U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-048
Drug Name:	Triesence™ (tiamcinolone acetonide injectable suspension)
Indication(s):	Treatment of [redacted] visualization during vitrectomy, sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids
Applicant:	Alcon, Inc.
Date(s): Submitted	May 29, 2007
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Review Priority:	Priority
Biometrics Division:	DBIV
Statistical Reviewer:	Mushfiqur Rashid, Ph.D.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmologic Drug Products (HFD-520)
Clinical Team:	Martin P. Nevitt, M.D., MPH, Clinical Reviewer
	William Boyd, M.D., Medical Team Leader
Project Manager:	Carmen DeBellas, Pharm, D.

Keywords: NDA review, Clinical studies, Safety studies, Meta Analysis

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1.0 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted a 505(b)(2) New Drug Application (NDA) for triamcinolone Acetonide (TA) Injectable Suspension 40 mg/mL for the treatment of [redacted] visualization during vitrectomy. In addition, the sponsor has also sought the indications which include sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids. Note that Triamcinolone Acetonide Injectable Suspension (KENALOG®-40, NDA 14-901) with a concentration of 40 mg/mL of triamcinolone acetonide was approved for sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids. The new formulation of Triamcinolone acetonide injectable suspension is being developed with no preservative. According to the sponsor, the preservative benzyl alcohol is removed since this will be a single-use, intravitreal dosage form.

This submission is based on the study report C-06-26 which included 300 peer reviewed articles (with no new clinical studies) and study C-05-62 (submitted for the clinical evaluation of the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension for the indication of visualization during vitreoretinal surgery). The meta-analysis in study report C-06-26 cited articles with the route of drug administration varying from intravitreal to periocular routes with the dose ranging from 1 to 40 mg of triamcinolone acetonide.

There are several issues and limitations in the meta analysis provided as the supportive information for the indications sought. The limitations include the following:

- *Evidence of efficacy was not based on adequate and well controlled trials*
- *Post-hoc analysis of the data with the potential of inflating the overall type-I error rate(s)*
- *The data sets reported from articles did not readily fit in the requirements for the traditional meta analysis involving the estimation of effect sizes and a summary across similarly-derived estimates of central tendency and variability. Therefore the analyses included in this central study report were based on descriptive summaries of weighted means. This analysis of summary statistics included means and percentages depending on the variables and subgroups. No test of homogeneity was performed. No unique estimate of treatment benefit with respect to placebo was reported. The interpretations based on these analyses could be very misleading and problematic.*
- *Submission included masked (single or double masked) or unmasked studies and has the potential to seriously bias the results*
- *Pooled studies with varying endpoint(s) and time of evaluations, differences in patient characteristics*
- *The pooled analysis lacks randomization protection*
- *The route of drug administration varied from intravitreal to periocular routes*
- *Dosing is not unique (ranged from 1 to 40 mg of triamcinolone acetonide)*

- *Potential publication biases*
- *Dose administration varied from single to multiple doses and may have been prior to, during, of after a surgery. This can seriously confound the results.*
- *Measurement of the primary endpoint (best corrected visual acuity) was reported using different eye charts whose values were then converted to logMAR units*
- *There were various follow-up periods reported by visit or by LMFU (last mean follow-up).*
- *Many of these studies were case series reports without comparator groups*

Visualization during Vitrectomy:

The evidence presented in protocol C-06-26 did not support that Triamcinolone Acetonide Injectable Suspension 40 mg/mL for the treatment of Triamcinolone for visualization during Vitrectomy. Although there is some beneficial effect observed in study C-05-62, the result is based on within patient comparison. Note that the study was only observer-blinded and there are potential for selection biases in the results. The outcome assessment was based on judgment of how visualization compares prior to and following instillation of the study medication. This can be very subjective and can introduce noise in the data. In addition, the comparative efficacy of TA could not be ascertained without a control arm (placebo) incorporated in the study design.

