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CADTH COMMON DRUG REVIEW

Clinical Review Report

Dexamethasone (Ozurdex)

(Allergan Inc.)

Indication: For the treatment of adult patients with diabetic macular edema who are pseudophakic

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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATE	arterial thrombotic event
AUC	area under the curve
BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
CCB	Canadian Council of the Blind
CDR	CADTH Common Drug Review
CI	confidence interval
CNIB	Canadian National Institute for the Blind
CRT	central retinal thickness
DME	diabetic macular edema
DR	diabetic retinopathy
EQ-5D	EuroQol 5-Dimensions Health Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
FFB	Foundation Fighting Blindness
IDC	indirect comparison
IOP	intraocular pressure
ITT	intention to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	last observation carried forward
LS	least squares
MCID	minimally clinically important difference
NA	not available
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NICE	National Institute for Health and Care Excellence
NR	not reported
OCT	optical coherence tomography
PP	per-protocol
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
SD-OCT	spectral domain optical coherence tomography
TD-OCT	time domain optical coherence tomography
VEGF	vascular endothelial growth factor
WDAE	withdrawal due to adverse event

Drug	Dexamethasone (Ozurdex)
Indication	For the treatment of adult patients with diabetic macular edema who are pseudophakic
Reimbursement Request	As per the Health Canada indication
Dosage Form	700 mcg intravitreal implant
NOC Date	April 16, 2015
Manufacturer	Allergan Inc.

Executive Summary

Introduction

Diabetic macular edema (DME) generally manifests as slowly progressive vision loss. Signs of DME include blurred vision, retinal hemorrhages, retinal detachment, colours appearing “washed out” or faded, changes in contrast sensitivity, impaired colour vision, gaps in vision (scotomas), and potentially permanent vision loss. Persistent elevation of blood glucose, characteristic of diabetes mellitus, can cause damage to blood vessels on a microvascular level such as those in the eye resulting in diabetic retinopathy (DR). Some patients with diabetic retinopathy (DR) and continued poorly managed blood glucose may then experience DME.[1] The prevalence of diabetes in Canada is 9.2%, and it is estimated that there are 528,524 patients with DME across Canada, 13,530 of whom experienced vision impairment.[2,3] Overall, more than 50% of patients with DME experiencing vision loss were older than 60 years and more than 22% of patients with DME experiencing vision loss are patients within the First Nation communities.[2] Furthermore, some patients with DME are pseudophakic (natural lens surgically replaced with an artificial lens) and would therefore comprise a subset of the overall DME population.

Macular laser photocoagulation therapy for DME was the standard of care for more than 25 years before the introduction of anti-vascular endothelial growth factor (VEGF) drugs, and is still widely used following anti-VEGF therapy.[4] Recently, clinical studies have shown robust efficacy and safety for frequent (monthly or bimonthly) anti-VEGF injections for the treatment of DME patients.[5-8] However, there is limited evidence of benefit and risk of continuous anti-VEGF injections among patients who did not respond well to prior anti-VEGF therapy.[9] Canadian evidence based guidelines and clinical treatment algorithms recommend anti-VEGF injections as therapy for most patients with clinically significant DME involving central vision. If there is no response after six months treatment, patients should switch to intravitreal steroids, vitrectomy, or laser.[10,11]

Dexamethasone is a synthetic glucocorticoid receptor agonist, analogue to the naturally occurring glucocorticoids hydrocortisone and cortisone, and is administered into the vitreous on an as-needed basis to mitigate the effects of DME.[12] Corticosteroids target multiple mediators in DME, possessing anti-inflammatory, anti-vascular permeability, and

anti-angiogenic properties.[13] These drugs act by decreasing the production of mediators such as interleukin-6 and VEGF, and may also directly stabilize the blood-retinal barrier.[14] In contrast to anti-VEGF drugs, which inhibit the actions of synthesized VEGF, corticosteroids act to directly decrease the synthesis of VEGF.[15] Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular edema.[16-18] In general, treatment with dexamethasone is associated with elevated intraocular pressure and secondary cataract, which is consistent with the adverse events (AEs) profile of intravitreal steroid therapies.[12,19]

Dexamethasone (Ozurdex) has a Health Canada–approved indication for the treatment of macular edema following central retinal vein occlusion, the treatment of noninfectious uveitis affecting the posterior segment of the eye, and for the treatment of adult patients with DME who are pseudophakic. The objective of this review is to perform a systematic review of the beneficial and harmful effects of dexamethasone 700 mcg intravitreal injection for the treatment of adults with DME who are pseudophakic.

Results and Interpretation

Included Studies

No trials were identified that exclusively enrolled the patient population of interest for this review (i.e., adults with DME who are pseudophakic). Rather, the evidence for this review as it pertains to the use of dexamethasone 700 mcg intravitreal injection was derived from subgroups of adult patients with DME who were pseudophakic from two similarly designed masked phase III multi-centre, multinational and sham-controlled pivotal randomized controlled trials (RCTs). MEAD-010 (N = 494) and MEAD-011 (N = 554) randomized DME patients to a 1:1:1 ratio of dexamethasone 700 mcg, dexamethasone 350 mcg (not of a Health Canada–approved dose) or sham treatment. Overall, only a subset of the enrolled population (a pre-specified subgroup of adult patients with DME who are pseudophakic [MEAD-010, n = 94; MEAD-011, n = 93] derived from the intent-to-treat population (ITT) and the safety population) met the Health Canada–approved indication. The primary efficacy outcome was the average best-corrected visual acuity (BCVA) mean change from baseline evaluated after three years of follow-up based on Early Treatment for Diabetic Retinopathy Study (ETDRS) charts using an area-under-the-curve (AUC) approach. The MEAD trials were not initially designed to assess the average BCVA mean change from baseline as the primary end point. Rather, the original end point was the proportion of patients who achieved at least a 15-letter improvement by end of study. Subsequent to a protocol amendment was the primary end point changed to include the average BCVA mean change from baseline. Secondary outcomes included other BCVA end points, retinal thickness, health-related quality of life, and vision-related quality of life.

Key limitations associated with the interpretation results of the subgroup of adult patients who are pseudophakic, as drawn from the MEAD trials, include lack of subgroup stratification leading to imbalances in patient characteristics and therefore concerns with randomization potentially leading to confounding; lack of adjustments for multiple statistical testing across end points, subgroups and sensitivity analyses; variability of treatment effect at different time points; imbalances in patient disposition and patient characteristics; and uncertain generalizability to the Canadian setting.

As there were no studies identified that compared dexamethasone against other active treatments for DME, according to the selection criteria outlined in Table 3, the results of the manufacturer's indirect comparison (IDC) for the treatment of adult patients with DME were reviewed. In addition, three non-pivotal phase II trials comparing dexamethasone with other active treatments for DME were reviewed.

Efficacy

The efficacy results presented from the MEAD trials are for the Health Canada–approved dose of dexamethasone, as a 700 mcg intravitreal injection for the subgroup of patients that are pseudophakic.

The adjusted least squares mean differences in average BCVA mean change from baseline between dexamethasone 700 mcg and sham treatment as measured by ETDRS and using the AUC approach (the primary outcome) in the intention-to-treat (ITT) population were 5.9 letters [redacted], $P < 0.001$ and 3.6 letters [redacted], $P = 0.018$ in MEAD-010 and MEAD-011, respectively. Sensitivity analyses using a per-protocol (PP) population in both MEAD-010 and MEAD-011 were consistent with the primary analysis. According to the clinical expert consulted for this review, the degree of improvement reported in the MEAD trials may be considered clinically relevant, especially for patient with poor visual acuity. However, between-group differences did not exceed a 10-letter improvement. The difference in the proportion of patients achieving a ≥ 15-letter improvement versus sham was 18.1% (95% confidence interval [CI], 0.8 to 35.4; $P = 0.043$) and 6.0% (95% CI, –5.7 to 17.8; $P = 0.461$) in MEAD-010 and MEAD-011, respectively.

The adjusted least squares mean differences in average central retinal thickness (CRT), as measured by optical coherence tomography (OCT) using the AUC approach, were [redacted] in MEAD-010 and MEAD-011, respectively. The changes from baseline in CRT as measured by OCT were also evaluated at the last study visit and in a sensitivity analysis using the PP population and were consistent with the AUC method.

The MEAD trials evaluated vision-related outcomes using the using the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25). Overall, no statistically significant differences were observed between treatment groups with adjusted average least squares mean differences for the overall composite score of [redacted] in MEAD-010 and MEAD-011, respectively. Minimal clinically important differences for the NEI-VFQ-25 (among the general DME population) between 3.3 and 6.13 points in the overall composite score have been reported.[20] No post-baseline data associated to health-related quality of life measures using the Short Form (36) Health Survey (SF-36) or the EuroQol 5-Dimensions Health Questionnaire (EQ-5D) were provided for the subgroup of patients who are pseudophakic in the MEAD trials.

No trials were identified that directly compared dexamethasone against other active treatments for DME according to the criteria outlined in the CADTH Common Drug Review protocol (Table 3). The manufacturer submitted an unpublished IDC to assess the comparative efficacy and safety of dexamethasone for use in the treatment of DME. The manufacturer–submitted IDC was originally prepared for the National Institute for Health and Care Excellence (NICE) in 2014. [redacted]

Three phase II studies (RAN study, BEVORDEX study and the COMB study) that evaluated the effects of dexamethasone compared with anti-VEGF therapies (ranibizumab, bevacizumab) for the treatment of adult patients with DME were also summarized in Appendix 7. The study findings suggested a similar change from baseline in the BCVA letters between treatment with dexamethasone and anti-VEGF therapy. However, these studies were designed to evaluate the effects of dexamethasone in the general DME population, not the pseudophakic subgroup of patients that is of interest for this review. Of the overall number of enrolled patients, 24% to 50% were pseudophakic. Some pseudophakic subgroup results were reported, however the lack of stratification at randomization based on this factor, as well as the absence of reporting on baseline characteristics for the pseudophakic population make it difficult to assess the comparative efficacy and harms between dexamethasone and anti-VEGF drugs (i.e., bevacizumab and ranibizumab). These studies were also likely underpowered to detect differences between treatments in the pseudophakic subgroup, there was no control for multiple statistical testing, study durations were short, and no Canadian sites were included.

Harms

Frequencies of AEs, serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and notable harms were provided for the individual MEAD trials; however, the most common AEs, SAEs, WDAEs, and notable harms were only reported based on a pooled analysis of the two MEAD trials.

A greater proportion of patients in the dexamethasone group experienced AEs compared with the sham group. AEs that occurred more frequently in the dexamethasone treatment

groups compared with the sham groups were elevated intraocular pressure (IOP) and secondary cataracts, which is consistent with the adverse event profile of intravitreal steroid therapies.[12,19].The frequency of blepharitis in the dexamethasone groups was lower than those observed in the sham groups. Similar frequencies of SAEs were reported in the dexamethasone groups compared with the sham groups. No data were provided for the subgroup of patients who are pseudophakic regarding the most common reasons for ocular SAEs. The overall WDAEs were similar between treatment groups, however; no data regarding the withdrawals due to ocular AEs were provided for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

The occurrence of the remaining notable harms — specifically, eye inflammation, retinal detachment, arterial thrombotic event (ATE), dislocated implants, glaucoma, damage to optic nerve, conjunctival hemorrhage, and vitreous hemorrhage — was similar in both treatment groups across the MEAD trials. Endophthalmitis, eye infection, defects in visual acuity and visual field, and necrotizing retinitis were not reported in the MEAD trials.

