BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The applicant Alcon Laboratories UK Ltd submitted on 2nd December 2004 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for the Evaluation of Medicinal Products Retaane, through the centralised procedure.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Scientific Advice
The MAH did not seek scientific advice at the CHMP.

Licensing status:
Retaane was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. Steffen Thirstrup Co-Rapporteur: Dr. Bengt Ljungberg

2. Steps taken for the assessment of the product

- The application was received by the EMEA on 2nd December 2004.
- The procedure started on 20th December 2004.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8th March 2005. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 28th February 2005.
- During the meeting 18th - 21st April 2005, the CHMP agreed on the consolidated List of Questions. The final consolidated List of Questions was sent to the applicant on 22nd April 2005.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12th December 2005.
- The manufacturing site Alcon Manufacturing Ltd. - 6201 South Freeway - Forth Worth, Texas – USA was inspected between 2nd to 4th August 2004 by inspectors by the Swedish Medical Products Agency. The report was issued on 29th November 2004.
- Non-clinical safety studies performed by Maxxam Analytics, 5540 McAdam Road L, Mississauga, Ontario L4Z IPI, Canada were inspected between 28th November to 2nd December 2005 by inspectors from the GLP monitoring authorities, the Swedish Medical Products Agency (MPA) and Danish Medicines Agency (DKMA). The report was issued on 18th January 2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27th January 2006.
- During the CHMP meeting on 20th - 23rd February 2006, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.

- The EMEA was formally notified by Alcon Labotatories UK Ltd of its decision to withdraw its application for marketing authorisation on 28th February 2006, at day 180 of the evaluation procedure.

- During the meeting 20th – 23rd March 2006, following the withdrawal of the application, the CHMP adopted an assessment report, which reflects the status of the CHMP evaluation at day 180 of the procedure.

- An EMEA press release document on the withdrawn of the application was published on 2nd March 2006.

- Questions and answers (Q&A) document, and the applicant's letter of withdrawal were published on 28th March 2006.

SCIENTIFIC DISCUSSION

1. Introduction

The aim of this discussion is to provide the status of the CHMP assessment at the time of the withdrawal of Retaane. As the assessment was not finalised at this stage, some of the issues raised were still under discussion. As a consequence the CHMP could not draw definite conclusions on the benefit/risk balance of the product.

Problem statement

Age-related macular degeneration (AMD) is one of several diseases of the retina characterised by neovascularisation being the immediate cause of visual loss when it is most severe.

AMD is a progressive degenerative macular disease attacking the region of highest visual acuity, the macula. AMD is the major cause of vision loss in the elderly population in the Western world. Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities.

AMD is classified as two different types: the non-exudative (or dry) form and the exudative (or wet) form. The dry form is the most prevalent, accounting for 90% of the cases. The onset and progression of either type do not follow any particular pattern. It is not uncommon that the dry form develops into the wet, neo-vascular form of AMD. The latter form causes the worst incapacity and accounts for approximately 90% of blindness in AMD. The consequences of the neo-vascularisation include formation of immature leaky vasculature, and haemorrhage into the sub-retinal space. Fluid collects beneath photoreceptors within the fovea and may result in scar formation. In this process, the oxygen supply to the macula is disrupted and as a response to ischemia, new, abnormal blood vessels are formed. These may grow through breaks of the membrane behind the retina, towards the macula, often lifting the retina.

A certain percentage of patients with exudative AMD can benefit from laser treatment with traditional photocoagulation laser or photodynamic therapy (PDT) and recently, therapy to block vascular endothelial growth factor (VEGF) was approved.

There is a very prominent clinical need for ocular antiangiogenesis therapy. The compartmentalization of the orbit and the eyeball, including the ensheathing of the eyeball in the capsule of Tenon, which resembles a joint-capsule, offer promising opportunities to bring to the inside of the eye the action of pharmaceuticals with remarkable potency that would likely have intolerable side-effects were they to be administered systemically. The newly developed antagonists of VEGF is one type of such drugs; anecortave is another, its action being related to the angiostatic effect of glucocorticoids, yet being without the prominent side-effects of glucocorticoids. Because neovascular AMD is treatable only for a limited period of time after the development of the new vessels, before natural involution of the neovascularisation, the incidence of the condition rather than the prevalence is of relevance in estimating the potential need for treatment.

About the product

Anecortave acetate is a synthetic analogue of cortisol acetate stated to be without glucocorticoid activity. The compound is an angiostatic cortisene that has been shown to be an inhibitor of pathologic new blood vessel growth in the eye (ocular neovascularisation) in different a wide variety of animal models of angiogenesis.

In vitro and *in vivo* studies have demonstrated that the antiangiogenic activity provided by anecortave acetate is multifactorial. Anecortave acetate is suggested to inhibit pathologic angiogenesis by:

1) suppressing extracellular proteinase expression and activity required for initiation of new blood vessel growth,
2) inhibiting induction of VEGF expression and production, and
3) Blocking proliferation of VEGF-stimulated retinal endothelial cells. Local ocular delivery of anecortave acetate in *in vivo* models inhibited both pre-retinal and choroidal neovascularisation (CNV).

Anecortave acetate was devoid of glucocorticoid agonist or antagonist activity *in vitro* inflammation assays.

In patients, the drug has in the clinical trials been administered via a posterior juxtascleral depot (PJD) injection of 15 mg/0.5 ml every 6th months.

An incision is made through the conjunctiva in the superotemporal quadrant, midway between the insertions of the superior and lateral rectus muscles 8 mm posterior of the limbus,

A special curved cannula has been developed for the route of administration.

The *in situ* placing of the cannula in connection with the drug application and important steps in the procedure are illustrated below.

The proposed therapeutic indication was: *RETAANE suspension is indicated for the treatment of exudative age-related macular degeneration.*

Main Concerns raised by the CHMP at the time of the withdrawal

At the time of withdrawal the CHMP raised the following main concerns:

Major concerns remained regarding the studies C-98-03 (also a dose-response study) and C-01-99, which were regarded as pivotal.

In Study C-98-03 the analysis of ITT with LOCF achieved study ends, while ITT without LOCF and the PP subset evaluations showed different results, in most cases non-significant. This is a matter of concern since almost half of the patients did not complete their 12-month visit (the primary endpoint) and was hence not retreated. In a progressive disease like exudative AMD, robust 1-year and 2-year treatment data are a definite prerequisite for a solid assessment of efficacy. C-98-03 does not provide such robust information.

