

No phototoxicity testing had been undertaken despite the fact that FA absorbs light in the visible spectrum. The applicant argued that methodologies recommended for nonclinical photosafety testing focus on the cutaneous route of administration, and that no methods relevant to intraocular use are currently available. The applicant further considered that in the one year studies in rabbits and dogs, no relevant local ocular reactions indicative of phototoxicity, photoallergy or photocarcinogenicity had

been seen. However, the *in vitro* phototoxicity test (3T3 NRU test) recommended in the Note for Guidance on Photosafety Testing (SWP/398/01) is not considered to be irrelevant for products for ocular administration. Photomutagenicity studies were also found to be lacking. *In vitro* phototoxicity testing as recommended in the guideline should be performed.

The applicant has provided a number of *in vitro* studies examining the biocompatibility of the device portion of the product under acute exposure conditions. *In vitro* mutagenicity studies were performed in accordance with the relevant standards. *In vitro* cytotoxicity was assessed using both Minimal Essential Media (MEM) extract and by direct contact, in accordance with EN/ISO 10993-5. While no evidence of cytotoxicity was seen with the MEM extract, some cytotoxicity was seen in the direct contact method. In addition, significant evidence of cell growth inhibition was noted when an MEM diluted aqueous extract was incubated with L-929 mouse fibroblast cell suspensions. Furthermore, DMSO extracts were also seen to impair cell growth in the *in vitro* mouse lymphoma assay. While the *in vivo* relevance of these findings is not known, they indicate that careful examination of the local tissue after animal eye implantation studies should take place to assess the relevance of these results *in vivo*.

In vitro haemolysis data was also provided, which indicated that the product is not haemolytic. However, these are considered irrelevant to this application.

The applicant also provided biocompatibility data from acute *in vivo* systemic toxicity studies using extracts administered intravenously and intraperitoneally. While these studies did not produce positive results it is noted that acute systemic toxicity is not recommended for a solid eye implant according to the general exposure route considerations in EN/ISO 10993-1 and more detailed guidance in the biocompatibility of an intraocular lens standard EN/ISO 11979-5 where the 20mg of an IOL is already considered too little to warrant systemic testing. However, ocular implantation testing should have been performed (in accordance with the principles from 10993-6 [tests for local effects after implantation] supplemented with detail in 11979-5), unless documented evidence can be presented about the safety of the product in the eye. Despite a long history of use of the ingredients in this implant, the applicant has not provided such evidence. Local tolerance testing performed in rabbit muscle has also been provided and is also inappropriate for this route of exposure. *In vivo* pyrogenicity testing was in accordance with EN/ISO 10993-11.

Chronic data (1 year rabbit and 1 year dog studies) were only performed with drug-containing implants. Delamination (separation of polymer layer from silicone cup) of the implant is reported not to have been seen during that time period. However, it was observed after 18-24 months of storage in medium and in three cases in a clinical trial (2 during explantation, one spontaneous). The adhesive bond has since been strengthened and no further delaminations were seen in the later clinical trials. However, in clinical practice, implant exposure is likely to be life-long. The strengthening of the adhesive bond will delay delamination, but it can be expected to occur at some point, leaving the silicon cup free to float in the vitreous humour. The risk of mechanical damage to the retina from the free floating silicone cup was a cause for concern and given the anticipated life-long exposure to the implant, a risk assessment of the ocular exposure to the breakdown products of the implant should have been provided. Additionally, as nonclinical studies with the empty implant were performed before the changes to the silicone adhesive, analytical data confirming that these changes have not adversely affected the leaching profile should have been provided.

With regards to carcinogenicity testing of the device portion of the product, given the clean results in the Ames, mouse lymphoma and *in vivo* micronucleus assay, none would be expected. However, given the life-long exposure in humans, long-term ocular implantation data is expected. This has been provided in the 1-year rabbit and dog studies using the functioning implant (i.e. containing FA).

Histopathology data from the 1-year rabbit study revealed localised tissue damage, retinal degeneration and fibrosis at the implant site in test and sham implanted eyes. Occasionally, focal retinal degeneration (minimal to slight) was seen in the same hemisphere but at some distance from the site of the implant. Focal lenticular degeneration and/or distortion by the implant was also seen in a few test and sham implanted eyes. Additionally, the presence of a fibrous membrane on the ganglion

cell layer of the retina was present in one test and one sham implanted eye. The applicant concluded that the findings represent minor changes related to mild focal trauma associated with the presence of the implant, although a discussion of these findings from a biocompatibility point of view has not been provided.

In the 1-year dog study the most common finding seen in the evaluation of the surgical site was a cavity through the ciliary body and into the sclera that varied in size and shape, opened into the vitreal cavity, and was enclosed by slight to moderate amounts of fibrous connective tissue. Single or multiple fragments of the suture tab were typically present in the cavity or were closely associated with it. Uncommonly, a large closed cyst was located at the surgical site and contained an implant and fragments of a suture tab. The incidence of these findings should have been clarified and the details of the incidence of these findings and their clinical significance should also have been provided. Peripheral cystic retinal degeneration was noted in a number of globes in all groups including the untreated controls.

Additionally, cataracts, graded as minimal to moderate, were seen in a number of test and sham-operated animals. The cataracts are reported to have started where the implant could be seen to be in contact with the lens posterior capsule. As no dose response effect was seen, the applicant attributed the cataracts to mechanical contact between the implant and the lens. The possibility that the cataracts may have been reflective of cytotoxic leachables has not been addressed.

In toxicity studies in both the rabbit and the dog the sham implant consisted of the suture tab only. Compared to the actual implant, the dimensions of the suture tab are much reduced, and it fails to provide exposure to the silicone elastomer and adhesive. It would have been more appropriate to use empty implants as sham implants. From a biocompatibility point of view, use of the suture tab in sham operated animals does not serve to provide a satisfactory negative control and nor does it provide information relating to a complete, drug-free implant. The use of the suture tab instead of the blank (empty) implant should have been justified.

The proposed product is not considered to represent a risk to the environment.

Clinical aspects

Pharmacokinetics

The clinical pharmacokinetic studies presented in this application dealt with the systemic or local levels of fluocinolone (FA).

Blood levels

In the pivotal clinical trial BLP 415-001, a total of 156 samples from 40 subjects were received and analysed. Blood samples were taken from selected subjects at baseline and at visits including Day 2, Week 1, Week 4 and Week 34. At none of these visits was the level of FA in the blood above the lower limit of quantitation.

Similar results were obtained in clinical study BLP 415-001J/JF. In none of the samples collected was the level of FA in the serum above the lower limit of quantitation.

FA amounts in explanted product

In several studies subjects in whom the implant was explanted, the explanted intravitreal implant was assayed in some patients. Analysis of the explants analysed from these studies demonstrated that there was an inverse relationship between the proportion of drug remaining in the implant and the number of days in the eye. The sample size makes it difficult to draw conclusions.

FA concentrations in ocular tissues

In several studies subjects in whom the implant was explanted, or another intraocular surgery was being performed, samples of aqueous humour and/or vitreous humour were requested for chemical analysis.

A total of 147 ocular tissue samples were obtained for analysis. In the aqueous humour samples taken up to two years after implantation, levels of FA ranged from 691 pg/mL to 86.7 ng/mL. In the vitreous humour samples taken up to three years after implantation, levels of FA ranged from below the lower limit of quantitation to 589 ng/mL. Six samples, (4 aqueous and 2 vitreous) were below the lower limit of quantitation of the assay. Due to the wide range, it was not possible to establish a clear relationship between the duration of implantation and the ocular tissue level.