Sympathetic Ophthalmia, Temporal Arteritis, Uveitis, and Ocular Inflammatory Conditions Unresponsive Corticosteroids:

The applicant reported that in total 30 peer reviewed publications that evaluated triamcinolone acetonide for the treatment of ophthalmic diseases and conditions supported by Kenalog -40 (NDA 14-901) were included in the clinical database of NDA 22-048. None of these 30 publications met all of the Agency's criteria for adequate and well controlled study design with adequate duration (≥1 year). Based on the nature of the diseases and rare conditions represented by these indications, most studies were case series reports without comparator groups. Although many reports noted visual acuity, data were reported for a limited number of patients at time points that varies substantially among publications. Furthermore, most studies did not present visual acuity data in a format suitable for integration. Dose ranged from <1 mg to 40 mg. Papers selected for review included studies that could either be of masked (single –or double masked) or

unmasked designs. Based on the above concerns as well as due to lack of prospectively designed clinical trial(s), the information submitted in this application did not provide substantial evidence of efficacy and safety.

1.2 Brief Overview of Clinical Studies

Triesence (triamcinolone acetonide injectable suspension) is a sterile, terminally sterilized, non-preserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide which is pharmaceutically and therapeutically equivalent to a marketed product KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ). The sponsor filied a 505(b)(2) New Drug Application (NDA) for triamcinolone acetonide injectable suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical steroids, and visualization during vitrectomy. Triamcinolone Acetonide Injectable Suspension (KENALOG®-40, NDA 14-901) with a concentration of 40 mg/mL of triamcinolone acetonide was approved for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids. Triamcinolone acetonide was also approved as a nasal spray (NDA 20-784, Nasacort HFA Nasal Aerosol).

The applicant's triamcinolone acetonide injectable suspension is being developed with no preservative. According to them, the preservative benzyl alcohol was removed since this will be a single-use, intravitreal dosage form. The concentration of 40 mg/mL of triamcinolone acetonide is the same as that in KENALOG-40. Based on the correspondence during a Pre-NDA (October 3, 2006 for NDA 22-048/PIND 73,462) meeting, the division agreed that a literature based clinical development program in conjunction with the cross-reference of NDA 14-901 (KENALOG® -40) would be acceptable to support the fileability of the proposed indications. On May 29, 2007 Alcon submitted a 505(b) (2) application cross-referencing information from NDA 14-901 (KENALOG® -40). NDA 22-048 contained a study report of C-06-26 which was based on a meta-analysis of published literature to support the safety and effectiveness of triamcinolone acetonide in the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive corticosteroids. For Visualization during vitreoretinal surgery, a clinical study report of C-05-62 was submitted in support of the meta analysis. This study was conducted to evaluate the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension when used for visualization during vitrectomy with or without membrane removal.

1.3 Statistical Issues and Findings

According to sponsor, published results from peer reviewed studies that met inclusion/exclusion criteria were analyzed. The data captured from articles did not readily fit the requirements for the traditional meta analysis involving the estimation of effect sizes and a summary across similarly-derived estimates of central tendency and variability. Therefore the analyses included in the current study report are based on descriptive summaries of weighted means. This analysis of summary statistics included means and percentages depending on the variables and subgroups.

No tests of homogeniety were performed. The interpretations based on these analyses could be very misleading.

There are several issues and limitations in the meta analysis provided as the supportive information for the indications sought. The limitations include the following:

- *Evidence of efficacy was not based on adequate and well controlled trials.*
- *Post-hoc analysis of the data with the potential of inflating the overall type-I error rate(s)*
- *The data sets reported from articles did not readily fit the requirements for the traditional meta analysis involving the estimation of effect sizes and a summary across similarly-derived estimates of central tendency and variability. Therefore the analyses included in this central study report are based on descriptive summaries of weighted means. This analysis of summary statistics included means and percentages depending on the variables and subgroups. No test of homogeneity was performed. No unique estimate of treatment benefit with respect to placebo was reported. The interpretations based on these analyses could be very misleading and problematic.*
- *Submission included masked (single or double masked) or unmasked studies and has the potential to seriously bias the results*
- *Pooled studies with varying endpoint(s) and time of evaluation, differences in patient characteristics*
- *The pooled analysis lacks randomization protection*
- *The route of drug administration varied from intravitreal to periocular routes*
- *Dosing is not unique (ranged from 1 to 40 mg of triamcinolone acetonide)*
- *Potential publication biases*
- *Dose administration varied from single to multiple doses and may have been prior to, during, of after a surgery. This can seriously confound the results.*
- *Measurement of the primary endpoint (best corrected visual acuity) was reported using different eye charts whose values were then converted to logMAR units*
- *There were various follow-up periods reported by visit or by LMFU (last mean follow-up).*

The findings and issues specific to each indication are outlined below.