In the 1-year study C-01-99, the results of the primary efficacy analysis did not support non-inferiority *vs.* active control. For at least one main secondary outcome measure, anecortave 15 mg was statistically significantly inferior to PDT. The Applicant has now submitted the 2-year data of C-01-99. These results basically replicate those of the 1-year evaluation. The levels of VA were quite stable during the second year of treatment, which is reassuring. The difference between the two arms remained the same without being statistically significant (% of responders being 40.9 with PDT and 34.7 with 15 mg of anecortave ($p = 0.23$).

Moreover, in the third study, C-00-07 a significant benefit of additional anecortave treatment to PDT with verteporfin was not shown. Thus, at present there is insufficient data to conclude that anecortave would be a valid treatment option in exudative AMD.

The applicant's claim that reflux influenced efficacy results, implying that less active drug was available in the juxtascleral space behind the eye to exert activity, is not convincing in light of the higher 30 mg dose being substantially less effective than the 15 mg dose in the study.

Anecortave acetate applied as a PJD injection may possess some clinical effect in the investigated AMD population; however, the exact population to profit remains to be accurately defined.

With regard to safety, no major concerns were identified in the current submission, at the time of withdrawal.

2. Quality aspects

Active Substance

Information on the active substance anecortave acetate has been presented in the form of a Master File (ASMF). It is a white powder, practically insoluble in aqueous buffers and is chiral but is used in this product as a single stereoisomer. The manufacture and specification of the active substance have been evaluated without giving rise to major objections. Considering the pharmaceutical form, attention has

focussed on the physical aspects of the active substance, in particular particle size and polymorphic form. Several polymorphic forms are known, but all of them convert to the same physical form on contact with water. Anecortave acetate appears to be a stable molecule, and stability studies according to the relevant CHMP/ICH guidelines have been submitted.

Medicinal Product

Retaane 15 mg suspension for injection is a single-dose injectable formulation for posterior juxtascleral injection. A volume of 0.82 ml suspension is filled in a 2 ml Type I clear glass vial with a grey butyl rubber stopper and a flip-off aluminium seal, allowing the administration of a 0.5 ml dose. Medical devices for administration are also included in the presentation, in order to place the suspension in the correct location for optimal therapeutic effect (juxta-scleral location). The product is formulated with mostly well-known excipients. Concerning the level of the wetting agent tyloxapol (4mg/ml), this is considered acceptable based on repeat dose toxicity studies. A satisfactory description of the pharmaceutical development has been provided and information has been provided to justify the choice of the final formulation and particle size distribution of the suspension and to justify the semi-aseptic manufacturing method. Choice of container closure has been justified and its compatibility with the Drug Product demonstrated. During manufacture, a heat-sterilised suspension of the drug substance and tyloxapol is ball milled and aseptically combined with a heat sterilised aqueous solution of the remaining excipients. This overall process has been evaluated as satisfactory (times, temperatures, and in-process controls etc.). There were some minor initial concerns relating to the specification, particularly the justification of impurity limits and validation of analytical methods according to CHMP/ICH guidelines on Analytical validation, although these were finally resolved before withdrawal. The description and choice of container is acceptable. The compatibility studies and the experience with the active substance and the data from the stability studies performed shows that the chosen primary packaging adequately protects the product. In general, the suspension for injection has been shown to be very stable when protected from freezing. Uniform particle size was demonstrated in the stability studies. Stability studies have been carried out on 8 batches of which some batches have been stored for a period covering the proposed shelf-life under long term conditions, i.e. real-time data. Results for storage at accelerated, intermediate and different cyclic conditions in addition to data on light stability studies have also been generated and the proposed 3 year shelf-life term was judged to be acceptable.

At the time of the withdrawal, the committee had raised questions regarding the following issues:

- *Confirmation of stability of the active substance. The committee felt that confirmatory stability data as generated by production scale batches should be provided when available.*
- *A number of minor issues concerning the closed (confidential) part of an ASMF for anecortave acetate.*
- *Confirmatory documentation is needed with regard to the medical device components of the medicinal product.*
- *The product shelf-life assay limits as proposed by the applicant are too wide and need to be tightened of the presentation of the product.*

These issues remained unresolved.

3. Non-clinical aspects

Pharmacology

The attempts to elucidate the proposed mechanism of action of AL-3789 are limited, even though there were some effects on members of the proteolytic cascade in a few studies. Additional mechanistic studies are ongoing. The cellular (RVEC, retinal vascular endothelial cells) and *in vivo* models (LPS –induced NV, the ROP model, laser induced CNV, growth factor induced choroidal and retinal NV) used are considered sufficiently relevant for the sought indication. *In vitro*, AL-4940 inhibited RVEC proliferation at 0.1 μM. However, a higher concentration stimulated cell growth. *In vivo*, AL-3789 (or AL-4940) inhibited ocular neovascularisation of various aetiologies, but the effect was not consistent. There were no clear dose-responses, rather, in a number of studies, there were bell-shaped, or inverse dose-response-relationships. AL-3789 may act on several levels and higher concentrations may counteract the desired anti-angiogenic effect. Therefore, the ongoing mechanistic studies should include efforts to explore whether anecortave have dual activities, i.e. besides the more potent activity that antagonise vascular growth, higher levels of anecortave may act on a target, i.e. a low affinity receptor, which stimulates angiogenesis/cell proliferation. For example, if there are activities stimulating nuclear receptors like the PPARs (reported to modulate angiogenesis, to decrease and to increase VEGF; Murata et al., IOVS 2000; Emoto et al., Diabetes 2001), the inconsistency in the non-clinical and clinical dose-response studies may be explained. AL-4940 and AL-3789 seem to have similar effects, but no systematic evaluation of their relative potencies in ocular neovascularisation has been performed.

There are no studies that confirm that the *in vitro* target concentration of 0.1 μM (~0.35 ng/ml) AL-4940 is effective also *in vivo*. There is one rabbit study (bFGF induced CNV) that supports efficacy and penetration of active substance through the sclera after the PJS route of administration, but in this study, there was an inverse dose-relationship. The lowest dose (0.5 mg) was the most effective, and at the high dose (50 mg), the effect was abolished. Unfortunately, tissue levels of AL-4940 were not measured in these studies.