Other Considerations

In consideration of the potential place in therapy for dexamethasone 700 mcg intravitreal injection (first- or second-line), the protocol for CADTH's Common Drug Review included the examination of a subgroup of patients with DME who are pseudophakic and who are either unsuitable for anti-VEGF therapy or have had an inadequate response to prior anti-VEGF therapy. However, only between [redacted] and [redacted] of patients included in the MEAD trials had prior experience with anti-VEGF therapy; therefore, it is unclear if the results of the MEAD trials can be generalized to patients with prior experience or prior inadequate response to anti-VEGF therapy. Studies by Pacella et al. and Gonzalez et al. as well as a systematic review and meta-analysis conducted by Khan et al. evaluated the effects of dexamethasone in the general DME population who were refractory to anti-VEGF therapy; however results in patients with DME who are pseudophakic were not reported.[9,21,22] Furthermore, the criteria for anti-VEGF therapy being unsuitable mostly remains unclear. The clinical expert consulted for this CDR review noted that there are different circumstances that may define a lack of suitability, such as history of glaucoma, allergies to anti-VEGF drugs and its components, pregnancy, phakic lens status with or without recent myocardial infarction, ischemic heart disease, or stroke. Similarly, patients may be considered unsuitable if they are unable to return for their regular monthly or bimonthly intraocular injection of anti-VEGF either due to transportation difficulties or work demands, which are especially common among younger patients who are actively employed.

Potential Place in Therapy[1]

The current standard of care for patients requiring treatment of center-involved DME is intraocular injection of anti-VEGF drugs. While the beneficial effects of anti-VEGF drugs typically only last between four and six weeks at the most, some patients may not adequately respond to treatment. Furthermore, treating DME with anti-VEGF drugs usually requires monthly or bimonthly injections which create barriers to adherence and therefore optimized treatment. In these cases, further improvement in BCVA is still possible; however, a switch to another anti-VEGF may not be effective or appropriate. According to the clinical expert consulted for this CDR review, all clinical studies associated to the treatment of DME with anti-VEGF therapy or intravitreal steroid therapy

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

compared favourably to laser treatment. Therefore, currently preferred clinical practice for center-involved DME is either anti-VEGF or intravitreal steroid injections, with laser therapy being reserved for those with non–center-involved DME.

For some patients, switching to treatment with an intravitreal steroid such as dexamethasone may be a reasonable alternative; however, the use of this medication class for many patients is currently limited due to elevated IOPs as well as the development and progression of cataracts. The clinical expert consulted for this CDR review highlighted potential issues in the prescribing of dexamethasone given that treatment is typically associated with increased frequency of elevated IOP, likely requiring IOP-lowering drugs, which may add to the treatment burden (number of concomitant treatments) and the overall cost of treatment. However, the expert noted that IOP-lowering treatments would mostly entail the use of topical medications, which should not be too bothersome. Furthermore, the development and progression of secondary cataracts as a result of intravitreal steroid injections would likely require further treatment to address the issue. For patients who have had complete removal of their natural lens, secondary cataracts will not form on the artificial lens. Generally, treatment regimens with intravitreal steroids are less frequent than those associated with anti-VEGF drugs (quarterly or biannual injections).

The clinical expert consulted for this CDR review noted that there are different circumstances where alternate therapies such as a dexamethasone implant should be considered, such as in patients who are allergic to anti-VEGF drugs and the components or in women during pregnancy given the teratogenicity of anti-VEGF therapies. In clinical practice, patients with DME who are pseudophakic without any history of glaucoma would be the best candidates to receive treatment with dexamethasone. The same clinical expert noted that intravitreal steroid injections should be particularly considered in those who are pseudophakic with or without recent myocardial infarction, ischemic heart disease, or stroke. Similarly, dexamethasone may also be considered in patients who are unable to return for their regular monthly or bimonthly anti-VEGF intraocular injection either due to transportation difficulties or work demands, which are especially common among younger patients who are actively employed. Patients who do not respond to the anti-VEGF treatment after 3 consecutive monthly intraocular injections or who have inadequate response to anti-VEGF therapy would also be considered for treatment with dexamethasone.

The clinical expert also highlighted that, overall, the effects of dexamethasone on BCVA reported in the MEAD trials (especially in MEAD-011) were found to be modest when compared with the change in BCVA that has been reported for anti-VEGF therapies. The same clinical expert noted that no specialized diagnostic test would be needed to identify patients in whom dexamethasone may be appropriate and that clinicians would likely base their decision on BCVA as well as OCT CRT, which would be routinely requested in this patient population.

Conclusions

The CDR systematic review included two masked, phase III, sham-controlled RCTs designed to assess the benefits and harms of dexamethasone in adult patients with DME. Given the Health Canada–approved indication for dexamethasone, the CDR review focused on the results of a subgroup of patients from the MEAD trials (i.e., adult patients with DME who are pseudophakic [MEAD-010 n = 94; MEAD-011 n = 93]).

Overall, dexamethasone was associated with a statistically significant improvement when compared with sham for the primary outcome (average BCVA mean change from baseline as measured by ETDRS based on the AUC approach) for patients with DME who are pseudophakic in both MEAD trials, while the proportion of patients achieving a ≥ 15 letter improvement was reported to be statistically significantly greater in the dexamethasone group in MEAD-010 only. However, between-group differences did not exceed a 10-letter improvement in either MEAD-010 or MEAD-011 (differences of 5.9 and 3.6 letters respectively) and were considered modest by the clinical expert consulted for this review. Further, the magnitude of improvement in visual acuity with dexamethasone compared with sham is uncertain, given the results are for a subgroup that was not subject to stratification at randomization and for which there was no adjustment for multiple testing. More patients in the dexamethasone group experienced AEs compared with the sham group in the MEAD trials. The most commonly reported AEs that occurred more frequently in the dexamethasone treatment groups compared with the sham groups were elevated IOP, which is consistent with the adverse event risk profile of intravitreal steroid therapies.

No data from the MEAD trials were available to assess the efficacy and safety of dexamethasone 700 mcg in adults with DME who are pseudophakic and who are either unsuitable for anti-VEGF therapy or have had an inadequate response to prior anti-VEGF therapy).

Due to the lack of direct evidence of dexamethasone versus other drugs in the MEAD trials, and the limitations with the supportive evidence including the manufacturer–submitted IDC, no definitive conclusions could be made regarding the comparative efficacy and safety of dexamethasone versus other drugs (including anti-VEGFs) for the treatment of patients with DME who are pseudophakic.

Table 1: Summary of the Efficacy Results for the MEAD Trials (Pseudophakic Subgroup)

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
Baseline BCVA				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Mean letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
BCVA average change from baseline[a,b]				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	8.1 [redacted]	2.1 [redacted]	4.9 [redacted]	1.3 [redacted]
Adjusted LS MD versus sham (95% CI)	5.9 [redacted]	*P* < 0.001	3.6 [redacted]	*P* = 0.018
BCVA ≥ 15 letter improvement from baseline (last visit)				
Proportion of patients, n/N (%)	15/44 (34.1)	8/50 (16.0)	5/42 (11.9)	3/51 (5.9)
Difference versus sham (95% CI)	18.1% (0.8 to 35.4) *P* = 0.042		6.0% (–5.7 to 17.8) *P* = 0.461	
CRT as measured by OCT average change from baseline[a,b]				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	50 (98)
Adjusted LS mean change from baseline, microns (SD)	–137.4 [redacted]	–43.3 [redacted]	–125.9 [redacted]	–58.3 [redacted]
Adjusted LS MD versus sham (95% CI)	[redacted] *P* < 0.001		[redacted] *P* = 0.007	
NEI-VFQ-25				
Overall composite score[c]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at last visit (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean average change from baseline (SD)[d]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS average MD versus comparator (95% CI)	[redacted]		[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; ITT = intention to treat; LS = least squares; MD = mean difference; OCT = optical coherence tomography; SD = standard deviation.

[a] Based on AUC approach and observed data.

[b] Missing data were not imputed.

[c] LOCF was used to impute missing data.

[d] Based on AUC approach and observed data and missing data were not imputed.

Last visit refers to either month 39 or month 36 which ever was the final visit.

Outcomes were evaluated using an ITT analysis

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic

LOCF was used to impute missing data. Patients without post-baseline BCVA were set to value 0 in the analysis

The overall composite score was calculated by averaging all 11 vision-targeted subscale scores, excluding general health score.

Means and mean differences were analyzed using an ANCOVA model stratified by treatment and study as fixed effects and baseline BCVA as the covariate, with the exception of OCT retinal outcomes which utilized baseline CRT as measured by OCT as the covariate.

P values from ANOVA with treatment as a factor for baseline and ANCOVA with treatment as a factor and baseline value as a covariate for post-baseline visits.

Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Table 2: Summary of the Harms for the MEAD Trials (Pseudophakic subgroup)

Outcome	Pooled data (MEAD-010 and MEAD-011)	
	DEX 700 N = 85	Sham N = 100
AEs, n (%)		
Subjects with > 0 AEs	63 (74.1)	61 (61.0)
Most common AEs[a]		
Conjunctival hyperaemia	[redacted]	[redacted]
Posterior capsule opacification	4 (4.7)	6 (6.0)
Blepharitis	[redacted]	[redacted]
SAEs, n (%)		
Subjects with > 0 SAEs	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]
WDAEs, n (%)	[redacted]	[redacted]
Most common reasons	[redacted]	[redacted]
Deaths		
Number of deaths, n (%)	1 (1.2)	2 (2.0)
Most common reasons		
Acute renal failure	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Myocardial ischemia	[redacted]	[redacted]
Notable Harms, n (%)		
Elevated IOP	25 (29.4)	9 (9.0)
IOP increased	[redacted]	[redacted]
Ocular hypertension	[redacted]	[redacted]
Open angle glaucoma	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]
Conjunctival hemorrhage	[redacted]	[redacted]
Secondary cataract	5 (5.9)	2 (2.0)
Vitreous detachment	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]
Anterior chamber inflammation	[redacted]	[redacted]
Detachment of retinal pigment epithelium	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]
Device dislocation	[redacted]	[redacted]
Optic nerve cupping	[redacted]	[redacted]
Endophthalmitis	[redacted]	[redacted]
Eye infection	[redacted]	[redacted]
Defects in visual acuity and visual field	[redacted]	[redacted]
Necrotizing retinitis	[redacted]	[redacted]

AE = adverse event; DEX = dexamethasone; IOP = intraocular pressure; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Frequency > 5%.

Ocular harms were evaluated in the safety population.