Sympathetic Ophthalmia, Temporal Arteritis, Uveitis, and Ocular Inflammatory Conditions Unresponsive Corticosteroids:

The applicant reported that in total 30 peer reviewed publications that evaluated triamcinolone acetonide for the treatment of ophthalmic diseases and conditions supported by Kenalog -40 (NDA 14-901) were included in the clinical database of NDA 22-048. None of theses 30 publications met all of the Agency's criteria for adequate study design, well controlled, and adequate duration (≥1 year). Based on the nature of the diseases and rare conditions represented by these indications, most studies were case series reports without comparator groups. Although many reports noted visual acuity, data were reported for a limited number of patients at time points that varies substantially among publications. Furthermore, most studies did not present visual acuity data in a format suitable for integration. Based on the above concerns as well as due

to lack of data from prospectively designed clinical trial(s), the information submitted in this application did not provide adequate evidence of efficacy and safety for these indications.

Triamcinolone Acetonide for Vsualization During the Vitrectomy

The sponsor reported that long term follow-up was not required for studies evaluating intraoperative use of triamcinolone acetonide as a visualization agent for vitreos and membranes, so all articles in support of this indication were considered to have adequate duration. Seven articles reported comparison of posterior segment surgeries using triamcinolone acetonide for visualization either to vitrectomies without a visualization. The sponsor claims that these seven articles collectively indicated that triamcinolone acetonide was useful for visualizing the viterous and/membranes in over 600 patients.

Reviewer's comments: *The listing of citation (see Table 8 of Section 3.1) which the sponsor considered as well controlled, adequate duration and adequate design but they lacked majority of the requirements for well controlled trials. Some of them were retrospective, single masked with no control. There are potential for introducing serious biases based on the results from these studies. In visualization studies, the primary efficacy assessment pertained to whether the injected triamcinolone acetonide was useful to the surgeon for visualization during virectomy. This is a subjective assessment and can vary from investigator to investigator.*

According to the sponsor, study C-05-62 provided benefit of triamcinolone acetonide. However, this was based on within patient comparison (pre and post) and there was no control group in the study. Therefore, the relative efficacy of the drug with respect to placebo could not be determined.

2.0 INTRODUCTION

2.1 Overview

Triesence (triamcinolone acetonide injectable suspension) is a sterile, terminally sterilized, non-preserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide which is pharmaceutically and therapeutically equivalent to a marketed product KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ). The sponsor is filing a 505(b)(2) New Drug Application (NDA) for triamcinolone acetonide injectable suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical steroids, and visualization during vitrectomy. Triamcinolone Acetonide Injectable Suspension (KENALOG®-40, NDA 14-901) with a concentration of 40 mg/mL of triamcinolone acetonide was approved for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids. Triamcinolone acetonide was also approved as a nasal spray (NDA 20-784, Nasacort HFA Nasal Aerosol).

2.2 Data Sources

The major sources of clinical data utilized in this review include:

- Literature references citing the use of the product Triamcinolone Acetonide Injectable Suspension in study report C-06-26, a meta-analysis of 300 peer-reviewed articles.
- Data from study C-05-62 (Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study C-06-26:

Description of the studies:

Clinical study report C-06-26 provides a meta-analysis of published peer reviewed literature to support the safety and effectiveness of triamcinolone acetonide in the treatment of ophthalmic disorders and diseases and for use in ocular surgery to enhance visualization of vitreous and membranes. Papers selected for review are based on the following criteria:

1) Evaluated triamcinolone acetonide by intravitreal, sub-Tenon's or retrobyulbar administration
2) Included dose ranged from <1 mg to 40 mg.
3)

Primary endpoints:

The efficacy and safety variables were reported in the published peer-reviewed literature.

Primary efficacy and safety were assessed by evaluating the reported effect of triamcinolone acetonide and making relevant comparisons to comparator treatments and/or untreated controls. Best or current corrected visual acuity were collected from patients using ETDRS/LogMAR, decimal, or Snellen charts and subsequently converted to logMAR equivalents. Visual acuity scores were summarized in this report as either mean visual acuity score (LogMar scale), mean change from baseline in visual acuity, and the percentage of patients with visual acuity improvement of at least 2 line (10 letters).

In visualization studies, the primary efficacy assessment pertained to whether the injected triamcinolone acetonide was useful to the surgeon for visualization during virectomy.