Pharmacodynamics

Due to the nature of the product, neither plasma concentration nor ocular tissue levels are readily available for measure, and thus one cannot ascertain PK/PD relationships.

Efficacy of the intended dose (590 micrograms) was studied in the pivotal clinical studies (BLP 415-002 and BLP 415-001)

Summary of clinical pharmacology studies

Various doses have been evaluated in several clinical pharmacology studies ranging from 0.59 mg to 6 mg in different disease entities.

Tabular summary of clinical pharmacology studies

Design Control type	Study & control drugs, Route & Regimen	# N by arm entered/ complete	Study Status: Type of Report	Gender M/F Mean age (Range)	Diagnosis	Primary endpoints	Duration of Treatment
Open	2.1 mg implant 6 mg implant	7/N.A. 6/N.A.	Complete, Abbreviated	2/11 42.4 (24-52)	CNV	Inflammation	3 years
1) Open 2) Investigator masked (Uveitis) 3) Investigator masked (BRVO) 4) Investigator masked (CRVO)	590 microgram implant 2.1 mg implant 15 mg implant	4 8 1 64 (Masked)	Ongoing, Interim, Abbreviated	11/30(26 Unk.) 48.7 (11-87)	Uveitis, CRVO, BRVO, CME, RP	Inflammation	3 years
Variable	590 microgram implant 2.1 mg implant 6 mg implant	2 1 10	Complete, Abbreviated	10/3 59.9 (28-88)	DME ARMD NEOV	Inflammation	3 years
Variable	2.1 mg implant	2	Complete, Abbreviated	2/0 21.5 (17-26)	Behcet's Uveitis	Inflammation	3 years
Variable	2.1 mg implant 590 microgram implant	1 1	Complete, Abbreviated	1/0 47 (N.A.)	CNV	Inflammation	3 years
Variable	6 mg implant	1	Complete, Abbreviated	0/1 Unk. (N.A.)	Retinal NV	Inflammation	3 years
Variable	6 mg implant	1	Complete, Abbreviated	0/1 38 (N.A.)	CNV	Inflammation	3 years
Variable	2.1 mg implant	1	Complete, Abbreviated	1/0 7 (N.A.)	Uveitis	Inflammation	3 years
Variable	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

Clinical efficacy

Two pivotal (BLP 415-002 and BLP 415-001) and two supportive (BLP 415-004 and BLP 415-001J/JF) studies were submitted in support of this application.

Two study designs were utilised by the applicant in the pivotal studies;

- BLP 415-002; 590 microgram FA implant vs standard of care (SOC) treatment
- BLP 415-001; 590 microgram FA implant vs 2.1 mg FA implant

In both pivotal study designs, subjects with either unilateral or bilateral non-infectious uveitis affecting the posterior segment of the eye were enrolled.

The control for BLP 415-002 was the group of subjects enrolled in the SOC arm, which required administration of systemic corticosteroids and if necessary, administration of systemic non-steroidal immunosuppressive agents for a minimum period of 6 months. The primary efficacy variable for the BLP 415-002 study design, was the time-to-first protocol defined recurrence of uveitis in the study eye occurring in the 24 months after randomisation for the SOC group and the 24 months after visit 7 (12 weeks) for the implant group.

For BLP 415-001, two types of controls were employed: (1) a historical control and; (2) a dose comparison for both safety and efficacy evaluations. The primary efficacy variable for the BLP 415-002 study design, was the time-to-first protocol defined recurrence of uveitis in the study eye occurring in the 24 months after randomisation for the SOC group and the 24 months after visit 7 (12 weeks) for the implant group. For the BLP 415-001 uveitis study, the primary efficacy analysis involved a comparison of the rates of protocol-defined recurrences of uveitis before and after implantation. The data from the year prior to implantation were collected retrospectively.

Study BLP 415-001 is seen to be a dose finding study rather than a pivotal for the following reasons: This study was planned to investigate the two different implant doses (2.1 mg and 0.59 mg). Thus it was rather a dose finding study, which was subsequently changed to a comparison with historic data. Hence, only BLP 415-002 can be regarded as pivotal.

The list of studies providing efficacy information is presented in the table below:

Study/Phase/Type	Locations	Study start/enrolment goal/total enrolment	Design	Study & control drugs	N by arm entered/complete	Duration	Primary endpoints
415-002 IIb/III Safety & efficacy	Multicentre (EU, Israel, Turkey, Saudi Arabia)	24 Apr 2002 150/146	Open label, parallel	0.59 mg vs SOC	72/NA 74/NA	3 years	Time to first recurrence
415-001 IIb/III Safety & efficacy	Multicentre (US and Singapore)	28 Dec 2000 250/278	Double (dose) Masked parallel	0.59 mg 2.1 mg	110/106 168/165	3 years	recurrence
415-004 IIb/III Safety & efficacy	(US, Canada, Hong Kong, India, Australia, Philippines)	28 May 2002 250/239	Double (dose) Masked parallel	0.59 mg 2.1 mg	117/NA 122/NA	3 years	recurrence
415-00J/JF IIb/III Safety & efficacy	Multicentre (Japan)	12 Jun 2002 100/30	Double (dose) Masked parallel	0.59 mg 2.1 mg	14/14 16/16	3 years	recurrence

STUDY BLP 415-002

Study BLP 415-002 was a three-year superiority, multicentre (sites in EU, the Middle East and Turkey), open-label randomised, controlled, safety and efficacy study. The applicant submitted the second year study report for the purposes of this application. The aim of this study was to evaluate the effect of the intravitreal fluocinolone acetonide (0.59 mg) implant compared to standardised therapy in subjects with unilateral or bilateral, non-infectious uveitis affecting the posterior segment of the eye.

The primary inclusion criteria were males and non-pregnant females of at least 6 years of age with a history of recurrent or recrudescing unilateral or asymmetric non-infectious posterior uveitis of at least

1 year duration, not associated with significant systemic activity of disease. The more severely affected eye had at least two separate recurrences of non-infectious uveitis (the last episode during the 8 months prior to enrolment) and was treated by systemic therapy (corticosteroids and/or immunosuppressants) for at least 1 month just before inclusion. At the time of enrolment the subjects had to have a 'quiet' eye (defined as ≤ 10 AC cells/high power field and a vitreous haze $\leq$ grade 2) and a visual acuity of at least 1.4 logMAR units. The less severely affected eye was controlled with only periocular injections for 1 year and the visual acuity was at least 0.7 logMAR.

Eligible subjects were randomised in a 1:1 ratio to receive SOC therapy or surgical implant. SOC therapy started at screening/randomisation with systemic corticosteroids, and if necessary an immunosuppressive agent to lower the steroid doses to a minimum dose of 100 microgram/kg/day was used for 6 months.

The primary efficacy variable was the time-to-first recurrence of uveitis in the study eye.

Recurrences were defined as:

- a ≥ 2 step increase in the number of cells from baseline in the anterior chamber per high power field, or
- an increase in the vitreous haze of ≥ 2 steps from baseline, or
- a deterioration in visual acuity (VA) of at least 0.3 logMAR units from the best improved VA since screening (baseline) not related to cataract formation or raised intraocular pressure or surgical sequelae or epiretinal membrane.