Source: MEAD-010 CSR,[23] MEAD-011 CSR.[24]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). The persistent elevation of blood glucose can cause damage to blood vessels on a microvascular level such as those in the eye resulting in diabetic retinopathy (DR).[25] Some patients with DR and continued poorly managed blood glucose can experience swelling in the retina, known as diabetic macular edema (DME).[1] Generally, DME manifests as a slowly progressive vision loss. The Early Treatment for Diabetic Retinopathy Study (ETDRS) chart is the gold standard in measuring changes in best-corrected visual acuity (BCVA).[26] Each line contains five letters, which proportionally decrease in size as the patient reads down the chart. 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 center of the macula.[2,4,11] Signs of DME include blurred vision, retinal hemorrhages, retinal detachment, colours appearing “washed out” or faded, changes in contrast sensitivity, impaired colour vision, gaps in vision (scotomas), and potentially permanent vision loss. The development of hard exudates are typically the culprit in the significant vision impairment associated with DME.[27] Untreated DME is considered the leading cause of visual loss, visual disability, and legal blindness in people with diabetes mellitus.[1,27,28] The Eye Diseases Prevalence Research Group reported that the prevalence of DR for adults in the US was 40.3%; whereas, sight-threatening retinopathy occurred in 8.2% of such individuals.[29] Prevalence of macular edema in patients with type 1 diabetes, patients with type 2 diabetes treated with insulin therapy, and patients treated with antihyperglycemic therapies were 11%, 15% and 4%, respectively.[30] Furthermore, higher prevalence rates were identified in First Nations populations in Canada.[31,32] An observational retrospective study using records from the Southwestern Ontario database suggested that the prevalence of DME was estimated to be 15.7% and of these, 2.56% experienced vision loss that required treatment.[2] 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 experienced vision impairment.[2,3] Overall, more than 50% of patients with DME experiencing vision loss were older than 60 years, and more than 22% of patients with DME experiencing vision loss are patients within the First Nation community.[2] Furthermore, patients with DME who are pseudophakic (natural lens surgically replaced with an artificial lens) would therefore only comprise a subset of the overall DME population.

Generally, vision loss is associated with significant morbidity, including increased falls, hip fracture and mortality.[33] In addition, it has been suggested that amputation and visual loss due to DR are independent predictors of early death among patients with type 1 diabetes.[34] Such progressive visual impairment typically results in significant decrements in daily functioning and quality of life and indirect costs due to lost productivity are high if left untreated.[35-37] Therefore, early detection and treatment of DME is vital.[26,38]

Vascular endothelial growth factor (VEGF) and inflammation (as a result from damaged retinal blood vessels caused by chronic hyperglycemia) are the leading factors in the pathophysiology of DME.[39] Specifically, VEGF induces angiogenesis/neovascularization, and increases vascular permeability. Besides VEGF, hypoxia-induced placental growth factor is instrumental in contributing to vascular permeability.[40] Hypoxia induces influx of

leukocytes into the retina, another potential source of leakage-promoting proteins.[41] It acts in synergy with VEGF and contributes to the vessel abnormalities and retinal changes occurring in early DR. Recent evidence also highlights the role of inflammation in the development of DME. Inflammation due to leukostasis (accumulation of leukocytes on the surface of retinal capillaries) leads to the upregulation of intracellular adhesion molecule (ICAM)-1, found to further enhance retinal leukostasis and vascular permeability.[41] Therefore, suppression of inflammatory mediators and other permeability factors in addition to VEGF is a more comprehensive treatment strategy for DME.

Standards of Therapy

The treatment strategies for DME encompass lifestyle modification including diet and exercise, smoking cessation as well as better blood sugar, blood pressure, blood lipids, and body mass index control. Current therapies for DME can be categorized into non-pharmacological and pharmacological interventions. Non-pharmacological therapies include laser photocoagulation and surgery (vitrectomy). While approved pharmacological treatments include an anti-VEGF drugs (ranibizumab, aflibercept).

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 anti-VEGF drugs, and is still widely used following anti-VEGF therapy.[4] Laser therapy has been shown to slow and/or stabilize vision loss, but has been minimally effective in restoring vision.[42] Laser therapy also has the disadvantage of causing permanent destruction of retinal tissue during treatment.[43-45] Recently, clinical studies have shown robust efficacy and safety data for frequent (monthly or bimonthly) anti-VEGF injections for the treatment of DME patients.[5-8] However, there is limited evidence of benefit and risk of continuous anti-VEGF injections among patients who did not respond well to prior anti-VEGF therapy.[9] The results from these trials demonstrated that treatment with anti-VEGF drugs substantially improved visual and anatomic outcomes compared with laser photocoagulation, and avoids the ocular side effects associated with laser treatment. Canadian evidence based guidelines and clinical treatment algorithm recommend anti-VEGF injections as therapy for most patients with clinically significant DME involving central vision. If there is no response after six months treatment, patients should switch to intravitreal steroids, vitrectomy, or laser.[10,11] The first of the anti-VEGF drugs to be approved in Canada for the treatment of DME was ranibizumab (a humanized recombinant monoclonal antibody fragment with anti-VEGF activity) and has since become standard of care.[4,46] The recommended dose of ranibizumab is 0.5 mg administered as a single intravitreal injection monthly until stable visual acuity is achieved for three consecutive monthly assessments. This is followed by monthly monitoring and a “treatment as-needed” regimen.[46] Other anti-VEGF therapies include aflibercept at the recommended dose of 2.0 mg administered by intravitreal injection monthly for the first five consecutive doses, followed by one injection every two months.[47] Bevacizumab, another anti-VEGF drug approved for the treatment of cancers such as colorectal and lung cancer, has been used off label as monotherapy as an intravitreal treatment for macular edema in some Canadian jurisdictions. Although not approved for use in DME patients in Canada, the 2016 CADTH Therapeutic Review examined the evidence on age-related macular edema, diabetic macular edema, retinal vein occlusion, or choroidal neovascularization due to pathologic myopia, and issued a recommendation suggesting bevacizumab as the preferred initial anti-VEGF therapy, based on similar clinical effectiveness and lower cost compared with other anti-VEGF treatments.[48] Triamcinolone acetonide monotherapy administered as an intravitreal steroid injection is also

considered for off label in Canada for the treatment of macular edema according to the clinical expert consulted for this CDR review.

Although anti-VEGF therapies are widely accepted as the standard of care for patients with DME, they require frequent (eight to 12 injections per eye, per year) to achieve desirable outcomes, acting as a barrier to compliance. Anti-VEGF therapies are also associated with an increased risk of cerebro- and cardiovascular events such as thromboembolic events; therefore, they may not be appropriate in all DME patients. Furthermore, studies have shown that around 40% of patients on anti-VEGF therapy have inadequate response to treatment.[9]

Drug

Dexamethasone is a synthetic glucocorticoid receptor agonist, analogue to the naturally occurring glucocorticoids hydrocortisone and cortisone and is administered into the vitreous on an as-needed basis to mitigate the effects of DME.[12] Corticosteroids target multiple mediators in DME, possessing anti-inflammatory, anti-vascular permeability, and anti-angiogenic properties.[13] These drugs act by decreasing the production of mediators such as interleukin-6 and VEGF, and may also directly stabilize the blood-retinal barrier.[14] In contrast to anti-VEGF drugs which inhibit the actions of synthesized VEGF, corticosteroids act to directly decrease the synthesis of VEGF.[15] Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular edema.[16-18]

According to the Health Canada–approved product monograph, dexamethasone can be used for the treatment of macular edema following central retinal vein occlusion, noninfectious uveitis affecting the posterior segment of the eye and adult patients with DME who are pseudophakic.[12] The indication under review is limited to the latter (for the treatment of adult patients with DME who are pseudophakic).[12] Dexamethasone is administered using the Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS), which consists of a sterile, single-use system intended to deliver one biodegradable implant into the vitreous, and was designed to prolong the duration of the dexamethasone effect in the eye. The biodegradable implant delivers a 700 mcg dose of dexamethasone to the vitreous with gradual release over time allowing for sustained drug levels to the target areas. Patients are eligible for retreatment on an as-needed basis. According to the product monograph of dexamethasone implant, no more than two consecutive injections should be used, and an interval of approximately six months should be allowed between the two injections.[12] In general, treatment with dexamethasone is associated with elevated intraocular pressure (IOP) and cataracts, which is consistent with the AEs profile of intravitreal steroid therapies.[12,19] There are currently no other approved steroids for the treatment of DME in Canada, however, according to the clinical expert consulted for this CDR review, triamcinolone acetonide may be considered for off label use.

Dexamethasone is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases, patients with advanced glaucoma, patients with known hypersensitivity to any components of this product or to other corticosteroids, patients who have aphakic eyes with rupture of the posterior lens capsule and patients with anterior chamber intraocular lens and rupture of the posterior lens capsule.[12]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of dexamethasone 700 mcg intravitreal injection for the treatment of adults with DME who are pseudophakic.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion criteria for the systematic review

Patient Population	Adults with diabetic macular edema who are pseudophakic Subgroups • Baseline visual acuity • Baseline A1C • History of cerebro- or cardiovascular disease • Patients who are either unsuitable for anti-VEGF therapy or have had inadequate response to prior anti-VEGF therapy
Intervention	Dexamethasone 700 mcg intravitreal injection
Comparators	Laser photocoagulation therapy Triamcinolone acetonide[a] Anti-VEGF drugs (e.g., bevacizumab, ranibizumab, aflibercept) Sham
Outcomes	**Key efficacy outcomes:** • Change from baseline in visual acuity • Health-related quality of life[b] • Vision-related function[b] • Blindness (legal) • Change in CRT **Other efficacy outcomes:** • Proportion of fellow eye involvement[c] **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality • Notable harms: endophthalmitis, eye inflammation, eye infections, retinal detachment, increased intraocular pressure, ATE, dislocated implants, glaucoma, damage to optic nerve, defects in visual acuity and visual field, necrotizing retinitis, conjunctival hemorrhage, vitreous hemorrhage
Study Design	Published and unpublished Phase III RCTs

AE = adverse event; ATE = arterial thrombotic event; CRT = central retina thickness; RCT = randomized controlled trial; SAE = serious adverse event; VEGF = vascular endothelial growth factor; WDAE = withdrawal due to adverse event.

[a] No Health Canada–approved indication for the treatment of DME.

[b] Assessed by validated measures.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946-) through Ovid; Embase (1974-) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ozurdex (dexamethasone) and DME.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year 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 October 27, 2017. Regular alerts were established to update the search until the meeting of CADTH's Canadian Drug Expert Committee (CDEC) on February 21, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* 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, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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 3.

