CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

FLUOCINOLONE ACETONIDE INTRAVITREAL IMPLANT (ILUVIEN)

(Knight Therapeutics Inc.)

Indication: For the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
BCVA	best-corrected visual acuity
CDR	CADTH Common Drug Review
CI	confidence interval
DME	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluocinolone acetonide
HRQoL	health-related quality of life
ITC	indirect treatment comparison
IOP	intraocular pressure
LOCF	last observation carried forward
OCT	optical coherence tomography
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
MCID	minimal clinically important difference
VEGF	vascular endothelial growth factor
VFQ	Visual Function Questionnaire
WDAE	withdrawal due to adverse event

Drug	Fluocinolone acetonide (Iluvien)
Indication	For the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.
Reimbursement Request	As per indication.
Dosage Form	Sterile intravitreal implant, 0.19.
NOC Date	November 23, 2018
Manufacturer	Knight Therapeutics Inc.

Executive Summary

Introduction

Diabetic macular edema (DME) is the result of retinal microvascular changes that occur in patients with type 1 or type 2 diabetes mellitus and is defined as macular retinal thickening caused by diabetic retinopathy.[1] DME is the leading cause of blindness in patients with diabetes.[1,2] Generally, DME manifests as slowly progressive vision loss. The degree of vision loss can vary considerably and depends on the severity, duration, and location of intraretinal fluid, among other factors. Clinically significant macular edema can be defined by retinal thickening at or within 500 µm of the centre of the macula.[2,3] DME can be categorized as centre-involved or non–centre-involved DME.

In Canada, the estimated prevalence of DME is 15.7% and it is estimated that 2.56% of patients with DME have experienced vision loss that required treatment.[3] Given that the prevalence of diabetes in Canada is 9.2%, it is estimated that there are 528,524 patients with DME across Canada, 13,530 of whom have experienced vision impairment.[2,4] According to the clinical expert consulted for this review, DME is likely under-diagnosed in Canada. Given the higher prevalence of diabetes and diabetic retinopathy in Indigenous populations in Canada compared with the general Canadian population, it is expected that Indigenous populations are similarly disproportionately impacted by DME.[4]

Iluvien is a non-biodegradable intravitreal implant containing 0.19 mg fluocinolone acetonide (FA) designed to release 0.2 mcg FA per day for 36 months. FA is a corticosteroid that acts to inhibit inflammatory responses to a variety of inciting agents. It is expected to reduce intravitreal vascular endothelial growth factor (VEGF) levels by turning off the gene for production of VEGF and causing regression of active neovascularization by direct inhibition of VEGF-producing cells. Iluvien is indicated for the treatment DME[5] in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (IOP).[6] The recommended dose of Iluvien is one 0.19 mg non-biodegradable intravitreal implant designed to release FA for 36 months.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of an FA 0.2 mcg/day intravitreal implant for patients with DME.

Stakeholder Engagement

Patient Input

Four patient groups, including the International Federation on Ageing, the Canadian Council of the Blind (CCB), Diabetes Canada (DC), and the Canadian Association for Retired Persons jointly provided input for this review.

The patient group input indicated that blindness and vision loss is the most important aspect/symptom to control. Other symptoms include vision impairment (e.g., blurry vision, floaters, double vision). Patients also indicated that DME impacts their vision-related function (e.g., reading, driving, and housework) and health-related quality of life.

No patients who provided input reported currently receiving any medications for the treatment of DME. One person had previously received Lucentis and Avastin. One patient was taking medications for diabetes. The patient who had previously taken Lucentis and Avastin rated both medications as "very effective." More specifically, both Lucentis and Avastin improved visual acuity, helped in retaining independence, and maintained their hope. The noted side effect of Lucentis was irritation and the side effect of Avastin was increased IOP.

Four patients (US residents) had treatment experience with Iluvien. These patients mentioned the following advantages of treatment with Iluvien: reduction in the number of injections (from one, every one to three months to one, every two to three years), less worry about infections, elimination of swelling, less time off work to attend appointments, and a decrease in discomfort due to less frequent injections. The patients noted increased independence, more happiness, a greater sense of "permanency" in their vision, ability to travel, a return to all personal and lifestyle activities, and more confidence. None of the patients mentioned experiencing any disadvantages with Iluvien. One patient indicated that Lucentis did not seem to last as long as Iluvien and required more frequent appointments.

Clinician Input[1]

The following input is a summary of information provided by one clinical specialist with expertise in the diagnosis and management of DME.

The current treatment paradigm for centre-involved DME involves first-line treatment with intravitreal anti-VEGF therapeutics (e.g., ranibizumab, aflibercept, bevacizumab). For non–centre-involved, clinically significant DME, laser treatment is considered first-line treatment. Current gaps in therapy exist for patients whose condition does not respond or is refractory to currently available treatments. Currently available treatments require regular injections; a novel efficacious therapy with fewer injections would benefit patients' health-related quality of life.

With respect to the current treatment paradigm, FA is not considered first-line treatment for DME. FA may be better suited for pseudophakic patients or those whose condition does not respond to anti-VEGF treatment. Treatment with FA can be considered in combination with anti-VEGF therapeutics or laser treatment if the treatment effect is not adequate. The introduction of FA in the Canadian setting is unlikely to cause a shift in the current treatment paradigm, as FA has been associated with more serious side effects (e.g., increase in IOP,

[1] This information is based on information provided in draft form by the clinical expert consulted by the CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

cataract formation) than the anti-VEGF treatment. Although FA is not expected to be used as a first-line treatment option, there is no clinical requirement for patients to try another treatment before initiating treatment with FA. However, if a patient exhibited a favourable response to previous steroid treatment (triamcinolone or dexamethasone implant), it would be expected to exhibit a favourable response with FA.

Patients best suited for treatment with FA include those who do not experience an increase in IOP with steroid treatment or those who are pseudophakic. Patients who should not be treated with FA include those who are pre-symptomatic, those with glaucoma, and those whose condition previously responded poorly to steroid treatment.

Treatment with FA can be administered in both community and hospital settings by ophthalmologists experienced in managing patients with diabetic retinopathy, including DME. To assess a patient's response to treatment, an assessment of visual acuity and an optical coherence tomography (OCT) measurement of central retinal thickness should be performed at three-month increments. Patients with a clinically meaningful response to treatment would show improvements in visual acuity, a reduction of the central retinal thickness toward normal, and a reduction in the frequency of injections and office visits.

Results and Interpretation

Included Studies

FAME-A (N = 481) and FAME-B (N = 475) were identically designed, multi-centre, double-masked, parallel-group, sham-controlled, phase III randomized controlled trials (RCTs) that enrolled adult patients with DME who had had at least one macular laser treatment more than 12 weeks before the screening visit. The primary objective of both trials was to determine if either dose level of FA intravitreal implant (daily release rate of 0.2 mcg or 0.5 mcg) was superior to the control group with respect to the proportion of patients with a greater than or equal to 15-letter increase in best-corrected visual acuity (BCVA) at month 24 compared with baseline (primary end point). Patients were randomized in a 2:2:1 ratio to receive treatment with a 0.2 mcg/day FA implant, 0.5 mcg/day FA implant, or sham injection, respectively. The Health Canada–recommended dose of 0.2 mcg/day is the focus of this review.

In FAME-A, patients (FA 0.2 mcg/day, N = 190; sham, N = 95) were enrolled from 49 sites across the US, Europe, India, and Canada (five sites). In FAME-B, 276 patients (FA 0.2 mcg/day, N = 186; sham, N = 90) were enrolled from 52 sites in the US, Europe, and India. In both studies, the majority of patients were enrolled from sites in the US, which accounted for 70.7% of the study population in FAME-A and 67.8% in FAME-B. The trials were of identical design. Among other criteria, patients were required to have a diagnosis of diabetes mellitus and DME.

Key limitations of the FAME trials included generalizability issues, differential trial discontinuation, and the use of a sham comparator.

Efficacy

According to the clinical expert consulted for this review, an improvement in visual acuity is key in determining a clinically meaningfully response to treatment in patients with DME, and this was echoed by the patient groups consulted for this review. The primary end point in the FAME trials was the difference in the proportion of patients with an increase from

baseline of 15 or more letters in BCVA at month 24. This difference was statistically significantly in favour of treatment with FA 0.2 mcg/day compared with sham in both trials (FAME-A: difference = −12.1%, 95% confidence interval [CI], −21.6 to −2.6, *P* = 0.029; FAME-B: difference = −12.9 %, 95% CI, −23.2 to −2.6, *P* = 0.030). The criterion of having an increase of 15 letters or more in BCVA is consistent with recommendations from the FDA. A criterion based on a 10-letter difference in BCVA has been identified as clinically relevant in the literature and by the clinical expert consulted in this review.[7] The difference in the proportion of patients with an increase from baseline of 10 or more letters was −7.9% (95% CI, −19.3% to 3.5%) in FAME-A and −15.9% (95% CI, −27.2% to −4.5%) in FAME-B; the 10-letter end point was outside of the statistical hierarchy. Visual acuity was also assessed based on the mean change from baseline in BCVA letter score. Results were inconsistent between trials, as only FAME-B was statistically significant in favour of FA 0.2 mcg/day compared with sham at month 24 (FAME-A: difference = −1.8 letters; 95% CI, −6.3 to 2.8, *P* = 0.444; FAME-B: difference = −6.1 letters; 95% CI, −10.8 to −1.4, *P* = 0.011). This outcome was influenced by several patients in both arms who experienced worsening in visual acuity. This is shown in detail in Table 17, where change from baseline in BCVA letter score by five-letter increments is presented.

Findings from subgroup analyses may suggest that the treatment effect of FA 0.2 mcg/day on BCVA was more pronounced in patients with poorer visual acuity at baseline or patients who were pseudophakic. The differences in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by baseline lens status were consistently greater in the pseudophakic subgroup compared with the phakic subgroup. Results by other subgroups were inconsistent between trials. The difference in the mean BCVA letter score was consistently greater in patients with a baseline visual acuity of less than or equal to 49 letters. While the subgroup analyses may indicate that the treatment effect of FA 0.2 mcg/day on visual acuity was likely more pronounced in patients with poorer visual acuity at baseline or patients who were pseudophakic, further study is needed to confirm the effect due to the exploratory nature of the subgroup analyses.

Other outcomes identified in the CADTH Common Drug Review (CDR) review protocol included the proportion of patients with a worsening from baseline of three or more steps in the Early Treatment Diabetic Retinopathy Study (ETDRS) multi-step eye scale of diabetic retinopathy which did not show a difference between those treated with FA 0.2 mcg/day and those treated with sham (FAME-A: difference = −1.7%, 95% CI, −3.5% to 0.2%, *P* = 0.216; FAME-B: difference = 0.0%, 95% CI, −2.7% to 2.7%, *P* = 0.964). In both FAME trials, the 39-item Visual Function Questionnaire (VFQ-39) change from baseline at month 24 was not different between treatment arms for FA 0.2 mcg/day compared with sham (FAME-A: difference = 0.5, 95% CI, −4.0 to 4.9; FAME-B: difference = −2.5, 95% CI, −7.5 to 2.5). Similar results were reported for the 25-item VFQ (VFQ-25). In the FAME trials, at month 24, the VFQ-25 change from baseline at month 24 was not different between treatment arms for FA 0.2 mcg/day compared with sham (FAME-A: difference = −0.0; 95% CI, −4.5 to 4.5; FAME-B: difference −0.9, 95% CI, −6.1 to 4.3).

In both trials, more patients in the sham arms at month 24 (FAME-A = 67.4%; FAME-B = 56.7%) received treatment with laser compared with the FA 0.2 mcg arms (FAME-A = 44.2%; FAME-B = 38.7%) during the double-masked period. In both trials, more patients in the sham arms (FAME-A = 34.7%; FAME-B = 31.1%) received disallowed treatments for DME (intravitreal steroids, posterior sub-Tenon's steroids, anti-VEGF therapy, vitrectomies) compared with the FA 0.2 mcg arms (FAME-A = 18.9%; FAME-B = 11.3%). The high use of laser and disallowed treatments for DME confound the

interpretation of the efficacy of FA and the differential use of these therapies could artificially inflate the efficacy findings for the sham arm and bias the results against FA. More patients in the sham arm were re-treated (with sham procedure) compared with the FA arm (re-treated with an additional FA 0.2 mcg implant); approximately one-quarter of patients in the FA arm received an additional implant after 12 months. The use of a sham intervention instead of an active comparator limits the ability to make comparisons with other treatments indicated for DME.

The FAME extension study was conducted [redacted]

A manufacturer-submitted indirect treatment comparison (ITC) comparing FA with other treatments for DME was reviewed and critically appraised. Findings from the ITC indicate [redacted]

Harms

Adverse events (AEs) were reported by most patients. In FAME-A, 96.8% of patients in the sham arm and 97.9% of patients in the FA 0.2 mcg/day arm experienced an AE. Similarly, 92.2% of patients in the sham arm and 98.9% of patients in the FA 0.2 mcg/day arm experienced an AE in FAME-B. Most AEs were ocular-related; these occurred more frequently in the FA 0.2 mcg/day arm in both trials. The most common ocular AEs in the study eye were related to cataracts, cataract operation, and an increase in IOP, which effected more patients in the FA 0.2 mcg/day arm compared with the sham arm in both trials.

Similarly, ocular serious adverse events (SAEs) in the study eye occurred more frequently in the FA 0.2 mcg/day arm in both trials. In FAME-A, 26.3% of patients in the sham arm and 60% of patients in the FA 0.2 mcg/day arm experienced an ocular SAE in the study eye. Similarly, in FAME-B, 26.7% of patients in the sham arm and 53.5% of patients in the FA 0.2 mcg/day arm experienced an ocular SAE in the study eye. Ocular SAEs were most commonly related to cataract operations. In both FAME trials, the following notable harms were reported more often in patients in the FA 0.2 mcg/day arm compared with the sham arm; these included increased incidence of cataracts, endophthalmitis, eye infections, retinal tear, increased IOP, and glaucoma.

In FAME-A, withdrawal due to adverse events (WDAEs) occurred in 9.5% of patients in the sham arm and 6.8% of patients in the FA 0.2 mcg/day arm. Conversely, in FAME-B, WDAEs occurred in 7.8% of patients in the sham arm and 9.7% of patients in the FA 0.2 mcg/day arm. In FAME-A, six patients (6.3%) in the sham arm and 12 patients (6.3%) in the FA 0.2 mcg/day arm died. In FAME-B, five patients (5.6%) in the sham arm and

16 patients (8.6%) in the FA 0.2 mcg/day arm died. No more than two deaths per treatment arm occurred in any single category.

Results of the FAME extension show [redacted]

Safety results from the manufacturer-submitted ITC comparing FA with other treatments for DME were reviewed and critically appraised. Results of the ITC indicated that patients treated with [redacted]

Conclusions

In two identically designed phase III RCTs of adult patients with DME, treatment with an intravitreal implant containing 0.19 mg FA with a daily release of 0.2 mcg demonstrated a difference of approximately 12% in the proportion of patients with an increase from baseline of 15 or more letters in BCVA compared with sham at month 24. While clinical and statistical significance was achieved using this outcome, other visual acuity assessments for mean change in BCVA letter score do not show a substantive clinically meaningful improvement.

The considerable use of re-treatments with the FA implant, including use of laser and use of disallowed treatments for DME, over the study period may confound the assessment of the treatment effect of the FA implant.

The generalizability of the study findings to the Canadian population is questionable, as the clinical expert consulted for this review identified differences regarding prior use of therapies for DME (namely VEGF inhibitors) between the study population in the FAME trials and the Canadian clinical population.

While it is recognized that the 0.19 mg FA implant provides the convenience of relatively fewer injections for patients, the safety profile in terms of eye-related complications was less favourable for FA 0.2 mcg/day compared with sham in the FAME-A and FAME-B trials. Most notably, patients treated with FA 0.2 mcg/day experienced more AEs related to cataracts and increased IOP.

Findings from the ITC indicate treatment with [redacted]

[redacted].

Table 1: Summary of Key Results (Full Analysis Population)

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Proportion of Patients With an Increase From Baseline of 15 or More Letters in BCVA				
Month 24				
n (%)	14 (14.7%)	51 (26.8%)	16 (17.8%)	57 (30.6%)
Difference (95% CI)	−12.1 (−21.6 to −2.6)		−12.9 (−23.2 to −2.6)	
P value[a]	0.029		0.030	
BCVA Letter Score				
Baseline				
Mean (SD)	54.8 (11.36)	53.4 (13.00)	54.7 (11.23)	53.3 (12.39)
Month 24				
Mean change (SD)	3.2 (13.07)	3.7 (18.74)	0.0 (15.62)	5.1 (17.95)
Difference estimate (95% CI)[b]	−1.8 (−6.3 to 2.8)		−6.1 (−10.8 to −1.4)	
P value[b]	[redacted]		[redacted]	
Proportion of Patients With a Worsening From Baseline of 3 Steps or More in the ETDRS Multi-Step Eye Scale of Diabetic Retinopathy				
Month 24				
n (%)	[redacted]		[redacted]	
Difference (95% CI)	[redacted]		[redacted]	
P value[a]	[redacted]		[redacted]	
VFQ-25 Overall				
Baseline				
Number of observations at baseline, n	[redacted]		[redacted]	
Baseline value, mean (SD)	[redacted]		[redacted]	
Month 24				
Number of observations at month 24, n	[redacted]		[redacted]	
Change at month 24, mean change (SD)	[redacted]		[redacted]	
Difference (95% CI)[c]	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Severe Adverse Events				
Patients with > 0 SAEs, N (%)	[redacted]		[redacted]	
Patients with > 0 ocular SAEs in study eye, N (%)	[redacted]		[redacted]	
Ocular SAEs (study eye)				
Cataract operation	[redacted]		[redacted]	
Glaucoma	[redacted]		[redacted]	
Glaucoma surgery	[redacted]		[redacted]	
IOP increased	[redacted]		[redacted]	

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Retinal detachment	[redacted]	[redacted]	[redacted]	[redacted]
Trabeculectomy	[redacted]	[redacted]	[redacted]	[redacted]
Trabeculoplasty	[redacted]	[redacted]	[redacted]	[redacted]
Vitrectomy	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms (Study Eye)				
Cataract	[redacted]	[redacted]	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]	[redacted]	[redacted]
Increased IOP	[redacted]	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; IOP = Intraocular pressure; SAE = severe adverse event; SD = standard deviation; VFQ = Visual Function Questionnaire.

Note: Excess centre-point thickness calculated by subtracting a value of 180 µm from the centre-point thickness for each patient; all negative values were set to zero.

[a] *P* value based on a Cochran–Mantel–Haenszel chi-square test stratified by baseline visual acuity.

[b] The between-treatment difference, 95% CI, and *P* value are based on an analysis of variance model with treatment and baseline visual acuity strata as fixed effects.

[redacted]

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). Diabetic macular edema (DME) is the result of retinal microvascular changes that occur in patients with type 1 or type 2 diabetes mellitus and defined as macular retinal thickening caused by diabetic retinopathy.[1] DME is the leading cause of blindness in patients with diabetes.[1,2] DME can be categorized as centre-involved or non–centre-involved DME, where centre-involved DME describes DME in which the central macular is involved.

Generally, DME manifests as slowly progressive vision loss. The degree of vision loss can vary considerably and depends on the severity, duration, and location of intraretinal fluid, among other factors. Clinically significant macular edema can be defined by retinal thickening at or within 500 µm of the centre of the macula.[3,4]

The most common presenting clinical symptom of DME is blurred vision. However, a patient can have clinically significant macular edema with no symptomatic loss of central visual acuity. Other symptoms can include metamorphopsia, change in contrast sensitivity, photophobia, changes in colour vision, and scotomas.[1]

Patient input submitted for this review combined with input from a clinical expert highlight the extensive psychological, physical, and financial burden associated with DME. Patients indicated that blindness, vision loss, and visual impairment were among their most concerning symptoms. Patients also indicated that DME impacted their vision-related function (e.g., reading, driving and housework), independence, and health-related quality of life (HRQoL).