The glucocorticoid activity of anecortave was assessed in two studies. In rabbits, anecortave acetate treatment inhibited and partially reversed dexamethasone-induced increase in IOP. The IOP of rabbits exposed to anecortave acetate only was unaltered. The mechanism of the IOP-lowering action is not clear, but the Applicant suggests that the trabecular meshwork, which may be clogged by steroids modulating the ECM, is normalised. Furthermore, anecortave acetate and anecortave desacetate did not inhibit LPS-induced macrophagal IL-1β secretion. No meaningful inhibition was observed in a standard receptor screen. The glucocorticoid-receptor was not included in the screen and the activity of AL-3789 and AL-4940 on this receptor was only briefly reported. AL-3789 and its metabolites were stated to be devoid of meaningful glucocorticoid agonist activity, but the lack of anti-inflammatory activity for AL-3789 and AL-4940 *in vivo* has not been sufficiently reported. Anecortave acetate treatment did not affect the hERG tail current in HEK293 cells stably transfected with hERG cDNA. Pulmonary function in anaesthetised, ventilated rats was not affected by AL-3789 treatment. The heart rate tended to be lower in anecortave acetate treated rats, beginning 90 minutes post-dose, although the difference was only significant in the high dose animals at a single time point. No significant difference in mean arterial blood pressure was seen between vehicle and anecortave acetate treated rats.

With respect to pharmacodynamic drug interactions, Retaane will be combined with PDT. This is addressed in the clinical assessment.

Pharmacokinetics

HPLC/MS/MS methods were developed and validated for AL-3789, AL-4940, and the major metabolites AL-38508 and AL-38512. Absorption studies were not performed using PJ injections, which is the intended way of administration in the clinic. Anecortave acetate is rapidly metabolised to anecortave desactetate. Due to first-pass metabolism, the bioavailability of 25 to 500 mg/kg p.o anecortave desacetate was very low (0.08 to 0.24%). The increases in C_{max} and AUC values were less than proportional to the increases in p.o dose level. S.c administration provided >10-fold higher maximal plasma concentrations of AL-4940 and >500-fold greater AUC levels compared to similar

oral doses. Also in the rabbit it seems like the oral bioavailability is low with a less than dose proportional increase in exposure. There were only minor gender differences.

Distribution studies performed in rabbits and cynomolgus monkeys showed that after juxtascleral dosing, anecortave acetate is absorbed through the sclera into the choroide, retina and other ocular tissues. Thus anecortave desacetate reaches the tissues of relevance. The highest C_{max} values for anecortave desacetate were seen in the sclera, chorioidea and then retina but relatively high levels were also found in the optic nerve. Rabbit choroidal and retinal levels did not increase with dose, but the duration of exposure increased with dose. There was no accumulation after two repeated doses three months apart. If extrapolating the obtained tissue levels, after 30 and 50 mg to monkey and rabbits respectively, retinal AL-4940 may remain close to 0.1 µM for 4-6 months. Choroidal concentrations were ~10-fold higher. However, the clinical dose is 15 mg. In a second monkey study, the administered 9 mg dose of ^{14}C-AL-3789 was based on scaling the human 15 mg dose (monkey:human ocular surface area). In this study, radioactivity remained at > 0.3 µM for 6 months, but unfortunately, AL-4940 was not measured. In a more recent study (study report not submitted), plasma and ocular tissue concentrations of AL-4940 were determined in monkeys following a single 15 mg PJS dose of AL-3789. The plasma half-life of anecortave desacetate was 1.9 weeks. The systemic exposure reflects the release of the drug from the scleral depot, and in theory, plasma levels would parallel choroid levels. The monkey data submitted essentially show such a relation. If extrapolating to humans, where the relatively rapid plasma T½ was only 3.5 days (15 mg juxtasclerally, Study C-00-041), the release rate from the depot may be substantially quicker in man, unless the relatively short half-life in humans reflects plasma levels below the limit of detection of the assay. Consequently, the data cannot be used to support the clinical dosing interval of 6 months. Correct placing of the drug depot is important since 6- to 7-fold lower concentrations were observed in the retina and choroid, when the drug depot was placed within the membrane layers of the Tenon´s capsule. AL-4940 bound moderately to plasma proteins (88-94%) without any major differences between species. Anecortave acetate and its metabolites crossed the placenta into foetal tissues and were detected in dam milk. Maternal tissue and blood levels were slightly (1.6 - 4-fold in brain, lung and blood) to substantially higher (25-fold in liver) than foetal levels. Radioactivity derived from ^{14}C-anecortave acetate had no affinity for melanin pigments in rabbit eye.

The *in vitro* and *in vivo* metabolism of AL-3789 was qualitatively and quantitatively similar in humans and monkeys (independent of route of administration) and resulted in AL-4940 and glucuronidated metabolites. In rodents, similar metabolites appear, but in rat they were in the form of hydroxylated variants. The major human and monkey metabolite is the glucuronide of AL-38508. The C9-11 double bond aimed to keep the compound devoid of glucocorticoid-activity and the 17α-hydroxyl group important for angiostatic activity remained in all metabolites.

In the rat (i.v), excretion of ^{14}C-anecortave acetate was primarily via faeces and, to a lesser degree, urine. Excretion was relatively rapid with more than 70% of the dose recovered at 24-hours post-dose. In humans (p.o) most of the radioactivity was recovered in urine. There are no mass-balance studies after the PJS route of administration but, considering the low expected clinical plasma levels no additional data is asked for.

Anecortave acetate inhibits CYP1A and CYP2B activity in hepatic microsomes following administration of 200 mg/kg s.c to rats. Although several drugs are substrates for CYP1A and CYP2B, it is considered unlikely that drug interactions would occur due to the expected low plasma concentration of anecortave desacetate (C_{max} in humans is 2.6 ng/mL).

In the clinic Retaane will be administered as a juxtascleral injection through a curved cannula while pressing a CPD against the conjunctiva to avoid reflux. Using the CPD while delivering a PJD to rabbits reduced the drug reflux by 62% when comparing to dosing without reflux control and has therefore proved effective.