Secondary efficacy outcomes included:

- The proportion of subjects with a visual acuity improvement of more than 15 letters on EDTRS charts from baseline.
- Percentage of subjects having had at least one recurrence
- Number of recurrences
- Number of recurrences compared to the 52 weeks prior to enrolment
- Change in quality of life indices
- Adjunctive treatment required
- Change in the size, if present at baseline, of the area of CME on fluorescein angiography.

The protocol was amended 3 times.

The primary efficacy measure in this study was the time-to-first recurrence of uveitis in the study eye occurring in the 24 months after randomisation for the standard therapy group, and the 24 months after visit 7 (12 weeks after surgery) for the implant group. The first 12 weeks to visit 7 were excluded for the implant group. As such, as events occurring in this first period are not regarded as recurrences, a bias is introduced.

Treatments:

The implant was inserted intra-vitreally by a surgical procedure within 14 days from the screening visit, and perioperatively, a subconjunctival antibiotic and steroid injection was administered. A standard postoperative regimen consisted of prednisolone acetate 1 % eye drops (or an equivalent topical steroid) at least 4 times daily, trimetoprim sulphate 0.1 %/polymyxin B, or a broad spectrum antibiotic excluding steroid combinations 4 times daily, and homatropine 2 % or 5 % daily or equivalent mydriatic was to be administered for 1 week thereafter.

Pre existing therapy was tapered off along with post-operative medications. Pre-existing systemic steroid and/or immunosuppressant use and topical steroid use in implanted subjects was then tapered according to the protocol defined tapering schedule.

After the end of the study, the decision to remove the implant or not, was left to the Investigator.

Concomitant medication:

The following medications were not permitted during the study: Oral, systemic, or ocular steroids, or immunosuppressive agents, other than those required to treat recurrences of uveitis. No sub-tenon injections of depot steroid preparations were to be given from the time the subject met the entry

criteria to the time of surgery. Any adjunctive therapy of chronic steroid treatment was to be recorded. Dose variation and concomitant treatments were recorded for the study duration.

The therapy in the Standard of Care (SOC) group: This included systemic steroids and any one of the following standardised immunosuppressant therapies cyclosporine A, methotrexate, cyclophosphamide, mycophenolatemofetil, azathioprine or tacrolimus. After 6 months, the treatment was tapered, if the disease had been controlled.

Results:

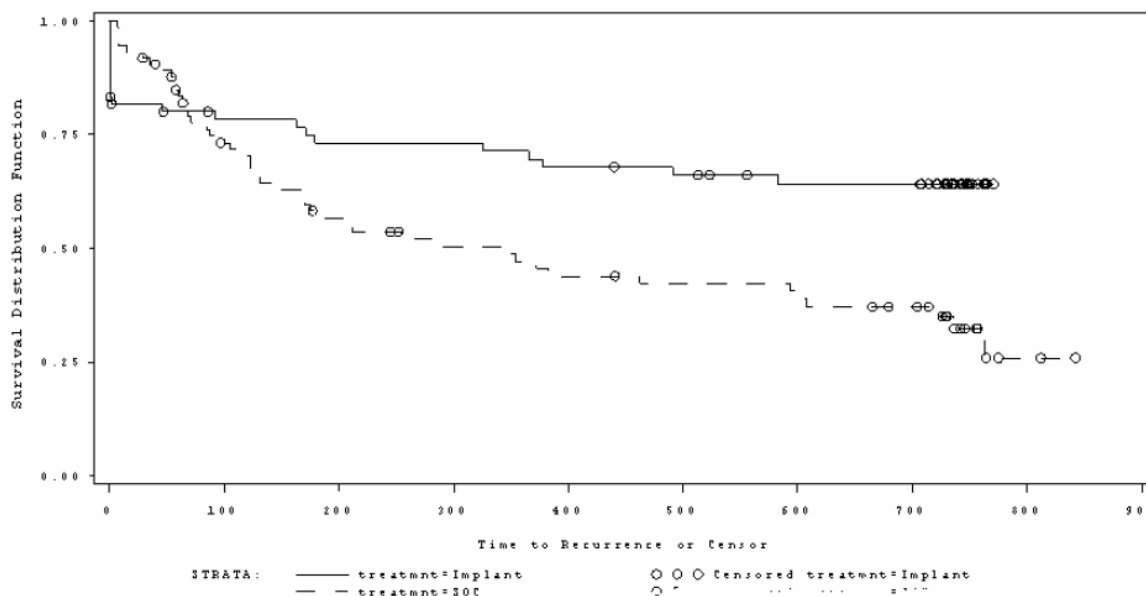
A total of 146 patients were enrolled with 72 in the implant group and 74 in the SOC group. A number of 140 patients were included in the ITT analysis. Of the 66 patients (92 %) who received treatment, three patients withdrew due to administrative problems, 2 withdrew consent and 1 experienced adverse events in connection to the surgery (failure of implantation). In the SOC group, all patients who were enrolled received treatment.

The time-to-recurrence of uveitis for implant versus SOC study eyes was evaluated by Kaplan-Meier methods (freedom from recurrence). The time-to-recurrence (x-axis) was presented in days. For this analysis, time 0 was visit 7 for the implant group and visit 1 for the SOC group. Each drop along the (y-axis) survival distribution function represented a failure.

In the Implant group, 61 patients completed the 2 years visit versus 70 in the SOC group.

For the primary endpoint a statistically superior outcome was not obtained. The Kaplan-Meier analysis did not demonstrate a statistically significant difference between the implant and SOC eyes; time to first recurrence of uveitis was 127 versus 208 days in the implant and SOC group, respectively. ($p=0.0652$)

Kaplan-Meier plot of time-to-first recurrence (stratified by pooled centres and prior systemic therapy): ITT population



Visual acuity (VA) improvements were a secondary efficacy measure in contrast to CHMP recommendations that a global measurement of ocular function such as visual acuity should have been a co-primary endpoint. The difference in the rate of improvement in VA at the 2-year visit was not statistically different. In fact, there was no difference in the mean VA between baseline and 24 months in either group.

As far as other secondary endpoints were concerned (percent of at least one recurrence, number of recurrences and number of recurrences compared to 52 weeks prior to enrolment, area of CME), the

implant group performed better in comparison to the SOC group. Quality of life surveys, however, scored worse in the implant group which possibly reflects the fact that this group underwent a surgical procedure associated with a period of discomfort from surgery and reduction in visual acuity.

The major concerns in this study include:

For namely visual acuity, no statistically significant difference between the implant group and the SOC group has been demonstrated. This is remarkable as a large part, i.e. 88 % (43/49) compared to 19 % (11/57) in the SOC group, has undergone cataract surgery, and was hence expected to achieve a gain in visual acuity. Moreover, at baseline fewer patients were phakic in the implant group than in the SOC group, namely 49 versus 57 eyes, meaning that the disposition of cataract surgery patients is even more skewed. In addition, 79 % of the Implant group as compared to 42 % in the SOC group experienced a decreased VA of at least 0.3 log MAR units relative to baseline. So, importantly, the overall outcome for the visual acuity is negative for the implant group

Furthermore, data for concurrent medication use were not analysed – according to a change in the analysis plan (Amendment 1), where the design was changed to one active group versus one SOC group. “Treatment failures were not only associated with recurrent ocular inflammation but were also inferred when efficacy of the study treatment could not be established due to concomitant anti-inflammatory therapy or explantation”. However, the Applicant did not consider the analysis of adjunctive therapy at 24 months relevant, and it was not performed. This is a clear shortcoming, as an important feature is the potential reduction in need for systemic glucocorticosteroid therapy.