In Canada, the estimated prevalence of DME is 15.7% and, of these patients, 2.56% experienced vision loss that required treatment.[3] Given that the prevalence of diabetes in Canada is 9.2%, it is estimated that there are 528,524 patients with DME across Canada, 13,530 of whom have experienced vision impairment.[2,4] According to the clinical expert consulted for this review, DME is likely under-diagnosed in Canada. Given the higher prevalence of diabetes and diabetic retinopathy in Indigenous populations in Canada compared with the general Canadian population, it is expected that Indigenous populations are similarly disproportionately impacted by DME.[4]

Standards of Therapy

The treatment strategies for DME encompass lifestyle modification, including diet and exercise and smoking cessation as well as improved control of blood sugar, blood pressure, blood lipids, and a lower body mass index. Current therapies for DME used in Canadian clinical practice include laser photocoagulation, pharmacologic treatment with vascular endothelial growth factor (VEGF) inhibitors (ranibizumab, aflibercept, and bevacizumab), triamcinolone acetonide, and intraocular steroids (dexamethasone), although bevacizumab and triamcinolone acetonide are used beyond their approved Health Canada indication.[4]

Macular laser photocoagulation (including focal or grid laser) therapy for DME was the standard of care for more than 25 years before the introduction of VEGF inhibitors and is

still widely used following VEGF inhibitors.[9] Laser therapy has been shown to slow and stabilize vision loss but has been minimally effective in restoring vision.[10]

The Canadian Ophthalmological Society states that more recently, use of intraocular steroid and intraocular VEGF inhibitors has demonstrated efficacy when used alone or as a supplement to laser.[4] There is increasing evidence that intraocular injections of anti-VEGF drugs are an effective treatment for DME and produce a larger gain in vision than focal or grid laser alone.[4] According to the clinician input provided for this review, the frequent administration (nine injections per eye per year) of anti-VEGF therapies required to achieve the desired outcomes may be a barrier to adherence and negatively impact quality of life. Anti-VEGF therapies are also associated with an increased risk of cerebrovascular and cardiovascular events such as thromboembolic events; therefore, they may not be appropriate for use in all patients with DME.[11] Furthermore, studies have shown that approximately 40% of patients on anti-VEGF therapy have an inadequate response to treatment.[11]

Intraocular injection of steroids has demonstrated rapid improvement of DME; however, the improvement is not sustained and is associated with a significant increase in the incidence of raised intraocular pressure (IOP) and cataract formation.[4] Intravitreal injection with a dexamethasone implant may be used for a period of approximately six months. Patients who provided input for this review highlighted the advantages of fewer injections for intraocular steroids (typically six injections per year) compared with intraocular VEGF inhibitors (typically nine injections per year); these included less worry about infections, elimination of swelling, less time off work to attend appointments, and a decrease in discomfort due to less frequent injections.

Drug

Iluvien is a non-biodegradable intravitreal implant containing 0.19 mg FA designed to release 0.2 mcg per day for 36 months. FA is a corticosteroid that acts to inhibit inflammatory responses to a variety of inciting agents and is expected to reduce intravitreal VEGF levels by turning off the gene for the production of VEGF and causing regression of active neovascularization by directly inhibiting VEGF-producing cells. Iluvien is indicated for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.

The recommended dose of Iluvien is 0.19 mg administered using a non-biodegradable intravitreal implant. Iluvien should be administered by an ophthalmologist who has experience administering intravitreal injections.

Table 2: Key Characteristics of Fluocinolone Acetonide, Dexamethasone, Aflibercept, Ranibizumab, and Bevacizumab

	Fluocinolone Acetonide (Iluvien)	Dexamethasone (Ozurdex)	Aflibercept (Eylea)	Ranibizumab (Lucentis)	Bevacizumab (Avastin)
Mechanism of Action	Corticosteroid; inhibits inflammatory responses and reduces intravitreal VEGF levels	Corticosteroid; glucocorticoid receptor agonist; acts directly to decrease VEGF synthesis	VEGF inhibitor	VEGF inhibitor	VEGF inhibitor
Indication[a]	Treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP	Treatment of adult patients with DME who are pseudophakic	Treatment of DME	Treatment of visual impairment due to DME	Not indicated in Canada for DME. Treatment of metastatic carcinoma of the colon or rectum; metastatic non-squamous non–small cell lung cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; glioblastoma
Route of Administration	Intravitreal implant	Intravitreal implant	Intravitreal injection	Intravitreal injection	Intravitreal injection
Recommended Dose	0.19 mg implant; up to 3-year duration	0.7 mg implant; every 6 months	2 mg every 8 weeks after initial 5 monthly injections	0.5 mg once a month	1.25 mg every 4 weeks

	Fluocinolone Acetonide (Iluvien)	Dexamethasone (Ozurdex)	Aflibercept (Eylea)	Ranibizumab (Lucentis)	Bevacizumab (Avastin)
Serious Side Effects / Safety Issues	SAE: increased IOP, cataracts, ocular infection. Contraindications: patients who are hypersensitive to this drug; patients who have active or suspected ocular or periocular infections, glaucoma, or aphakic eyes with rupture of the posterior lens capsule	SAE: endophthalmitis, eye inflammation, increased IOP, glaucoma, cataracts, and retinal detachments Contraindications: Patients with active or suspected ocular or periocular infections, advanced glaucoma, hypersensitivity to components in this product or corticosteroids, or aphakic eyes with rupture of the posterior lens capsule	SAE: endophthalmitis, traumatic cataract, increased IOP, and vitreous detachment Contraindications: patients who are hypersensitive to this drug, or have ocular or periocular infection or active intraocular inflammation	SAE: endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract, intraocular inflammation, and increased IOP Contraindications: patients who are hypersensitive to this drug or have active or suspected ocular or periocular infections or have active intraocular inflammation	SAE: hypertension, seizures, pulmonary embolism, dyspnea, lung infection Contraindications: patients who are hypersensitive to this drug

DME = diabetic macular edema; IOP = intraocular pressure; SAE = severe adverse event; VEGF = vascular endothelial growth factor.

[a] Health Canada indication.

Source: Product monographs for Iluvien,[5] Ozurdex,[10] Eylea,[11] Lucentis,[12] and Avastin.[13]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Four patient groups, including the International Federation on Ageing (IFA), the Canadian Council of the Blind (CCB), Diabetes Canada (DC), and the Canadian Association for Retired Persons (CARP) jointly provided input for this review.

The IFA is an international non-governmental organization. IFA has general consultative status at the United Nations and its agencies and a formal working agreement with the World Health Organization. The vision of the IFA is a world of healthy older people whose rights are both protected and respected. IFA aims to inform good policy and practice across the course of life. The IFA encourages and supports research, policy, and practice to advance the management and treatment of Canadians with eye conditions.

The CCB was founded by blind war veterans and graduates from schools for the blind. It has more than 80 chapters across Canada and more than 1,500 members. All officers and directors are blind or visually impaired, which gives the organization a unique sensitivity to the needs of the blind community. The CCB deals with the ongoing effects of vision loss by encouraging active living and rehabilitation through peer support and social and recreational activities. It also promotes measures to conserve sight, create a close relationship with the sighted community, and provide employment opportunities, and is committed to an integrated proactive health approach for early detection of vision impairment. CCB is dedicated to improving the quality of life for Canadians with vision loss.

DC is a national health charity representing 11 million Canadians living with diabetes or prediabetes. The priorities of the DC mission are diabetes prevention, care, and cure. Its focus on research and policy initiatives helps to deliver impact at a population level, while partnerships broaden reach in communities across the country. DC drives excellence in disease management by putting practical, evidence-based tools into the hands of health care providers and advocates for environments that make the healthy choice the easy choice. DC continues to search for a cure and better prevention and treatment strategies by funding the work of innovative scientists.

CARP is Canada's largest advocacy association for older Canadians. As a non-partisan not-for-profit association, CARP is committed to advocating for the rights and well-being of older Canadians. CARP has more than 320,000 members aged 50 and over and 30 chapters across the country. CARP's focus includes advocacy, policy development, community engagement, research, and outreach. CARP has members in every jurisdiction of the country and has an outreach of approximately two million older Canadians. CARP's national policy platform, the FACES of Canadian Seniors, identifies five priority areas: financial security, abuse prevention, caregiving and housing supports, exceptional health care, and social inclusion. CARP's commitment to vision health falls squarely in line with the key priorities of the organization.

IFA declared receiving funding (total amount of $10,000 to more than $50,000 over the past two years) from three pharmaceutical companies, including Bayer Canada, Bayer Global, and Roche Canada. CCB declared receiving funding of more than $50,000 from Bayer

Canada. DC and CARP declared not receiving funding from any company. The patient groups also indicated that they received assistance from Impetus Digital, but not from pharmaceutical companies, to design, collect, and analyze the survey results.

2. Condition-Related Information

The information was gathered through an online survey and telephone interviews. In the online survey, all of the data were contributed anonymously. IFA developed and designed a 10-minute, 22-question online survey that was disseminated in English and French. Recruitment was undertaken by IFA, CCB, DC, and CARP through social media and other online platforms. The online survey was open from April 8 to 19, 2019. There were five respondents in total (three DME patients and two DME caregivers). The respondents were from Canada (4) and Australia (1). The telephone interviews were conducted from April 11 to 23, 2019. Three patients and one caregiver (on behalf of one patient) were interviewed; all four patients had experience with Iluvien. All four people interviewed were from the US.

Patients were asked to describe how DME impacts their daily life on a scale of 0 to 5, with 0 being “no impact on daily life” and 5 being “very significant impact on daily life.” Attending medical appointments was rated as the most significant impact at 4.7/5.0, followed by reading (4.3/5.0), driving (4.0/5.0) and housework (3.3/5.0). When the caregivers were asked the same question, the most significant impact was taking their loved one to medical appointments and their employment (both 4.5/5.0), followed by housework and taking care of family (both 3.5/5.0). Patients were asked to describe how DME impacts their quality of life. Relying on others and isolation rated as the most significant impacts at 4.3/5.0, followed by independence and enjoyment of family (4.0/5.0), self-worth (3.7/5.0), and contributing to society (3.3/5.0). For caregivers, the most significant impact was mental health (depression, anxiety) and isolation (both at 4.5/5.0), followed by time to self (3.5/5.0).

The survey asked patients to choose those aspects/symptoms of DME that were of greatest concern to them. The respondents chose each of the four options: blurry vision, floaters, double vision, and blindness/vision loss. When asked to rank those same choices, all of the patients ranked blindness/vision loss as the most important aspect/symptom to control (4.0/4.0), followed by double vision (2.7/4.0), blurry vision (2.0/4.0) and floaters (1.3/4.0).

3. Current Therapy–Related Information

It was indicated that none of the patients were currently receiving any medications for the treatment of DME. One person had previously received Lucentis and Avastin. One patient was taking medications for diabetes. For the patient who had previously taken Lucentis and Avastin, they rated both medications as “very effective.” More specifically, both Lucentis and Avastin improved visual acuity, helped retain independence, and maintained their hope. The noted side effect of Lucentis was irritation and the side effect of Avastin was increased IOP.

When patients were asked about other challenges, they mentioned travel time and distance required to receive treatment and cost of treatment. Challenges specified by caregivers included taking time off work to take patients to appointments and difficulty with administering treatment (e.g., swallowing pills). Survey respondents specified anxiety about the injection, cost of transportation, and illness as reasons for missing appointments.

The one patient and two caregivers with current or previous experience with treatments were asked what improvements they would like to see in a new treatment. All three wanted a halt to vision loss, longer-term vision improvement (e.g., beyond three months) and

decreased wait times for procedures. Two respondents also hoped for improvement for their double vision and blurry vision. Thinking further about desired improvements, all patients were asked how a new treatment option would impact their quality of life. Driving, reading, and housework ranked highest at 4.7/5.0, followed by taking care of family and attending medical appointments (both at 4.0/5.0). When the caregivers were asked the same question, the most desired improvement related to their employment at 5.0/5.0, followed equally by taking care of family and housework (both at 4.0/5.0). All patients were then asked how the desired improvements in a new treatment option would impact their quality of life. Relying on others, independence, contributing to society, and isolation all averaged a 4.7/5.0 response rate, indicating that the new treatment option would greatly improve overall quality of life. This trend was also seen with respect to self-worth and enjoyment of family, which came in at 4.3/5.0, followed by mental health (depression, anxiety) at 4.0/5.0. In the case of the two caregivers, mental health (depression, anxiety) averaged 5.0/5.0, followed by isolation and time to self (4.5/5.0), and physical health (4.0/5.0). The respondents were asked how important it is for a new treatment option for DME to have less frequent injections; three out of five people ranked this as either "important" or "extremely important." When asked how important it is for a new treatment option for DME to result in longer-term vision improvement, all five patients ranked this as "extremely important."

4. Expectations About the Drug Being Reviewed

Based on a telephone interview, four patients (all residents of the US) had treatment experience with Iluvien. Two patients had received one Iluvien injection in the left eye since May 2016. The third patient had one injection of Iluvien in each eye in May 2016 and, since then, has had no need for further injections. The fourth patient received one injection of Iluvien in one eye in April 2018, with no further need for injections since that time. These patients mentioned the following advantages of the treatment with Iluvien: the reduction in the number of injections (from once every one to three months to once every two to three years), less worry about infections, elimination of swelling, less time off work to attend appointments, and a decrease in discomfort due to less frequent injections. The patients noted increased independence, more happiness, a greater sense of "permanency" in their vision, ability to travel, a return to all personal and lifestyle activities, and more confidence.

None of the patients mentioned that they experienced any disadvantages with Iluvien. One patient indicated that the effects of Lucentis did not seem to last as long as Iluvien and required more frequent appointments.

Below are a few examples of quotes from the patients regarding their experience and expectations for new treatments:

"Treatment with Iluvien is superior because I can see a lot better and can then be independent to do my own thing."

"Iluvien has been easy, with little or no impact on my lifestyle."

"Iluvien is far superior because of the vision and lifestyle outcomes."

"Iluvien is far better . . . no caring from family is required."

"Iluvien has given me the confidence to focus on management of the disease, so my weight has decreased, I exercise more, volunteer part-time, and have the incentive to be as well as I can."

"As part of my diabetes management, Iluvien has enabled me to continue my active lifestyle while monitoring my diet, exercise, and medication regimes."

"Iluvien has opened doors again. It's made my life easier; less swelling has meant my vision is a lot better, I am less depressed and optimistic about the future. Iluvien has given me a new life."

"It's been life-changing. Iluvien has meant less swelling . . ."

Clinical Expert Input

All CADTH review teams include at least one clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input is a summary of information provided by one clinical specialist with expertise in the diagnosis and management of DME.

Description of the Current Treatment Paradigm for the Disease

The current treatment paradigm for centre-involved DME involves first-line treatment with intravitreal anti-VEGF therapeutics (e.g., ranibizumab, aflibercept, bevacizumab). For non–centre-involved, clinically significant DME, laser treatment is considered first-line. Bevacizumab intravitreal injection does not have a Health Canada indication for use in patients with DME; however, it is used in the Canadian clinical setting and is associated with a lower cost. Intravitreal triamcinolone is also not approved by Health Canada for patients with DME; however, in the Canadian clinical setting, it is used in pseudophakic patients with DME. Intravitreal injection of dexamethasone implant is also limited to use in pseudophakic patients or patients waiting for cataract surgery. In patients whose condition does not respond to typical treatments, vitrectomy can be considered if there is taut epimacular membrane in combination with DME.

Treatment Goals

An ideal treatment would improve vision and HRQoL, modify the severity of diabetic retinopathy, and reduce the frequency of treatments and clinic visits.

Unmet Needs

Current gaps in therapy exist for patients whose condition does not respond to or is refractory to currently available treatments. Currently available treatments require regular injections; a novel therapy with fewer injections would benefit patients' HRQoL.

Place in Therapy

FA is a therapeutic drug that has a combined anti-inflammatory and anti-VEGF effect; this may enhance the treatment benefit experienced by patients. With respect to the current treatment paradigm, FA is not considered first-line treatment for DME. FA may be better suited for pseudophakic patients or patients whose condition did not respond to anti-VEGF treatment. Treatment with FA can be considered in combination with anti-VEGF therapeutics or laser treatment if the treatment effect is not adequate. The introduction of FA in the Canadian setting is unlikely to shift in the current treatment paradigm, as FA has been associated with more serious side effects (e.g., increase in IOP, cataract formation) than anti-VEGF treatment.

Although it is not expected that FA would be used as first-line treatment, there is no requirement for patients to try other treatments before starting treatment with FA. Patients whose condition previously responded to treatment with steroids (triamcinolone or dexamethasone implant) would be expected to respond to treatment with FA.

Patient Population

Patients best suited for treatment with FA include those who do not exhibit an increase in IOP with steroid treatment or are pseudophakic. Patients suitable for treatment with FA are typically identified via clinical examination; this includes IOP measurement and slit lamp and fundus examination. Retinal thickness and the presence or absence of edema fluid can be assessed using OCT, which is considered standard practice. Patients who should not be treated with FA include those who are pre-symptomatic, those with glaucoma, and those whose condition has previously responded poorly to steroid treatment.

Assessing Response to Treatment

To assess a patient's response to treatment, a visual acuity test and OCT measurement of central retinal thickness should be performed. Patients with a clinically meaningful response to treatment would show improvement of visual acuity (e.g., an improvement of five or more letters in BCVA), reduction of the central retinal thickness toward normal, and reduction in the frequency of injections and office visits. Treatment response should be assessed at three-month increments.

Discontinuing Treatment

Treatment with FA may be discontinued if any of the following factors are present: lack of improvement of the central retinal thickness measured by OCT; lack of improvement in visual acuity; development of uncontrolled increased IOP.

Prescribing Conditions

Treatment with FA can be administered in both community and hospital settings, as the injection is usually given in an outpatient treatment room. FA should be administered by ophthalmologists with experience in managing patients with diabetic retinopathy, including DME.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of a 0.19 mg FA intravitreal implant for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with diabetic macular edema who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP. Subgroups: • baseline visual acuity • baseline A1C • duration of disease • history of cerebrovascular or cardiovascular disease • lens status (phakic versus pseudophakic)
Intervention	Fluocinolone acetonide 0.19 mg intravitreal implant designed to release fluocinolone acetonide for 36 months
Comparators	Laser photocoagulation therapy Triamcinolone acetonide[a] Dexamethasone intravitreal administration Anti-VEGF therapies (ranibizumab, aflibercept, bevacizumab[a]) Sham injection
Outcomes	**Efficacy outcomes:** • Change from baseline in visual acuity[b] • HRQoL[b] • Vision-related function[b] (e.g., NEI VFQ-25) • Blindness (legal)[b] • Change in CRT **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality • Notable harms: Cataract formation, endophthalmitis, eye inflammation, eye infections, retinal tear, retinal detachment, increased IOP, ATE, glaucoma, surgical intervention for glaucoma treatment, damage to optic nerve, defects in visual acuity and visual field, necrotizing retinitis, conjunctival hemorrhage, vitreous hemorrhage
Study Design	Published and unpublished phase III and IV RCTs

A1C = glycated hemoglobin; AE = adverse event; ATE = arterial thrombotic event; CRT = central retina thickness; HRQoL = health-related quality of life; IOP = intraocular pressure; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; VEGF = vascular endothelial growth factor; WDAE = withdrawal due to adverse event.

[a] Not approved for the treatment of DME in Canada.

[b] These outcomes were identified in the input received by CADTH from patient groups as being of particular importance to patients.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[14]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were fluocinolone acetonide and diabetic macular edema. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal (ICTRP).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 2, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on August 21, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (Free)
- Internet Search[15]

Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional Internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4, excluded studies (with reasons) are presented in Appendix 2.