Toxicology

Single-dose toxicity studies were performed in rabbits and cynomolgus monkeys treated orally, posterior juxtasclerally or by injection into the anterior chamber of the eye. Generally, conjunctival congestion and discharge occurred as a response to the dosing procedure. Even though only measured after a single PJS administration, ERG, was not affected in rabbits. Anecortave acetate given as a PJD caused a localised inflammatory response with scleral and periscleral inflammation seen in rabbits 35

days following administration of 30 and 50 mg. At three months following treatment, no inflammation was observed, indicating full reversibility of the lesion.

Repeat-dose toxicity studies were performed in mouse, rat, rabbit and cynomolgus monkey with either posterior juxtascleral, topical ocular or oral dosing of an anecortave acetate formulation. The formulation used was in essence identical to the formulation intended for marketing.

Based on the results, anecortave acetate treatment is not expected to lead to adverse systemic effects.

However periscleral inflammation and fibrosis was a consistent, dose-dependent finding after repeated PJ dosing. Other adverse effects included scleral inflammation and degeneration, ocular muscle inflammation and a single case of inflammation in the capsule of the lacrimal gland. The severity of the findings and the number of cases increased with dose frequency. Consequently, anecortave acetate treatment of patients should not be considered with dose intervals of less than 6 months. In several instances, residual drug material was detected in the high dose groups and may have elicited the inflammatory response.

Two 1-year topical ocular studies in rabbits and monkeys addressed the safety of the anterior segment of the eye, including the cornea and anterior sclera. At 1.6 mg given three times a day, no significant effects were observed on corneal thickness and corneal endothelial cell count. There were no effects on the pupil IOP or any increased incidence of cataracts in any of the ocular studies, but it is not clear whether there were any effects on the pupil, as observed clinically.

Anecortave acetate was reported to be non-genotoxic in tests for gene mutations in bacteria and mammalian cells, transformation of mammalian cells and chromosomal abberrations *in vivo*. Exposure to the test substance was not demonstrated in the *in vivo* chromosomal aberrations study. In a 2-year rat carcinogenicity study, 10, 20 and 40 mg/kg were administered once a week via the s.c route to increase systemic exposure. The formulation injected was essentially identical to that intended for marketing, but with 5, 10 and 20 mg/ml instead of 30 mg/ml. Besides visible masses at or around the injection site, there were few clinical signs. Liver and kidney weights were slightly increased in high dose males and spleens and lymph nodes were enlarged. Histopathology revealed the masses as accumulation of compound, fibrinoid necrosis, chronic active inflammation, fibrosis, mineralisation and fibrosarcomas. The fibrosarcomas appeared in mid and high dose animals, mostly males, and were likely to be the result of a foreign body reaction, which is probably of low clinical relevance.

In high dose males, pituitary gland adenomas, an increased frequency of MCL and cystic degeneration in the liver were observed. According to the Applicant, the findings were not significantly increased compared to controls (liver changes and MCL) or were within the historical control range in F344 rats (pituitary gland adenoma). The justification is accepted since in addition, at NOEL for these tumours, there was a 13-fold exposure margin to clinical use.

No treatment-related neoplastic findings were made after oral dosing to hemizygous Tg.rasH2 mice and their wild-type littermates CbyB6F1 in a 26-week carcinogenicity study. Toxicokinetics in CByB6F1 mice showed an acceptable exposure at all dose levels (6-15-fold over clinical exposure).

Based on its pharmacological action, AL-3789 has a potential to adversely impact reproduction and development. In a conventional fertility study, parental toxicity was noted occasionally in rats administered 500 and 1000 mg/kg/day p.o as evidenced by reduced food consumption and decreased body weight gain. Male fertility was not affected. In high-dose female rats, a decrease in uterine weight and in the number of corpora lutea and live and total implants were seen. As such, anecortave acetate may cause a small reduction in the number of eggs being ovulated. No toxicokinetic sampling was performed, but based on the bioavailability of anecortave it is likely that animal exposure was low. A mild maternal toxicity was detected in one out of the three pivotal embryo-foetal development studies as a reduction in food consumption. There were no treatment-related effects on litter viability, size or body weight or increase in foetal malformations or anomalies. After oral administration, the exposures were very low in both the rat and rabbit. Fortunately, in the study employing the s.c route, plasma levels ~20-fold higher than expected clinically were obtained. No treatment-related effects on pre- and postnatal development, including maternal function were observed in the s.c embryo-foetal development study. Overall, only in the s.c rat embryo/foetal development study, the animals reached an exposure that was higher than clinically expected. On the other hand, considering that Retaane is aimed for an elderly patient population.

Local tolerance at the injection site was investigated in the course of the single- and repeat-dose toxicity studies and has been addressed. Anecortave acetate did not cause contact sensitisation when tested in a guinea pig model.

The major human metabolites AL-38508 and AL-38512 have been present at acceptable exposure multiples in toxicity studies in monkeys and mice and no concern is identified. The major synthetic impurity is 21-acetyloxy-17α-hydroxypregna-1,4,9(11)-triene-3,20-dione (AL-39058) which has a proposed limit of 0.2% in the final product. No ocular irritation or toxicity specifically related to AL-39058 (up to 2%) was seen after co-administration with anecortave acetate posterior juxtasclerally in rabbits. Moreover, AL-39058 was not genotoxic. Consequently, the suggested limit of 0.2 % is acceptable. Retaane contains 4 mg/mL of the excipient Tyloxapol. Tyloxapol is currently used in several ocular solutions though not in concentration above 1 mg/mL. Still, the Tyloxapol content in Retaane is considered qualified since formulations with 4 mg/mL Tyloxapol were used in the repeat-dose toxicity studies.

L-3789 does not, nor is AL-4940 expected to absorb light in the range of 290-700 nm. Consequently, no photosafety testing is warranted despite that high levels of AL-3789-related compounds reach tissues that are exposed to light. There is no environmental concern.

4. Clinical aspects

Pharmacokinetics (PK)

For development of anecortave acetate 15 mg, the Applicant conducted 7 clinical pharmacokinetic studies to characterize the plasma pharmacokinetics and disposition of the active metabolite anecortave desacetate following either topical ocular (C-93-77), oral (C-02-12) or subcutaneous (C-03-08, C-03-09) routes as well as periocular posterior juxtascleral depot (PJD) administration (C-98-03, C-02-47, C-00-41).