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 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

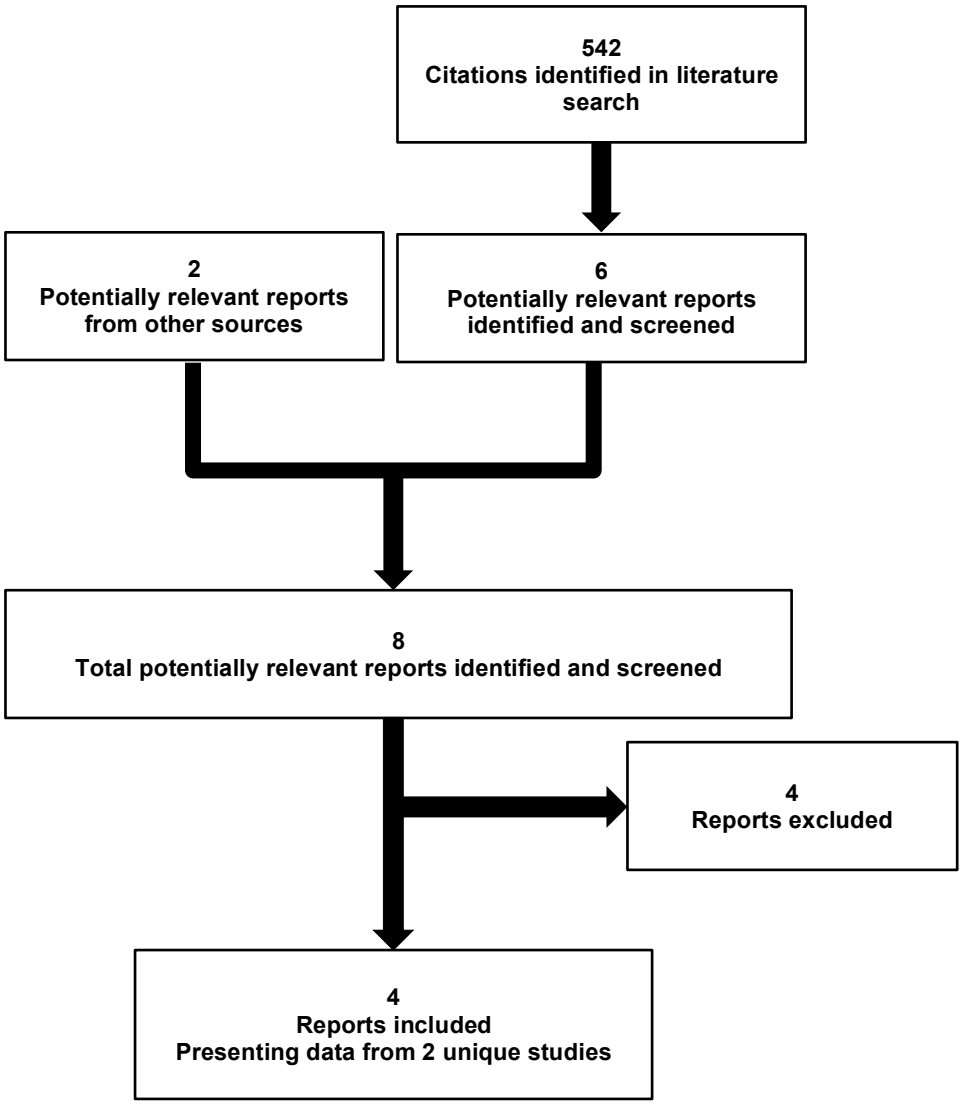

Table 4: Details of Included Studies

		MEAD-010	MEAD-011
Designs and Populations	**Study Design**	Masked, multi-centre, multinational, sham-controlled, Phase III, RCT	
	Locations	59 centres in 10 countries Australia, Canada, Israel, Philippines, South Africa, US, and Western Europe	72 centres in 14 countries Asia, Canada, India, New Zealand, South America, UK, US, and Western Europe
	Randomized (N)	494[a]	554[b]
	Inclusion Criteria	Adults with type 1 or type 2 diabetes mellitus defined as any one of the following: • Current regular use of insulin for the treatment of diabetes • Current regular use of oral hypoglycemic drug(s) for the treatment of diabetes • Diabetes defined by the presence of any one or combination of the following ADA guidelines: o Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus plasma glucose concentration at any time of the day regardless of time since last meal ≥ 11.1 mmol/L o 8-hour fasting plasma glucose ≥ 7.0 mmol/L o 2-hour postload (75 g) glucose ≥ 11.1 mmol/L during an oral glucose tolerance test. DME in the study eye defined as clinically observable macular edema involving the center of the macula (fovea) associated with diabetic retinopathy with any of the following characteristics: • Prior medical therapy for DME • Prior macular laser(s) for DME with the most recent laser at least 3 months prior to qualification/baseline when, in the opinion of the investigator, the patient would be able to improve 15 or more letters in BCVA from baseline with the resolution of the macular edema despite the presence of macular laser scars • In the investigator's opinion the patient would not benefit from macular laser treatment • The patient refused laser treatment BCVA score between 34 letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye measured by the ETDRS method at qualification/baseline Retinal thickness of ≥ 300 µm as measure by OCT in the 1 mm central macular subfield of the study eye at qualification/baseline as determined by the investigator Patients who had received intravitreal triamcinolone acetonide must have satisfied the following: • The intended dose for each injection was 4.0 mg or less • The most recent dose was at least 6 months prior to the qualification/baseline visit • No treatment-related adverse event was seen that, in the opinion of the investigator, had the potential to worsen or reoccur with study treatment	
	Exclusion Criteria	A1C > 10.0% at the qualification/baseline visit Any ocular condition in the study eye that, in the opinion of the investigator, would have prevented a 15-letter improvement in visual acuity (e.g., severe macular ischemia, extensive macular laser scarring or atrophy) Presence of BRVO, CRVO, uveitis, pseudophakic cystoid macular edema, or any other condition in the study eye that could have been contributing to macular edema Glaucoma, optic nerve head or visual field damage consistent with glaucoma Aphakia or an anterior chamber intraocular lens in the study eye	

		MEAD-010	MEAD-011
		History of intraocular laser or incisional surgery in the study eye within 90 days before study entry History of pars plana vitrectomy, active iris, or retinal neovascularization in the study eye Other systemic disease History of IOP elevation in response to steroid treatment in either eye that resulted in any of the following: • ≥ 10 mm Hg increase in IOP from baseline with an absolute IOP ≥ 25 mm Hg Ocular hypertension in the study eye at qualification/baseline with any of the following: • IOP > 23 mm Hg if taking no anti-glaucoma medications • IOP > 21 mm Hg if taking 1 anti-glaucoma medication • Use of 2 or more anti-glaucoma medications (combination products were to be considered 2 medications). Periocular depot of steroids to the study eye within 6 months prior to qualification/baseline Current use or anticipated use of systemic steroids during the study History of use of intravitreal steroids in the study eye other than triamcinolone acetonide History of use of intravitreal bevacizumab, ranibizumab, or pegaptanib in the study eye within 3 months before the qualification/baseline visit History of use of any intravitreal drug in the study eye other than triamcinolone acetonide, bevacizumab, ranibizumab, or pegaptanib, or intravitreal doses of triamcinolone acetonide > 4 mg, bevacizumab > 1.25 mg, ranibizumab > 0.5 mg, or pegaptanib > 0.3 mg Previous enrolment in a DEX PS DDS applicator system clinical trial	
DRUGS	**Intervention**	Dexamethasone 350 mcg and 700 mcg intravitreal injection at day 0[c] Patients were eligible for retreatment if retinal thickness in the 1 mm central macular subfield by OCT was > 175 µm, or upon investigator interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the center subfield)[d] Study treatment procedure was not to be performed more often than approximately every 6 months	
	Comparator(s)	Sham procedure using a needleless applicator pressed against the conjunctiva.	
DURATION	**Phase**		
	Treatment	3 years	
	Follow-up	1, 7, and 21 days post injection Regular visits every 1.5 months for the first year and every 3 months thereafter	
OUTCOMES	**Primary End Point**	Average BCVA mean change from baseline in BCVA as measured by ETDRS (AUC approach)[e]	
	Secondary End Points	• BCVA change from baseline at each visit • Proportion of patients with improvement/worsening of 10 or more letters from baseline • Proportion of patients with improvement/ worsening of 15 or more letters from baseline • Categorical change from baseline • Average change from baseline in retinal thickness of the central subfield during the study (AUC approach) • Change from baseline in retinal thickness of the central subfield at each visit	

		MEAD-010	MEAD-011
	Other End points	• NEI-VFQ-25 • EQ-5D • SF-36	
NOTES	**Publications**	Boyer 2014[49]	

A1C = glycated hemoglobin; ADA = American Diabetes Association; AUC = area under the curve; BCVA = best-corrected visual acuity; BRVO = branched retinal vein occlusion; CRVO = central retinal vein occlusion; DEX = dexamethasone; DDS = drug delivery system; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; EQ-5D = EuroQol 5 Dimension Health Questionnaire; IOP = intraocular pressure; OCT = optical coherence tomography; PS = posterior segment; RCT = randomized controlled trial; SF36v1 = Short Form (36) Health Survey version 1; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.

[a] 166 patients randomized to dexamethasone 350 mcg.

[b] 181 patients randomized to dexamethasone 350 mcg.

[c] The Health Canada–approved indication for dexamethasone is for 700 mcg dexamethasone intravitreal injection and therefore the dexamethasone 350 mcg intravitreal injection will not be discussed in this CDR review.

[d] Original retreatment criteria based on CRT as measured by OCT was > 225 µm. Threshold was changed to > 175 µm subsequent to a protocol amendment.

[e] Original primary end point was the proportion of patients with ≥ 15 letter improvement. The protocol was subsequently amended and the primary end point changed to the average BCVA mean change (AUC approach) from baseline during the study.

Source: Boyer 2014,[49] MEAD-010 CSR,[23] MEAD-011 CSR,[24] CDR Submission.[50]

Included Studies

Description of Studies

No trials were identified that exclusively enrolled the patient population of interest for this review (adults with DME who are pseudophakic). Thus this review includes two phase III randomized controlled trials (RCTs) that were pivotal in the Health Canada submission (Table 4).

Studies 206207-010 and 206207-011, hereafter referred to as MEAD-010 (N = 494) and MEAD-011 (N = 554), respectively, were similarly designed masked, sham-controlled, phase III superiority RCTs. Both trials were multi-centre and multinational, and recruited patients from centres located in North America (including Canada).

Populations

Inclusion and Exclusion Criteria

The inclusion criteria across both MEAD trials were similar, and enrolled a broader patient population than the patient population for which a Health Canada indication was granted; i.e., the trials were not restricted to DME patients who were pseudophakic. Rather, both trials included adults with type 1 or type 2 diabetes mellitus with fovea-involved DME and BCVA score between 34 letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye as measured by the ETDRS method at qualification/baseline. Lens status was determined using retroillumination photography and biomicroscopy. Retinal thickness ≥ 300 µm as measured by OCT in the 1 mm central macular subfield of the study eye at qualification/baseline was also required for enrolment. Additional inclusion and exclusion criteria are detailed in Table 4.

If both eyes were eligible for the studies, the eye with shorter duration of macular edema was to be selected. The study eye was identified at the qualification/baseline visit and remained the same throughout the entire study duration in both MEAD trials. Only the study eye was treated in the studies.

Both MEAD trials were initially designed to assess the efficacy and safety of dexamethasone in the general DME population (MEAD-010 [N = 494] and MEAD-011 [N = 554]). However, due to lack of efficacy due to confounding associated with cataracts, the Health Canada–approved indication is limited to adult patients with DME who are pseudophakic, based on findings for the relevant subpopulation enrolled in the MEAD trials (MEAD-010, n = 141; MEAD-011, n = 134 across the dexamethasone 700 mcg, 350 mcg and sham treatment groups), that were derived from the intent-to-treat population (ITT) and the safety population of the overall DME population.[51] Accordingly, the results presented in this CDR review are for a subgroup of patients from the MEAD trials that are pseudophakic.