Results

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

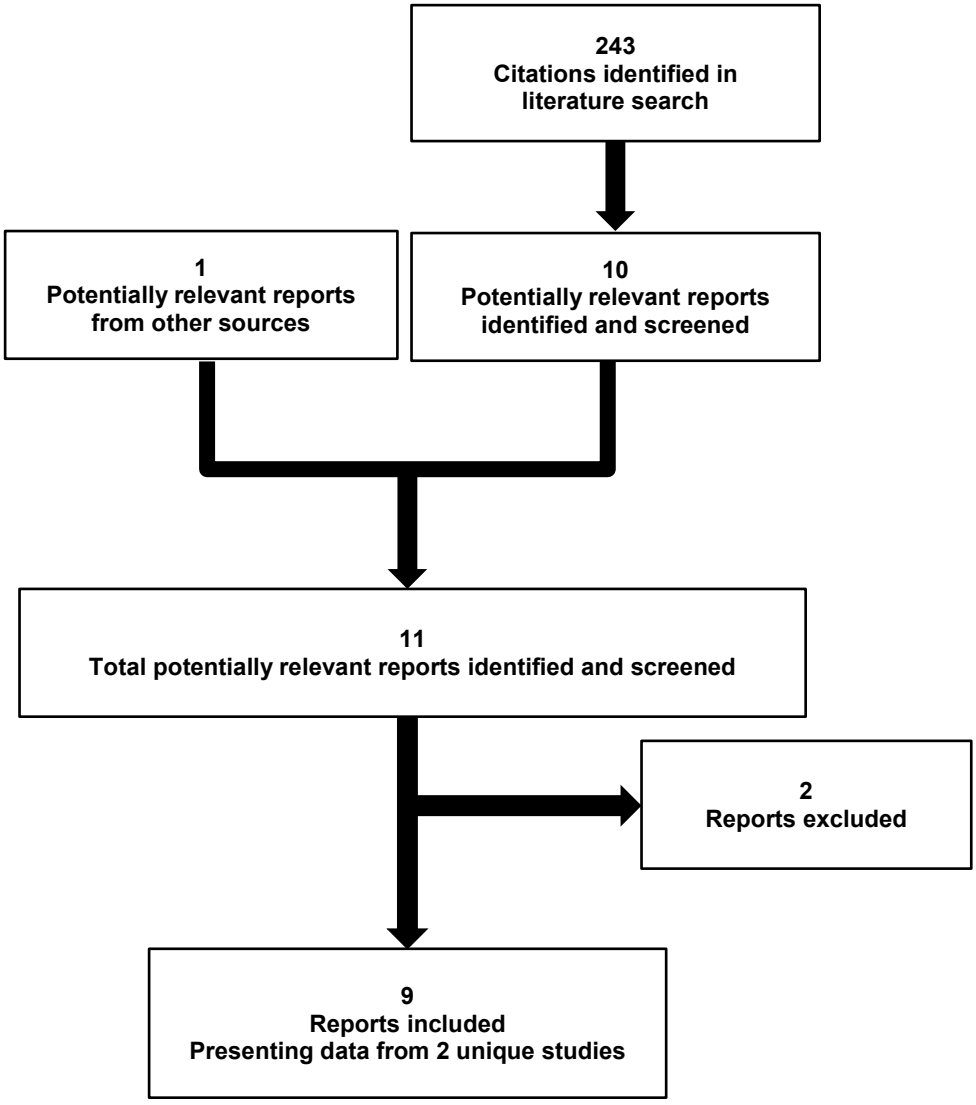


Table 4: Details of Included Studies

		FAME-A	FAME-B
Designs & Populations	**Study Design**	Double-masked, sham injection–controlled, parallel-group, multi-centre, phase III, randomized trial	
	Locations	Canada, US, Western Europe, India	US, Western Europe, India
	Randomized (N)	481	475
	Inclusion Criteria	• Study eye BCVA of ≥ 19 and ≤ 68 letters ETDRS • Patient diagnosed with diabetes mellitus as evident by insulin or oral antihyperglycemic treatment for at least three months • Patient had undergone at least one macular laser treatment more than 12 weeks before the screening visit[a] • Positive determination of the presence of DME based on investigators' clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and OCT • Mean foveal thickness of at least 250 µm measured through OCT in study eye	
	Exclusion Criteria	• Laser treatment within 12 weeks of screening, or expected to be done within 6 weeks of screening • Ocular surgery within 12 weeks of screening • Yag capsulotomy in the study eye within 15 days of screening • Prior intravitreal, sub-Tenon, or periocular steroid therapy within 3 months before enrolment • Prior anti-VEGF treatment within 2 months of enrolment • Retinal or choroidal neovascularization due to ocular condition other than diabetic retinopathy • Glaucoma, ocular hypertension, IOP > 21 mm Hg or concurrent therapy at screening with IOP-lowering drugs • History of uncontrolled IOP elevation with steroid use not responding to topical therapy • History of vitrectomy in the study eye • Resting systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 105 mm Hg at the screening visit	
Drugs	**Intervention**[b]	• Fluocinolone acetonide at a release rate of 0.2 mcg per day via intravitreal implant, implanted on study day 0 • Fluocinolone acetonide at a release rate of 0.5 mcg per day via intravitreal implant, implanted on study day 0	
	Comparator	Sham procedure using a needleless syringe pressed against the conjunctiva	
Duration	**Phase**		
	Run-in	21 days 36 months 12 months (extension study)	
	Double-mask		
	Follow-up		
Outcomes	**Primary End Point**	Proportion of patients with an improvement of 15 letters or more in BCVA on the ETDRS scale at month 24	
	Other End Points	• Mean change from baseline in visual acuity letter score as measured by the ETDRS chart (secondary outcome) • Mean change from baseline in the excess centre-point thickness (in micrometres) as assessed by OCT (secondary outcome) • Proportion of patients with ≥ 3-step worsening in the study eye compared with baseline in the ETDRS multi-step eye scale of diabetic retinopathy (secondary outcome) • HRQoL using VFQ-25 and VFQ-39 for English-speaking patients (exploratory outcome)	

		FAME-A	FAME-B
Notes	**Publications**	• Campochiaro et al., 2011[16] • Campochiaro et al., 2012[17] • Cunha-Vaz et al., 2014[18] • Yang et al., 2015[19] • Parrish et al., 2016a[20] • Parrish et al., 2016b[21] • Veritti et al., 2017[22] • Wykoff et al., 2017[23] • Chakravarthy et al., 2018[24]	

BCVA = best-corrected visual acuity; CDR = CADTH Common Drug Review; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; HRQoL = health-related quality of life; IOP = intraocular pressure; OCT = optical coherence tomography; VEGF = vascular endothelial growth factor; VFQ = vision function questionnaire.

Note: Two additional reports were included (CDR submission[25] and Health Canada reviewers report[26]).

[a] Per the protocol, initially, all patients were required to have had prior macular laser; however, in an attempt to increase enrolment, the protocol was amended to permit patients with no prior laser into the study. This amendment was in force for approximately seven months before the sponsor amended the protocol again to remove this change because there was concern that the response of the population without prior laser might be significantly different from those with prior laser. Twelve patients were enrolled who had not received prior laser.

[b] Health Canada–indicated dose. The FA 0.5 mcg/day dose will not be approved in Canada and will not be included in the present review.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Included Studies

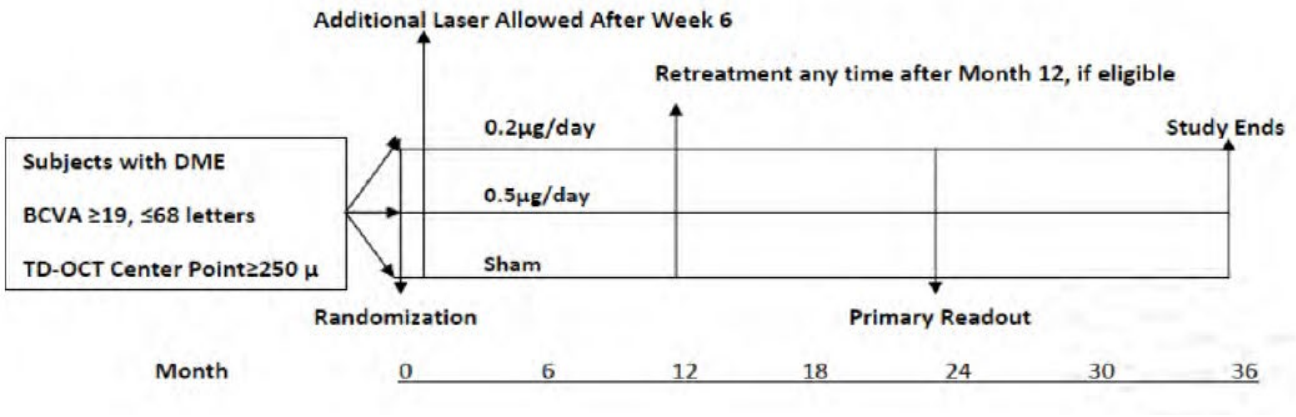
Description of Studies

Two phase III, 36-month randomized controlled trials (RCTs) were identified and included in this systematic review (FAME-A and FAME-B).[8,9] The two trials were identical in design and included a 12-month safety extension study described in Appendix 5.

FAME-A and FAME-B were identically designed, multi-centre, double-masked, parallel-group, sham-controlled, RCTs in adult patients with DME who had previously undergone laser therapy. The primary objective of both trials was to determine if either dose level of the FA intravitreal implant (daily release rate of 0.2 mcg or 0.5 mcg) was superior to sham injection with respect to the proportion of patients with a greater than or equal to 15-letter increase in BCVA at month 24 compared with baseline. The studies included patients from the US, Western European countries, and India. In addition, FAME-A included patients from five Canadian sites. In FAME-A, patients were enrolled from 49 sites across the US, Europe, India, and Canada. In FAME-B, patients were enrolled from 52 sites in the US, Europe, and India. In both studies, the majority of patients were enrolled from sites in the US, which accounted for 70.7% of the study population in FAME-A and 67.8% in FAME-B. FAME-A took place between November 7, 2005 and September 27, 2010, while FAME-B took place between September 9, 2005 and September 22, 2010. The randomization for each study was generated using an automated validated system. Patients were randomized using an interactive voice response system (IVRS) using standard blocked randomization. Randomization was stratified by site and baseline visual acuity (less than or equal to 49 letters, or greater than 49 letters). In both trials, patients were randomized in a 2:2:1 ratio to treatment with a 0.2 mcg/day FA implant, 0.5 mcg/day FA implant, or sham injection, respectively. The Health Canada–recommended 0.2 mcg/day FA implant is the focus of this review; the 0.5 mcg/day FA implant will not be reviewed in this report as it is beyond the dosing recommended by Health Canada.

Patients enrolled in both trials were treated for 36 months; afterward, patients were followed in a safety extension study for an additional 12 months. Figure 2 shows a visual representation of the study design for the FAME trials.

Figure 2: Study Design for the FAME Trials



BCVA = best-corrected visual acuity; TD-OCT = time-dependent optical coherence tomography.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Populations

Inclusion and Exclusion Criteria

The study populations in FAME-A and FAME-B consisted of patients with DME who were 18 years of age or older. The patients' study eye was required to have a BCVA of greater than or equal to 19 letters and fewer than or equal to 68 letters assessed by an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Patients were required to have a diagnosis of diabetes mellitus (type 1 or 2) indicated by insulin or oral antihyperglycemic treatment for at least three months. Patients had to have a positive determination of the presence of DME based on investigators' clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and OCT. A mean foveal thickness of at least 250 µm measured through OCT in the study eye was required for participation. In the original protocol, patients were required to have undergone at least one macular laser treatment more than 12 weeks before the screening visit. This criterion was briefly amended (removed to increase study enrollment) for approximately seven months, which resulted in the inclusion of 12 patients in FAME-A and 21 patients in FAME-B who had not received prior treatment with laser. Patients were excluded from the trials if they had laser treatment for DME or any ocular surgery in the study eye within 12 weeks of screening. Patients were excluded if they had prior intravitreal, sub-Tenon, or periocular steroid therapy within three months of enrollment, or prior anti-VEGF treatment within two months of enrollment. Patients with a history of uncontrolled IOP elevation with steroid use that did not respond to topical therapy were excluded. Patients with glaucoma, ocular hypertension, IOP greater than 21 mm Hg or concurrent therapy at screening with IOP-lowering drugs in the study eye were excluded from the trials. Patients with a resting a systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 105 mm Hg at the screening visit were excluded from the trials.

Baseline Characteristics

The baseline characteristics were generally balanced between arms for each study. Across studies, males accounted for [redacted]% to [redacted]% of the patients, and the majority were white. The mean age of patients ranged from [redacted]years to [redacted]years. The mean duration of DME was between [redacted]years and [redacted]years, while the mean duration of diabetes was between [redacted]years and [redacted]years. For [redacted]% to [redacted]% of patients, the lens status in the study eye was pseudophakic. Patients with prior intravitreal anti-VEGF treatment ranged from [redacted]% to [redacted]% of the population. Patients with prior treatment with steroid injection ranged from [redacted]% to [redacted]%. Baseline eye characteristics for BCVA ranged from [redacted] letters to [redacted]letters. IOP in the study eye ranged from [redacted]mm Hg to [redacted]mm Hg, and centre-point macular thickness ranged from [redacted]µm to [redacted]µm. Table 5 summarizes the baseline characteristics for FAME-A and FAME-B.

Table 5: Summary of Baseline Characteristics

Characteristics	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Age, Mean Years (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
DME Duration, Years				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (minimum, maximum)	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes Duration, Years				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Missing, n	[redacted]	[redacted]	[redacted]	[redacted]
Lens Status of the Study Eye, n (%)				
Pseudophakic	[redacted]	[redacted]	[redacted]	[redacted]
Aphakic	[redacted]	[redacted]	[redacted]	[redacted]
Phakic	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Prior Treatment, n (%)				
Intravitreal anti-VEGF	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Steroid injection	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
A1C				
Mean, % (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median, % (minimum, maximum)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
BCVA in the Study Eye at Baseline, Letters				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (minimum, maximum)	[redacted]	[redacted]	[redacted]	[redacted]
> 49 letters (n, %)	[redacted]	[redacted]	[redacted]	[redacted]
IOP in the Study Eye, mm Hg				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Centre-Point Macular Thickness, Micrometres				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (minimum, maximum)	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; BCVA = best-corrected visual acuity; DME = diabetic macular edema; FA = fluocinolone acetonide; IOP = intraocular pressure; SD = standard deviation; VEGF = vascular endothelial growth factor.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Interventions

In FAME-A and FAME-B, patients received treatment with a single 0.2 mcg/day FA intravitreal implant, a 0.5 mcg/day FA intravitreal implant, or a sham injection in the study eye. The 0.5 mcg/day FA intravitreal implant is not approved by Health Canada for use in patients with DME and is not included in this review. The patients' "study eye" was defined as the affected eye for patients with unilateral DME, and the more severely affected eye for patients with bilateral DME. For patients with equally affected and eligible eyes, the study eye was determined by the patient number (even, right eye and odd, left eye). The FA intravitreal implants were administered by the treating investigator via injection through the pars plana into the vitreous using a 25-gauge needle. The sham injection consisted of pressing the hub of a needleless syringe against the sclera of the eye with approximately the same pressure as for an injection of an implant. The patients in the sham arm were prepared for injection in the same manner as those in the FA implant arms. Following the FA or sham procedure, all patients were prescribed a topical antibiotic for use for the following three to five days.

Patients were permitted the use of additional laser treatment in the study eye at the six-week visit if the eye showed no improvement in edema compared with baseline, assessed via fundus photography. At any later study visit, additional laser treatment was allowed if recommended by the investigator. Throughout the trials, laser treatments in the non-study eye could be administered if recommended by the investigator. Table 6 presents data from patients treated with laser for any reason in the study eye. In both trials, more patients in the sham arms (FAME-A = [redacted]%; FAME-B = [redacted]%) received treatment with laser compared with the FA 0.2 mcg arms (FAME-A = [redacted]%; FAME-B = [redacted]%).

Use of non-approved treatments for DME (e.g., ranibizumab) and systemic treatments for DME were discouraged; however, if deemed necessary at the discretion of the investigator, patients were permitted to continue their previously administered treatment (FA 0.2 mcg/day or sham) in the study. Table 7 presents data from patients treated with disallowed treatments (intravitreal steroids, posterior sub-Tenon's steroids, anti-VEGF therapy, vitrectomies) for DME in the study eye. In both trials, more patients in the sham arms (FAME-A = [redacted]%; FAME-B = [redacted]%) received disallowed treatments for DME compared

with the FA 0.2 mcg arms (FAME-A = [redacted]%; FAME-B = [redacted]%). Treatment with intravitreal steroids was the most commonly used disallowed treatment for DME in both trials.

Table 6: Patients Treated With Laser for Any Reason (Study Eye)

Additional Laser Treatments	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Laser Treatments Administered				
Number of treatments, n	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients receiving at least one laser treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Laser Treatments Administered by Time Period, n (%)				
Baseline to month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 to month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 to month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 9 to month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 to month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 15 to month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 18 to month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 to month 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 30 to month 36	[redacted]	[redacted]	[redacted]	[redacted]

FA = fluocinolone acetonide.

Note: Full analysis population.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Table 7: Patients With Disallowed Treatments for Diabetic Macular Edema (Study Eye)

Disallowed Treatments	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Disallowed Treatments Administered				
Number of treatments, n	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients receiving at least one disallowed treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Disallowed Treatments Administered by Time Period, n (%)				
Baseline to month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 to month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 to month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 9 to month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 to month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 15 to month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 18 to month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 to month 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 30 to month 36	[redacted]	[redacted]	[redacted]	[redacted]

Disallowed Treatments	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Type of disallowed treatment, n (%)				
Intravitreal steroids	[redacted]	[redacted]	[redacted]	[redacted]
Posterior sub-Tenon's steroids	[redacted]	[redacted]	[redacted]	[redacted]
Anti-VEGF therapy	[redacted]	[redacted]	[redacted]	[redacted]
Vitrectomies	[redacted]	[redacted]	[redacted]	[redacted]

FA = fluocinolone acetonide; VEGF = vascular endothelial growth factor.

Note: Full analysis population.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Outcomes

Across the two FAME trials, several end points related to visual acuity were assessed using ETDRS charts. See Appendix 4 for a full description and appraisal of the ETDRS and other outcomes. The ETDRS chart is the most widely used outcome measure in clinical trials to assess changes in visual acuity from a therapeutic intervention. ETDRS charts present a series of five letters of equal difficulty on each row with standardized spacing between letters and rows, for a total of 14 lines (70 letters).[27-31] The ETDRS letter score results in a maximum score of 100.[32,33] ETDRS charts may reliably identify changes in visual acuity of two lines (10 letters) or more, but not changes of one line (five letters) or fewer; however, the reliability of ETDRS charts depends on the baseline visual acuity.[7] For macular edema, the FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with a greater than or equal to 15-letter change in visual acuity as clinically relevant outcome measures in trials of interventions.[34] The clinical expert consulted for this review highlighted the clinical relevance of a 10-letter change.

The primary end point in FAME-A and FAME-B was the proportion of patients with a greater than or equal to 15-letter increase from baseline in BCVA in their study eye at month 24. In the FAME trials, for each dose of FA that was clinically and statistically superior to sham at month 24, a numerical comparison was made to its corresponding month 18 result. If the proportion of patients with a 15-letter or greater improvement from baseline in BCVA at month 24 was equal to or greater than that observed at month 18, it was declared that clinical evidence of efficacy had been demonstrated for that dose.

The mean change from baseline in BCVA was a secondary efficacy end point in the FAME trials.

The mean change from baseline in the excess average foveal thickness assessed via OCT was another secondary efficacy end point in the FAME trials. The excess centre-point thickness was calculated by subtracting a value of 180 µm from the centre-point thickness for each patient; all negative values were set to zero. OCT is a validated, fast, non-invasive technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[35] In a previous meta-analysis analyzing the discriminatory power of foveal thickness for the diagnosis of DME, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of OCT were 0.81, 0.85, 5.4, and 0.22, respectively.[36] OCT is modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient-reported outcomes.[37,38] No minimal

clinically important difference (MCID) information on central retinal thickness changes measured by the OCT was identified.