Statistical Methodology:

Published results from peer reviewed studies that met inclusion/exclusion criteria were analyzed. The analyses included in this Central Study report are based on descriptive summaries of weighted means. This analysis of summary statistics included means and percentages depending on the variables. No test of homogeniety was performed.

Reviewer's Comments:

The primary endpoints were based on different scales and durations. The publish data were to be used in the meta analysis to assess treatment group differences. However, the data captured from articles did not readily fit the requirements for the traditional meta analysis involving the estimation of effect sizes and a summary across similarly-derived estimates of central tendency and variability. There were numerous issues and limitations in the analysis.

Efficacy:

Sympathetic Ophhalmia, Temporal Arteritis, Uveitis, and Ocular Inflammatory Conditions Unresponsive Corticoteroids:

The applicant reported that in total 30 peer reviewed publications that evaluated triamcinolone acetonide for the treatment of ophthalmic diseases and conditions supported by Kenalog -40 (NDA 14-901) were included in the clinical database of NDA 22-048. None of theses 30 publications met all of the Agency's criteria for adequate study design, well controlled, and adequate duration (≥1 year). Based on the nature of the diseases and rare conditions represented by these indications, most studies were case series reports without comparator groups. Although many reports noted visual acuity, data were reported for a limited number of patients at time points that varies substantially among publications. Furthermore, most studies did not present visual acuity data in a format suitable for integration. Based on the above concerns as well as due to lack of data from prospectively designed clinical trial(s), the information submitted in this application did not provide adequate evidence of efficacy and safety for these indications.

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Visualization of the Vitreous and Pathologic Membranes during Vitrectomy

Meta analysis:

The following table summarizes the percentage of eyes in TA was declared useful for visualization during vitrectomy:

Table 7: Percentage of Eyes in which TA was declared useful for Visualization (Study C-06-26)

			TA was safe and effective for visualization	
	Articles	Total N	N	%
All Reported Techniques Combined	33	3051	3040	99.6
Membrane(s)	19	2753	2742	99.6
Vitrectomy	19	2462	2461	100
Vitrectomy and Membrane(s)	8	2199	2198	100

Reviewer's comments:
There were no control groups in the above mentioned articles. Therefore, the comparative efficacy of the drug with respect to placebo could not be determined.

The following table provides the listing of citations provided by the sponsor for what they called well controlled, with adequate duration and adequate design. However, these trials failed to meet the standards for well controlled trials.

Table 8: Listing of Peer-reviewed Articles Evaluated- Triamcinilone Acetonide for Aiding in Visualizing and Removal of Vitreous and Membranes

Citation	Study type	Randomized	Masking	Adequate Study design	Well-Controlled	Adequate Duration	Agency Criteria Achieved
Aritomi et al (2004)	Retrospective	Yes	Unmasked	Yes	Yes (no treatment concurrent control)	Yes (intraoperative use)	Yes
Enaida et al (2003)	Prospective	No	Single masked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Enaida et al (2003)	Prospective	No	Single masked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Enaida et al (2003)	Prospective	No	Single masked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Kaynak et al (206)	Retrospective	No	Unmasked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Wang et al (2005b)	Prospective	Yes	Unmasked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Watanabe et al (2005b)	Prospective	Yes	Not reported	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Yamakiri et al (2007)	Prospective	Yes	Single masked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes
Bardak et al (2006)	Retrospective	Yes	Unmasked	Yes	Yes (active treatment concurrent control)	Yes (inoperative use)	Yes
Bardak et al (2006)	Retrospective	Yes	Unmasked	Yes	Yes (no treatment concurrent control)	Yes (inoperative use)	Yes

Reviewer's Comments:

The articles submitted in the above table have the following limitations::

- *Studies may have been masked (single or double masked) or unmasked*
- *The route of drug administration varied from intravitreal to periocular routes*

- *Dosing ranged from 1 to 40 mg of triamcinolone acetonide*
- *Dose administration varied from single to multiple doses and may have been prior to, during, of after a surgery*
- *Measurement of the primary endpoint (best corrected visual acuity) was reported using different eye charts whose values were then converted to logMAR units.*

3.1.2 Study C-05-62

The objective of this study was to evaluate the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension when used for visualization during pars plana vitrectomy with or without membrane removal.