Baseline Characteristics

Details of patients' baseline characteristics are presented in Table 5.Generally, the distributions of patient characteristics for the pseudophakic subpopulation were imbalanced across treatment groups and across trials.

Patients in the pseudophakic subgroup enrolled in the MEAD trials had a mean age that ranged between [redacted] and [redacted] years (SD ranged between [redacted] and [redacted]) of whom the majority ([redacted] to [redacted]) was older than 65 years of age. In the MEAD-010 trial, there were differences in the distribution of ages between groups. More than half of the patients enrolled in the MEAD trials were male ranging between [redacted] and [redacted] in both MEAD trials; however, MEAD-010 enrolled more male patients than MEAD-011. The majority of patients in both trials were Caucasian (50.0% to 90.0%); however, MEAD-011 had a greater representation of patients from different races/ethnicities (up to [redacted] Asian and [redacted] Hispanic). Overall, patients had mean IOP that ranged between [redacted] and [redacted] (SD ranged between [redacted] and [redacted]), mean systolic blood pressure that ranged between [redacted] and [redacted] (SD ranged between [redacted] and [redacted]), mean diastolic blood pressure that ranged between [redacted] and [redacted] (SD ranged between [redacted] and [redacted]).

Most patients received prior therapy in both MEAD trials, the most common being laser therapy ([redacted] to [redacted]). Only a minority of patients had prior anti-VEGF therapy ([redacted] to [redacted]), and a greater percentage of patients (approximately 7% difference) in the sham group had prior anti-VEGF therapy compared with the dexamethasone group in MEAD-010.

The majority of patients in both MEAD trials had type 2 diabetes (88.0% to 100%) with differences between treatment groups in MEAD-010 with respect to the percentage of patients with type 1 versus type 2 diabetes. Patients had a mean A1C that ranged between [redacted] and [redacted] (SD ranged between [redacted] and [redacted]), with most patients having an A1C ≤ 8.0% ranging between 69.0% and 79.5%. [redacted]

Generally, most patients had moderately severe DR or better ([redacted] to [redacted]). However, MEAD-010 and MEAD-011 had differences up to approximately [redacted] and [redacted] between

treatment groups in severity of DR, respectively. [redacted]

Patients in the pseudophakic subgroup of the MEAD trials had mean BCVA that ranged between [redacted] and [redacted] letters (SD ranged between [redacted] and [redacted]). Most patients had BCVA [redacted] letters in both MEAD trials; [redacted]. Although the inclusion criteria of the MEAD trials are restricted BCVA scores between 34 letters and 68 letters in the study eye as measured by the ETDRS method at qualification/baseline, patients with BCVA scores greater than the inclusion thresholds were enrolled. Overall, the ≥ 36 to ≤ 45 and ≥ 46 to ≤ 55 BCVA categories had differences of approximately [redacted] and [redacted] in between treatment groups in MEAD-011, respectively. [redacted]

Table 5: Summary of Baseline Characteristics (Pseudophakic Subgroup)

Characteristics	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
Age, mean years (SD)	[redacted]	[redacted]	[redacted]	[redacted]
< 45 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 45 to ≤ 65, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
> 65, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Hispanic	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
DME duration, months				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes duration, years				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
Lens status of the study eye, pseudophakic, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Study eye was the better-seeing eye, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment, n (%)				
Laser	[redacted]	[redacted]	[redacted]	[redacted]
Anti-VEGF	[redacted]	[redacted]	[redacted]	[redacted]
Intravitreal steroid injection	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]
A1C				
Mean, % (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median, % (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
≤ 8.0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
> 8.0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Type of diabetes, n (%)				
Type 1	[redacted]	[redacted]	[redacted]	[redacted]
Type 2	[redacted]	[redacted]	[redacted]	[redacted]
Severity of diabetic retinopathy in the study eye, n (%)				
Moderately severe NPDR or better	[redacted]	[redacted]	[redacted]	[redacted]
Severe NPDR or worse	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Type of DME[a], n (%)				
None	[redacted]	[redacted]	[redacted]	[redacted]
Focal	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]
Diffuse	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
BCVA in the study eye at baseline				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
≤ 35 letters, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 to ≤ 45 letters, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 46 to ≤ 55 letters, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 56 to ≤ 65 letters, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 66 to ≤ 75 letters, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 76 letters, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
IOP in the study eye, mm Hg				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
SBP, mm Hg				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
DBP, mm Hg				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
OCT retinal thickness at center subfield, microns				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
History of cardiovascular disease, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
History of cerebrovascular disease n (%)	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; BCVA = best-corrected visual acuity; DEX = dexamethasone; DBP = diastolic blood pressure; DME = diabetic macular edema; IOP = intraocular pressure; max = maximum; min = minimum; NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography; SBP = systolic blood pressure; SD = standard deviation; VEGF = vascular endothelial growth factor.
[a] Based on fluorescein angiography.

Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Interventions

Patients were randomized (1:1:1) to dexamethasone 700 mcg intravitreal injection, dexamethasone 350 mcg intravitreal injection or sham. Randomization was conducted using the Interactive Voice Response System (IVRS) or the Interactive Web Response System (IWRS). The intervention of interest for this CDR review is the dexamethasone 700 mcg administered by intravitreal injection; therefore, the dexamethasone 350 mcg intravitreal injection will not be discussed.

The treatment procedures in both MEAD trials were performed by treating investigators in a controlled and sterile setting according to a standardized protocol. Patients randomized to dexamethasone had the study drug (Ozurdex; dexamethasone 700 mcg) or dexamethasone 350 mcg placed into the vitreous (posterior segment of the eye) through the pars plana using the Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS). Patients randomized to sham treatment had the needleless applicator pressed against the conjunctiva to preserve masking. Ozurdex was embedded into an inactive biodegradable polymer matrix that slowly releases dexamethasone while gradually degrading over time. Treatments occurred at randomization (day 0) followed by assessments for retreatment eligibility every 3 months. Patients were eligible for retreatment if retinal thickness in the 1 mm central macular subfield as measured by optical coherence tomography (OCT) was > 225 µm, or upon investigator interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the center subfield). The original retreatment retinal thickness threshold as measured by OCT was amended during the trial, reducing the required thickness from 225 µm to 175 µm.

Follow-up was conducted at one, seven and 21 days post injection, and regular treatment visits occurred every 1.5 months in the first year and every three months thereafter. Starting from the six-month visit and every three months thereafter, patients were evaluated for retreatment eligibility. Retreatment could occur no sooner than at six months, and patients could receive up to seven treatments during the three-year duration of the studies. Patients could have been treated with escape therapy and withdrawn from the studies or withdrawn due to visual acuity at the investigator's discretion at any time during the studies.

IOP treatments, panretinal photocoagulation, cataracts surgeries, topical steroids or nonsteroidal anti-inflammatory drugs were permitted in the study eye during the trials.

Macular edema in the non-study eye could be treated with laser and/or local therapies (e.g., topical, periocular, intravitreal). Systemic therapies (e.g., oral or parenteral steroids, systemic anti-VEGFs) and doses of intravitreal anti-VEGFs higher than the doses detailed in the exclusion criteria were not to be used. Additionally, systemic steroids, additional non-study procedures or surgeries in the study eye with the exception of those related to cataracts were not permitted. Escape therapy for macular edema including intravitreal steroids other than the study medication, periocular steroids, laser or surgical treatments for macular edema, anti-VEGF therapy, systemic anti-VEGF therapy, and other pharmacologic therapies for macular edema in the study were also prohibited.

The use of escape therapy was permitted anytime during the trial; however, patients who received escape therapy in the study eye were considered study treatment failures and were no longer be eligible to receive study medication, and were withdrawn from the study. Reasons for use of escape therapy resulting in study withdrawal could have included:

- intravitreal steroids other than the study medication in the study eye
- periocular steroids in the study eye
- Laser and/ or surgical treatments for macular edema in the study eye
- intravitreal anti- VEGF therapy in the study eye
- systemic anti-VEGF therapy
- other pharmacologic therapies for macular edema in the study eye.

Outcomes

Efficacy

The primary efficacy outcome in both MEAD trials was the average BCVA mean change from baseline in the study eye based on the ETDRS method using an area-under-the-curve (AUC) approach. The ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows. There are a total of 14 lines (i.e., 70 letters). Reading more lines (i.e., more letters) indicates better visual acuity. 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 15 or greater letter change in visual acuity, as clinically relevant outcome measures in trials of interventions for macular edema.[52] For more information regarding the ETDRS refer to Appendix 5.

Secondary efficacy outcomes included mean change in BCVA from baseline at each study visit, proportion of patients achieving a 10-letter change in BCVA, proportion of patients achieving a 15-letter change in BCVA, average change in central retinal thickness (CRT) from baseline during the study as measured by OCT (AUC approach), and mean change in CRT from baseline at each study visit as measured by OCT. OCT is a validated technique used to create cross sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[43] CRT is defined as the thickness of the center subfield (the area of the retina using a 1mm diameter around the center of the macula). For more information regarding the retinal thickness as measured by OCT refer to Appendix 5.

Other efficacy end points included patient reported outcomes for health-related quality of life as measured by the EuroQol 5-Dimensions Health Questionnaire (EQ-5D) and Short

Form (36) Health Survey (SF-36) questionnaires and visual function evaluated through the NEI-VFQ-25 questionnaire were also evaluated in the MEAD trials. However, post-baseline results for the EQ-5D and SF-36v1 were not provided for adult patients with DME who were pseudophakic, and therefore no descriptions are provided in this CDR report.

The NEI-VFQ-25 was developed to measure vision-targeted quality of life and consists of 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component. The NEI-VFQ-25 was developed with a number of common eye conditions in mind (e.g., age-related cataracts, age-related macular degeneration, and DR) and is comprised of 11 subscales related to general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision and colour vision, in addition to a subscale for general health. 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. Although, the minimal clinically important difference (MCID) for the NEI-VFQ-25 in adult patients with DME who are pseudophakic remains unclear, differences between 3.3 and 6.1 points in the overall composite scores are typically clinically meaningful in the general DME population.[20] More information regarding the NEI-VFQ-25 can be found in Appendix 5.

Harms

Both MEAD trials collected safety data, including the occurrence of adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), mortality and notable harms.

AEs were defined as any untoward medical occurrence in a patient that was administered a pharmaceutical product and that did not necessarily have a causal relationship with treatment, and therefore captured any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of treatment, whether or not related to the therapy.

SAEs were defined as any event occurring at any dose and resulting in any of the following outcomes: death, life threatening AEs, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect. However, important medical events may have been considered a serious adverse despite not meeting the previously defined criteria based on appropriate medical judgment or requirement for medical or surgical intervention to prevent one of the outcomes listed in the definition.

Severity of AEs was defined using the following definitions:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or do usual activity

IOP was measured in both eyes using Goldmann applanation tonometry.

Withdrawal due to visual acuity in patients who had a confirmed 15-letter or more decrease in BCVA from baseline in the study eye attributable to macular edema (e.g., not

due to cataract or media opacity) were at the investigator's discretion and considered a treatment failure. This 15 or more letter decrease in BCVA was confirmed and documented at two consecutive visits at least four weeks apart using the ETDRS method. The patient did not receive study treatment between or during these two visits.