Another secondary efficacy end point was the proportion of patients with greater than or equal to three-step worsening in the study eye compared with baseline in the ETDRS Multi-Step Eye Scale of diabetic retinopathy. This validated scale was developed to categorize the severity of diabetic retinopathy based on several fundus photographic characteristics and has become the reference standard for diabetic retinopathy grading in clinical trials.[39,40] There are 13 levels in the original ETDRS scale and a severity step or level increase is associated with an increased risk of retinopathy progression. The ETDRS Diabetic Retinopathy Severity Scale (DRSS) has a reported MCID of two steps of progression at one-year follow-up.[41] The FDA recommended the percentage of patients with a greater than or equal to three-step change at three years on the ETDRS DRSS as an outcome for diabetic retinopathy clinical trials.[42]

HRQoL (specific to vision-related function) was assessed using the 25-item Vision Function Questionnaire (VFQ-25) or the 39-item VFQ-39 for English-speaking patients. The VFQ was developed to measure vision-targeted quality of life.[43] The VFQ was reported to be a valid and reliable measure of HRQoL among patients with a wide range of eye conditions; however, recent studies have suggested that it may be more appropriately identified as a measure of visual functioning. The VFQ-25 has a reported MCID of between 3.3 points and 6.13 points for the overall composite score.[5] No validity information or MCID information on the VFQ-39 were identified from the literature.

Harms outcomes assessed included adverse events (AEs), severe adverse events (SAEs), withdrawal due to adverse events (WDAEs) and deaths.

Subgroup analysis based on baseline visual acuity was performed for primary and secondary end points. For the primary efficacy end point, additional subgroup analysis was performed based on baseline lens status (phakic, pseudophakic), duration of DME, and baseline glycated hemoglobin (A1C).

Statistical Analysis

In the FAME trials, the sample size was calculated based on the primary end point (proportion of patients with a greater than or equal to 15-letter increase from baseline in BCVA in their study eye at month 24). An estimated 400 patients were required to achieve 89% power and detect a 16% difference between the FA arm and the sham arm. To account for a dropout rate of approximately 10%, the sample size was increased to 450 patients. The power calculation was performed using the Pearson chi-square test for comparing two proportions (each FA dose group versus sham control). The Hochberg–Bonferroni multiple-comparison procedure was used to adjust for the comparison of two dose groups with the control. The calculation was based on the 2:2:1 randomization ratio for the 0.5 mcg/day FA implant, 0.2 mcg/day FA implant, and sham control. The 16% difference in the primary end point between the FA arm and the sham arm was derived from the results of a trial of DME patients who used a 0.59 mcg/day FA implant. The trial assumed that both the 0.2 mcg/day and 0.5 mcg/day FA implant would be equally effective.

The primary end point was analyzed using two pairwise comparisons to evaluate the between-treatment differences for each FA dose and the sham control arm. The pairwise comparisons were made using a Cochran–Mantel–Haenszel (CMH) chi-square test

stratified by the baseline visual acuity score in the study eye (less than or equal to 49 letters, greater than 49 letters) presented with 95% CIs. Multiple comparisons were accounted for using the Hochberg–Bonferroni correction. Sensitivity analyses for the primary end point were performed for an unstratified Pearson's chi-square test, and a CMH chi-square test stratified by baseline visual acuity and site. Missing data were imputed using last observation carried forward (LOCF) methodology. Sensitivity analyses were also performed for the primary end point based on alternative imputation methods: worst-case imputation (i.e., missing data were imputed by carrying forward the patient's worst value observed prior to the missing data), observed-case (i.e., no data imputation method was applied to missing data), and non-response imputation (i.e., values were imputed by setting all missing data as failures for the response variable of gaining 15 letters or more in ETDRS visual acuity).

Both the first secondary efficacy end point (the mean change from baseline in BCVA) and the second secondary efficacy end point (the mean change from baseline in the excess average foveal thickness) were assessed using an analysis of variance (ANOVA) model with treatment group and baseline visual acuity strata as fixed effects. The third secondary efficacy end point (the proportion of patients with greater than or equal to three-step worsening in the study eye compared with baseline in the ETDRS multi-step eye scale of diabetic retinopathy) was assessed with pairwise comparisons between-treatment groups using a CMH chi-square test stratified by baseline visual acuity strata in the study eye with 95% CIs. For secondary outcomes, missing data were imputed using LOCF methodology.

The analysis in the FAME trials was performed according to a pre-specified hierarchy to control the overall type I error. For each FA dose arm that was significantly superior (*P* value was greater than 0.0491) to the sham arm, the next end point was tested according to the following hierarchy:

- primary end point (the proportion of patients with a greater than or equal to 15-letter increase from baseline in BCVA in their study eye at month 24)
- first secondary end point (the mean change from baseline in BCVA at month 24)
- second secondary end point (the mean change from baseline in the excess average foveal thickness at month 24)
- third secondary end point (the proportion of patients with a greater than or equal to three-step worsening in the study eye compared with baseline in the ETDRS multi-step eye scale of diabetic retinopathy at month 24).

Multiple comparisons for the testing of the three treatment arms for the primary and secondary end points were accounted for using the Hochberg–Bonferroni correction. All other end points, including those pertaining to HRQoL (e.g., VFQ-25, VFQ-39), were not adjusted for multiplicity.

The efficacy results from time points other than month 24 (e.g., month 36) were meant to provide supportive evidence for the primary end point and were tested at a type I error rate of 0.050, although no claims of efficacy can be made at these time points.

Subgroup analysis was preplanned and included: baseline visual acuity (less than or equal to 49 letters versus greater than 49 letters), baseline lens status (phakic versus pseudophakic), duration of DME (less than the median or greater than or equal to the median), baseline A1C (less than the median or greater than or equal to the median). Subgroup analysis was not taken into account in the statistical analysis plan.

Analysis Populations

FAME-A and FAME-B included the following five analysis populations:

- The all-randomized population included all-randomized patients who received any study drug. Missing data were imputed using LOCF methodology.
- The intention-to-treat data set included all-randomized patients who received any study drug. For patients treated with disallowed therapy (e.g., anti-VEGFs, intravitreal steroids) for DME, the efficacy data after treatment with the disallowed therapy was set to missing. Missing data were imputed using LOCF methodology.
- The per-protocol (PP) data set included all-randomized patients who received any study drug. Data after use of disallowed therapies or significant protocol deviation were set to missing. Missing data were not imputed.
- The full analysis data set included all-randomized patients. Missing data were imputed using LOCF methodology. Approvals of the study drug in Europe and the US were based on this data set. The full analysis set was used for the primary analysis.
- The safety data set included all-randomized patients who received the initial injection and had at least one safety measurement. All data were used; missing data were not imputed.

Patient Disposition

Data for the number of patients screened for FAME-A and FAME-B were not available. In FAME-A, the proportion of patients who discontinued the trial were similar between the sham arm and the FA 0.2 mcg/day arm. In FAME-B, more patients discontinued in the sham arm ([redacted]%) compared with the FA 0.2 mcg/day arm ([redacted]%). The most common reasons for discontinuation were attributed to loss to follow-up, withdrawal of consent, and death. In FAME-A, [redacted] patients died, and in FAME-B, [redacted] patients died. Table 8 presents the patient disposition for the FAME trials.

Table 8: Patient Disposition

	FAME-A			FAME-B		
	Sham	FA 0.2 mcg/day	FA 0.5 mcg/day	Sham	FA 0.2 mcg/day	FA 0.5 mcg/day
Screened, N		[redacted]			[redacted]	
Randomized, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed study, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unsatisfactory therapeutic effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	FAME-A			FAME-B		
	Sham	FA 0.2 mcg/day	FA 0.5 mcg/day	Sham	FA 0.2 mcg/day	FA 0.5 mcg/day
Full Analysis, N	95	190	196	90	186	199
ITT, N	95	190	195	90	185	198
PP, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FA = fluocinolone acetonide; ITT = intention-to-treat; PP = per-protocol.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Exposure to Study Treatments

The study drug was administered as an implant that provided sustained delivery of FA. In FAME-A, the implant was removed by vitrectomy in one patient in the FA 0.2 mcg/day arm (due to IOP elevation). Two other patients underwent vitrectomy, but it was not confirmed if the implant was removed. In FAME-B, no patients had the implant removed.

Patients in both treatment arms were eligible for re-treatment with their assigned treatment after 12 months if they experienced vision loss (i.e., documented reduction of five or more letters in ETDRS visual acuity) or retinal thickening (i.e., OCT indicating a minimum increase of 50 µm at the centre of the fovea) compared with their best status during the previous 12 months. Over the 36-month period, [redacted]% of patients in the sham arm and [redacted]% in the FA 0.2 mcg arm in FAME-A were re-treated. In FAME-B, [redacted]% of patients in the sham arm and [redacted]% in the FA 0.2 mcg arm were re-treated.

Table 9: Patients Re-Treated With Sham or Fluocinolone Acetonide 0.2 mcg/day

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Re-treatments Administered[a]				
Number of treatments, n	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients receiving at least one re-treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Re-treatments Administered by Time Period, n (%)				
Month 12 to 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 15 to 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 18 to 21	[redacted]	[redacted]	[redacted]	[redacted]
Month 21 to 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 to 27	[redacted]	[redacted]	[redacted]	[redacted]
Month 27 to 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 30 to 33	[redacted]	[redacted]	[redacted]	[redacted]
Month 33 to 36	[redacted]	[redacted]	[redacted]	[redacted]

ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; OCT = optical coherence tomography.

[a] Patients were eligible for re-treatment after month 12 if they experienced vision loss (documented reduction of five or more letters in ETDRS visual acuity or retinal thickening per OCT) (minimum increase of 50 µm at the centre of the fovea) compared with their best status during the previous 12 months.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Critical Appraisal

Internal Validity

Baseline and demographic characteristics were generally well balanced across the treatment arms in both trials.

The FAME trials were conducted using double-masked methodology. The patients, assessing investigator, visual acuity assessor, and personnel involved in the monitoring and conduct of the studies were masked. To preserve masking in the trials, one investigator performed the treatments and another investigator performed the assessments. In both trials, masking methodology was reasonable, with steps taken to ensure the sham procedure was as similar to the FA implant procedure as possible. This helped protect against potential bias, particularly bias related to subjectivity in the assessment of the patients' HRQoL. The clinical expert consulted for this review described the method of masking as reasonable; however, a limitation with the methodology was identified: the patients who received the FA implant may have noticed a change in their vision (depicted as a new shadow or floater attributed to the implant), while those in the sham arm would not have any of these changes.

In the original protocol, patients were required to have undergone at least one macular laser treatment more than 12 weeks before the screening visit. This criterion was briefly amended (removed) in an effort to increase enrolment. It was later determined that removing the criterion could result in a significantly different response between the population without prior laser compared with those with prior laser. The amendment was applicable for approximately seven months and resulted in 12 patients in FAME-A and 21 patients in FAME-B who had not received prior treatment with laser; their presence in the trial created a subpopulation that was likely different from the patients who had received previous laser treatment, although the impact of this on the overall results is expected to be minimal.

Patients in both trials were permitted the use of laser in either the study or non-study eye at the discretion of the investigator. In both trials, more patients in the sham arms received treatment with laser compared with the FA 0.2 mcg arms (FAME-A: 67.1% versus 44.2%; FAME-B: 56.7% versus 38.7%). Use of non-approved treatments (e.g., ranibizumab) and systemic treatments for DME were discouraged; however, if non-approved therapy was deemed necessary, patients were permitted to continue in the study. In both trials, more patients in the sham arms received disallowed treatments (e.g., intravitreal steroids, anti-VEGFs) for DME compared with the FA 0.2 mcg arms. In particular, anti-VEGF was used by 16.8% of patients in the sham arm compared with 2.6% in the FA 0.2 mcg arm in the FAME-A trial, and 12.2% of patients in the sham arm compared with 3.8% in the FA 0.2 mcg arm in FAME-B. Intravitreal steroids were used by 18.9% of patients in the sham arm compared with 9.5% of patients in the FA 0.2 mcg arm in FAME-A. Similarly, in FAME-B, this percentage was 22.2% for patients in the sham arm and 5.9% for patients in the FA 0.2 mcg arm. The differential use of laser and disallowed DME treatments could have biased the efficacy findings against FA, potentially leading to an underestimate of treatment effect.

For the primary end point, 26.3% of patients in the sham arm and 22.6% of patients in the FA 0.2 mcg arm had missing data in FAME-A. In FAME-B, 28.9% of patients in the sham arm and 24.7% of patients in the FA 0.2 mcg arm had missing data. Relevant sensitivity analyses were performed for the primary end point based on alternative imputation

methods: worst-case imputation, observed-case, and non-response imputation. For the primary and three secondary end points, an analysis was performed using the PP population. Overall, these analyses corroborated the findings of the primary analysis on BCVA but also revealed high variation, including inconsistency of the PP analysis findings (statistically non-significant), which signals the modest quality of the trial data (i.e., a substantial proportion of patients were excluded from the PP analysis).

In both trials, more patients in the sham arm discontinued the trial compared with patients in the FA 0.2 mcg/day arm. In FAME-A, 29.5% of patients in the sham arm compared with 25.8% of patients in the FA 0.2 mcg arm discontinued the trial. In FAME-B, 34.4% of patients in the sham arm compared with 28.5% of patients in the FA 0.2 mcg arm discontinued the trial. Lost to follow-up was the leading cause of discontinuations and was particularly notable in FAME-B (16.7% in the sham arm compared with 12.4% in the FA 0.2 mcg arm), followed by patients who withdrew consent and death. The exact reasons for the patients who withdrew or were lost to follow-up remains unknown. AEs or unsatisfactory therapeutic effect represented 5.3% of patients in the sham arm compared with 1.1% of the FA 0.2 mcg arm in FAME-A, and 3.3% of patients in the sham arm compared with 1.1% of patients in the FA 0.2 mcg arm in FAME-B. The high proportion of discontinuation in both trials may have compromised the assessment of treatment effect at 24 and 36 months.

Missing data were imputed using LOCF methodology. This method of imputation may be problematic, as it assumes data are missing at random and that the efficacy will remain constant over time (e.g., patients' condition does not worsen). Given DME is a progressive disease, such a method is likely conservative and would tend not to overestimate the treatment effect.

A total of 28.9% and 22.0% of patients in the FA arm and FAME-A and FAME-B, respectively, were re-treated due to treatment failure (i.e., reduction of five or more letters in ETDRS visual acuity or an OCT measurement of retinal thickening showing a minimum increase of 50 µm at the centre of the fovea) after 12 months (Table 9). Re-treatment of sham in the sham arm would not generate any treatment effect for the patients, whereas re-treatment of patients in the FA arm (doubled dose) may have benefited at least a proportion of the patients who did not show any treatment effect with the initial FA implant at 12 months. Therefore, it is likely that re-treatment with FA may have attributed additional treatment effect and therefore biased the assessment of a single dose of 0.19 mg FA at 36 months (designed to release 0.2 mcg FA per day). The re-treatment of nearly 25% of patients in both trials after 12 months in combination with laser treatment and/or use of intravitreal steroid (FAME-A: 67.1% versus 44.2%; FAME-B: 56.7% versus 38.7%, sham versus FA 0.2 mcg, respectively), complicated the efficacy assessment of FA treatment with the effect from other additional alternative treatments. In other words, the treatment effect of FA as observed in both trials was likely a result of a combination of re-treatment and/or an additional use of laser treatment or intravitreal steroid, especially among those patients whose condition was refractory to FA treatment, if such treatment was deemed necessary by the investigator.

External Validity

The demographic characteristics of patients included in the FAME trials generally reflected the Canadian clinical population. FAME-A included patients from five Canadian sites. The mean age of patients ranged from 61.1 years to 64.0 years with a mean duration of DME of 3.3 years to 4.4 years. The mean duration of diabetes was between 16.3 years and 17.4 years. The clinical expert consulted for this review noted that the population studied was older than what is seen in clinic and had disease durations applicable to an older population.

Both the FAME-A and FAME-B studies had relatively stringent inclusion and exclusion criteria for patient enrolment, even though they were similar to other DME trials. Such restrictions compromised the generalizability of findings to those who were not studied in these trials. For example, only patients with a baseline BCVA of 19 to 68 letters and a mean foveal thickness of at least 250 µm measured by OCT were eligible to participate in the trials. Patients were excluded from the trials if they had laser treatment for DME or any ocular surgery in the study eye within 12 weeks of screening. Patients with a history of uncontrolled IOP elevation with steroid use that did not respond to topical therapy were excluded, although these patients would not be eligible for treatment with corticosteroids in clinical practice. Patients with glaucoma, ocular hypertension, IOP greater than 21 mm Hg, or concurrent therapy at screening with IOP-lowering drugs in the study eye were excluded from the trials. Patients with a resting systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 105 mm Hg at the screening visit were excluded from the trials. Therefore, the study population included in both trials was highly selective and may represent a treatment population that was more likely to respond to the treatment and was not at an increased risk of potential treatment-related AEs, including comorbidities, which rendered the benefit–harm profile to be more optimal than what could be seen in real-world clinical practice.

The population in the trials included almost all patients previously treated with laser, with relatively few patients previously treated with intravitreal anti-VEGF treatment. According to the clinical expert, the proportion of patients treated with anti-VEGF treatment compared with steroids was not consistent with the Canadian population. In Canada, it is expected that clinicians would see a greater proportion of patients with previous intravitreal anti-VEGF treatment compared with steroids, as anti-VEGF is considered first-line therapy because AEs are associated with steroid use. Thus, prior treatment experience may limit generalizability to the Canadian patient population.

The trials used sham intervention as the comparator for FA. The use of a sham intervention instead of an active comparator limits the ability to make comparisons with other treatments indicated for DME.

The subgroups analyzed in the FAME studies were based on baseline visual acuity, baseline lens status, duration of DME, and baseline A1C. The analyses were performed for the primary efficacy end point (the proportion of patients with a greater than or equal to 15-letter increase from baseline in BCVA in their study eye at month 24) and were deemed clinically relevant by the clinical expert consulted for this review.

The FAME trials based several efficacy end points on visual acuity, which is consistent with clinical practice in Canada. Although efficacy data were collected up to month 36, the trials were designed to assess the end points at month 24. The clinical expert consulted for the review indicated that the duration of the trials was sufficient to determine the efficacy of FA.

Data from a 12-month safety extension study were also available. The FAME trials used an FA implant that was not consistent with the FA implant marketed for use in Canada; the extension study was conducted using the FA implant consistent with market use in Canada. No new safety signals emerged over the course of the extension study that used the commercially available injector to administer the implant.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. Blindness was also identified as an outcome in the protocol but was not measured in either of the FAME studies. See Appendix 3 for detailed efficacy data.

Best-Corrected Visual Acuity

In both FAME trials, at month 24 the difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA was statistically significantly greater in the FA 0.2 mcg/day arm compared with the sham arm (FAME-A: difference = −12.1%, 95% confidence interval [CI], −21.6% to −2.6%, *P* = 0.029; FAME-B: difference = −12.9%, 95% CI, −23.2% to −2.6%, *P* = 0.030) (Table 10). Similar findings in favour of treatment with FA 0.2 mcg/day were reported at month 36. Results at month 24 for the PP population are reported in Appendix 3 (Table 18), where a similar pattern of change was observed in both trials (FAME-A: difference = −14.2%, 95% CI, −27.6% to −0.9%; FAME-B: difference = −20.9 (−35.0 to −6.8).

At month 24, the difference in the proportion of patients with an increase from baseline of 10 or more letters in BCVA was −7.9 % (95% CI, −19.3% to 3.5%) in FAME-A, and −15.9% (95% CI, −27.2% to −4.5%) in FAME-B (Table 10). Similar findings were reported at month 36. Statistical testing for this outcome was outside of the statistical hierarchy.