Study Design:

This study was a multi-center, observer-masked study of preservative-free triamcinolone acetonide sterile injectable suspension. Patients received unpreserved triamcinolone acetonide as a surgical adjunct for enhancing visualization of transparent tissue during pars plana vitrectomy with or without membrane removal. An independent masked observer will evaluate the primary efficacy. There were 60 patients enrolled in this study.

Primary Endpoints:

Primary efficacy consisted of the evaluation of the visualization of posterior segment structures in pars plana vitrectomy before and after instillation of triamcinolone acetonide. The assessment was based upon a masked review of videos images taken before and after use of triamcinolone acetonide. Secondary efficacy was determined by the surgeon's assessment of triamcinolone acetonide's ability to improve visualization. This assessment was based on judgment of how visualization compares prior to and following instillation of the study medication.

Safety Endpoints:

Safety variables included intraocular pressure, slit-lamp assessment of anterior segment inflammation (aqueous cells, aqueous flare, and corneal edema), and dilated fundus assessment of vitreous haze, retina, macula, choroid and optic nerve. Patients were examined preoperatively, in addition to Days 1 and 7, following surgery.

Dosage:
Approximately 1-4 mg (0.025-0.1 cc) as needed was used for visualization during pars plana vitrectomy with or without membrane removal. Sixty patients had undergone pars plana vitrectomy with or without membrane removal. The trial was observer masked (neither patient masked or double masked). There was no concurrent control.

Statistical Methodology:

Independent masked reader evaluations of pre and post-study medication video images were performed. The independent reader reviewed the images with respect to the selected posterior segment structure (vitreous edge, vitreous body or membrane). The reader was then asked to indicate the degree of visualization of the relevant posterior segment structure on a 5 point scale ranging from "Not Visible 0 ' to Clearly Delinated 4". Descriptive statistics were calculated for the pre and post study medication reader evaluations. A paired t-test comparing visualization of posterior segment structures before and after use of study medication (during pars plana viterctomy surgery) was presented.

Efficacy:

The following table summarizes mean visualization score for the ITT population:

Table 9– Mean Visualization Score (ITT): Study C-05-62

	Mean	Std	N	P-value* (paired t test)
Pre-instillation	0.5	0.6	60	
Post-instillation	3.7	0.8	60	
Change	3.2	0.9	60	0.0001

Reviewer's Comments:

Although there is some beneficial effect observed, the result is based on within patient comparison. The study was only observer-blinded and there were potential for selection biases in the outcome assessments. The outcome assessment was also based on judgment of how visualization compares prior to and following instillation of the study medication. This can be very subjective and can introduce noise in the data. In addition, the comparative efficacy of TA could not be ascertained without a control arm (placebo) incorporated in the study design.

3.2 Evaluation of Safety

See medical review for details.

4.0 Conclusions and Recommendations

In summary, the evidence submitted in this application does not support the effectiveness of Triamcinolone Acetonide Injectable Suspension 40 mg/mL for the treatment of treatment of [redacted] visualization during vitrectomy, sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids. There were several issues identified and discussed in the review based on the meta analysis and results from study C-05-62.

It is strongly recommended that the evidence submitted be based on well controlled, prospective studies with endpoints consistent with Agency's current guidelines for each indication.

SIGNATURES/DISTRIBUTION LIST

Mushfiqur Rashid, Ph.D.
Primary Statistical Reviewer

Concurring Reviewer:

Thamban Valappil, Ph.D
Statistical Team Leader

cc:
HFD-520/Project Manager/Carmen DeBellas, Pharm, D.
HFD-520/DAIOP Acting Division Director/Wiley Chambers, M.D.
HFD-520/ DAIOP Deputy Division Director/Katherine Laessig, M.D.
HFD-520/ Clinical Reviewer/Martin P. Nevitt, M.D., MPH
HFD-520/ Medical Team Leader/William Boyd, M.D.
HFD-725/Primary Statistical Reviewer/Mushfiqur Rashid, Ph.D.
HFD-725/Statistical Team Leader/Thamban Valappil, Ph.D
HFD-725/Deputy Division Director: Daphne Lin, Ph.D
HFD-725/Division Director: Mohammad Huque, Ph.D
HFD-700/Lillian Patrician, MS, MBA
HFD-700/ Office of Biostatistics Deputy Director/Edward Nevius, Ph.D

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Mushfiqur Rashid
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