Different investigators were used to perform the study treatment procedure, follow-up, data collection, and data analysis throughout the trial to maintain masking with the exception of post-injection safety visits at days one, seven and 21, which were conducted by the treating investigator resulting in unblinded safety evaluations. Other safety evaluations performed at regular study visits (excluding post-injection visits at day one, seven and 21) were performed by an investigator which was not involved in the study treatment procedure to maintain masking. Patients were also masked to the treatment arm assignment throughout the trial.

Statistical Analysis

Originally, the study was designed to assess the effect of dexamethasone using the proportion of patients with ≥ 15 letter improvement as the primary end point and required a sample size of [redacted] in total. The protocol was subsequently amended and the primary end point changed to the average BCVA mean change (AUC approach) from baseline during the study. Therefore a new sample size of 170 patients per treatment arm (510 patients in total) would have provided a power of 86% to detect a 4-letter mean difference in average BCVA mean change from baseline between dexamethasone 700 mcg and sham based on a 2-sided test at the 5% significance level in the primary efficacy end point assuming a standard deviation of 12 letters (standard deviation was based on two single-dose 6-month retinal vein occlusion studies reporting an observed standard deviation of 10 letters). No specific power calculation conducted for the pre-specified subgroup of interest for this CDR review and there was no specific power calculation for the subgroup of adult patients with DME who are pseudophakic.

The primary analysis of efficacy in the MEAD trials was performed based on measurements obtained during the masked treatment phase for the general DME population. Originally, the primary analysis of the MEAD trials was to be assessed after 12 months of follow-up. The trial duration was subsequently amended several times to include the possibility of a final assessment after 39 months of follow-up. The primary efficacy end point in both MEAD trials was the average BCVA mean change from baseline in the study eye based on the ETDRS method using an AUC approach. The primary efficacy end point was analyzed in the ITT population using an ANCOVA model stratified by treatment as fixed effects and baseline BCVA as the covariate. Although the manufacturer suggests that no imputation for missing data was performed for the primary analysis, the average BCVA mean change from baseline for patients with no post-baseline BCVA assessment was set to zero. To avoid confounding effects of other therapies, all patients in the MEAD study who required escape therapies were discontinued from the study and their values set to missing (not imputed); therefore, were not included in the final analyses. Data are presented as mean difference in the change from baseline compared with sham, with corresponding 95% CIs.

A gate-keeping procedure was used to control the overall type I error at the 5% level for between-group comparisons. The comparison of dexamethasone 700 mcg versus sham was considered significant if the *P* value was ≤ 0.05. Only if the comparison of dexamethasone 700 mcg versus sham was significant at the 0.05 level was the comparison of dexamethasone 350 mcg versus sham to be performed, at a significance

level of 0.05. If the comparison of dexamethasone 700 mcg versus sham was not statistically significant, the comparison of dexamethasone 350 mcg versus sham was not to be considered statistically significant regardless of its *P* value.

Sensitivity analyses were also performed for the primary outcomes in the general DME population and included:

- Per-protocol (PP) population
- Multiple imputation for missing values (Markov chain Monte Carlo [MCMC] method)
- Using “as is” observed data.

Secondary efficacy analyses were also assessed in the general DME population using the ITT population; however, no adjustments were made to control for type I error. Contrary to the primary analysis, the secondary analyses used last observation carried forward (LOCF) methods to impute for missing data with the exception of the average change from baseline in retinal thickness of the central subfield during the study end point which did not impute for missing data (only based on observed data). Secondary efficacy outcomes included:

- BCVA change from baseline at every study visit (ANCOVA using baseline BCVA as a covariate)
- proportion of patients with Improvement/worsening of 10 or more letters from baseline at every study visit (Pearson’s chi-square test)
- proportion of patients with Improvement/ worsening of 15 or more letters from baseline at every study visit (Pearson’s chi-square test)
- categorical change from baseline at every study visit (Wilcoxon Rank Sum Test)
- average change from baseline in retinal thickness of the central subfield during the study (AUC approach, observed cases [ANCOVA using baseline central subfield retinal thickness as a covariate])
- change from baseline in retinal thickness of the central subfield during the study at every study visit (ANCOVA baseline with central subfield retinal thickness as a covariate instead of BCVA).

Other efficacy analyses were also conducted in the general DME population based on patient reported outcomes using health-related quality of life measures (EQ-5D, SF-36v1, and NEI-VFQ-25) in the ITT population; however, no adjustments were made to control for type I error. For analyses of mean change from baseline at every study visit, missing values were imputed by LOCF methods, while the analyses of average change from baseline using AUC approaches were performed on observed data which did not impute for missing data. Post-baseline data for the EQ-5D and SF-36v1 were not provided for adult patients with DME who were pseudophakic, therefore no descriptions are provided in this CDR report. NEI-VFQ-25 was assessed using time-weighted average change from baseline derived from observed data using the AUC approach. Comparisons between treatment arms were performed using an ANCOVA model with treatment as a fixed effect and the baseline NEI-VFQ-25 score as a covariate. In addition, the proportions of patients with at least 5-point and at least 10-point improvement from baseline at each follow-up visit were analyzed using Pearson’s chi-square test or Fisher’s exact test.

Safety results were presented by treatment group (dexamethasone 700 mcg and sham) and summarized as a frequency distribution for all adverse events (regardless of causality) and treatment-related AEs, each broken down by ocular adverse events (study eye and non-study eye) and non-ocular adverse events analyzed using the safety population.

Pre-specified subgroups of patients defined by duration of diabetes, duration of DME, baseline A1C, prior laser treatment, treatment-naïve patients, lens status at baseline (phakic and pseudophakic), nonproliferative diabetic retinopathy severity at baseline, and country were also conducted. Only the duration of DME subgroup was analyzed in the pseudophakic subpopulation. The primary, secondary and other efficacy outcomes evaluated in subgroups were performed in a similar way as for the general DME population. Furthermore, only the PP sensitivity analysis was performed in the subgroup of adult patients with DME who were pseudophakic. Overall, subgroup analyses in both MEAD trials were not adjusted for multiple statistical tests and are therefore subject to inflated type I error. Randomization was not stratified for any of the pre-specified subgroups. No analyses were conducted for the subgroup of adult DME patients who are pseudophakic and either unsuitable for anti-VEGF therapy or have had inadequate response to prior anti-VEGF therapy.

Overall, no interim analyses were planned or conducted in any of the MEAD trials.

Analysis Populations

The intention-to-treat (ITT) population was defined as all randomized patients. Analyses based on the ITT population were performed based on the treatment to which the patient was randomized.

The PP population was defined as randomized patients with no major protocol violations. Analyses based on the PP population were based on the treatment which the patient received.

The safety population was defined as all patients who received treatment. Analyses based on the safety population were performed based on the treatment which the patient received.

The focus of this CDR review is based on a pre-specified subgroup of the enrolled MEAD population, specifically those with DME who are pseudophakic derived from the ITT and safety populations.

Patient Disposition

Of the 929 and 961 patients screened in MEAD-010 and MEAD0-011, 47% and 42% did not meet the criteria for enrolment, respectively. A total of 94 and 93 patients in the MEAD-010 and MEAD-011 trials satisfied the Health Canada indication (i.e., adults with DME who are pseudophakic). Generally, more patients discontinued the study in the sham groups compared with the dexamethasone groups (and compared with and in MEAD-010 and MEAD-011, respectively). Data associated with treatment discontinuation were not provided in the subgroup of patients with DME who were pseudophakic. Details in regards to patient disposition in the MEAD trials are provided in Table 6.

Table 6: Patient Disposition

	MEAD-010		MEAD-011	
	DEX 700	Sham	DEX 700	Sham
Full trial population				
Screened[a]	929		961	
Enrolled, N (%)[a]	494[b] (53.2)		554[c] (57.6)	
Randomized, N (%)	163[d]	165[e]	188[f]	185[g]
Pseudophakic subgroup				
Randomized, N (%)	44	50	42	51
Treated, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed 3 year study, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for discontinuation, N (%)				
Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]
Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Non-Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Lack of Efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Lost to Follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Personal Reasons	[redacted]	[redacted]	[redacted]	[redacted]
Protocol Violation	[redacted]	[redacted]	[redacted]	[redacted]
Other[h]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment[i], N (%)				
Reasons for discontinuing treatment[i], N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Ocular	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Personal reasons	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Need for escape therapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Need for escape therapy in study eye, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
ITT, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
PP, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N (%)	[redacted]	[redacted]	[redacted]	[redacted]

DEX = dexamethasone; ITT = intention to treat; NA = not available; PP = per-protocol.

[a] Patients screened in the overall DME population.

[b] 166 patients randomized to dexamethasone 350 mcg.

[c] 181 patients randomized to dexamethasone 350 mcg.

[d] Three patients were randomized to DEX 700 but never received treatment.

[e] One patient was randomized to Sham but never received treatment.

[f] One patient was randomized to DEX 700 but never received any treatment.

[g] One patient was randomized to DEX 350 but actually received sham and was counted in the DEX 350 group for analyses based on the ITT population and in the sham group for analyses based on the safety population.

[h] Other reasons for patient discontinuation included patient withdrawal of consent, patient relocation, site closure, etc.

[i] Data were requested but not provided by the manufacturer.

Source: MEAD-010 CSR[23], MEAD-011 CSR[24]

Exposure to Study Treatments

The majority of patients in the MEAD in trials were treated with [redacted] or more doses (ranging between [redacted] and [redacted]), with the exception of the DEX 700 group in MEAD-011 wherein the majority of patients were treated with [redacted] or more doses ([redacted]). Overall, [redacted] and [redacted] were treated with [redacted] or more doses of dexamethasone in both MEAD trials. Only between [redacted] and [redacted] of patients in the MEAD trial received a [redacted] treatment. The mean number of treatments per patients ranged between [redacted] and [redacted] doses (SD ranged between [redacted] and [redacted]) and the median number of treatments ranged between [redacted] and [redacted] doses (range 1 to 7). Overall, the majority of patients achieved [redacted] months or more of follow-up during the MEAD trials ([redacted] to [redacted]) with the exception of the sham group in MEAD-011 ([redacted]). Details in regards to exposure in the MEAD trials are provided in Table 7, Table 8 and Table 12.

Table 7: Number of Patients Categorized by the Total Number of Injections Received During the Study (Pseudophakic subgroup)

Number of treatments, N (%)	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]

DEX = dexamethasone.

Exposure was based on the safety population.

Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Table 8: Cumulative and Average Study Follow-up (Pseudophakic subgroup)

Number of treatments, N (%)	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
≥ 1.5 Months (study days ≥ 45)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 Months (study days ≥ 90)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4.5 Months (study days ≥ 135)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6 Months (study days ≥ 180)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 7.5 Months (study days ≥ 225)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 9 Months (study days ≥ 270)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 10.5 Months (study days ≥ 315)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 Months (study days ≥ 360)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 15 Months (study days ≥ 450)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 18 Months (study days ≥ 540)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 21 Months (study days ≥ 630)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 Months (study days ≥ 720)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 27 Months (study days ≥ 810)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 30 Months (study days ≥ 900)	[redacted]	[redacted]	[redacted]	[redacted]

Number of treatments, N (%)	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
≥ 33 Months (study days ≥ 990)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 36 Months (study days ≥ 1080)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 39 Months (study days ≥ 1170)	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of treatments/patient (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median number of treatments/patient (min, max)	[redacted]	[redacted]	[redacted]	[redacted]

DEX = dexamethasone; max = maximum; min = minimum; SD = standard deviation.