Following PJD administration of 15 mg anecortave acetate to AMD (age-related macular degeneration) patients, measurable plasma concentrations were observed at the first collection time (0.5 hour), indicating relatively quick absorption and distribution from the administration site. Peak plasma concentrations (C_{max}) of anecortave desacetate were typically observed within 12 hours post-dose and declined thereafter in a biphasic manner. Absolute bioavailability, clearance and volume of distribution have not been determined. Plasma protein binding determined *in vitro* is moderate (93.5%) and independent of concentration in the range 10-300 ng/ml. The terminal $t_{1/2}$ of anecortave desacetate after PJD administration of anecortave acetate is about 3.5 to 5 days.

In study C-02-47 (PJD 15 mg in AMD patients), reflux of the dose at the injection site following administration was observed in several subjects and more often after the first than after the second injection. Systemic exposure of anecortave decacetate was lower in patients with reflux than in patients without reflux. In the other PK studies in AMD patients, reflux did not seem to be specifically documented nor evaluated and the clinical significance of reflux has not been further elucidated.

A mass-balance study of limited quality (e.g. dosing errors and low recovery) following a single oral administration of ^{14}C-anecortave acetate suspension has revealed that urinary excretion is the major route of elimination, accounting for on average 52% of the dose. Anecortave acetete is rapidly hydrolyzed to anecortave desacetate. Nine inactive metabolites of anecortave desacetate in glucoronidated forms have been identified and less than 1% of a dose is recovered as unchanged anecortave desacetate in urine. The metabolic processes are likely to involve NADPH-dependent reductases, but have not been fully characterized. The P450 does not catalyse the metabolism and anecortave acetate does not inhibit human CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 *in vitro*. As both the molecule and its metabolism seems similar to cortisol and its metabolic pathways, which do not involve CYP450 isozymes, drug interaction studies were not conducted.

A linear dose-concentration relationship has been demonstrated within the dose range of 3 to 30 mg and no clinical significant accumulation occurs with repeated administrations every 6 months, but dose-proportionality with respect to AUC has not be addressed.

PK studies of relevance to the clinical application form (PJD) have not been made in special populations, but the effect of hepatic impairment on the pharmacokinetics of anecortave desacetate has

been evaluated after s.c. administration. Mild or moderate hepatic impairment had no effect, but in patients with severe hepatic impairment an approximately 2-fold increase in exposure was observed. Considering the seemingly large safety margin for anecortave acetate, no precautions are needed in patients with severe hepatic impairment. No gender differences were seen in the pharmacokinetics of anecortave desacetate. There is no information regarding the influence of renal function, race, weight or age on the pharmacokinetics of anecortave desacetate.

Photodynamic treatment following PJD administration of anecortave acetate does not affect the plasma pharmacokinetics of anecortave desacetate**.**

Pharmacodynamics

The applicant has not submitted pharmacodynamic studies. This is to some degree justifiable as no obvious surrogate marker exists that allows for a reasonable study. The pharmacodynamics hence relies on *in vitro* data and animal studies and human efficacy studies.

No uniform dose-response pattern could be concluded in the preclinical program, since both linear relationships, inverse linearity and bell-shaped curves were observed. The latter was replicated in the clinical phase II study C-98-03, where the 15 mg dose, compared with 3 mg and 30 mg doses, achieved the best results on the primary endpoint, change in VA. This bell-shaped curve was, however, in contrast to seemingly equal effects on the pharmacodynamic endpoint, i.e. growth in % of the choroidal neovascularisation (CNV) lesion (statistics provided for the 15 mg arm only). The inconsistencies of C-98-03 are dealt with in more detail in the efficacy section.

The absence of glucocorticoid activity, e.g. anti-inflammatory properties, has been suggested in the *in vitro* and *in vivo* non-clinical studies. The typical glucocorticoid-induced adverse effects seen with topical administration such as elevated IOP and cataract formation/progression do not seem to have occurred in the clinical programme, which is reassuring.

The pharmacodynamic interaction between anecortave and a preceding photodynamic therapy (PDT) was explored in another dose-finding study C-00-07. No PDT + anecortave proof-of-concept was shown, in spite of the hypothesis that a destruction of pathological vessels with PDT combined with the angiostatic anecortave should have delayed the need for re-treatment with PDT.

Clinical efficacy

The clinical development of anecortave started in 1998 and coincided with the publication of data from the pivotal studies on PDT, a licensed therapeutic mode combining verteporfin, a photosensitising agent with low-powered laser application. This had a considerable impact on the selection of patients for the studies with anecortave. Two of the main studies in this application, a study with anecortave as an add-on treatment to PDT and a non-inferiority study with PDT as the active comparator, recruited patients with CNV lesions covered by the approved PDT indication. The effect of anecortave on other forms of CNV is largely unknown.

Dose-response studies and main clinical studies

Three main clinical studies were conducted to establish the efficacy and safety of anecortave acetate 15 mg administered as a periocular posterior juxtascleral depot (PJD) according to the claimed indication, i.e. treatment of subfoveal CNV secondary to AMD.

Study C-98-03 compared anecortave acetate, 3 mg, 15 mg, or 30 mg with placebo.

In Study C-00-07 anecortave 15 mg and 30 mg was compared to placebo, adjunctive photodynamic therapy (PDT) with verteporfin being permitted throughout the study in all groups.

Study C-01-99 compared anecortave 15 mg to verteporfin PDT.

Studies C-98-03 and C-01-99 are regarded as pivotal. One of the pivotal studies, Study C-98-03, was also a dose-response study.

Two open-label pharmacokinetic studies (C-02-47 and C-00-41) also contributed efficacy and safety data. In addition, several smaller Investigator-sponsored studies were conducted. An overview of conducted studies is presented in the table below.

In addition, randomised, double-masked placebo controlled studies are presently ongoing (C-02-27 and C-02-29).