For the SOC group, according to the protocol, in all cases systemic therapy should be tapered after 6 months, if the disease was controlled. Unfortunately, such information about therapy in the SOC-group cannot be identified in the report. Furthermore, registration of concurrent medication is close to useless as the information is presented as “medication used at least once” (including use in the immediate vicinity of the implantation procedure). Glucocorticosteroids were used in 100 % in both groups. There is no distinction between topical, sub-tenon injection and systemic use. Therefore, the major question if the implant would possess a “glucocorticosteroid-sparing” effect cannot be answered. This is a severe draw-back of the dossier. The planned tapering of systemic therapy in the SOC group after 6 months may well have elicited some recurrence, which is another bias in the design. As the implant group also received systemic therapy in the first weeks of the study, they might have a better outcome. It is not possible to evaluate to which extent this would be counteracted by the surgical implantations and the sequelae hereof, but some bias is likely.

Major protocol amendments and changes in SAP may likely interfere with the results.

Interpretation of bilateral comparison is questionable.

Data as to compare to prior 12 months uveitis were collected retrospectively.

Reservations are also appropriate concerning the open design of the study, though the reasons for this design are acknowledged.

The applicant has not adhered to the SA in the choice of primary variable efficacy parameter, but chosen “time to first uveitis recurrence”. CHMP did not agree with the applicant’s choice of end point and the reasons for this choice.

In addition, the visual acuity results derive from the 2 years observation point, however, the study is planned to obtain 3 years data. This is especially important considering that the expected time of a persistent efficacy is 3 years. Thus, a final evaluation of the visual acuity outcome is not possible with the submitted data.

Investigations to explore the optimal regimen, i.e. whether explant or not after 3 years, have not been conducted.

In conclusion, the pivotal study appears to have failed in the primary hypothesis and is furthermore marred by significant insufficiencies in the whole conduct of the study.

STUDY BLP 415-001

This study was a multicentre, double-masked, controlled safety and efficacy study in subjects with either unilateral or bilateral non-infectious uveitis affecting the posterior segment of the eye, conducted in the USA and in Singapore. Clinical evaluations took place over a period of approximately 3 years following surgical implantation of the fluocinolone acetonide (FA) intravitreal implant 0.59 mg or 2.1 mg.

The primary efficacy measure was the change in disease status of the eye receiving the FA implant, from the period of assessment prior to implantation, to the period following surgical implantation. This was an amendment to the original protocol, which was introduced at a late stage while the trial was ongoing. The trial was originally designed as a comparison of 2 doses of FA. The primary analysis was conducted after all subjects completed 34 weeks post-implantation. An additional analysis was conducted when all subjects had completed one-year post-implantation. The report submitted presented data after all subjects had completed the study (3 years post-implantation).

Subjects eligible for participation in this study included males or non-pregnant females at least 6 years of age who had been diagnosed and treated for recurrent, non-infectious uveitis affecting the posterior segment of one or both eyes for at least 1 year prior to the commencement of the study. The subjects had to have clinically 'quiet' eyes at surgery, and no coexistent medical (e.g. AIDS or other immunosuppressive conditions) or ocular conditions (e.g. iritis, glaucoma, vitreous haemorrhage, infectious uveitis etc) and a visual acuity of at least 1.4 logMAR in the study eye.

Three lots of the 2.1 mg implant were used, having two different designs. The original design was found *in vitro* to allow more rapid release of FA into the eye than was desirable, which could allow FA delivery to the eye to cease at an earlier time than with the 0.59 mg implant.

The primary efficacy variable was the recurrence of uveitis before and after implantation. Data from the year prior to implantation were collected retrospectively. A recurrence with onset within 1 year prior to implantation was defined by the assessment of the Investigator that the episode satisfied the definition of a "protocol-defined" recurrence as recorded on the Uveitis History CRF. This could have been contradicted by the following: a maximum AC cell score < 2 , as recorded on the Uveitis History CRF and a maximum vitreous haze score < 2 , as recorded on the Uveitis History CRF and a maximum change in VA of < 0.3 logMAR or Snellen equivalent, as recorded on the Uveitis History CRF.

Post-implantation recurrences were evaluated based upon changes in VA (deterioration of ≥ 0.30 logMAR), vitreous haze (≥ 2 step increase in grade from baseline) and the presence of cells in the anterior chamber of the eye (≥ 2 step increase in number of cells per high-power field). For purposes of analysis, any eye not observed past the 24-week visit was assumed to have had a recurrence of uveitis. Primary analyses of efficacy were conducted at 34 weeks post-implantation at 1 year and at 3 years. The report submitted included analyses of efficacy performed after all subjects remaining in the study had completed 3 years of post-implantation follow-up.

Secondary efficacy outcomes included:

- o between-dose group comparisons of the rate of uveitis recurrence post-implantation;
- o within-subject comparisons of study eye to fellow eye for recurrence of uveitis post-implantation;
- o time to first post-implantation recurrence of uveitis;
- o the need for adjunctive uveitis treatment for the study eye (pre- versus post-implantation);
- o reduction in the area of cystoid macular oedema (within subject comparison of study eye versus fellow eye);
- o Quality of Life surveys (QoL) pre- versus post-implantation

Subjects who satisfied the inclusion criteria and entered the study were randomly assigned to have one of the 2 intravitreal implants. A total of 278 subjects were randomised; all of these subjects received FA intravitreal implants (110/278, 0.59 mg; 168/278, 2.1 mg). A total of 241 subjects (86.69%)

completed the study. A total of 37 subjects did not complete the study. The most common reason for discontinuation was the occurrence of an adverse event. The most common adverse event resulting in discontinuation was explantation due to uncontrolled IOP; this was reported for 5 of the 14 subjects who discontinued due to an adverse event.

Primary efficacy measure: Pre- versus post-implantation recurrence of uveitis

Study eyes

The table below summarises uveitis recurrence rates for 1 year pre-implantation, 34 weeks post-implantation, 1 year post-implantation, 2 years post-implantation and 3 years post implantation.

The 2.1 mg dose group is divided into: recurrence data from subjects who received the original 2.1 mg implant (enrolled prior to January 2002) and recurrence data from subjects who received the redesigned 2.1 mg implant. Overall, 42% (70/168) of study eyes received the original 2.1 mg implant and 58% (98/168) received the redesigned 2.1 mg implant.