Note: Exposure was based on the safety population.

Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Critical Appraisal

Internal Validity

The MEAD trials were similarly designed masked, sham-controlled RCTs that used appropriate methods to randomize patients (Interactive Voice/Web Response System). The MEAD trials were not initially designed to assess the average BCVA mean change from baseline as the primary end point. Rather, the original end point was the proportion of patients who achieved at least a 15-letter improvement by end of study, which the FDA still considered as the primary end point. Only subsequent to a protocol amendment was the primary end point changed to be the average BCVA mean change from baseline. The manufacturer provided adjustments to the sample size to accommodate the new end point. Based on the sample size calculations, the MEAD studies were designed as a superiority trial with the expectation to show a between-treatment difference of at least four letters. The primary end point used in the MEAD trials (average BCVA mean change from baseline) used the AUC approach. Although this method was considered to be more reliable and was expected to result in a more appropriate control of type I error compared with analysis at every individual time point according to the Health Canada reviewer report, it can also mask the variability of treatment effects across all time points.[51] The FDA also commented on the robustness of the AUC approach, noting that the average mean change in BCVA during the study does not differentiate the short-term treatment effect (which the FDA indicated was prior to 36 months) from the long-term treatment effect.[52] The FDA refused to accept the amendment to the primary end point and considered the original primary end point (i.e., proportion of patients who achieved at least a 15-letter improvement by end of study) more appropriate.[52]

The use of the ANCOVA method of analysis would have ensured that the results were adjusted for variables including baseline BCVA and CRT as measured by OCT. All efficacy analyses were conducted using ITT analysis defined as all randomized patients analyzed according to the treatment to which the patient was randomized. In the ANCOVA model, missing data were imputed using the LOCF approach for all end points with the exception of those based on the AUC approach. Excluding patients with missing data is inconsistent with the true definition of an ITT analysis, in which all randomized participants are included. The exclusion of these patients can potentially bias the results, given the pattern of missing data. Overall, more withdrawals occurred in the sham groups compared with the dexamethasone groups in both MEAD trials, especially due to lack of efficacy (more prominently in MEAD-011). Given that missing data were not imputed in the AUC approach used for the primary analysis, the treatment effect may have been

biased in favour of dexamethasone 700 mcg given that patients that were doing well would be overrepresented in that group. Furthermore, patients were excluded from the primary analysis if they received escape treatment. Excluding these patients can bias the results if withdrawals due to escape therapy were imbalanced between treatment groups, although this was not the case given that the numbers were well balanced between treatment groups in both MEAD trials. In addition, a sensitivity analysis using a PP population was also conducted; however, this does not lessen the concerns related to exclusion of patients. Furthermore, given that more than 50% of patients discontinued the studies in the both MEAD trials, the LOCF method for imputing data may be biased given that it does not account for patients who had an initial response but could not tolerate treatment. Given that the reasons for withdrawal are related to the study drug and are not balanced between study groups, using the LOCF alone as an imputation method for certain end points may not be sufficient to address the missing data. Sensitivity analyses using multiple imputation methods were evaluated in the overall DME population; however, the results were not reported for the pre-specified subgroup of patients with DME who are pseudophakic. The Health Canada reviewers report states that the results were no longer statistically significant in the overall DME population when using the multiple imputation method to handle missing data.[51] The lack of a statistically significant difference from the multiple imputation analysis is due to the larger variance produced by the analysis compared the LOCF method which artificially reduces variance by repeating the same data point when data are missing.[51] Overall, per Health Canada, had the missing data actually been captured, they would have been expected to have had some variance — which indicates that the multiple imputation model may be more appropriate than the LOCF method.

Although, different investigators were used to perform the study treatment procedure, follow-up, data collection and data analysis throughout the trial to maintain masking, post-injection safety visits at day one, seven and 21 which were conducted by the treating investigator, resulting in unblinded safety evaluations. Furthermore, the adverse event profile associated with intravitreal steroids (i.e., IOP) is well known, therefore some accidental unblinding may have occurred.[12,19] Given that prior intravitreal steroid experience was not an exclusion criterion in any of the trials, some patients with prior experience may have surmised that the allocated treatment was dexamethasone. However, considering that the primary end point of the MEAD trials is relatively objective, the potential for bias is of lesser concern. Unblinding may, however, lead to biases such as under or over reporting of subjective outcomes (i.e., AEs or health-related quality of life measures) which can impact the overall impressions with dexamethasone treatment. Treatment discontinuations during the studies were not reported in any of the MEAD trials. Overall, there were numerically more study discontinuations in the sham groups compared with the dexamethasone groups in both MEAD trials. The European Medicines Agency's guideline on missing data in confirmatory clinical trials suggests that patients who do not complete a clinical trial may be more likely to have extreme values than patients who complete a trial.[53] Therefore, excluding these patients could underestimate the variability and artificially narrow the confidence interval for the treatment effect, and neither the LOCF method nor sensitivity analysis using the PP population would have overcome this potential limitation.

Dexamethasone response at each study visit varied considerably across both MEAD trials. The reason for the relatively large difference in response rate between the two trials remains unclear; however, it may be due to underlying confounders due to the imbalance in baseline characteristics between treatment groups and across studies. In

the MEAD trials, the ANCOVA model only adjusted for BCVA and retinal thickness as measure by OCT as covariates. Other baseline line factors which may confound the results were not adjusted, such as duration of diabetes, duration of DME, severity of DR, and type of DME among others. If not adjusted appropriately, such confounding factors may influence the comparative efficacy, though the direction of bias is unclear.

In the MEAD trials, only the primary analyses were controlled for multiple statistical testing using a gate-keeping procedure (i.e., average BCVA mean change from baseline in the general DME population). Adjustments for type I error were conducted using a hierarchical approach for the dexamethasone 700 mcg versus sham comparison at the 0.05 level of significance first, followed by the dexamethasone 350 mcg versus sham comparison (also at the 0.05 level of significance) if the prior analysis was statistically significant. As a result, all other outcomes were not appropriately adjusted for multiplicity, which increases the risk of making a type I error. Further, subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was not the case). Inadequate randomization introduces biases through the presence of confounders (known and unknown). The imbalances present in the baseline characteristics of the subgroup of adult patients who are pseudophakic may suggest that randomization may have been compromised. Given the distribution of known and unknown confounders, the direction of the bias remains unclear; however, these biases may explain the differing treatment affect between MEAD-010 and MEAD-011. Subgroups are also likely underpowered (small sample size) to detect a statistically significant difference.

The MEAD trials were originally designed to evaluate the effects of dexamethasone in the general DME population. This CDR report is based on the results of a subgroup (i.e., adults with DME who are pseudophakic) which only consisted of approximately 20% of overall enrolled patients. While the risks of type I error and bias remain, the validity of the results for the subgroup of adult patients with DME who are pseudophakic are strengthened by its pre-specified nature and the biological plausibility of the interaction effect. It is known that intravitreal steroid injections result in the development and progression of cataracts (clouding of the natural lens) in eyes that are phakic (natural lens).[19] Furthermore, treatment with dexamethasone has been shown to be associated with increased frequency of cataracts, which is outlined in the warning and precautions section of the Health Canada–approved product monograph.[12] It is believed that the formation of cataracts can potentially confound the overall treatment effect on the BCVA in patients with DME who are phakic; therefore, patients who have had their natural lens surgically replaced with an artificial lens (pseudophakic) would be expected to further benefit from treatment with dexamethasone given that the formation and progression of cataracts is no longer possible.[51]

External Validity

In the MEAD trials, 42% to 47% of patients were screening failures when considering the overall DME population. Stringent inclusion and exclusion criteria can result in a highly enriched population, which may not be completely representative of the DME population in Canada and can potentially limit the generalizability of the trial results. Furthermore, the MEAD trials were initially designed to assess the effects of dexamethasone in the general DME population. Only after a notice of non-compliance was issued (due to lack of efficacy due to confounding associated with cataracts) was an analysis subsequently conducted in the pre-specified subgroup of adult patients with DME who are

pseudophakic. The Health Canada–approved indication was consequently limited to the treatment of patients with DME who are pseudophakic. Therefore, the focus of this CDR review is based on a subset of the overall DME population. In addition, the protocol for the present review considered further subgroups, including patients who are either unsuitable for anti-VEGF therapy or have had inadequate response to prior anti-VEGF therapy. Between [redacted] and [redacted] of the pseudophakic patients included in the MEAD trials had prior experience with anti-VEGF therapy, and it remains unclear if these patients responded to these treatments and were truly anti-VEGF refractory. It is also unclear if there were any patients included in the MEAD trials that were considered unsuitable for anti-VEGF therapy. According to the clinical expert consulted for this review, the date of conduct of the trials (between February 2005 to June 2012) was prior to the adoption of anti-VEGF therapies and may therefore may have influenced the number of patients having access to anti-VEGF therapy. It is therefore unclear if the results of the MEAD trials can be generalized to patients who are unsuitable for anti-VEGF therapy or have had an inadequate response to anti-VEGF therapy.

Both MEAD trials were multinational and included sites from Canada. The clinical expert consulted by CDR for this review highlighted that the MEAD trials appear to have recruited patients with characteristics similar to those of the overall DME population in Canada with some exceptions, however, the expert noted that the majority of patients recruited in the MEAD trials were aged > 65 years ([redacted] to [redacted]), which may represent an older DME population than what would be observed in Canadian clinical practice.

With respect to the study duration, the FDA suggested that 36 months is considered short term. The FDA recommends that the treatment effect be demonstrated at a time point of at least 36 months or later for the indication of DME given that earlier treatment success is not necessarily a good indicator of a later success.[52] Therefore, it is unclear if the results of the MEAD trials would be representative of the long-term treatment effect.

Overall, the relatively large and imbalanced number of discontinuations in the MEAD trials may have led to a DME population that was generally healthier than those initially randomized into the study given that mostly patients who were doing well remained in the trial. This effect is artificially high in the sham groups of the MEAD trials because only patients who did not develop substantial visual deterioration without any treatment were included in the final analyses. Therefore, it remains unclear if the dexamethasone treatment effect observed in the MEAD trials is truly representative of the effect potentially observed in clinical practice.

The dexamethasone retreatment regimen could not occur more frequently than every six months in both MEAD trials. However, the clinical expert consulted for this CDR review suggests that the effects of intravitreal dexamethasone injections wane over time and are rarely sustained at month six, therefore dexamethasone may be used more frequently than every six months in clinical practice. The same expert suggested a retreatment regimen closer to every four months rather than a similar regimen included in the trials. The effects of dexamethasone associated with a more frequent injection regimen were not evaluated in the MEAD trials and therefore remain unclear.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported below. See Appendix 4 for detailed efficacy data.