Protocol Number	Number, Location of **Study Centers**	**Start Date, Enrollment Status, Enrollment Goal**	**Study Design, Study Controls**	**Study Medication, Dosage, Route and Regimen**	**Study Objectives**	**Patients per Arm enrolled and Completed**	**Duration of Treatment and Follow-up**	**Gender, Mean Age (ITT)**	**Diagnosis, Inclusion Criteria**	**Primary End-points**
C-98-03	18 centers in US and EU	4/12/1999 128 enrolled 120 goal Completed 128 ITT	Multi-center, double-maskedrandomized placebo-controlled, parallel-group, dose duration	Anec acet 30 mg, 15 mg or 3 mg versus vehicle as PJD every 6 months	Safety and duration effect of Anec Acet versus vehicle for CNV	For 30 mg: (N=33; 12 completed) For 15 mg: (N=33; 16 completed) For 3 mg: N=32; 12 completed For vehicle: (N=30; 12 completed)	Up to 2 years	59 M 69 F Mean age: 76.9 (58 to 93 years)	Subfoveal CNV secondary to AMD	Mean change from baseline in logMAR visual acuity
C-00-07	11centers in North America & EU	5/5/2000 136 enrolled 120 goal Completed 136 ITT	Multi-center, double-maskedrandomized, placebo controlled, parallel-group	Anec acet 15 mg, 30 mg or vehicle as single PJD within 5-8 days after PDT	Effect of single administration of Anec Acet versus placebo on need for additional PDT at Months 3,4,5 and 6	For 30 mg: (N=45; all completed) For 15 mg: (N=45; all completed) For vehicle: (N=46; 45 completed)	6 months, with a single PJD of Anec Acet or vehicle and up to 2 treatments with PDT	53 M 83 F Mean age: 76.6 (58 to 91 years)	Subfoveal CNV secondary to AMD	Mean change from baseline in logMAR visual acuity
C-01-99	52 centers in North America, EU, Israel & Australia	6/18/2002 530 enrolled 522 goal Ongoing 522 ITT	Multi-center, double-masked randomized, parallel-group, active-controlled	Anec acet 15 mg plus sham PDT versus PDT plus sham PJD	Demonstrate non-inferiority of Anec Acet 15 mg versus PDT	For 15 mg: (N=259; 231 completed) For PDT: (N=267; 204 completed)	12 months with additional 12 months follow-up with study treatment	248 M 274 F (51 to 96 years)	Subfoveal CNV secondary to AMD eligible for PDT	Percentage of responders (< 3 line loss) at the Month 12 visits.
C-00-41	2 centers in North America	2/27/2001 36 enrolled 34 goal Completed 34 ITT	Multi-center, open label	Anec acet 30 mg, as PJD every 6 months	Pharmacokinetics of anecortave Acetate and AL-4940 following 2 PJD administrations	N=34; 32 completed	12 months	19 M 15 F (59 to 86 years)	Subfoveal CNV secondary to AMD eligible for PDT	Pharmaco-kinetics; LogMAR VA was collected as safety variable
C-02-47	1 center in North America	12/2/2002 20 enrolled 20 goal Completed 20 ITT	Single-center, open label	Anec acet 15 mg, as PJD every 6 months	Pharmacokinetics of anecortave Acetate and AL-4940 following 2 PJD administrations	N=20; 16 completed	12 months	5 M 15 F (57 to 91 years)	Exudative AMD (classic, occult or mixed CNV)	Pharmaco-kinetics; LogMAR VA was collected as safety variable

Anec Acet = Anecortave Acetate; PJD = Posterior Juxtascleral Depot

Study population
Patients of ≥50 years with a clinical diagnosis of exudative AMD and a primary or recurrent subfoveal choroidal neovascular membrane were included. In Studies C-98-03 and C-00-07 the lesions were predominantly or minimally classic, in Study C-01-99 lesions were predominantly classic. The best corrected baseline visual acuity should be 0.3 (20/40 Snellen) to 1.3 (20/320 Snellen). The visual acuity of the contralateral (non-study) eye had to be 0.6 (20/800 Snellen) or better.

Relevant exclusion criteria pertaining to ocular and systemic conditions were followed. The dose selection and the dosing interval do not appear to have been well founded.

Treatment procedure for anecortave acetate study medication
The study drug is injected following a posterior juxtascleral depot procedure.

The presence of reflux (backflow of material along the cannula track and out of the incision site) might influence the obtained efficacy of the anecortave acetate. Therefore, the Applicant has introduced a number of ways to oppose the consequences of reflux, e.g. a counter pressure device (CPD), a smaller incision in the conjunctiva, use of a smaller syringe, and a slow rate of infusion. These measures have been introduced in the ongoing study programme, but the revised instructions are not part of the submitted data.

Endpoints
The primary efficacy endpoints were:

a. Studies C-98-03 and C-00-07; change from baseline in visual acuity,
b. Study C-01-99; percent patients who lost less than 3 lines from baseline (responders)

RESULTS

C-98-03
The vast majority of patients had predominantly classic CNV lesions at baseline, and the population was well balanced across the treatment groups. The ITT population encompassed 128 patients and the PP-population included 118 patients.

At month 12, the logMAR visual acuity change from baseline was 0.14 and 0.31 in the anecortave acetate 15 mg and the placebo group, respectively (lower 95 % CI -0.32, upper 95 % CI -0.02; p=0.0246). However, the actual difference was logMAR 0.17, meaning roughly 8 letters (1 ½ lines in the ETDRS chart), which is inferior to the hypothesised relevant difference of 0.21. The inhibition of CNV lesion growth appears similar among all groups precluding additional conclusions on dose selection.

The considerable drop-out rate and the imbalances of the reasons for discontinuation (e.g. 30% drop-outs in the 30 mg arm due to disease progression) between treatment arms, hamper meaningful assessment, especially since the primary analysis set of ITT using LOCF imputation is questionable in conditions with a natural worsening in the efficacy variable.

The statistically superior effect of PJD-injected anecortave acetate 15 mg to that of placebo was evident for both mean change in visual acuity from baseline and for percentage of patients who lost less than 3 lines of visual acuity, both in the total study population and in the subgroup with predominantly classic lesion at baseline. The results from the ITT analysis have, though, not been confirmed by the PP analysis.

The VA results seem to support the 15 mg dosage level, but the study groups were small. Taken together, the amount and character of the many amendments may weaken the credibility of this rather limited sized pivotal trial.

C-01-99:
A number of 522 and 511 patients contributed to the ITT and to the PP population, respectively. The number of patients who lost less than 3 lines in visual acuity from baseline at Month 12 was 44.9 % in the anecortave group and 48.6 % in the verteporfin PDT treatment group, respectively (p=0.4305).

The non-inferiority criterion was not met and PDT was nominally slightly better at all time-points. The finding that both arms performed considerably worse than the PDT group in the reference TAP trial,

where in fact a 67% responder rate in patients with predominantly classic lesions was documented, points to a variability in treatment susceptibility of CNV lesions.
The lack of a placebo arm in this pivotal study is judged to be a major deficiency in this application.