Uveitis recurrence rates for the 1 year pre-implantation period and during the 3 year post-implantation period; study eyes; ITT

Post-implantation Period	FA Intravitreal Implant Dose	N	1 Year Pre-implantation N (%)	Post-implantation N (%)	p-value ¹
34 Weeks ²	0.59 mg	110		2 (1.82%)	
	All 2.1 mg	168		8 (4.76%)	
	Original 2.1 mg	70		4 (5.71%)	
	Redesign 2.1 mg	98		4 (4.08%)	
	Both Doses	278		10 (3.60%)	
1 Year ²	0.59 mg	110	68 (61.82%)	4 (3.64%)	
	All 2.1 mg	168	98 (58.33%)	11 (6.55%)	
	Original 2.1 mg	70	50 (71.43%)	5 (7.14%)	
	Redesign 2.1 mg	98	48 (48.98%)	6 (6.12%)	
	Both Doses	278	166 (59.71%)	15 (5.40%)	
2 Years	0.59 mg	110	68 (61.82%)	11 (10.00%)	<0.0001
	All 2.1 mg	168	98 (58.33%)	28 (16.67%)	<0.0001
	Original 2.1 mg	70	50 (71.43%)	19 (27.14%)	<0.0001
	Redesign 2.1 mg	98	48 (48.98%)	9 (9.18%)	<0.0001
	Both Doses	278	166 (59.71%)	39 (14.03%)	<0.0001
3 Years	0.59 mg	110	68 (61.82%)	22 (20.00%)	<0.0001
	All 2.1 mg	168	98 (58.33%)	69 (41.07%)	0.0006
	Original 2.1 mg	70	50 (71.43%)	40 (57.14%)	0.0588
	Redesign 2.1 mg	98	48 (48.98%)	29 (29.59%)	0.0038
	Both Doses	278	166 (59.71%)	91 (32.73%)	<0.0001
3 Years ³	0.59 mg	110	68 (61.82%)	33 (30.00%)	<0.0001
	All 2.1 mg	168	98 (58.33%)	80 (47.62%)	0.0314
	Original 2.1 mg	70	50 (71.43%)	44 (62.86%)	0.2207
	Redesign 2.1 mg	98	48 (48.98%)	36 (36.73%)	0.0768
	Both Doses	278	166 (59.71%)	113 (40.65%)	<0.0001

¹ p-value (from McNemar's test), comparing recurrence rates for the pre- and post-implantation periods noted.

² Statistical comparisons for 34 weeks pre- and post-implantation and 1 year pre- and post-implantation have been previously presented (FSR BLP 415-001, version 1.1 [34-week report] and FSR BLP 415-001 [1-year report]) and are not repeated here.

³ Results presented include imputed recurrences. Recurrences were imputed when a subject was not seen within 10 weeks of their final scheduled visit. Imputed recurrences are not included in Listing 16.2.6.

For study eyes in the 0.59 mg group 8.18% (9/110) of eyes had more than 1 uveitis recurrence within the 3 year post-implantation period, compared to 42.73% (47/110) of eyes that experienced more than 1 recurrence during the 1 year pre-implantation period. For the 2.1 mg group 14.29% (24/168) of eyes had more than 1 uveitis recurrence within the 3 year post-implantation period, compared to 30.36% (51/168) of eyes that experienced more than 1 recurrence during the 1 year pre-implantation period. The comparison of the two groups is of particular interest as, paradoxically, the 0.59 mg implant performs better than the 2.1 mg implant and this was also seen with the redesigned 2.1 mg implant.

This analysis defined as primary by the applicant is subject to substantial bias. The patients were recruited into the trial based upon having had uveitis recurrences that required treatment over the previous 6 months. So as a group when their disease over the last year is assessed the recurrence rate is extremely likely to be high, as this is the basis on which they were recruited. If a group is selected on the basis of having had a bad year, it is almost certain that on average the next year will be an improvement for them. This phenomenon is known as “regression to the mean”, and is one reason why concurrent controls are the preferred choice in a clinical trial (see statistical assessment report page 78 of day 70 clinical assessment report). In addition, the evaluation of the results is difficult as the comparison of uveitis recurrences post-implantation is conducted against a period where treatment was not standardised and it is unknown whether it was what would be considered the standard of care for the disease

Visual acuity:

The incidence of improvement in visual acuity from baseline of at least 0.3 log MAR is shown below.

Table 17: Incidence of improvement in visual acuity (from Baseline) of at least 0.30 logMAR at the 3-year visit; Intent-to-Treat sample

FA Intravitreal Implant Dose	Study Eyes		Fellow Eyes		p-value ¹
	N	Improvement N (%)	N	Improvement N (%)	
0.59 mg	94	22 (23.4%)	90	5 (5.6%)	<0.0001
2.1 mg	141	26 (18.4%)	137	6 (4.4%)	0.0004
Both Doses	235	48 (20.4%)	227	11 (4.8%)	<0.0001

¹ p-value from McNemar's test.

Source: Statistical Appendix 14.2.7.1.

Importantly, this should be seen in the perspective that the percentage of loss ≥ 3 lines in VA was greater in the study eye 70 % and 75 % (0.59 and 2.1 mg group, respectively) than in the fellow eye 44 % for both groups fellow eye ($p < 0.0001$) at 3 years. It should also be noted that a large part of patients had undergone cataract surgery during the 3 years study period.

Table 12: Use of systemic medications for control of uveitis at enrollment and at the 3-year visit; Intent-to-Treat sample

FA Intravitreal Implant Dose	N	At Enrollment N (%)	At 3-Year Visit ¹ N (%)	p-value ²
0.59 mg	110	48 (43.6%)	9 (8.2%)	<0.0001
2.1 mg	168	95 (56.5%)	22 (13.1%)	<0.0001
Both Doses	278	143 (51.4%)	31 (11.2%)	<0.0001

¹ Data imputed for subjects who did not complete 3-year visit.

² p-value from McNemar's test.

Source: Statistical Appendix 14.2.4.

The above table, and data for peri-ocular steroid injections and peri-ocular injections applied to the fellow eye, support the assumption of an effect on the inflammation.

For fellow, non-implanted eyes, uveitis recurrence rates were higher during the 3 year post-implantation period in comparison to the year pre-implantation.

Similar results (the 0.59 mg implant performing better than the 2 mg implant) were observed for secondary efficacy measures such as between-treatment group comparison and area of CME.

BLP 415-004

This was a 3-year, randomised, double-masked, controlled, safety and efficacy study to evaluate 2 dose levels of FA intravitreal implants conducted in sites across US, Canada, Hong Kong, Australia and Philippines. Patients were randomised in a 1:1 ratio between 2.1 mg and 0.59 mg dose. The 1 year interim clinical study report was included in this dossier.

The primary inclusion criteria were males and non-pregnant females at least 6 years of age, with one or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of ≥ 1 year duration requiring either:

- systemic corticosteroid or other equivalent systemic therapy for at least three months prior to enrolment OR
- at least 2 sub-Tenon's injections of corticosteroid for the management of uveitis during the six months prior to enrolment OR
- at least 2 separate recurrences within the six months prior to enrolment requiring either systemic corticosteroid therapy or sub-Tenon's injection of corticosteroid and at the time of enrolment in the study eye, ≤ 10 anterior chamber cells/HPF and a vitreous haze $\leq$ grade 2 (i.e. a relatively quiet eye prior to surgery for implantation of implant) and best corrected visual acuity of at least 1.4 logMAR units.

Subjects were to be followed for at least 3 years following implantation. In the event of a clinical recurrence in either eye subjects were treated as follows: Peri-ocular corticosteroid injections were the preferred first-line treatment, with systemic corticosteroids being the second choice. Once the recurrence was under control, therapy was tapered. Each recurrence was to be treated in the same manner and the progress of recurrences in each eye was documented.

The primary efficacy endpoint in this study, similarly to study 415-001, was the comparison of uveitis rates pre and post-implantation. The data prior to implantation were obtained retrospectively.

Secondary efficacy endpoints included comparison of the dose response and comparison to fellow non-implanted eye in bilateral cases. Secondary efficacy variables were: change in visual acuity, number of recurrences, change in Quality of Life indices, adjunctive treatment required, change in the size if present at baseline of CME on fluorescein angiography and change in a- and b- wave amplitude and implicit time.