The difference in mean change in BCVA letter score at month 24 was statistically significant and in favour of treatment with FA 0.2 mcg/day compared with sham in the FAME-B trial. The difference in the FAME-A trial, however, was not statistically significant (FAME-A: difference = −1.8 letters, 95% CI, −6.3 to 2.8, *P* = 0.444; FAME-B: difference = −6.1 letters, 95% CI, −10.8 to −1.4, *P* = 0.011) (Table 10). Similar findings were reported at month 36. Results for the PP population are reported in Appendix 3 (Table 18) and show no difference associated with mean change in BCVA letter score between-treatment arms at month 24.

Results for BCVA letter score by five-letter increments are reported in Appendix 3, Table 17.

Early Treatment Diabetic Retinopathy Study Multi-Step Eye Scale of Diabetic Retinopathy

In both FAME trials, at month 24 the proportion of patients with a worsening from baseline of three or more steps in the ETDRS multi-step eye scale of diabetic retinopathy did not show a difference between-treatment arms for FA 0.2 mcg/day compared with sham (FAME-A: difference = −1.7%, 95% CI, −3.5% to 0.2%, *P* = 0.216; FAME-B: difference = 0.0%, 95% CI, −2.7% to 2.7%, *P* = 0.964) (Table 10). Based on the pre-specified hierarchy for statistical testing, statistical findings cannot be confirmed for this outcome for either FAME study, as previous outcomes tested in the hierarchy did not achieve statistical

significance. Similar findings were reported at month 36 and for the PP population at month 24 (Table 18).

Visual Function Questionnaire

In both FAME trials, the VFQ-39 change from baseline at month 24 was not different between-treatment arms for FA 0.2 mcg/day compared with sham (FAME-A: difference = 0.5, 95% CI, −4.0 to 4.9; FAME-B: difference = −2.5, 95% CI, −7.5 to 2.5) (Table 10). Similar findings were reported at month 36.

Similar results were reported for the VFQ-25. In the FAME trials, the VFQ-25 change from baseline at month 24 was not different between-treatment arms for FA 0.2 mcg/day compared with sham (FAME-A: difference = −0.0; 95% CI, −4.5 to 4.5; FAME-B: difference = −0.9; 95% CI, −6.1 to 4.3) (Table 10). Similar findings were reported at month 36.

The VFQ end points were not accounted for in the statistical hierarchy.

Excess Centre-Point Thickness

Results of the difference between FA 0.2 mcg/day compared with sham in mean change in excess centre-point thickness at month 24 were not consistent between FAME-A and FAME-B. In FAME-A, the difference was 77.4 µm (95% CI, 25.1 µm to 129.6 µm, $P = 0.004$). In FAME-B, the difference was 0.9 µm (95% CI, −5.1 µm to 6.9 µm, $P = 0.222$) (Table 10). Statistical findings cannot be confirmed for this outcome for FAME-A, as an outcome previously tested in the statistical hierarchy did not achieve statistical significance. Similar findings were reported at month 36 and for the PP population at month 24 (Table 18).

Efficacy Outcomes by Subgroup

Best-Corrected Visual Acuity

Table 13 in Appendix 3 presents the difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA at month 24 for the following subgroups: baseline visual acuity, baseline lens status, duration of DME, baseline A1C.

The difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by subgroup for baseline visual acuity (fewer than or equal to 49 letters versus greater than 49 letters) showed inconsistent results between trials.

The difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by baseline lens status were consistently greater in the pseudophakic subgroup compared with the phakic subgroup.

The difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by subgroup for duration of DME (less than the median or greater than or equal to the median) showed inconsistent results between the trials.

The difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by baseline A1C status (less than the median or greater than or equal to the median) showed inconsistent results between trials.

The mean change from baseline BCVA letter score was assessed using subgroups for visual acuity. The difference in the mean BCVA letter score was consistently greater in patients with a baseline visual acuity of less than or equal to 49 letters.

ETDRS Multi-Step Eye Scale of Diabetic Retinopathy

Table 15 in Appendix 3 presents data on the proportion of patients with a worsening from baseline of three or more steps in the ETDRS multi-step eye scale of diabetic retinopathy by baseline visual acuity at month 24. In both trials, no numerical difference was observed between the FA 0.2 mcg/day arm versus the sham arm, regardless of baseline BCVA (fewer than or equal to 49 letters; greater than 49 letters).

Excess Centre-Point Thickness

Table 16 presents the difference in the mean change from baseline in excess centre-point macular thickness by baseline visual acuity at month 24. The difference in mean change from baseline in excess centre-point macular thickness by subgroup for baseline visual acuity (fewer than or equal to 49 letters versus greater than 49 letters) showed inconsistent results between trials.

Table 10: Efficacy Outcomes (Full Analysis Population)

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Proportion of Patients With an Increase From Baseline of 15 or More Letters in BCVA				
Month 24				
n (%)	14 (14.7%)	51 (26.8%)	16 (17.8%)	57 (30.6%)
Difference (95% CI)	−12.1% (−21.6 to −2.6)		−12.9% (−23.2 to −2.6)	
P value[a]	0.029		0.030	
Month 36				
n (%)	18 (18.9%)	54 (28.4%)	17 (18.9%)	54 (29.0%)
Difference (95% CI)	−9.5% (−19.6 to 0.7)		−10.1% (−20.5 to 0.2)	
P value[a]	0.106		0.086	
Proportion of Patients With an Increase From Baseline of 10 or More Letters in BCVA				
Month 24				
n (%)	[redacted]		[redacted]	
Difference (95% CI)	[redacted]		[redacted]	
P value[a]	[redacted]		[redacted]	
Month 36				
n (%)	[redacted]		[redacted]	
Difference (95% CI)	[redacted]		[redacted]	
P value[a]	[redacted]		[redacted]	
BCVA Letter Score				
Baseline				
Mean (SD)	54.8 (11.36)	53.4 (13.00)	54.7 (11.23)	53.3 (12.39)
Month 24				
Mean change (SD)	3.2 (13.07)	3.7 (18.74)	0.0 (15.62)	5.1 (17.95)
Difference estimate (95% CI)	−1.8 (−6.3 to 2.8)		−6.1 (−10.8 to −1.4)	
P value[b]	[redacted]		[redacted]	

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Month 36				
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Proportion of Patients With a Worsening From Baseline of Three Steps or More in the ETDRS Multi-Step Eye Scale of Diabetic Retinopathy				
Month 24				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value[a]	[redacted]		[redacted]	
Month 36				
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value[a]	[redacted]		[redacted]	
VFQ-39 Overall				
Baseline				
Number of observations at baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
Number of observations at month 24, n	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 24, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value[c]	[redacted]		[redacted]	
Month 36				
Number of observations at month 36, n	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 36, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value[c]	[redacted]		[redacted]	
VFQ-25 Overall				
Baseline				
Number of observations at baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
Number of observations at month 24, n	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 24, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value[c]	[redacted]		[redacted]	
Month 36				
Number of observations at month 36, n	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 36, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value[c]	[redacted]		[redacted]	

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Excess Centre-Point Thickness (in Micrometres)				
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	
P value[d]	[redacted]		[redacted]	
Month 36				
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	
P value[d]	[redacted]		[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; SD = standard deviation; VFQ-25 = 25-item Visual Function Questionnaire; VFQ-39 = 39-item Visual Function Questionnaire.

Note: Excess centre-point thickness calculated by subtracting a value of 180 µm from the centre-point thickness for each patient; all negative values were set to zero.

[a] *P* value based on a Cochran–Mantel–Haenszel chi-square test stratified by baseline visual acuity.

[b] The between-treatment difference, 95% CI, and *P* value are based on an analysis of variance model with treatment and baseline visual acuity strata as fixed effects.

[c] [redacted]

[d] [redacted]

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Harms

Table 11 contains detailed harms data for the FAME trials.

Adverse Events

In FAME-A, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an AE (Table 11). In FAME-B, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an AE.

Ocular AEs in the study eye occurred more frequently in the FA 0.2 mcg/day arm in both trials. In FAME-A, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an ocular AE in the study eye. Similarly, in FAME-B, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an ocular AE in the study eye. The most common ocular AEs in the study eye were related to cataracts and cataract operation, which affected more patients in the FA 0.2 mcg/day arm than in the sham arm in both trials. Similarly, an increase in IOP affected more patients in the FA 0.2 mcg/day arm than in the sham arm in both trials.

Systemic AEs were reported in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A. In FAME-B, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced a systemic AE. The most commonly reported systemic AE was related to eye disorders, which was reported more often in patients treated with FA 0.2 mcg/day. In FAME-A, eye disorders were reported by

[redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-B, eye disorders were reported by [redacted]% patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Serious Adverse Events

In the FAME trials, more patients in the FA 0.2 mcg/day arm reported SAEs than in the sham arm (Table 11). In FAME-A, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an SAE. In FAME-B, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an SAE.

Ocular SAEs in the study eye occurred more frequently in the FA 0.2 mcg/day arm in both trials. In FAME-A, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an ocular SAE in the study eye. In FAME-B, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an ocular SAE in the study eye. The most common ocular SAEs in the study eye were related to cataract operations, which affected more patients in the FA 0.2 mcg/day arm than in the sham arm in both trials.

Withdrawal Due to Adverse Events

In FAME-A, WDAEs occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm (Table 11). Conversely, in FAME-B, WDAEs occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. The most common WDAEs were attributed to cardiac arrest, cardiac failure, and myocardial infarction; however, no clear pattern emerged in either treatment arm in either trial.

Mortality

In FAME-A, [redacted] patients ([redacted]%) in the sham arm and [redacted] patients ([redacted]%) in the FA 0.2 mcg/day arm died (Table 11). In FAME-B, [redacted] patients ([redacted]%) in the sham arm and [redacted] patients ([redacted]%) in the FA 0.2 mcg/day arm died. No more than two deaths per treatment arm occurred in any single category in either trial. In FAME-B, [redacted] patients ([redacted]%) in the sham arm and [redacted] patients ([redacted]%) in the FA 0.2 mcg/day arm had deaths attributed to myocardial infarction. No deaths in FAME-A were attributed to myocardial infarction.

Notable Harms

Notable harms identified in the protocol for this review included the following: cataract formation, endophthalmitis, eye inflammation, eye infections, retinal tear, retinal detachment, increased IOP, arterial thrombotic event, glaucoma, surgical intervention for glaucoma treatment, damage to optic nerve, defects in visual acuity and visual field, necrotizing retinitis, conjunctival hemorrhage, and vitreous hemorrhage.

In the FAME trials, cataracts, endophthalmitis, eye infections, retinal tears, increased IOP, glaucoma, and vitreous hemorrhages were reported more often in patients in the FA0.2 mcg/day arm compared with the sham arm (Table 11). The frequency of eye inflammation, retinal detachment, optic nerve disorder, reduced visual acuity, and visual field defect were similar between-treatment arms.

In FAME-A, cataracts occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-B, cataracts occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Endophthalmitis occurred in [redacted] patients in the sham arm in both trials and [redacted]% and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A and FAME-B, respectively.

Eye inflammation occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A. In FAME-B, eye inflammation occurred in [redacted] patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Eye infections occurred in [redacted] patients in the sham arm in both trials and [redacted]% and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A and FAME-B, respectively.

Retinal tears occurred in [redacted] patients in the sham arm in both trials and [redacted]% and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A and FAME-B, respectively.

In FAME-A, increased IOP occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-B, increased IOP occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Glaucoma occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A. In FAME-B, glaucoma occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Surgical interventions for glaucoma occurred in [redacted] patients in the sham arm in both trials and [redacted]% and [redacted]% of patients in the FA 0.2 mcg/day arm in FAME-A and FAME-B, respectively.

Optic nerve disorders occurred in [redacted]% of patients in the sham arm and [redacted] patients in the FA 0.2 mcg/day arm. In FAME-B, optic nerve disorders occurred in [redacted] patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

A reduction in visual acuity was reported in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-B, a reduction in visual acuity was reported in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Visual field defects occurred in [redacted]% of patients in the sham arm and [redacted] patients in the FA 0.2 mcg/day arm. In FAME-B, visual field defects occurred in [redacted] patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Conjunctival hemorrhages occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-B, conjunctival hemorrhages occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Vitreous hemorrhages occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-B, vitreous hemorrhages occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm.

Table 11: Harms (Safety Population)

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 95)	FA 0.2 mcg/day (N = 190)
AEs				
Patients with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 ocular AEs in study eye, N (%)	[redacted]	[redacted]	[redacted]	[redacted]

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 95)	FA 0.2 mcg/day (N = 190)
Patients with > 0 ocular AEs in non-study eye, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 systemic AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Ocular AEs (Study Eye)				
Most Common AEs[a]				
Cataract	[redacted]	[redacted]	[redacted]	[redacted]
Cataract operation	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]	[redacted]
Myodesopsia	[redacted]	[redacted]	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 ocular SAEs in study eye, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 ocular SAEs in non-study eye, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 systemic SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Ocular SAEs (Study Eye)[b]				
Cataract operation	[redacted]	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Glaucoma surgery	[redacted]	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]	[redacted]	[redacted]
Trabeculectomy	[redacted]	[redacted]	[redacted]	[redacted]
Trabeculoplasty	[redacted]	[redacted]	[redacted]	[redacted]
Vitrectomy	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Systemic SAEs[b]				
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Convulsion	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]	[redacted]	[redacted]
Femoral neck fracture	[redacted]	[redacted]	[redacted]	[redacted]
Gangrene	[redacted]	[redacted]	[redacted]	[redacted]
Hip fracture	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 95)	FA 0.2 mcg/day (N = 190)
WDAEs				
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most Common Reasons				
Cardiac arrest	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
Number of Deaths, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms				
Study Eye				
Cataract	[redacted]	[redacted]	[redacted]	[redacted]
Endophthalmitis	[redacted]	[redacted]	[redacted]	[redacted]
Eye inflammation	[redacted]	[redacted]	[redacted]	[redacted]
Eye infections	[redacted]	[redacted]	[redacted]	[redacted]
Retinal tear	[redacted]	[redacted]	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]	[redacted]	[redacted]
Increased intraocular pressure	[redacted]	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]	[redacted]
Surgical intervention for glaucoma treatment	[redacted]	[redacted]	[redacted]	[redacted]
Optic nerve disorder	[redacted]	[redacted]	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]	[redacted]
Visual field defect	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Necrotizing retinitis	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; FA = fluocinolone acetonide; SAE = severe adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 10%.

[b] Frequency ≥ 2%.

Note: Safety population.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Discussion

Summary of Available Evidence

Two identically designed, phase III RCTs were included in this CDR review. FAME-A (N = 481) and FAME-B (N = 475) were 36-month, multi-centre, double-masked, parallel-group, sham-controlled, RCTs conducted in adult patients with DME who had at least one macular laser treatment more than 12 weeks before the screening visit. Patients were randomized in a 2:2:1 ratio for treatment with a 0.2 mcg/day FA implant, 0.5 mcg/day FA implant, or sham injection, respectively. Randomization was stratified by site and baseline visual acuity (fewer than or equal to 49 letters or greater than 49 letters). The primary objective of both trials was to determine if either dose level of the FA intravitreal implant (daily release rate of 0.2 mcg or 0.5 mcg) was superior to sham injection with respect to the proportion of patients with a greater than or equal to 15-letter increase in BCVA at month 24 compared with baseline. Subgroup analyses were based on baseline visual acuity, baseline lens status, duration of DME, and baseline A1C. Only the 0.2 mcg/day FA implant is approved by Health Canada and is the focus of this review; data for the 0.5 mcg/day FA implant is not presented.

Key limitations of the FAME trials included generalizability issues related to the baseline characteristics of the included patients (e.g., use of prior medications not consistent with the Canadian clinical population), differential trial discontinuation, and the lack of evidence comparing FA 0.2 mcg/day with other treatments used for DME in Canada. The manufacturer-submitted indirect treatment comparison (ITC) in this report (Appendix 6) summarized the indirect evidence comparing FA with other treatments for DME. The outcomes evaluated in this analysis included [redacted].

Interpretation of Results

Efficacy

Based on the primary outcome (the difference in the proportion of patients with an increase from baseline of 15 or more letters in BCVA), treatment with FA 0.2 mcg/day showed statistically and clinically significant improvement compared with sham in both trials at month 24. The criterion of a 15-letter or more improvement is consistent with recommendations from the FDA. Testing the difference in the proportion of patients with an increase from baseline using a criterion of 10 letters or more in BCVA was identified as clinically relevant in the literature and by the clinical expert consulted in this review. At month 24, an improvement in the 10-letter end point was observed for FA 0.2 mcg/day compared with sham (based on 95% CI) in the FAME-B study but not in FAME-A; however, this outcome measure was outside of the statistical hierarchy. Visual acuity was also assessed based on the mean change from baseline in BCVA letter score. Results for this outcome were inconsistent between trials; in FAME-B, patients who received the 0.2 mcg/day implant exhibited a statistically significant improvement (difference = −6.1 letters, 95% CI, −10.8 to −1.4, $P = 0.011$), while this effect was not observed in the FAME-A study (difference = −1.8 letters, 95% CI, −6.3 to 2.8, $P = 0.444$). The other visual

acuity–based outcome for mean change in BCVA letter score did not show a clinically meaningful improvement associated with FA 0.2 mcg/day compared with sham treatment.

According to the clinical expert consulted for this review, an improvement in visual acuity is key in determining a clinically meaningfully response to treatment in patients with DME; this was echoed by the patient groups that provided input for this review. In both trials, the mean proportion of patients who experienced a 15-letter or more improvement in BCVA at month 24 was 12%; this improvement was observed in even fewer patients at month 36 (approximately 8% to 9%). Using a lower criterion of 10 letters as a cut point, the percentage of patients who experienced clinical meaningful improvements was inconsistent between trials.

Several subgroup analyses were performed in the FAME trials. The differences in the proportion of patients with an increase from baseline of 15 or more letters in BCVA by baseline lens status were consistently greater in the pseudophakic subgroup compared with the phakic subgroup. Results by other subgroups were inconsistent between trials. The difference in the mean BCVA letter score was consistently greater in patients with a baseline visual acuity of fewer than or equal to 49 letters. These subgroup analyses showed that the treatment effect on visual acuity was likely more evident in patients with poorer visual acuity at baseline or patients who were pseudophakic; however, further study is needed to confirm the effect due to the exploratory nature of the subgroup analyses.

The proportion of patients with a worsening from baseline of three or more steps in the ETDRS multi-step eye scale of diabetic retinopathy was less than 3% in the FA arm and not different from the sham arm. There was no consistent improvement in mean change in excess centre-point thickness in favour for treatment with FA 0.2 mcg/day compared with sham across the two trials. The ETDRS multi-step eye scale of diabetic retinopathy has a reported MCID of two steps of progression at one-year follow-up and the three-step criteria is consistent with FDA recommendations.

The visual-function outcomes (VFQ-25 and VFQ-39) showed no difference in change from baseline to month 24 between-treatment arms for FA 0.2 mcg/day compared with sham. However, visual-function and HRQoL outcomes were identified as important, based on patient input provided for this review.

The outcomes investigated in the FAME trials were designed to be statistically tested for efficacy at month 24. This limits the ability to draw conclusions for the efficacy of FA mcg/day at month 36, which would be useful, as the Health Canada indication states the FA implant is designed to release the drug over the course of 36 months.

The generalizability of the efficacy findings from the FAME trials to Canadian patients with DME is questionable. The baseline characteristics of the study population regarding prior use of DME therapies observed in the trials is inconsistent with the treatment history of Canadian patients with DME. According to the clinical expert, the proportion of patients who received anti-VEGF treatment compared with steroids was not consistent with the Canadian population. In Canada, one would expect to see a greater proportion of patients with previous intravitreal anti-VEGF treatment compared with steroids, as anti-VEGF is considered first-line therapy due to the AEs associated with steroid use. However, in the FAME trials, less than 10% of patients had previously received treatment with intravitreal anti-VEGF drugs, and approximately 20% of patients had received prior treatment with intravitreal steroids. The prior treatment received by patients in the trial may limit the generalizability of the study population to the Canadian clinical population, although it

should be noted that the studies were conducted in 2005 and the availability of therapeutics for DME differed compared with what is currently available for Canadians.