So, this study failed to show non-inferiority of anecortave 15 mg to PDT with verteporfin in the prospectively planned analyses.

C-00-07:
A number of 136 and 122 patients, respectively, constituted the ITT and the PP population.

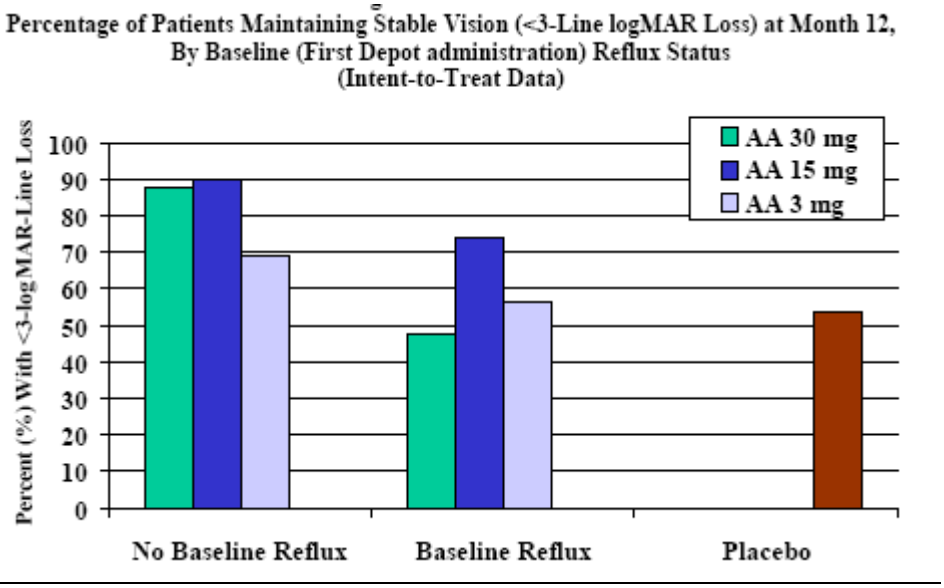
As for the primary endpoint, in the anecortave 15 mg plus PDT and the PDT alone groups the mean change in logMAR score from baseline to month 6 was 0.10 and 0.14, respectively (p= 0.4630).

This study, thus, failed to show any statistically significant benefit of the addition of anecortave acetate to PDT. The short study duration, in view of the protracted course of the disease may be responsible for this negative result. Unfortunately, no follow-up or extension was planned in this trial.

Almost half of the patients were ineligible for PDT with verteporfin, by indications approved by the regulatory bodies in the EU as their lesions were not predominantly classic or occult-only. This is an important problem, because minimally (<50%) classic failed to obtain approval because of lack of efficacy.

Post-hoc analyses
C-98-03
A challenge in the clinical program of anecortave has been the proper administration of the treatment resulting in optimal bioavailability of the drug. It is given as a PJD aimed at delivering the compound as closely as possible to the scleral area covering the retinal fundus, i.e. the macular region. Early on in the clinical program it was evident that a considerable amount of the injected substance refluxed to the ocular surface, confirming non-clinical experience with this administration form. Reflux was hence documented and when analysing treatment response relative to reflux and non-reflux administrations *post-hoc*, some efficacy results were better in the non-reflux group.

The following figure presents a responder analysis in relation to baseline reflux status within C-98-03.



Given the withdrawal rates and the option to retreat at month 6, which was used in about 60% of patients, the data cannot be interpreted. Moreover, further reflux analyses in the other clinical studies have yielded contradictory results and seem to invalidate the applicant's claim that non-reflux is a predictor of a favourable outcome.

C-00-07:
In a *post-hoc* analysis, baseline reflux was associated with a better VA outcome, contradicting the applicant's claim that this procedure-dependent variability influences efficacy results in a consistent way.

C-01-99:
Post-hoc analyses regarding reflux status showed that non-reflux at baseline did not translate into a better visual outcome at the Month 6 evaluation, while non-reflux at Month 6 was associated with a better visual outcome at Month 12 than for the reflux group. These inconsistencies are confirmed by the contradictory results of reflux analyses in C-98-03 and C-00-07.

The bioavailability of Anecortave is in all likelihood a key issue in achieving efficacious doses but it is not proven beyond doubt that the reflux status reflects the appropriate deposition of the compound.

Supportive studies
It is notable that there are still at this point randomised placebo controlled trials ongoing: C-02-27 and C-02-29 in which anecortave acetate 15 mg is compared to placebo in patients with predominantly classic, minimally classic and occult CNV lesions due to exudative AMD in a 12 months study with 12 months follow-up in 268 patients and 122 patients, respectively.

The Sponsor has also conducted trials with a topical formulation in patients with glaucoma.and pterygium.

Investigator sponsored studies
A total of 132 patients have been included in Investigation New Drug applications (INDs) studies. These studies were small and uncontrolled, and mainly non-randomised. Of these 106 had AMD but were either not eligible for the Alcon sponsored clinical studies, or they had retinal angiomatous proliferation, or they received anecortave/triamcinolone. A number of 8 patients with other choroidopathies participated in 4 trials and 16 patients with retinopathies were enrolled in 7 trials. Two patients had anterior segment treatment. The doses were 3, 15 or 30 mg. These studies will not be evaluated here.

Clinical studies in special populations
The pharmacokinetics of anecortave following a single-dose subcutaneous administration in subjects with hepatic impairment was studied. With the exception of Child-Pugh class C subjects, no significant differences between pharmacokinetic parameters were found. With severe hepatic impairment, drug exposure is about doubled following s.c. administration.

Mild or moderate hepatic impairment is unlikely to be of clinical relevance to the pharmacokinetics of anecortave. The study performed is unlikely to be of relevance to the clinical use of PJD-administrated anecortave as the systemic exposure in terms of AUC is many times less following the clinically relevant administration.

No gender differences were seen in the pharmacokinetics of anecortave desacetate or the glucuronide conjugates of its metabolites (AL-38508, AL-38512) after PJD administration of anecortave Acetate in AMD patients.

The influence of neither race nor weight has not been studied.

Thus at the time of the withdrawal, the questions raised regarding the following clinical issues remained unresolved:

Convincing evidence of clinical efficacy is still lacking.