A total of 239 patients were enrolled. Of these, 232 (97.2%) completed 1 year of the study. Of the 7 subjects that did not complete the year, 6 discontinued prior to one year due to adverse events, 2 of these subjects died (deaths judged unrelated to study treatment) and 1 was lost to follow up.

Primary efficacy measure: Pre- versus post-implantation recurrence of uveitis.

Study eyes:

For both doses, 42.3% (101/239) had recurrences during the period prior to implantation, while 13.8% (33/239) presented with recurrences during the period subsequent to implantation.

Uveitis recurrence: 1 year periods prior to and subsequent to implantation: Intent-to-treat patients

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	117	51 (43.6%)	17 (14.5%)	<0.0001
2.1 mg	122	50 (41.0%)	16 (13.1%)	<0.0001
Both doses	239	101 (42.3%)	33 (13.8%)	<0.0001

¹ P-value is from McNemar's test.

The same limitations to evaluation of the primary efficacy measure as in study 415-001 apply to this study

BLP 415-001J/JF

This was a randomised, double masked, controlled, safety and efficacy study to evaluate 2 dose levels of FA intravitreal implants conducted in Japanese sites. Patients were randomised in a 1:1 ratio to 2.1mg or 0.59 mg of FA intravitreal implant.

The primary inclusion criteria were males and non-pregnant females of at least 18 years of age, with one or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of ≥ 1 year duration. Enrolment was stratified according to whether or not subjects were receiving systemic or local therapy consisting of corticosteroids or other immunosuppressive medicinal products at the time of their enrolment. Blood sampling in selected subjects for determination of FA plasma concentration was performed on day 2 and weeks 1, 4 and 34.

Treatment began with implantation on day 1. Previous treatment was tapered over 6 weeks. Scheduled visits were day 2, weeks 1, 4, 8, 12, 18, 24, 30 and 34. At the 34 week visit, subjects were to be exited from the BLP 415-001J study and subsequently enrolled into the long-term follow up study BLP 415-001JF. The long-term follow up visits were every 3 months $\pm$ 1 month starting with the one-year follow up visit.

Subjects were to be followed for at least 3 years following implantation. In the event of a clinical recurrence in either eye, subjects were treated as in study 415-004 with corticosteroid injections as first line and systemic corticosteroids as second line.

The primary efficacy endpoint in this study, similarly to studies 415-001 and 415-004, was the comparison of uveitis rates pre and post implantation. The data prior to implantation were obtained retrospectively. Secondary efficacy endpoints included comparison of the dose response and comparison to fellow non-implanted eye in bilateral cases.

Secondary efficacy variables were: change in visual acuity, number of recurrences, change in Quality of Life indices, adjunctive treatment required, change in the size if present at baseline of CME on fluorescein angiography and change in a- and b- wave amplitude and implicit time.

A total of 30 subjects were enrolled and implanted in the study (14 in the 0.59 mg and 16 in the 2.1mg group) and included in the intent-to-treat analysis.

Primary outcome measures: Intrasubject comparison of the presence or absence of uveitis recurrence before and after implantation (ITT)

Implant eyes

The rates of uveitis recurrence during the 34-week period before and after implantation are presented in the table below:

Dose groups	Number of subjects	Before implantation			After implantation			McNemar test p value
		Number of subject with recurrence	%	95% confidence interval	Number of subject with recurrence	%	95% confidence interval	
0.5 mg	14	7	50.0	{23.0%-77.0%}	0	0.0	{0.0%-23.2%}	-
2 mg	15	9	60.0	{32.3%-83.7%}	1	6.7	{0.2%-31.9%}	0.0114
Overall	29	16	55.2	{35.7%-73.6%}	1	3.4	{0.1%-17.8%}	0.0003

The number of subjects of presence or absence of recurrence over 34-week period

Dose groups			After implantation	
			Absent	Present
0.5 mg	Before implantation	Absent	7	0
		Present	7	0
2 mg	Before implantation	Absent	5	1
		Present	9	0
Overall	Before implantation	Absent	12	1
		Present	16	0

Overall conclusions on clinical efficacy

The applicant submitted two pivotal studies utilising Retisert in the treatment of non-infectious uveitis affecting the posterior segment of the eye. In one study Retisert was compared to SOC and conducted mainly in Europe and in the other mainly US based study, two doses of Retisert (0.59 mg and 2.1 mg) were compared against historical data from the year prior to implantation.

Study 415-002 was a randomised, open-label, controlled study comparing the Retisert 0.59 mg implant to standardised therapy in patients with unilateral or bilateral uveitis. A major amendment to the protocol (clarification of the definition of recurrence to take into account the 12 week post-operative period) occurred at a very late stage. This is an important drawback and it may have introduced bias to the efficacy results, as this amendment was introduced only five months before the last 2-year visit occurred.

The study was open label due to the differences in the treatments utilised. A ‘double-dummy’ design could have been used, but considering the fact that patients would have to be subjected to a surgical procedure and the limitations therein, the current design of the study could be accepted as the best possible option.

The primary efficacy endpoint in this study was time-to-first recurrence of uveitis. The applicant obtained scientific advice from CHMP on the design of this study and CHMP advised that time-to-first recurrence as a primary efficacy variable does not adequately reflect the disease and the proposed treatment. Damage to a uveitic eye can occur without a full recurrence and additionally the harmful effects of the actual device on ocular function need to be considered. Therefore, a global measurement of ocular function, such as visual acuity, should have been used as a co-primary endpoint. Additionally, considering the fact that the treatment in the implanted group is continuous for approximately three years, delaying the first recurrence does not automatically mean that the outcome at three years is superior to that of the SOC group. In conclusion, the choice of primary endpoint is not considered appropriate as the time-to-first recurrence would not adequately reflect the treatment proposed, which is over a prolonged period of time and a global measurement of ocular function was not utilised as a co-primary endpoint.

The applicant has not presented the population at risk at any time point. The duration of exposure of each patient should have been presented, by Kaplan-Meier plots or tables, to enable some understanding of the duration of follow up for each patient.

The primary efficacy analysis (the time-to-recurrence of uveitis analysis shown as the Kaplan-Meier plot) did not demonstrate a statistically significant difference between the implant and SOC eyes. The applicant argues that the primary efficacy analysis was not statistically significant due to failures being recorded as uveitis recurrences that were not due to clinical signs of inflammation but because of incorrect tapering of systemic immunosuppression. The results were only statistically significant when a supplemental analysis was conducted considering the failed cases censored instead of failed.

Uveitis recurrences were only being recorded for the implant group 12 weeks after surgery so that the eye could recover from the surgical procedure. However, for SOC eyes recording of uveitis recurrences started on day 1. It would have been more useful if recording of uveitis recurrences commenced at the same time for both study groups.

A negative impact in visual acuity has not been excluded in patients without recurrences, which was a request in the Scientific Advice. For a considerable part of the study population with implants the visual acuity outcome seems to be impaired. It is not clear to what extent this is correlated to recurrence of uveitis.

With respect to the Quality of Life surveys the implant group scored worse than the SOC group in a number of them, which possibly reflects the fact that the implant group had to endure a surgical procedure which for a considerable amount of time affected their vision and other aspects of their daily life.

Study 415-001 was a historical-controlled study. Initially the study was designed to provide a comparison between 0.59 mg and 2.1 mg of FA implant. While the trial was ongoing a major amendment to the original protocol was conducted and the primary efficacy analysis was modified to the comparison of uveitis recurrence rates prior to and after implantation. Information on uveitis recurrences for the year prior to enrolment was provided retrospectively.