During the FAME trials, the use of laser was permitted in either eye (study or non-study) for all patients if the eye showed no improvement in edema compared with baseline. The decision to use laser was at the discretion of the investigator. In both trials, more patients in the sham arms (FAME-A = 67.4%; FAME-B = 56.7%) received treatment with laser compared with the FA 0.2 mcg arms (FAME-A = 44.2%; FAME-B = 38.7%). The differential use of these therapies could artificially inflate the efficacy findings for the sham arm and bias the results against FA, and the high use of laser in the FA arm could introduce confounds and complicate the interpretation of the efficacy of FA.

Use of non-approved treatments for DME (e.g., ranibizumab) and systemic treatments for DME were discouraged; however, if deemed necessary, patients who had such treatments were permitted to continue in the study. In both trials, more patients in the sham arms (FAME-A = 34.7%; FAME-B = 31.1%) received disallowed treatments for DME (intravitreal steroids, posterior sub-Tenon's steroids, anti-VEGF therapy, vitrectomies) compared with the FA 0.2 mcg arms (FAME-A = 18.9%; FAME-B = 11.3%). The high use of disallowed treatments for DME could introduce confounds and complicate the interpretation of the efficacy of FA.

In the FAME trials, patients in either arm were eligible for re-treatment with their assigned treatment after 12 months if they experienced vision loss (i.e., documented reduction of five or more letters in ETDRS visual acuity) or retinal thickening (i.e., a minimum increase of 50 µm at the centre of the fovea as measured by OCT) compared with their best status during the previous 12 months. While more patients in the sham arm were re-treated (with sham procedure) compared with the FA arm (re-treated with an additional FA 0.2 mcg implant), approximately one-quarter of patients in the FA arm received an additional implant after 12 months. However, there is limited evidence on patients who received more than two treatments with FA implants, and the total number of devices that can be implanted in the eye remains unknown. Additionally, there is no evidence on patients treated with FA in both eyes simultaneously.

The trials used sham intervention as the comparator for FA. The sham procedure was designed to be as similar to the FA procedure as possible. The sham procedure consisted of patient prep that was similar to that used for those with the FA implant, which was followed by pressing the hub of a needless syringe against the sclera of the eye with approximately the same pressure as for an injection of an implant, followed by a prescription for a topical antibiotic. The clinical expert consulted for this review described the method of masking as reasonable; however, the expert identified a limitation with the methodology: the patients who received the FA implant would likely have noticed a change in their vision depicted as a new shadow or floater attributed to the implant, while those in the sham arm would not likely observe such changes.

The use of a sham intervention instead of an active comparator limits the ability to make comparisons with other treatments indicated for DME. A manufacturer-submitted ITC comparing FA with other treatments for DME was reviewed and critically appraised. Findings from the ITC indicate that treatment with [redacted]

[redacted].

Harms

AEs were reported by most patients. In FAME-A, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an AE. Similarly, [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm experienced an AE in FAME-B. Most AEs were ocular-related; these occurred more frequently in the FA 0.2 mcg/day arm in both trials. The most common ocular AEs in the study eye were related to cataracts, cataract operation, and an increase in IOP, which affected more patients in the FA 0.2 mcg/day arm compared with the sham arm in both trials. Similarly, ocular SAEs in the study eye occurred more frequently in the FA 0.2 mcg/day arm in both trials and were most commonly related to cataract operations. In both FAME trials, the following notable harms were reported more often in patients in the FA 0.2 mcg/day arm compared with the sham arm: cataracts, endophthalmitis, eye infections, retinal tears, increased IOP, and glaucoma.

In FAME-A, WDAEs occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. Conversely, in FAME-B, WDAEs occurred in [redacted]% of patients in the sham arm and [redacted]% of patients in the FA 0.2 mcg/day arm. In FAME-A, [redacted] patients ([redacted]%) in the sham arm and [redacted] patients ([redacted]%) in the FA 0.2 mcg/day arm died. In FAME-B, [redacted] patients ([redacted]%) in the sham arm and [redacted] patients ([redacted]%) in the FA 0.2 mcg/day arm died. No more than two deaths per treatment arm occurred in any single category.

In the FAME extension study, the safety profile of the commercially available FA implant was assessed in patients with DME. [redacted] In a 12-month follow-up post-FA treatment, [redacted]

The manufacturer-submitted ITC comparing FA with other treatments for DME [redacted]

Conclusions

In two identically designed phase III RCTs in adult patients with DME, treatment with an intravitreal implant containing 0.19 mg FA with a daily release of 0.2 mcg FA demonstrated a difference of approximately 12% in the proportion of patients with an increase from baseline of 15 or more letters in BCVA compared with sham at month 24. While clinical and statistical significance was achieved using this outcome, other visual acuity assessments for mean change in BCVA letter score do not show a substantive clinically meaningful improvement.

The considerable use of re-treatments with the FA implant over the study period, including use of laser and use of disallowed treatments for DME, may confound the assessment of the treatment effect of the FA implant.

The generalizability of the study findings to the Canadian population is questionable, as the clinical expert consulted for this review identified differences regarding prior use of therapies for DME (namely VEGF inhibitors) between the study population in the FAME trials and the Canadian clinical population.

While it is recognized that the 0.19 mg FA implant provides the convenience of relatively fewer injections for patients, the safety profiles in terms of eye-related complications were less favourable for FA 0.2 mcg/day compared with sham in the FAME-A and FAME-B trials. Most notably, patients treated with FA 0.2 mcg/day experienced more AEs related to cataracts and increased IOP.

Findings from the ITC indicate treatment with [redacted].

Appendix 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 2, 2109
Alerts:	Weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CDSR and DARE)
.pt	Publication type
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. exp fluocinolone acetonide/
2. iluvien*.ti,ab,kf,ot,rn,nm.
3. (fluocinolon* or flucinolon* or 0CD5FD6S2M).ti,ab,ot,rn,nm,kf.
4. (((macula* or fovea* or retina* or luteal* or interretina*) adj2 (edema* or oedema* or dystroph*)) or dme or dmo).ti,ab,kf.
5. exp macular edema/
6. exp diabetic retinopathy/
7. 1 or 3
8. 4 or 5 or 6

MULTI-DATABASE STRATEGY
9. 7 and 8
10. 2 or 9
11. 10 use medall
12. *fluocinolone acetonide/
13. iluvien*.ti,ab,dq,kw.
14. (fluocinolon* or flucinolon*).ti,ab,kw,dq.
15. exp macular edema/
16. (((macula* or fovea* or retina* or luteal* or interretina*) adj2 (edema* or oedema* or dystroph*)) or dme or dmo).ti,ab,kw.
17. exp diabetic retinopathy/
18. 12 or 14
19. 15 or 16 or 17
20. 18 and 19
21. 13 or 20
22. 21 use oemezd
23. 11 or 22
24. conference abstract.pt. 25. 23 NOT 24 26. Remove duplicates

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies with results | (fluocinolone OR Iluvien*) AND diabetic macular edema]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.

Grey Literature

Dates for Search:	May 26 to 29, 2019
Keywords:	Fluocinolone, Iluvien, diabetic macular edema
Limits:	No limits used.

Relevant websites from the following sections of the CADTH grey literature checklist, Grey matters: a practical tool for evidence-based searching (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines

- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Excluded Studies

Table 12: Excluded Studies

Reference	Reason for Exclusion
Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multi-centre, randomized, controlled clinical trial. *Ophthalmology*. 2011;118(8):1580-1587. [44]	Intervention not identified in the CDR review protocol.

CDR = CADTH Common Drug Review.

Appendix 3: Detailed Outcome Data

Table 13: Proportion of Patients With an Increase From Baseline of 15 or More Letters in Best-Corrected Visual Acuity by Subgroup (Full Analysis Population)

Outcome	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Proportion of Patients With an Increase From Baseline of 15 or More Letters in BCVA				
Baseline Visual Acuity at Month 24				
≤ 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
> 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
Baseline Lens Status at Month 24				
Phakic, N	61	124	60	112
Responders, n (%)	11 (18.0%)	37 (29.8%)	11 (18.3%)	32 (28.6%)
Pseudophakic, N	34	66	30	74
Responders, n (%)	3 (8.8%)	14 (21.2%)	5 (16.7%)	25 (33.8%)
Duration of DME at Month 24				
< median, N	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ median, N	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline A1C at Month 24				
< median, N	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ median, N	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; BCVA = best-corrected visual acuity; DME = diabetic macular edema; FA = fluocinolone acetonide; SD = standard deviation.

Note: Median duration of DME FAME-A = 3 years for sham and FA 0.2 mcg/day; FAME-B = 3 years for sham and FA 0.2 mcg/day.

Note: Median baseline A1C: FAME-A = 7.5 for sham, 7.4 FA 0.2 mcg/day; FAME-B = 7.4 for sham, 7.7 FA 0.2 mcg/day.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Table 14: Best-Corrected Visual Acuity Letter Score by Baseline Visual Acuity at Month 24 (Full Analysis Population)

Outcome	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Best-Corrected Visual Acuity Letter Score				
Baseline Visual Acuity at Month 24				
≤ 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 24, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
> 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 24, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	

CI = confidence interval; FA = fluocinolone acetonide; SD = standard deviation.

Note: Full analysis population.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Table 15: Proportion of Patients With a Worsening From Baseline of Three Steps or More in the ETDRS Multi-Step Eye Scale of Diabetic Retinopathy by Baseline Visual Acuity at Month 24 (Full Analysis Population)

Outcome	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Percentage of Patients With a Worsening From Baseline of 3 Steps or More in the ETDRS Multi-Step Eye Scale of Diabetic Retinopathy				
Baseline Visual Acuity at Month 24				
≤ 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
> 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
N (%)	[redacted]	[redacted]	[redacted]	[redacted]

ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide.

Note: Full analysis population.

Source: CSRs for FAME-A[8] and FAME-B.[9]

Table 16: Mean Change From Baseline in Excess Centre-Point Macular Thickness by Baseline Visual Acuity at Month 24 (Full Analysis Population)

Outcome	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
Excess Centre-Point Macular Thickness				
Baseline Visual Acuity at Month 24				
≤ 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 24, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
> 49 letters, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change at month 24, mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	

CI = confidence interval; FA = fluocinolone acetonide; SD = standard deviation.

Note: Full analysis population.

Source: CSRs for FAME-A[8] and FAME-B.[9]

Table 17: Other Efficacy Outcomes (Full Analysis Population)

	FAME-A		FAME-B	
	Sham (N = 95)	FA 0.2 mcg/day (N = 190)	Sham (N = 90)	FA 0.2 mcg/day (N = 186)
BCVA Letter Score				
Month 24, n (%)				
≥ 15-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
10- to 14-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
5- to 9-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
1- to 4-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
0-letter change	[redacted]	[redacted]	[redacted]	[redacted]
1- to 4-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
5- to 9-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
10- to 14-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
≥ 15-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
Month 36				
≥ 15 letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
10- to 14-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
5- to 9-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
1- to 4-letter decrease	[redacted]	[redacted]	[redacted]	[redacted]
0-letter change	[redacted]	[redacted]	[redacted]	[redacted]
1- to 4-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
5- to 9-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
10- to 14-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
≥ 15-letter increase	[redacted]	[redacted]	[redacted]	[redacted]
Excess Centre Subfield Thickness (in Micrometres)				
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	
Month 36				
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; FA = fluocinolone acetonide; SD = standard deviation.

Note: Full analysis population.

Excess centre subfield thickness was calculated by subtracting a value of 212 µm for the centre subfield thickness for each patient; all negative values were set to zero.

Source: CSRs for FAME-A[8] and FAME-B.[9]

Table 18: Efficacy Outcomes (Per-Protocol Population)

	FAME-A		FAME-B	
	Sham	FA 0.2 mcg/day	Sham	FA 0.2 mcg/day
Proportion of Patients With an Increase From Baseline of 15 or More Letters in BCVA				
Month 24				
N	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
BCVA Letter Score				
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Proportion of Patients With a Worsening From Baseline of 3 Steps or More in the ETDRS Multi-Step Eye Scale of Diabetic Retinopathy				
Month 24				
N	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Excess Centre-Point Thickness (in Micrometres)				
Baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 24				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference estimate (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluocinolone acetonide; SD = standard deviation.

Source: Clinical Study Reports for FAME-A[8] and FAME-B.[9]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures (Table 20) and review their measurement properties (validity, reliability, responsiveness to change, and minimal clinically important difference [MCID]). Outcome measures included in the FAME-A and FAME-B studies are presented in Table 18: Efficacy Outcomes (Per-Protocol Population).

Table 19: Outcome Measures Included in Each Included Study

Outcome Measure	FAME-A	FAME-B
BCVA: percentage of patients with improvement of 15 letters (measured by ETDRS chart)	Primary	Primary
BCVA: mean change from baseline	First secondary	First secondary
Excess centre-point thickness: change from baseline (in micrometres, measured by OCT)	Second secondary	Second secondary
ETDRS multi-step eye scale of diabetic retinopathy (≥ 3-step worsening)	Third secondary	Third secondary
Centre macular thickness (micrometres)	Exploratory	Exploratory
VFQ-39 (English-speaking patients only)	Exploratory	Exploratory
VFQ-25 (for non–English-speaking patients)	Exploratory	Exploratory

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; VFQ-25 = 25-item Visual Functioning Questionnaire; VFQ-39 = 39-item Visual Functioning Questionnaire.

Findings

The validity and MCID information of the relevant instruments listed in Table 19 are presented in Table 20.

Table 20: Validity and Minimal Clinically Important Difference of Instruments to Assess Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
ETDRS charts	Developed to measure visual acuity. Patients are presented a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows (total of 14 lines [70 letters]).	Yes	10 to 15 letters	Kniestedt, 2003[27] FDA Statistical Review[34] Lucentis medical review[45] Rosser, 2003[7]
OCT	A technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.	Yes	Unknown	Goatman, 2006[35]

Instrument	Type	Evidence of Validity	MCID	References
ETDRS multi-step eye scale of diabetic retinopathy	The ETDRS DRSS was developed to categorize the severity of diabetic retinopathy based on several fundus photographic characteristics. There are 13 levels in the original ETDRS scale, and a severity step or level increase is associated with an increased risk of retinopathy progression.	Yes	≥ 2 steps of progression (at one-year follow-up)	ETDRS Research Group, 1991[39] Klein et al., 2001[41]
VFQ-25	Developed as a means to measure vision-targeted quality of life. It includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general-health component.	Yes	3.33 points (SEM-based method) or 6.13 points (one-half SD-based method) for the composite score	Mangione, 1998[43] Mangione, 2001[46] Dougherty, 2010[47] Lloyd, 2013[5]
VFQ-39 (English-speaking patients only)	VFQ-39 includes 39 items that are grouped into 12 vision-specific subscales that include general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision, and peripheral vision.[48]	No	No	Mollazadegan, 2014[48]

DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; MCID = minimal clinically important difference; OCT = optical coherence tomography; SD = standard deviation; SEM = standard error of measurement; VFQ-25 = 25-item Visual Functioning Questionnaire; VFQ-39 = 39-item Visual Functioning Questionnaire.

Early Treatment Diabetic Retinopathy Study Charts

Early Treatment Diabetic Retinopathy Study (ETDRS) charts are based on a design by Bailey and Lovie and are commonly used in clinical research.[27-31] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows, for a total of 14 lines (70 letters). ETDRS letter score can be calculated when 20 or more letters are read correctly at 4.0 metres; the visual acuity letter score is equal to the total number of letters read correctly at 4.0 metres plus 30. If fewer than 20 letters are read correctly at 4.0 metres, the visual acuity letter score is equal to the total number of letters read correctly at 4.0 metres (number of letters recorded on line 1.0), plus the total number of letters in the first six lines read correctly at 1.0 metre. Therefore, the ETDRS letter score could result in a maximum score of 100.[32,33]

Charts are used in a standard light box with a background illumination of approximately 150 cd/m^2. Standard chart testing distance is four metres; however, shorter distances may be used when vision is severely impaired.[27,49] ETDRS results can be converted to Snellen fractions, another common measure of visual acuity, in which the numerator indicates the distance at which the chart was read, and the denominator the distance at which a person may discern letters of a particular size. A larger denominator indicates worsening vision. ETDRS letters range from 58.18 mm to 2.92 mm in height, corresponding to Snellen visual acuity fractions of 20/200 to 20/10, respectively. Further, letter size increases geometrically and equivalently in every line by a factor of 1.2589 (or 0.1 log unit), moving up the chart. Scoring for ETDRS charts is designed to produce a logarithmic score (logarithmic minimal

angle of resolution [logMAR]), suitable for statistical analysis, in which individual letters score 0.02 log units.

ETDRS charts may reliably identify changes in visual acuity of two lines (10 letters) or more, but not changes of one line (five letters) or fewer.[7] The reliability of ETDRS charts depends on the baseline visual acuity. For eyes with acuity better than 20/100, a change in visual acuity of five or more letters has a greater than 90% probability of being a real change, while for eyes worse than 20/100, a change of 10 or more letters is required for the same reliability.[50] A loss or gain of three lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials.[51] For macular edema, the FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with a greater than or equal to 15-letter change in visual acuity as clinically relevant outcome measures in trials of interventions.[34]

With regard to the relationship between visual acuity measurement and visual function, a loss of three or more lines (greater than or equal to 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered moderate visual loss, while a loss of six or more lines (greater than or equal to 30 letters) corresponds to a quadrupling of the visual angle and is considered severe. However, visual acuity is only one component contributing to overall visual function and the ability to perform everyday visual tasks (e.g., reading, recognizing faces, driving, and using the telephone). Overall visual function also depends upon variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare.[52] The various components of visual function will affect the performance of different vision-related tasks by varying degrees. For example, the use of distance acuity to measure the success of treatments for age-related macular degeneration is not optimal, given that distance vision is usually two ETDRS lines better than reading vision,[51] and difficulties with reading is a common complaint among people with eye disease.[43] Rather, contrast sensitivity is a more important contributor to reading performance.[51,53]

Optical Coherence Tomography

Optical coherence tomography (OCT) is a fast, non-invasive technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[35] OCT uses lasers centred on infrared wavelengths to record light reflected from interfaces between materials with different refractive indices, and from materials that scatter light. OCT3 machines are able to differentiate three reflecting layers thought to be the vitreous/retina, inner/outer photoreceptor segments, and the retinal pigment epithelium/choriocapillaris interfaces. Ultra–high resolution machines can differentiate a fourth layer. During the OCT scan, a series of intersecting, radial cross sections of the retina are measured. Resolution depends on the software as well as the hardware used and is better around the central axis than lateral areas.[35,54] A recent advancement in OCT device technology has been the shift from time-domain (TD-OCT) to spectral-domain OCT (SD-OCT), as the latter can acquire data at a higher speed with better image resolution and reduced motion artifact.[55]

In a previous meta-analysis analyzing the discriminatory power of foveal thickness for the diagnosis of diabetic macular edema (DME), the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of OCT were 0.81, 0.85, 5.4, and 0.22, respectively.[36] Intra-device repeatability and inter-device reproducibility of measurements depend on a number of factors, including retinal pathology, retinal region, region size, OCT model, equipment settings, manual or automated analysis, and operator experience.[35] In eyes with

DME, a comparison of measurements with four different OCT devices found good intra-device repeatability, but statistically significant differences in retinal thickness values across different devices.[56] Another study that compared the reproducibility of retinal thickness measurements from OCT images of eyes with DME obtained by TD-OCT and SD-OCT instruments found that SD-OCT devices demonstrated less test–retest variability.[55] Inter-device differences in retinal thickness were also reported in this study, though they were expected due to the different algorithms used by SD-OCT and TD-OCT machines that define the anatomical structures serving as the boundaries for measurement. Additionally, the presence of macular edema can influence OCT measurement precision. In one study, the 95% limits of agreement (the scale at which an instrument can detect changes in a patient) for average foveal thickness in healthy eyes was 8 µm, while in patients with DME, it was 36 µm.[57] In patients with DME, the association between OCT-measured retinal thickness and best-corrected visual acuity (BCVA) has been evaluated. A moderate correlation between visual acuity and OCT centre-point thickness has been observed (r = 0.52). [58] For every 100 µm decrease in centre-point thickness, visual acuity increased by 4.4 letters (95% CI, 3.5 to 5.3).[58] Other studies have shown similarly modest correlations between visual acuity and central retinal thickness determined by OCT.[37,38] In eyes with DME treated with laser photocoagulation, changes in centre-point thickness were associated with changes in visual acuity, with correlation coefficients of 0.44, 0.30, and 0.43 at 3.5, 8, and 12 months, respectively.[58] Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes in DME, but it is only modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient-reported outcomes. No MCID information on central retinal thickness changes measured by OCT was identified.