In general terms the major objection remains. The applicant has presented the same arguments as previously, regarding the non-conclusive studies C-98-03 and C-00-07 and supplied the 2-year efficacy data from C-01-99. Nothing new of decisive importance has actually transcended.

Concerning C-98-03, the analysis of ITT with LOCF achieved study ends, while ITT without LOCF and the PP subset evaluations showed different results, in most cases non-significant. This is a matter of concern since almost half of the patients did not complete their 12-month visit (the primary endpoint) and was hence not retreated. In a progressive disease like exudative AMD, robust 1-year and 2-year treatment data are a definite prerequisite for a solid assessment of efficacy. C-98-03 does not provide such robust information. The claim that reflux influenced efficacy results, implying that less active drug was available in the juxtascleral space behind the eye to exert activity, is not convincing in light of the higher 30 mg dose being substantially less effective than the 15 mg dose in the study.

In the 1-year study C-01-99, the results of the primary efficacy analysis did not support non-inferiority vs. active control. For at least one main secondary outcome measure, anecortave 15 mg was statistically significantly inferior to PDT.

The 2-year data of C-01-99 basically replicated those of the 1-year evaluation. The levels of visual acuity (VA) were quite stable during the second year of treatment, which is reassuring. The difference between the two arms remained the same without being statistically significant (% of responders being 40.9 with PDT and 34.7 with 15 mg of anecortave, ($p = 0.23$). The mean VA was low at 24 months. While the CHMP is aware of the need for improved therapy of neovascular AMD, it does not find that anecortave acetate 15 mg monotherapy has been shown to be sufficiently non-inferior in the studied patient population.

As regards C-00-07, the study did not demonstrate proof of concept. Regardless of dose, anecortave did not exhibit enough efficacy. While the CHMP also acknowledges the potential value of a Visudyne PDT-adjuvant, the data submitted for anecortave acetate is also insufficient to approve this indication.

Clinical safety

Overall, a number of 883 patients were included in the application with the sought AMD therapeutic indication. A number of 459 patients had at least 6 months, and 269 had 12 months of exposure. In the 3 main studies 791 patient contributed safety data. Additionally, 876 patients were treated with anecortave acetate via the topical ocular route for open angle glaucoma or pterygium. Several investigator IND studies included moreover a number of 132 patients.

Patient exposure

Overview of Patient Exposure to Study Drug by Protocol - All Clinical Studies
(C-98-03, C-00-07, C-00-41, C-01-99, C-02-12, C-02-47, C-03-08, C-03-09)

Protocol Number	Safety N	AA 3 mg	AA 15 mg	AA 30 mg	AA 15 mg + PDT	AA 30 mg + PDT	AA 15 mg SQ	AA 50 mg p.o	PDT + Sham	Vehicle + PDT	Vehicle
AMD Studies											
C-98-03	128	32	33	33							30
C-00-07	136				45**	45**				46**	
C-01-99	527		260*						267		
Subtotal	791	32	293	33	45	45	0	0	267	46	30
PK Studies											
C-00-41	34			34							
C-02-12	8							8			
C-02-47	20		20								
C-03-08	6						6				
C-03-09	24						24				
Subtotal	92	0	20	34	0	0	30	8	0	0	0
Total	883	32	313	67	45	45	30	8	267	46	30

* All patients receiver sham PDT
** All patients received one dose of study drug plus either one, two, or three administrations of PDT
AMD = Age-related Macular Degeneration
PK = Pharmacokinetic
AA = Anecortave Acetate
PDT = Photodynamic therapy with VISUDYNE®
SQ = Subcutaneous dosing
p.o = Oral dosing

- Adverse events (AEs)

The most common are decreased visual acuity, cataract, eye pain, vitreous detachment, hyperaemia, and vision abnormal

Overall, the observed adverse events in the study population are not unexpected. Of special interest would be any adverse events indicative of glucocorticoid side effects.

No indications of an increased frequency of cataract in any of the anecortave groups were seen.

For increased IOP the limits used as a clinically significant increase is ≥10 mm Hg, which is too high to exclude such an effect. Based on mean baseline and exit IOP values there are no indications of an increased risk of elevated IOP with anecortave acetate.

The information presented in the Clinical Summary is too limited to exclude an effect on the blood pressure, which however is not very likely.

A few ocular adverse events need further exploration, i.e. the attribution or not to the treatment in some cases of visual loss of more than 4 lines, a few cases of ptosis and of anisocoria.

- Serious adverse events and deaths

Serious adverse events were reported for 177 patients, mainly of unnotable nature in the context of the test drug. For two patients vision decrease were reported as serious.

- Laboratory findings

Laboratory evaluations of haematology, serum chemistry and urine analyses were performed without noteworthy findings.

- Safety in special populations

Studies in special populations have not been conducted. Analyses to study the influence of age, sex, and race have not revealed notable findings.

- Immunological events

Not studied.

- Safety related to drug-drug interactions and other interactions

No formal interaction studies were conducted. With the allowed use of concomitant medication no specific concerns are raised. No dose relationship concerns were raised in the studies using 3, 15, or 30 mg doses.

- Discontinuation due to AEs

A number of 59 patients (6.7 %) were withdrawn because of an adverse event. Five patients were withdrawn because of ocular events: retinal arterial occlusion, retinal detachment, vitreous haemorrhage, optic neuritis and vision change, of which the two first mentioned were considered to be treatment-related.

Overall, no major safety concerns were identified in the current submission, at the time of withdrawal.

Abbreviations

AMD	Age-related macular degeneration
AUC	Area under the curve
bFGF	basic fibroblast growth factor
C_{max}	Maximum drug concentration
CNV	Choroidal neovascularisation
CPD	Counter pressure device
ERG	Electroretinogram
GLP	Good laboratory practice
IOP	Intraocular pressure
ITT	Intent-to-treat
LOCF	Last observation carried forward
LPS	Lipopoly saccharide
MCL	Mononuclear cell leukaemia
NOEL	No observed effect level
PDT	Photodynamic therapy
PJD	Posterior juxtascleral depot
PJS	Posterior juxtascleral
PK	Pharmacokinetics
p.o	Per os (oral administration)
PP	Per protocol
PPAR	Peroxisome Proliferator Activated Receptor
ROP	Retinopathy of prematurity
s.c	Subcutaneous
VA	Visual acuity
VEGF	Vascular endothelial growth factor