The primary efficacy measure was the pre- versus post-implantation recurrence of uveitis. The 0.59 mg implant performed better in terms of efficacy in comparison to the 2.1 mg implant. The applicant argues that this was due to the technical problems with the original 2.1 mg implant. However, the 0.59 mg had better efficacy results even when compared to the redesigned 2.1 mg implant. The applicant would need to justify and explain this unexpected finding. The implant with the larger dose of fluocinolone would have been expected to have better efficacy results, but have a worse safety profile than the implant with the lower dose. However, this was not the case in this study. It is not clear that the ideal dose of fluocinolone has been identified as doses lower than 0.59 mg have not been studied and it is quite possible that a smaller dose could lead to similar efficacy with an improved safety profile.

Similar results (the 0.59 mg implant performing better than the 2 mg implant) were observed for secondary efficacy measures such as between-treatment group comparison and area of CME.

Comparison of improvement in visual acuity was conducted between study and fellow eye. This is not a very useful comparison as the fellow eye was only receiving periodic treatment of uveitis flares whereas the study eye was treated continuously. However, other comparisons were limited by the fact that fellow eyes could not have possibly been treated continuously with systemic agents in this type of study.

The results of this study demonstrated a reduction of the number of uveitis recurrences in patients implanted with the 0.59 mg implant when compared to the year prior to implantation. However, the significance of these results is limited by the fact that the main comparison in this study was with the year prior to implantation. This primary efficacy measure was only introduced at a late stage in the trial, when it was considered by the applicant that a comparison between the 2 doses of the fluocinolone implant would not demonstrate statistically significant differences. In the year prior to implantation patients were not receiving standardised care and it is unknown whether they were receiving optimum treatment prior to the commencement of the study. The evaluation of the results is difficult as the comparison of uveitis recurrences post-implantation is conducted against a period

where treatment was not standardised and it is unknown whether it was what would be considered the standard of care for the disease. In addition, there was a paradox in this study and the implant with the higher fluocinolone dose performed worse than the implant with the lower dose.

Similar limitations apply to supportive studies 415-004 and 415-001 J/JF, as with study 415-001, since the main comparison was to a historical period (year prior to implantation).

The CHMP agree that qualitatively and quantitatively major methodological shortcomings hamper conclusions to be drawn for study BLP 415-002, which failed in the primary efficacy parameter, and for study BLP 415-001, which is inconclusive. Even considering the orphan designation, the methodological shortcomings are so grave that they preclude final evaluation.

There is a suggestion from the studies submitted, that a fluocinolone implant could be a useful tool to ophthalmologists in the treatment of non-infectious posterior uveitis. However, the results have not demonstrated compelling evidence of efficacy and it is not clear at this stage that the ideal dose has been identified, as doses lower than 0.59 mg have not been evaluated. The evidence so far suggests that a lower dose could be as efficacious as the 0.59 mg dose and possibly have a better safety profile

Overall statistical conclusion

There is some evidence of efficacy post-surgery provided, mainly from trial 415-001. The applicant's primary analysis of the trial, comparison to pre-treatment recurrent rates was not considered to be useful as it was subject to large biases. However, the 0.59mg implant was superior to the 2.1mg implant. This demonstrates that the 0.59mg implant has some effect, although it does raise important questions regarding the choice of dose, as this inverse relationship was not anticipated prior to the trial. In addition the study eye had fewer recurrences than the fellow eye, although this was not a randomised comparison.

So there is evidence that from 12-weeks onward use of the 0.59mg implant reduces the recurrence rate. However it is not clear (from trial 415-002) that Retisert is superior to the standardised treatment. And consideration of efficacy only beyond week 12 does not truly assess the efficacy of the overall strategy of using the implant, which should include assessment from the time of implant onwards.

The analysis of efficacy excludes consideration of the first 12 weeks of treatment, where it was not considered possible to distinguish the occurrence of post-operative inflammation from recurrences of uveitis. The data from 415-002 needs to be reconsidered. The current analysis does not give a fair comparison of the implant and standardised treatments as the two treatment arms are not compared over identical treatment periods (and even with the non-equivalent treatment periods the analysis just failed to reach statistical significance). Once this study is re-analysed it must be considered whether the reduction in events post week 12 is sufficient considering the effects of surgery

Clinical safety

The safety review of Retisert was prepared from data collected from 21 clinical studies submitted with this application. These studies included patients with chronic non-infectious posterior uveitis and other ocular disease entities such as diabetic macular oedema (DME) and age related macular degeneration (AMD).

The studies in this submission included 1276 eyes of 1268 subjects. Of the 1276 eyes, 1061 eyes were assigned to receive the FA intravitreal implant: 549 to the 0.59 mg implant, 340 to the 2.1 mg, 18 to the 6 mg implant, 1 to the 15 mg implant and 153 for whom the dose assigned was still masked.

There were approximately 3500 patient-years of exposure for controlled studies sponsored by the applicant, of which approximately 2800 patient-years were with the intravitreal implant, at the intended marketed strength of 0.59 mg or higher.

Adverse events

The most frequently reported adverse events in the uveitis studies in the study eye were increased IOP (57.3% in 0.59 mg group and 65.4% in 2.1 mg group) and eye pain. For SOC study eyes the most common ocular adverse event was worsened cataract (28.4%).

Ocular adverse events reported at an incidence of 30 to 55% in implanted eyes included eye pain, cataract (worsened or *de novo*), conjunctival haemorrhage and reduced visual acuity.

Ocular adverse events in the study eyes reported at an incidence of 15 to 30% for both implant groups were maculopathy, hypotony, post-operative wound complications, glaucoma, eye irritation, unusual sensation in the eye and pruritis.

Ocular adverse events in the study eyes reported at an incidence of 5 to 15% for both implant groups were vitreous haemorrhage, retinal haemorrhage, retinal detachment, wound site dehiscence, vitreal opacities, eyelid oedema, macular oedema, ptosis, inflammation, dry eye, increased tear production, discharge and photophobia.

Some ocular AEs in the fellow eye (increased IOP, reduced visual acuity) occurred at a higher rate in the Retisert group. A potential explanation could be that the benefit of the Retisert implant in the study eye prompted a reduction of systemic treatment which again put the fellow eye at greater risk of uveitis and uveitis-related events.

In addition, also some non ocular AEs (e.g. headache, nasopharyngitis, arthralgia, nausea, pyrexia) seem to be more frequent in the Retisert group.

The most frequent ocular serious adverse events with an incidence of >5% from the uveitis studies were cataracts, increased intraocular pressure, glaucoma, hypotony and retinal detachment. A similar pattern of SAEs was seen in DME and AMD studies, with cataracts being reported more frequently from those studies.

Other significant adverse events

Explants

There were 96 explants in the 1061 subjects (9%) in the 21 studies presented in this submission. There were approximately an equal number of explants in the 0.59 mg group and the 2.1 mg group.

Cataract extractions

- Uveitis studies

Cataracts were extracted in 95.9% (173/182) and 91.1% (150/161) of 0.59 mg and 2.1 mg implanted eyes, respectively, that were phakic at the time of implantation. In the SOC study eyes and in fellow eyes, cataracts were extracted from 22.8% (13/57) and 24.9% (111/499) of eyes respectively. The surgeries generally occurred between the week 24 and 24 month visits.

- DME and AMD studies

Similar results were observed in DME and AMD studies and almost all patients that were phakic at the time of implantation required extraction of their cataracts.