Early Treatment Diabetic Retinopathy Study Multi-Step Eye Scale of Diabetic Retinopathy

The ETDRS Research Group modified the Airlie House classification of diabetic retinopathy to create a diabetic retinopathy grading system based on stereoscopic fundus photographs.[59] Fundus photography displays ocular abnoermalities, such as microaneurysms, hemorrhages, hard and soft exudates, venous abnormalities, new vessels, fibrous proliferations, retinal thickening, and clinically significant macular edema; these abnormalities are graded independently from single or multiple photographic fields.[59] A comparison of fundus photograph characteristics in patients with diabetic retinopathy over time led to the identification of photographic risk factors for progression from non-proliferative to proliferative diabetic retinopathy.[39] As a result of these analyses, the ETDRS multi-step eye scale of diabetic retinopathy was created. The ETDRS multi-step eye scale of diabetic retinopathy consists of 13 levels of graded photographic characteristics that were defined to categorize severity of diabetic retinopathy for individual eyes, ranging from no retinopathy to severe vitreous hemorrhage.

Complete inter-rater agreement of fundus photography grading in the ETDRS was demonstrated with a frequency of 38%, agreement within one level occurred in 71%, and agreement within two levels in 87%.[39] The unweighted kappa statistic was 0.31, which increased to 0.71 with a weighting of 1.00 for exact agreement, 0.94 for one-level disagreement, and 0.75 for two-level disagreement.[39] Since its introduction, the ETDRS severity scale has been used extensively in research and has demonstrated sufficient reproducibility and validity to establish it as the “gold standard” instrument for diabetic retinopathy grading in clinical trials.[40]

Step progression refers to an increase in photographic level that can be used to describe change in diabetic retinopathy over time.[39,41] In the ETDRS, the proportion of eyes with progression of two or more levels at follow-up was relatively similar among all severity categories at the one-year follow-up time point, establishing two-step progression as a reasonable outcome measure for all baseline retinopathy levels.[39] When assessing change in overall retinopathy severity for the patient and not just individual eyes, the scale was reproducible for progression in three or more steps for a longer period than one-year follow-up.[39] The FDA-recommended end points for diabetic retinopathy clinical trials include a "statistically significant difference in the percentage of patients at 3 years with a ≥ 3-step change on the ETDRS retinopathy scale."[42] The Wisconsin Epidemiology Study of Diabetic Retinopathy evaluated whether fewer than three steps of ETDRS Diabetic Retinopathy Severity Scale (DRSS) progression were clinically meaningful in a population-based study of diabetic patients with 10 years of follow-up.[41] The results indicated that patients with one or more or two or more steps of ETDRS DRSS progression over six years (four years to 10 years of follow-up) were significantly more likely to develop proliferative diabetic retinopathy than those without ETDRS DRSS step progression.[41]

National Eye Institute Visual Function Questionnaire

The National Eye Institute (NEI) Visual Function Questionnaire (VFQ) was developed as a means to measure vision-targeted quality of life. The original 51-item questionnaire was developed based on focus groups composed of people with a number of common eye conditions (e.g., age-related cataracts, age-related macular degeneration, and diabetic retinopathy); thus, the questionnaire may be used to assess quality of life for a broad range of eye conditions.[43] The original 51-item questionnaire comprises 12 subscales related to general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, colour vision, and expectations for future vision. In addition, the questionnaire includes one general-health subscale.[60]

A shorter version of the original instrument, the VFQ-25, was subsequently developed, which retained the multidimensional nature of the original and is more practical and efficient to administer.[46] With the exception of the expectations for future vision, all the constructs listed previously were retained in the shortened version, with a reduced number of items within each subscale. Thus, the VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general-health component. Responses for each item are converted to a 0 to 100 scale, with 0 representing the worst, and 100 the best visual functioning. Items within each construct, or subscale, are averaged to create 12 subscale scores, and averaging of the subscale scores produces the overall composite score. Different scoring approaches for the VFQ-25 have been proposed.[47] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring with Rasch analysis and using an algorithm to approximate Rasch scores, all methods were highly correlated.[47] However, standard scoring is subject to floor and ceiling effects whereby the ability of the least visually able is overestimated and the ability of the most visually able is underestimated.[47]

Determination of what constitutes a clinically meaningful change in the VFQ-25 appears to be linked to its correlation with visual acuity. A three-line (15-letter) change in visual acuity has been used as the outcome of interest in clinical trials, and corresponding changes in the VFQ-25 are suggested as clinically meaningful end points. A psychometric validation study of the VFQ-25 specifically in patients with DME has more recently been conducted, and two distribution-based methods were employed to determine an MCID from baseline to

week 54.[5] Using a one-half standard deviation–based approach, the MCID for each VFQ-25 domain ranged from 8.80 (general vision) to 14.40 (role difficulties) and produced a composite score MCID of 6.13 points. The MCID for the near-vision and distance-vision subscales were 10.24 and 11.07, respectively. A standard error of measurement approach yielded similar MCID estimates from 8.79 (driving) to 14.04 (role difficulties), with a composite score MCID estimate of 3.33 points. This technique lowered the MCID estimates for the near- and distance-vision domains, which were reported as 9.17 and 10.19, respectively.[5]

Both versions (the original 51-item questionnaire and the VFQ-25) of the VFQ were reported to be valid and reliable measures of health-related quality of life among patients with a wide range of eye conditions, including DME,[5,46,60,61] and all but two subscale scores (general health and ocular pain) have been shown to be responsive to changes in visual acuity in the better-seeing eye.[61,62] However, some assessments of the psychometric validity of the VFQ-25 using Rasch scoring and principal component analysis in patients with various eye conditions have identified issues with multidimensionality (measurement of more than one construct) and poor performance of the subscales.[40,62,63] The NEI VFQ-25 subscales were found to have too few items and were unable to discriminate among the population under measurement, and thus were not valid. [40,63] Re-engineering the VFQ-25 into two constructs (visual functioning and socio-emotional factors) and removing misfit items (e.g., pain around eyes, general health and driving in difficult conditions) improved the psychometric validity of the scale in individuals with low vision.[40,63] Considering the evidence of multidimensionality, the validity of the single composite score of the VFQ-25 may be questioned.

Limitations of internal consistency due to the presence of single-item domains were also noted in a validation study specific to the DME population.[5] The near-vision and distance-vision subscales are three-item domains on the VFQ-25; their internal reliability as represented by Cronbach's alpha was reported as 0.73 and 0.58, respectively. A convergent validity analysis to examine the relationship between VFQ-25 scores and other disease-related variables provided mixed results, and the VFQ-25 domains collectively showed low-to-moderate correlations with the ETDRS visual acuity score for both study eyes and untreated eyes. The Pearson correlation with ETDRS total letters in the study eye was reported as 0.35 for the near-vision subscale and 0.34 for the distance-vision subscale. A slightly stronger correlation was observed between the VFQ-25 and the EuroQol 5-Dimensions (EQ-5D) questionnaire Visual Analogue Scale (VAS), and the EQ-5D VAS along with the ETDRS was a significant predictor of near- and distance-vision subscale scores, suggesting that general health-related quality of life was captured by the VFQ-25 more so than strictly vision-related information. However, in support of known group validity, patients who saw more ETDRS letters also scored higher on the NEI VFQ-25 near and distance subscales as well as on the VFQ-25 composite. Overall, the authors concluded that despite its documented limitations and the need for an improved instrument, the VFQ-25 demonstrated a degree of validity for measuring health-related quality of life in patients with DME.[5]

Very limited information on the VFQ-39 (another shorter version of the original VFQ) was found from the literature search.[48,63] The 39 items of the NEI VFQ-39 are also grouped into 12 vision-specific subscales (similar to the VFQ-25) that include general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision, and peripheral vision.[48] However, no validity information and MCID information on the VFQ-39 were identified from the literature.

Conclusion

The validity of various instruments to measure visual acuity (ETDRS charts and ETDRS multi-step eye scale of diabetic retinopathy), retinal thickening (OCT), and vision-related function (VFQ-25) was reviewed.

The ETDRS chart is the most widely used outcome measure to assess changes in visual acuity from a therapeutic intervention. It is a modified version of the Snellen chart and ETDRS scores are based on the number of letters correctly read by a patient. A loss or gain of two to three lines (10 to 15 letters) is the most commonly used MCID in clinical studies.

Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes, but it is only modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient-reported outcomes.

The ETDRS multi-step eye scale of diabetic retinopathy was developed to categorize severity of diabetic retinopathy based on several fundus photographic characteristics and has become the reference standard for diabetic retinopathy grading in clinical trials. There are 13 levels in the original ETDRS scale, and a severity step or level increase is associated with an increased risk of retinopathy progression. The FDA recommended the percentage of patients with a greater than or equal to three-step change at three years on the ETDRS DRSS as an outcome for diabetic retinopathy clinical trials.

The VFQ was developed to measure vision-targeted quality of life. The VFQ was reported to be a valid and reliable measure of health-related quality of life among patients with a wide range of eye conditions; however, recent studies have suggested that it may be more appropriately identified as a measure of visual functioning. The VFQ-25 has a reported MCID of between 3.3 and 6.13 points for the overall composite score. No validity information and MCID information on the NEI VFQ-39 were identified from the literature.

Appendix 5: Summary of Other Studies

Objective

To summarize and critically appraise the safety for fluocinolone acetonide (FA) intravitreal implant, 0.19 mg in patients with diabetic macular edema (DME) reported in the open-label, multi-centre FAME extension study.[64]

Description of the Study

[redacted]

Study Characteristics

The FAME extension[64] was a phase IIIb, open-label study for patients with DME [redacted]. The main inclusion and exclusion criteria are presented in Table 21.

Only FAME study sites in the US were allowed to enrol patients [redacted]. The study duration consisted of a 12-month post-treatment period. [redacted]

[redacted]

Table 21: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Patients who previously participated in the FAME studies who would benefit from re-treatment, in the medical opinion of the investigator.	Glaucoma, defined as glaucomatous anatomical changes of the optic disc and/or visual field changes at screening in the study eye.
Patients with chronic DME considered insufficiently responsive to available therapies and who were expected to benefit from treatment with 0.2 mcg/day FA, in the medical opinion of the investigator.	History of uncontrolled IOP elevation with steroid use that did not respond to topical therapy or IOP-lowering procedure.
Ability and willingness to comply with the treatment and follow-up procedures.	Any viral, fungal, or bacterial disease of the cornea or conjunctiva, or any history of a potentially recurrent infection that could be activated by treatment with a steroid (e.g., ocular herpes simplex virus).
Ability to understand and sign the informed consent form. No expectation that the patient would be moving out of the area of the clinical centre to an area not covered by another clinical centre during the next 12 months.	Any lens opacity which significantly impairs vision, in the opinion of the investigator. Peripheral retinal detachment in prospective area of insertion.

DME = diabetic macular edema; FA = fluocinolone acetonide; IOP = intraocular pressure.

Source: Clinical Study Report for FAME Extension Study.[64]

Results

Patient Disposition

Patient disposition is summarized using the questionnaire population (Table 22). Of 121 patients enrolled into the study across 30 sites in the US, [redacted]. A total of 17 patients discontinued from the study. Of the 121 patients in the study, 104 (86%) completed the study and 17 (14%) prematurely discontinued. [redacted]

Table 22: Summary of Patient Disposition (Questionnaire Population)

	0.2 mcg/day FA		
	[redacted]	[redacted]	Total
Enrolled, N	[redacted]	[redacted]	121
Treatment received, n (%)	[redacted]	[redacted]	120 (99.2)
[redacted]	[redacted]	[redacted]	[redacted]
Completed, n (%)	[redacted]	[redacted]	104 (86.0)
Discontinued from study, n (%)	[redacted]	[redacted]	17 (14.0)
Adverse event [redacted]	[redacted]	[redacted]	2 (1.7)
Unsatisfactory therapeutic effect	[redacted]	[redacted]	1 (0.8)
Subject withdrew consent	[redacted]	[redacted]	3 (2.5)
Lost to follow-up	[redacted]	[redacted]	7 (5.8)
Death	[redacted]	[redacted]	3 (2.5)
Other	[redacted]	[redacted]	1 (0.8)

FA = fluocinolone acetonide.

Source: Clinical Study Report for FAME Extension Study.[64]

Baseline Characteristics

[redacted] Overall, the majority of the patients were [redacted] male (60%). The mean age was 65.2 years [redacted].

Table 23: Demographics and Baseline Characteristics (Safety Population)

	0.2 mcg/day FA		
	[redacted]	[redacted]	Total (N = 120)
Age (years), n (%)			
Mean (SD)	[redacted]	[redacted]	65.2 (9.29)
Range	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	72 (60.0)
Female	[redacted]	[redacted]	48 (40.0)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black/African-American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Iris colour, n (%)			
Brown	[redacted]	[redacted]	[redacted]
Hazel	[redacted]	[redacted]	[redacted]
Green	[redacted]	[redacted]	[redacted]

	0.2 mcg/day FA		
	[redacted]	[redacted]	Total (N = 120)
Blue	[redacted]	[redacted]	[redacted]
Study Eye, n (%)			
Right eye	[redacted]	[redacted]	[redacted]
Left eye	[redacted]	[redacted]	[redacted]
Study eye lens status, n (%)			
Pseudophakic	[redacted]	[redacted]	[redacted]
Phakic	[redacted]	[redacted]	[redacted]
Duration of DME (years)			
Number of patients, n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of missing patients, n (%)	[redacted]	[redacted]	[redacted]
Treatment received in FAME, n (%)			
Sham control	[redacted]	[redacted]	[redacted]
0.2 mcg/day FA	[redacted]	[redacted]	[redacted]
0.5 mcg/day FA	[redacted]	[redacted]	[redacted]
Patients not previously enrolled in FAME-A or -B, n (%)	[redacted]	[redacted]	[redacted]

DME = diabetic macular edema; FA = fluocinolone acetonide; SD = standard deviation.

Source: Clinical Study Report for FAME Extension Study.[64]

[redacted]

Figure 3: [redacted]

Figure 3 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Table 24: [redacted]

	[redacted]	
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

[redacted]

Table 25: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Table 26: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Harms

Extent of Exposure

[redacted]

Overall Adverse Events

[redacted]

Table 27: Treatment-Emergent Adverse Events (Safety Population)

	[redacted]	
	[redacted]	[redacted]
≥ 1 TEAE,[a] n (%)	[redacted]	[redacted]
Study eye, n (%)	[redacted]	[redacted]
Non-study eye, n (%)	[redacted]	[redacted]
Systemic, n (%)	[redacted]	[redacted]
SAEs (non-fatal), n (%)	[redacted]	[redacted]
Study eye, n (%)	[redacted]	[redacted]
Non-study eye, n (%)	[redacted]	[redacted]
Systemic, n (%)	[redacted]	[redacted]
WDAE,[b] n (%)	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]

FA = fluocinolone acetonide; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Ocular Treatment-Emergent Adverse Events

[redacted]

Table 28: [redacted]

	[redacted]	
	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Systemic Treatment-Emergent Adverse Events

[redacted]

Table 29: [redacted]

	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Searious Adverse Events (Non-Fatal)

[redacted]

Table 30: [redacted]

	[redacted]	
	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for FAME Extension Study 25.

Table 31: [redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Report for FAME Extension Study.[64]

Deaths/Discontinuations

[redacted]

Limitations

Due to the limitation of the nature of the single-arm study design (i.e., open-label study design, no active comparator, [redacted].

Summary

[redacted].

Appendix 6: Summary of Indirect Comparisons

Introduction

Fluocinolone acetonide (FA) has been approved by Health Canada for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (IOP). There is an absence of comparative studies for FA versus other treatments for DME. The objective of this review was to summarize and critically appraise the indirect evidence comparing FA with other drugs used in the treatment of DME.

Methods

One manufacturer-supplied systematic review and indirect treatment comparison (ITC) met the criteria for inclusion.[65] CADTH conducted an independent literature search to identify relevant ITCs that included the patients, interventions, and outcomes as identified in the CADTH Common Drug Review (CDR) Clinical Review protocol (Table 3).

Description of Indirect Treatment Comparisons Identified

One ITC submitted by the manufacturer was included for critical appraisal.[65] Table 32 summarizes the key aspects of the ITC. No other ITCs were identified in the literature search.

Table 32: Overview of Included Indirect Treatment Comparison

Population	Intervention	Comparators	Outcomes	Study Design
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Manufacturer-supplied indirect treatment comparison.[65]

Review and Appraisal of Indirect Treatment Comparisons

The manufacturer-submitted ITC[65] was critically appraised using recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons as a guide.[66]

Review of Manufacturer-Supplied Indirect Treatment Comparison

Objectives and Rationale for the Manufacturer-Supplied Indirect Treatment Comparison

[redacted]

Methods

Study Eligibility, Selection Process, and Data Extraction

[redacted]

Comparators

[redacted]

Outcomes

[redacted]

Quality Assessment of Included Studies

[redacted]

Indirect Comparison Methods

[redacted]

Results

[redacted]

An overview of study characteristics and a summary of the patient characteristics included in the ITCs are provided in Table 33 and Table 34, respectively. The included studies took place across the US, UK, Brazil, Australia, Canada, Turkey, Iran, Germany, and Switzerland.