Glaucoma filtering surgery

- Uveitis studies

Filtering surgeries were required to manage the pressure increase in 30.9% (95/307) and 41.2% (126/306) of the 0.59 mg and 2.1 mg implanted eyes, respectively. The pressure increase was managed with explantation in 2.1% (13/613) of eyes. The surgeries generally occurred between the week 12 and week 34 visits. By comparison, in SOC study eyes and in fellow eyes, filtering surgeries to manage pressure increases were performed in 2.7% (2/74) and 2.2% (15/688) of eyes, respectively.

- **SOC controlled DME studies**

Filtering surgeries were required to manage the pressure increase in 32.8% (47/158) and 33.3% (51/133) of the 0.59 mg and 2.1 mg implanted eyes, respectively. The pressure increase was managed with explantation in 1.8% (6/316) of eyes. For the most part, these procedures occurred starting one year or more after implantation. By comparison, there were no filtering surgeries performed in SOC study eyes and filtering surgeries to manage pressure increases in fellow eyes were performed in 1.4% (4/315) of eyes.

- **Placebo Controlled DME Study**

There were 22 trabeculectomies (24.7%, 22/89) reported in the study eye up to 10 March 2006. For the most part, these procedures occurred starting one year or more after implantation. There are no cases reported of the pressure increase being managed by explantation. By comparison, no fellow eye trabeculectomies have been reported for this study.

- **AMD Studies**

Filtering surgeries were reported in 21.9% (7/32) and 50.0% (2/4) in study eyes of 0.590 mg and combination therapy treatment groups, respectively. No filtering surgeries have been reported in SOC study eyes. For fellow eyes, surgeries were reported for 1.5% (1/65) of eyes. These procedures mainly occurred starting one year or more after implantation. There are no cases reported of the pressure increase being managed by explantation.

Endophthalmitis

Up to 10 March 2006, a total of 29 cases of endophthalmitis have been reported for the Phase 2b/3 clinical studies presented in this submission. Ten of these events have occurred in subjects treated in the uveitis studies.

In the pivotal uveitis study BLP 415-002, endophthalmitis was reported for 7.5% (5/67) of implanted eyes with the average time to occurrence of 1.7 years post-implantation. In contrast, no cases were reported for SOC study eyes or fellow eyes.

In the pivotal uveitis study BLP 415-001, endophthalmitis was reported for one eye (0.9%; 1/110) in the 0.59 mg group with an onset date of 4 weeks post-implantation. No cases were reported for 2.1 mg study eyes (0%; 0/168) or fellow eyes (0%; 0/278) in study BLP 415-001.

In uveitis study BLP 415-004, the rates of endophthalmitis were 1.7% (2/117) and 8.2% (10/122) for 0.59 mg and 2.1 mg implanted eyes, respectively. The average time to onset for all cases in BLP 415-004 was 42 weeks (range 3 weeks to 2.9 years). No cases of endophthalmitis have been reported for fellow eyes in BLP 415-004. There have been no cases of endophthalmitis reported for BLP 415-001J/JF.

Visual acuity

A decrease in visual acuity (by at least 0.30 logMAR) was observed in 79% of implant study eyes and 42% of SOC study eyes at least at one visit. It is suggested by the applicant that these decreases are associated to implantation and cataract progression. However, after cataract extraction visual acuity should be improved again. The 3-year data are indispensable to elucidate this issue.

Overall conclusions on clinical safety

Safety data were available from a total of 21 studies involving 1276 eyes. Of these 1061 received either the 0.59 or 2.1 mg implant. Most studies were conducted in patients suffering from non-infectious posterior uveitis, however, safety data are available from studies of patients with diabetic macular oedema and age related macular degeneration.

Ocular adverse events were reported in almost all implanted eyes. Those reported in implanted study eyes were considerably more profound in number, frequency and severity in comparison to SOC eyes. In more than 50% of patients, increased intraocular pressure was recorded and in 31% of these patients filtering surgery was required. In 2.1% of patients explantation was necessary as it was impossible to control intraocular pressure with other methods.

Cataracts were extracted in 95.9% of eyes implanted with the 0.59 mg implant that were phakic at the time of implantation in the uveitis studies. It is not known whether the recovery from surgery in implanted eyes is compromised by the presence of corticosteroids in ocular tissue. Details of post-operative complications and a comparison of the post-operative period of implanted versus SOC eyes that underwent cataract extraction have not been provided.

Endophthalmitis, a serious, eye sight threatening adverse event was observed in a considerable number of implanted eyes. In contrast, no patients in SOC group experienced endophthalmitis.

Approximately 10% of implanted eyes were explanted for various reasons (e.g. increased intraocular pressure that was not controlled with medications or surgical procedures, endophthalmitis etc). A large proportion of the explanted eyes recovered with sequelae, which in a number of patients resulted in loss of visual acuity.

There is concern regarding the safety of the actual device. In the safety update of study BLP 415-001 which included the period after the end of the study, in a number of patients in both dose groups implant/stunt separation occurred which lead to explant surgery. This is in contrast with the applicant's claim that these technical problems were seen only in the original 2.1 mg implant. The implications to the eye from implant/stunt separation are not known.

This is potentially a life-long treatment. Data are available for 3 years post implantation and the implications in terms of safety for eyes that will require insertion of further implants are not known.

There was an extremely large proportion of patients with debilitating ocular adverse events. Patients treated with standard of care therapy experienced considerably less ocular adverse events. Overall, the applicant has not provided compelling evidence that the risk to the patient from ocular adverse events is lower than that of the systemic adverse events associated with treatment with systemic immunomodulators.

Orphan Medicinal Products

On 7 March 2005, orphan designation (EU/3/05/261) was granted by the European Commission to Bausch & Lomb (UK) Ltd, for fluocinolone acetonide (prolonged-release intravitreal implant) for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The disease is considered to affect between 13,800 and 46,000 persons in the European Union.

BENEFIT RISK ASSESSMENT

With respect to quality, the applicant has not fully discussed and justified the steps taken to minimise the risks of delamination, which principally relate to improvements in the bonding process during manufacture.

From a nonclinical point of view, the lack of a thorough investigation into the distribution and elimination of fluocinolone acetonide and its metabolites is considered to represent a serious safety concern. Additionally, available data suggest that the device portion of the product may eventually break into smaller parts, exposing the patient to the risk of mechanical damage from free floating device fragments. The applicant has not explained why it considers this risk to be acceptable. There are outstanding questions regarding the applicant's non-clinical data package.

The efficacy and safety of Retisert in the treatment of non-infectious uveitis affecting the posterior segment of the eye have been investigated in a number of studies. Despite this there are several issues related to both efficacy and safety that need to be thoroughly discussed and preclude a marketing authorisation at this stage. Compelling evidence of efficacy has not been provided and at this point it is not clear that Retisert is superior to standard of care. In terms of safety the majority of patients experienced ocular adverse events, which in a large percentage of patients were serious and in certain cases resulted in temporary or permanent loss of visual acuity. Overall, the applicant has not provided

evidence that the risk to the patient from ocular adverse events is lower than that associated with systemic adverse events from treatment of uveitis with systemic immunomodulators. Only an outstanding improvement of efficacy parameters including an improvement or lack of deterioration in visual acuity and/or a corticosteroid sparing effect might potentially justify the extremely unfavourable safety profile.

The risk benefit balance at this point for Retisert in the treatment of non-infectious uveitis affecting the posterior segment of the eye, is considered negative.