[redacted]

[redacted]

[redacted]

Table 33: Overview of Included Studies

Study	Country	Design	Population	Trial Length	N Randomized Eyes
BEVORDEX (NCT01298076)	Australia and UK	Phase II, prospective, multi-centre, randomized, single-masked clinical trial	DME affecting the central fovea	12 months	61
BOLT (2007-000847-89)	UK	Prospective, randomized, masked, single-centre, 2-year, 2-arm clinical trial	Persistent clinically significant macular edema and at least one previous laser treatment	24 months	80
DA VINCI (NCT00789477)	US, Canada, and Austria	Randomized, double-masked, active-controlled multi-centre, phase II clinical trial	Centre-involved DME	12 months	221
FAME-A and -B (NCT00344968)	FAME-A: US, Canada, European Union, and India FAME-B: US, India, European Union	Two parallel, prospective, randomized, sham injection–controlled, double-masked, multi-centre, 36-month clinical trials	Persistent DME despite ≥ 1 macular laser treatment	36 months	956
IBERA-DME (NCT01487629)	Brazil	Prospective randomized clinical trial	Centre-involved DME	48 weeks	48
IBeTA (NCT00997191)	Brazil	NR (prospective, randomized, controlled clinical trial)	DME	52 weeks	49
LUCIDATE (NCT01223612)	UK	Single-centre, prospective, randomized clinical trial	Centre-involved DME	48 weeks	37
MEAD (NCT00168337 and NCT00168389)	Worldwide	Two randomized, multi-centre, masked, sham-controlled, phase III clinical trials with identical protocols	DME	3 years	1,048
NCT00370669	Iran	3-arm, randomized, phase III clinical trial	Treatment-naive DME	2 years	150
Protocol I (NCT00445003)	US	Phase III, randomized, multi-centre clinical trial	DME involving the fovea	5 years	854

Study	Country	Design	Population	Trial Length	N Randomized Eyes
NCT00490815	US	Phase II, prospective, randomized, interventional, multi-centre clinical trial	Persistent DME despite ≥ 1 focal/grid laser therapy	12 months	37
NCT00502541	US	4-year, prospective, multi-centre, randomized, evaluator-masked, parallel-group, controlled phase II/III clinical trial	Persistent or recurrent DME	4 years (3-year results)	196
NCT00799227	Australia, US	Randomized double-masked study	Diffuse DME	12 months	153
Protocol T (NCT01627249)	US, Canada	Multi-centre, randomized, phase III clinical trial	DME involving the macular centre	2 years	660
OZDRY (NCT01892163)	UK	Multi-centre, prospective, randomized, active-controlled, noninferiority, phase III study	Refractory DME	12 months	100
OZLASE (EudraCT 2011-003339-74)	UK	Phase III, single-centre, prospective, randomized, active-controlled trial	Centre-involving DME	56 weeks	80
PLACID (NCT00464685)	US, Canada	Randomized, controlled, multi-centre, double-masked, parallel-group, 12-month, phase III trial	Diffuse DME	1 year, with up to 3 months of additional follow-up	253
READ-2 (NCT00407381)	US	Prospective, interventional, multi-centre follow-up of a phase II randomized clinical trial	DME	3 years	126
RELATION (NCT01131585)	Germany	Multi-centre, 12-months, two-armed, double-masked, parallel-group, active-controlled, phase III clinical trial	DME	12 months	128
RESOLVE (NCT00284050)	Switzerland	12-month, randomized, controlled, double-masked, multi-centre, phase II study	DME involving the foveal centre	12 months	151

Study	Country	Design	Population	Trial Length	N Randomized Eyes
RESPOND (NCT01135914)	Canada	12-month, multi-centre, open-label, 3–parallel treatment arm, randomized, phase IIIb study	DME	12 months	237
RESTORE (NCT00687804)	10 European countries, Turkey, Canada, and Australia	12-month, phase III, randomized, double-masked, multi-centre, laser-controlled study	DME	12 months	345
RETAIN (NCT01171976)	International	24-month, phase IIIb, single-masked, controlled, three-arm, parallel-group study	DME	2 years	372
REVEAL (NCT00989989)	China, Hong Kong, Japan, South Korea, Singapore, Taiwan	12-month, randomized, double-masked, laser-controlled, multi-centre, phase III study	DME (Asian patients)	12 months	396
RIDE and RISE (NCT00473382, NCT00473330)	US and South America	Methodologically identical, phase III, randomized, multi-centre, double-masked, trials that were sham injection–controlled for the first 2 years	Centre-involving DME	36 months	759
VISTA and VIVID (NCT01363440, NCT01331681)	VISTA: US VIVID: Europe, Japan, Australia	Two similarly designed double-masked, randomized, active-controlled, 148-week, phase III trials	Centre-involving DME	148 weeks	VISTA: 466 VIVID: 406
Ekinci 2014	Turkey	Prospective, randomized trial	DME	12 months	100
Maturi 2015	US	Prospective, single-masked, randomized, controlled trial	DME with incomplete response to multiple antivascular endothelial growth factor injections	12 months	30
Jorge 2012	Brazil	NR (randomized clinical trial)	Centre-involving DME	48 weeks	63

DME = diabetic macular edema; NR = not reported.

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 34: Demographics and Baseline Characteristics by Treatment for Studies Included in Indirect Treatment Comparison

Study	Treatment Arm	N	Age (Years, mean (SD)	Gender (Male %)	Type of Diabetes	A1C (mean, SD)	Previous Treatments	Lens Status	Baseline BCVA (Letters)
BEVORDEX (NCT01298076)	Bevacizumab 1.25 mg	42	–	62%	-	7.8 (2.1)	–	–	56.3
	Dexamethasone 0.7 mg	46	–	65%	-	7.7 (2.5)	–	–	55.5
BOLT (2007-000847-89)	Bevacizumab 1.25 mg	42	64.9 (9.4)	71%	Type1: 10% Type 2: 90%	7.6 (1.4)	Laser: 100%	Pseudophakic: 11.9% Phakic: 88.1%	55.8
	Laser	38	63.5 (8.1)	66%	Type1: 11% Type 2: 89%	7.5 (1.2)	Laser: 100%	Pseudophakic: 21.1% Phakic: 78.9%	55.4
DA VINCI (NCT00789477)	Aflibercept 0.5q4	44	62.3 (10.7)	54.5%	Type 1: 2.3% Type 2: 97.7%	8.10 (1.91)	Laser: 47.7% Anti-VEGF: 11.4%	–	59.3
	Aflibercept 2q4	44	62.1 (10.5)	61.4%	Type 1: 6.8% Type 2: 93.2%	8.08 (1.94)	Laser: 52.3% Anti-VEGF: 22.7%	–	59.9
	Aflibercept 2q8	42	62.5 (11.5)	52.4%	Type 1: 4 (9.5%) Type 2: (90.5%)	7.85 (1.72)	Laser: 66.7% Anti-VEGF: 14.3%	–	58.8
	Aflibercept 2PRN	45	60.7 (8.7)	64.4%	Type 1: 4.4% Type 2: 95.6%	7.97 (1.71)	Laser: 57.8% Anti-VEGF: 13.3%	–	59.6
	Laser	44	64 (8.1.)	61.4%	Type 1: 11.4% Type 2: 88.6%	7.93 (1.84)	Laser: 50.0% Anti-VEGF: 22.7%	–	57.6
FAME-A and -B (NCT00344968)	Fluocinolone acetonide 0.2 mcg/day	375	63.0 (9.3)	57.3%	Type 1: 7.7% Type 2: 90.7%	7.8 (2.1)	–	Pseudophakic: 37.3% Phakic: 62.7%	53.3
	Fluocinolone acetonide 0.5 mcg/day	393	62.2 (9.3)	61.8%	Type 1: 5.3% Type 2: 93.1%	7.7 (2.5)	–	Pseudophakic: 32.6% Phakic: 67.4%	52.9
	Sham	185	61.9 (9.6)	58.4%	Type 1: 7.0% Type 2: 91.9%	7.6 (1.4)	–	Pseudophakic: 34.6% Phakic: 65.4%	54.7

Study	Treatment Arm	N	Age (Years, mean (SD)	Gender (Male %)	Type of Diabetes	A1C (mean, SD)	Previous Treatments	Lens Status	Baseline BCVA (Letters)
IBERA-DME (NCT01487629)	Bevacizumab 1.5 mg	32	63.8 (SE 8.8)	40.6%		8.6 (1.3)	Laser: 100% Triamcinolone: 3.6% Bevacizumab: 10.7% Ranibizumab: 7.1%	Phakic 71.9% Pseudophakic 28.1%	logMAR 0.60
	Ranibizumab 0.5 mg	28	63.7 (SE 9.0)	50.0%		8.7 (2.0)	Laser: 100% Triamcinolone: 6.3% Bevacizumab: 9.4% Ranibizumab: 6.3%	Phakic: 75.0% Pseudophakic: 25.0%	logMAR 0.63
IBeTA (NCT00997191)	Bevacizumab 1.5 mg	21	–	–	–	–	–	–	logMAR 0.63
	Laser	23	–	–	–	–	–	–	logMAR 0.65
LUCIDATE (NCT01223612)	Ranibizumab 0.5 mg	24	64.9 (58.4 to 71.0)	68%	Type 1: 18.2% Type 2: 81.8%	7.93 (1.31)	Laser: 100%	–	70.4
	Laser	12	67.4 (62.8 to 74.6)	55%	Type 1: 0% Type 2: 100%	7.25 (0.92)	Laser: 100%	–	63.8
MEAD (NCT00168337 and NCT00168389)	Dexamethasone 0.35 mg	347	62.3 (9.2)	59.4%	Type 1: 6.3% Type 2: 93.7%	7.5 (1.1)	Laser: 64.6% Anti-VEGF: 11.2%	Phakic:74.9% Pseudophakic: 25.4%	55.5
	Dexamethasone 0.7 mg	351	62.5 (8.3)	60.7%	Type 1: 9.7% Type 2: 89.5%	7.6 (1.2)	Laser: 65.8% Anti-VEGF: 7.1%	Phakic:75.5% Pseudophakic: 24.5%	56.1
	Sham	350	62.5 (9.5)	62.0%	Type 1: 8.0% Type 2: 92.0%	7.5 (1.1)	Laser: 69.4% Anti-VEGF: 7.4%	Phakic:71.1% Pseudophakic: 28.9%	56.9
NCT00370669	Bevacizumab 1.25 mg	50	60.5 (5.9)	46%			naive	–	logMAR 0.71
	Laser	50	61.0 (5.3)	56%			naive	–	logMAR 0.55

Study	Treatment Arm	N	Age (Years, mean (SD)	Gender (Male %)	Type of Diabetes	A1C (mean, SD)	Previous Treatments	Lens Status	Baseline BCVA (Letters)
Protocol I (NCT00445003)	Sham + prompt laser	293	Median 63 (IQR, 57, 69)	58%	Type 1: 9% Type 2: 89% Uncertain: 3%	Median 7.3 (IQR, 6.6 to 8.3)	Anti-VEGF: 8%	Phakic: 66% AC IOL: 1% PC IOL: 33%	Median 65
	Ranibizumab 0.5 mg + prompt laser	187	Median 62 (IQR, 56 to 70)	55%	Type 1: 6% Type 2: 92% Uncertain: 2%	Median 7.3 (IQR, 6.6 to 8.4)	Anti-VEGF: 13%	Phakic: 70% AC IOL: 1% PC IOL: 29%	Median 66
	Ranibizumab 0.5 mg + deferred laser	188	Median 54 (IQR, 58 to 70)	59%	Type 1: 8% Type 2: 90% Uncertain: 2%	Median 7.5 (IQR, 6.7 to 8.4)	Anti-VEGF: 11%	Phakic: 71% AC IOL: 1% PC IOL: 28%	Median 66
NCT00490815	Fluocinolone acetonide 0.2 mcg/day	20	66.6 (2.10)	50.0%			–	Phakic: 70% Aphakic: 0% Pseudophakic: 30%	61.6
	Fluocinolone acetonide 0.5 mcg/day	17	67.4 (2.50)	64.7%			–	Phakic: 41.1% Aphakic: 6% Pseudophakic: 53%	54.9
NCT00502541	Fluocinolone acetonide 0.59 mg	127	62.7 (10.23)	58.3%			–	–	–
	SOC (additional laser or observation)	60	61.4 (9.88)	58.0%			–	–	–
NCT00799227	Dexamethasone + laser	126	–	–			–	–	–
	Laser	127	–	–			–	–	–
Protocol T (NCT01627249)	Aflibercept 2.0 mg	208	60 (10)	51%	Type 1: 10% Type 2: 88% Uncertain: 3%	Median 7.6 (IQR, 6.8 to 9.1)	Laser: 36% Anti-VEGF: 11%	Phakic: 74% Pseudophakic: 26%	65
	Bevacizumab 1.25 mg	206	62 (10)	53%	Type 1: 6% Type 2: 94% Uncertain: < 1%	Median 7.7 (IQR, 6.8 to 8.8)	Laser: 39% Anti-VEGF: 14%	Phakic: 73% Pseudophakic: 27%	64.8
	Ranibizumab 0.3 mg	206	60 (11)	57%	Type 1: 7% Type 2: 90% Uncertain: 3%	Median 7.8 (IQR, 6.9 to 9.2)	Laser: 37% Anti-VEGF: 13%	Phakic: 79% Pseudophakic: 21%	65.1

Study	Treatment Arm	N	Age (Years, mean (SD)	Gender (Male %)	Type of Diabetes	A1C (mean, SD)	Previous Treatments	Lens Status	Baseline BCVA (Letters)
OZDRY (NCT01892163)	Fixed Dexamethasone 0.7 mg	50	63.8 (11.1)	80%	Type 1: 14% Type 2: 86%	8.1 (1.4)	Laser: 92% Anti-VEGF: 34%	Pseudophakic: 32% Phakic: 68%	57.5
	PRN dexamethasone 0.7 mg	50	65.4 (9.8)	68%	Type 1: 4% Type 2: 96%	7.7 (1.3)	Laser: 96% Anti-VEGF: 34%	Pseudophakic: 22% Phakic: 78%	61.2
OZLASE (EudraCT 2011-003339-74)	Dexamethasone 0.7 mg + laser	40	65.6 (10.6)	85%	Type 1: 5.0% Type 2: 95.0%	7.9 (1.2)	Laser: 100% Anti-VEGF: 5%	Phakic: 67.5% Pseudophakic: 32.5%	66.1
	Laser	40	61.1 (12.8)	80%	Type 1: 10.0% Type 2: 90.0%	7.9 (1.2)	Laser: 100% Anti-VEGF: 5%	Phakic: 67.5% Pseudophakic: 32.5%	66.6
PLACID (NCT00464685)	Dexamethasone 0.7 mg + laser	126	61.8 (11.1)	49.2%	–	–	Laser: 64.0% Anti-VEGF: 3.2%	Phakic: 72.2% Pseudophakic: 27.8%	57
	Laser	127	61.3 (9.3)	52.0%	–	–		Phakic: 74.8% Pseudophakic: 25.2%	57.5
READ-2 (NCT00407381)	Ranibizumab 0.5 mg	33	–	–	–	–	–	–	–
	Laser	34	–	–	–	–	–	–	–
	Ranibizumab 0.5 mg + laser	34	–	–	–	–	–	–	–
RELATION (NCT01131585)	Ranibizumab + laser	85	–	–	–	–	–	–	–
	Laser	43	–	–	–	–	–	–	–
RESOLVE (NCT00284050)	Ranibizumab 0.3 mg to 0.6 mg	51	63.2 (range, 37 to 85)	56.9%	Type 2: 98.0%	7.3 (range, 5.5 to 11.1)	Laser: 19.6%	–	59.2
	Ranibizumab 0.5 mg to 1.0 mg	51	62.8 (range, 32 to 84)	52.9%	Type 2: 96.1%	7.6 (range, 5.6 to 10.0)	Laser: 17.6%	–	61.2
	Sham	49	65.0 (range, 41 to 82)	51.0%	Type 2: 98.0%	7.5 (range, 5.3 to 9.7)	Laser: 18.4%	–	61.1

Study	Treatment Arm	N	Age (Years, mean (SD)	Gender (Male %)	Type of Diabetes	A1C (mean, SD)	Previous Treatments	Lens Status	Baseline BCVA (Letters)
RESPOND (NCT01135914)	Ranibizumab 0.5 mg	75	61.5 (9.9)	56.0%	Type 1: 12.0% Type 2: 88.0% Other: 0.0%	7.8 (1.3)	–	–	63.1
	Ranibizumab 0.5 mg + laser	73	60.8 (10.2)	64.4%	Type 1: 15.1% Type 2: 79.5% Other: 5.5%	7.7 (1.1)	–	–	64.8
	Laser	72	62.8(9.4)	59.7%	Type 1: 11.1% Type 2: 87.5% Other: 1.4%	7.6 (1.3)	–	–	61.9
RESTORE (NCT00687804)	Ranibizumab 0.5 mg	115	62.9 (9.29)	62.9%	Type 1: 11.2% Type 2: 88.8%	–	–	–	64.8
	Ranibizumab 0.5 mg + laser	118	64.0 (8.15)	59.3%	Type 1: 12.7% Type 2: 86.4%	–	–	–	63.4
	Laser	110	63.5 (8.81)	52.3%	Type 1: 11.7% Type 2: 87.4%	–	–	–	62.4
RETAIN (NCT01171976)	T&E ranibizumab 0.5 mg + laser	121	63.7 (9.1)	64.5%	Type 1: 8.3% Type 2: 91.7%	7.8 (1.4)	–	–	61.7
	T&E ranibizumab 0.5 mg	128	63.0 (9.8)	60.2%	Type 1: 9.4% Type 2: 90.6%	7.9 (1.3)	–	–	63.9
	PRN ranibizumab 0.5 mg	123	64.5 (9.7)	62.6%	Type 1: 8.1% Type 2: 91.9%	8.0 (1.2)	–	–	64.7
REVEAL (NCT00989989)	Ranibizumab 0.5 mg	133	60.7 (9.37)	60.9%	Type 1: 0.8% Type 2: 99.2%	7.5 (1.02)	–	–	58.8
	Ranibizumab 0.5 mg + laser	132	61.2 (10.52)	50.8%	Type 1: 1.5% Type 2: 98.5%	7.4 (1.05)	–	–	58.5
	Laser	131	61.5 (9.68)	57.3%	Type 1: 1.5% Type 2: 98.5%	7.5 (1.10)	–	–	58.4
RIDE and RISE (NCT00473382, NCT00473330)	Ranibizumab 0.3 mg	250	–	–	–	–	–	–	–
	Ranibizumab 0.5 mg	251	–	–	–	–	–	–	–
	Sham	253	–	–	–	–	–	–	–
	Aflibercept 2q4	290	–	–	–	–	–	–	–
	Aflibercept 2q8	286	–	–	–	–	–	–	–

Study	Treatment Arm	N	Age (Years, mean (SD)	Gender (Male %)	Type of Diabetes	A1C (mean, SD)	Previous Treatments	Lens Status	Baseline BCVA (Letters)
VISTA and VIVID (NCT01363440, NCT01331681)	Laser	286	–	–	–	–	–	–	–
Ekinci 2014	Bevacizumab 1.25 mg	50	68 (9)	36%	–	–	–	–	logMAR 0.22
	Ranibizumab 0.05 mg	50	65 (14)	28%	–	–	–	–	logMAR 0.24
Maturi 2015	Dexamethasone 0.7 mg + bevacizumab 1.25 mg	21	61 (10)	43%	Type 1: 7.5% Type 2: 92.5%	–	Bevacizumab: 95%	Pseudophakic: 38.1% Phakic: 61.9%	65
	Bevacizumab 1.25 mg	19	–			–	Bevacizumab: 89%	Pseudophakic: 36.8% Phakic: 63.2%	64
Jorge 2012	Bevacizumab 1.5 mg	–	–	–	–	–	–	–	logMAR 0.6
	Ranibizumab 0.5 mg	–	68 (9)	–	–	–	–	–	logMAR 0.63

2q4 = 2 mg monthly; 2q8 = 2 mg every 8 weeks; A1C = glycated hemoglobin; AC IOL = anterior chamber intraocular lens; BCVA = best-corrected visual acuity; IQR = interquartile range; logMAR = logarithmic minimal angle of resolution; PC IOL = posterior chamber intraocular lens; PRN = pro re nata (as needed); SE = standard error; SOC = standard of care; T&E = treat and extend; VEGF = vascular endothelial growth factor.

Source: Manufacturer-supplied indirect treatment comparison.[65]

[redacted]

Figure 4: [redacted]

Figure 4 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 35: [redacted]

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Source: Manufacturer-supplied indirect treatment comparison.[65]

Figure 5:

Figure 5 contained confidential information and was removed at the request of the manufacturer.

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 36:

Source: Manufacturer-supplied indirect treatment comparison.[65]

Figure 6:

Figure 6 contained confidential information and was removed at the request of the manufacturer.

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 37: [redacted]

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Source: Manufacturer-supplied indirect treatment comparison.[65]

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Figure 7: [redacted]

Figure 7 contained confidential information and was removed at the request of the manufacturer.

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Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 38: [redacted]

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Source: Manufacturer-supplied indirect treatment comparison.[65]

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Figure 8: [redacted]

Figure 8 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 39: [redacted]

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Source: Manufacturer-supplied indirect treatment comparison.[65]

Figure 9: [redacted]

Figure 9 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 40:

Source: Manufacturer-supplied indirect treatment comparison.[65]

Figure 10:

Figure 10 contained confidential information and was removed at the request of the manufacturer.

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 41:

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Source: Manufacturer-supplied indirect treatment comparison.[65]

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Figure 11: [redacted]

Figure 11 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Source: Manufacturer-supplied indirect treatment comparison.

Table 42:

Source: Manufacturer-supplied indirect treatment comparison.[65]

Figure 12:

Figure 12 contained confidential information and was removed at the request of the manufacturer.

Source: Manufacturer-supplied indirect treatment comparison.[65]

Table 43: [redacted]

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Source: Manufacturer-supplied indirect treatment comparison.[65]

Critical Appraisal

[redacted]

[redacted]

Conclusion

Based on the results of the submitted ITC, treatment with [redacted]

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