This CDR review focused on the pre-specified subgroup of patients who were pseudophakic in the MEAD trials (MEAD-010 n = 94; MEAD-011 n = 93), according to the Health Canada–approved indication. No efficacy data were available for patients who were considered inadequate responders to, or unsuitable for, anti-VEGF therapy.

Best-Corrected Visual Acuity

Details pertaining to BCVA outcomes for the pseudophakic subpopulation in MEAD trials are provided in Table 9.

Compared with sham, the adjusted least squares mean differences in average BCVA mean change from baseline using the AUC approach (the primary outcome) were 5.9 letters (95% CI, [redacted]), $P < 0.001$ and 3.6 letters (95% CI, [redacted]), $P = 0.018$ in MEAD-010 and MEAD-011, respectively. The results of sensitivity analyses (using a PP population instead of the ITT population) were consistent with the primary analyses: the adjusted least squares mean difference, versus sham, were[redacted], respectively (Table 16).

In both trials, the change from baseline in BCVA was also measured at different times during the study, including at months 3, 6 9, 12, 18, 24, 30, 36, and 39. Assessments of BCVA at these time points (95% CI) ranged between [redacted] (Table 15).

Other BCVA outcomes included ≥ 15 letter improvement from baseline at the last study visit. Overall, 15 (34.1%) patients in the dexamethasone group and eight (16.0%) patients in the sham group achieved a ≥ 15 letter improvement in MEAD-010 (difference versus sham of 18.1% [95% CI, 0.8 to 35.4] $P = 0.043$). In MEAD-011, five (11.9%) patients in the dexamethasone group and three (5.9%) patients in the sham group achieved a ≥ 15 letter improvement (difference versus sham of 6.0% [95% CI, –5.7 to 17.8] $P = 0.461$). Patients achieving other categories of BCVA change at the last study visit including ≥ 5 and < 15 letter improvement, no change (includes 5 letter improvement or worsening), ≥ 5 and < 15 letter worsening and ≥ 15 worsening (additionally reported as ≥ 15 letter worsening from baseline any time during the trial) were also evaluated and detailed in Table 15. Similarly 10-letter change analyses were also reported and detailed in Table 15.

Table 9: Visual Acuity Efficacy Outcomes (Pseudophakic Subgroup; ITT analysis)

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
Baseline BCVA				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Mean letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
BCVA average change from baseline[a]				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	8.1 [redacted]	2.1 [redacted]	4.9 [redacted]	1.3 [redacted]
Adjusted LS MD versus sham (95% CI)	5.9 [redacted] *P* < 0.001		3.6 [redacted] *P* = 0.018	
BCVA ≥ 15 letter improvement from baseline (last visit)				
Proportion of patients, n/N (%)	15/44 (34.1)	8/50 (16.0)	5/42 (11.9)	3/51 (5.9)
Difference versus sham (95% CI)	18.1% (0.8 to 35.4) *P* = 0.042		6.0% (–5.7 to 17.8) *P* = 0.461	
CRT as measured by OCT average change from baseline[a]				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	50 (98)
Adjusted LS mean change from baseline, microns (SD)	–137.4 [redacted]	–43.3 [redacted]	–125.9 [redacted]	–58.3 [redacted]
Adjusted LS MD versus sham (95% CI)	[redacted] *P* < 0.001		[redacted] *P* = 0.007	

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; ITT = intention to treat; LS = least squares; MD = mean difference; OCT = optical coherence tomography; SD = standard deviation.

[a] Based on AUC approach and observed data, missing data were not imputed

Last visit refers to either month 39 or month 36 which ever was the final visit.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic

LOCF was used to impute missing data unless otherwise specified. Patients without post-baseline BCVA were set to value 0 in the analysis

Means and mean differences were analyzed using an ANCOVA model stratified by treatment as fixed effects and baseline BCVA as the covariate, with the exception of CRT as measured by OCT outcomes, which used baseline CRT as measured by OCT as the covariate.

Source: MEAD-010 CSR[23], MEAD-011 CSR[24]

National Eye Institute Visual Functioning Questionnaire 25 (NEI-VFQ-25)

The MEAD trials also evaluated vision-related outcomes using the National Eye Institute Visual Functioning Questionnaire-25. In general, NEI-VFQ-25 overall composite scores at baseline were similar across both treatment groups across both trials and ranged between [redacted] and [redacted]. The adjusted average least squares mean differences for the overall composite score were [redacted] in MEAD-010 and MEAD-011, respectively. Details pertaining to BCVA outcomes in the MEAD trials are provided in Table 10. In addition, the percentage of patients achieving five-point or more and 10-point or more improvement in the NEI-VFQ-25 overall composite score and its subscales were reported and detailed in Table 10; Overall, number of patients achieving the 10 or 5 letter thresholds were similar between treatment groups with few exceptions. However, the anomalies were not consistent across the MEAD trials.

Table 10: National Eye Institute Visual Functioning Questionnaire-25 (Pseudophakic Subgroup)

Subscales (ITT)	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
Overall composite score[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at last visit (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean average change from baseline (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS average MD versus comparator (95% CI)	[redacted]		[redacted]	
General vision[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at last visit (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean average change from baseline (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS average MD versus comparator (95% CI)	[redacted]		[redacted]	
Difficulty with near-vision activities[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at last visit (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean average change from baseline (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS average MD versus comparator (95% CI)	[redacted]		[redacted]	
Difficulty with distance-vision activities[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at last visit (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean average change from baseline (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS average MD versus comparator (95% CI)	[redacted]		[redacted]	
Mental health symptoms due to vision[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at last visit (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean average change from baseline (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS average MD versus comparator (95% CI)	[redacted]		[redacted]	
Patients with ≥ 10-point improvement from baseline at last visit[a]				
Overall composite score	[redacted]	[redacted]	[redacted]	[redacted]
General vision	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with near-vision activities	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with distance-vision activities	[redacted]	[redacted]	[redacted]	[redacted]
Mental health symptoms due to vision	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 5-point improvement from baseline at last visit[a]				
Overall composite score	[redacted]	[redacted]	[redacted]	[redacted]

Subscales (ITT)	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
General vision	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with near-vision activities	[redacted]	[redacted]	[redacted]	[redacted]
Difficulty with distance-vision activities	[redacted]	[redacted]	[redacted]	[redacted]
Mental Health Symptoms due to Vision	[redacted]	[redacted]	[redacted]	[redacted]

[a] LOCF was used to impute missing data.

[b] Based on AUC approach and observed data and missing data were not imputed.

NEI-VFQ-25 was evaluated using an ITT analysis.

Last visit refers to either month 39 or month 36 which ever was the final visit.

Data for non-reported subscales were not available.

The composite score was calculated by averaging all 11 vision-targeted subscale scores, excluding general health score.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic.

P values from ANOVA with treatment as a factor for baseline and ANCOVA with treatment as a factor and baseline value as a covariate for post-baseline visits.

CI = confidence interval; DEX = dexamethasone; ITT = intention to treat; LS = least squares; MD = mean difference; SD = standard deviation.

Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Short Form 36 Health Survey Version 1(SF-36v1)

No health-related quality of life post-baseline data using the SF-36v1 was provided for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

EuroQol 5 Dimensions Health Questionnaire (EQ-5D)

No health-related quality of life post-baseline data using the EQ-5D was provided for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

Retinal Thickness As Measured by Optical Coherence Tomography (CRT As Measured by OCT)

Compared with sham, the adjusted least squares mean difference in average CRT as measured by OCT were [redacted] in MEAD-010 and MEAD-011, respectively. The change from baseline in CRT as measured by OCT was also measured at the last study visit in both MEAD trials and was consistent with the AUC approach in MEAD-010, but not in MEAD-011(adjusted least squares mean differences were [redacted]). Sensitivity analyses were also performed for this outcome using a PP population instead of the ITT population in both MEAD-010 and MEAD-011 (adjusted least squares mean differences were [redacted], respectively). For detailed outcome data in regards to CRT as measure by OCT and the PP sensitivity analyses refer to Table 15 and Table 16.

Harms

Only those harms identified in the review protocol (Table 3) are reported below. See Appendix 4 for detailed harms data.

Individual trial harms data were provided (Table 20); however, the most common AEs, SAEs, WDAEs and notable harms were not reported. Therefore, this section focuses on the pooled data across MEAD-010 and MEAD-011. However, given the differences in frequency of harms for the individual trials (MEAD-010 and MEAD-011), it is uncertain if the pooled harms analyses are generalizable to the patients included in both trials.

This CDR review focused on the pre-specified subgroup of patients who were pseudophakic in the MEAD trials (MEAD-010 n = 94; MEAD-011, n = 93), according to the Health Canada–approved indication. No safety data were available for patients who were considered inadequate responders to, or unsuitable for, anti-VEGF therapy.

Adverse Events

A total of 74.1% and 61.0% of patients experienced AEs in the dexamethasone and sham groups, respectively. Overall, 29.4% and 9.0% of patients experienced elevated IOP, 5.9% and 2.0% experienced secondary cataracts and [redacted]experienced blepharitis in the dexamethasone and sham groups, respectively. Overall, the frequencies of other AEs were relatively similar across treatment groups.

Serious Adverse Events

Similar frequencies of SAEs were reported in the dexamethasone groups compared with the sham groups ([redacted] respectively). No data were provided regarding the most common reasons for ocular SAEs for the subgroup of adult patients with DME who are pseudophakic.

Withdrawal Due to Adverse Events

The overall WDAEs were similar between treatment groups, however, no data regarding the withdrawals due to ocular AEs was provided for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

Mortality

A total of three deaths occurred in the MEAD trials in the pseudophakic subgroup, however, none of the deaths were considered to be related to study treatment by the investigators. Two deaths occurred in MEAD-010 (one in the dexamethasone group and one in the sham group) and one death occurred in MEAD-011 (one death in the sham group). [redacted]

Notable Harms

The occurrence of the remaining notable harms (other than elevated IOP and secondary cataracts), specifically, eye inflammation, retinal detachment, ATE, dislocated implants, glaucoma, damage to optic nerve, conjunctival hemorrhage, and vitreous hemorrhage, was approximately equivalent in both treatment groups across the MEAD trials. Endophthalmitis, eye infection, defects in visual acuity and visual field, and necrotizing

retinitis were not reported for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

Table 11: Ocular Harms (Pseudophakic Subgroup)

Outcome	Pooled data (MEAD-010 and MEAD-011)	
	DEX 700 N = 85	Sham N = 100
AEs, n (%)		
Subjects with > 0 AEs	63 (74.1)	61 (61.0)
Most common AEs[a]		
Conjunctival hyperaemia	[redacted]	[redacted]
Posterior capsule opacification	4 [redacted]	6 [redacted]
Blepharitis	[redacted]	[redacted]
SAEs, n (%)		
Subjects with > 0 SAEs	[redacted]	[redacted]
Treatment related	2 (2.4)	0
WDAEs, n (%)	[redacted]	[redacted]
Most common reasons	[redacted]	[redacted]
Deaths		
Number of deaths, n (%)	1 (1.2)	2 (2.0)
Most common reasons		
Acute renal failure	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Myocardial ischemia	[redacted]	[redacted]
Notable Harms, n (%)		
Elevated IOP	25 (29.4)	9 (9.0)
IOP increased	[redacted]	[redacted]
Ocular hypertension	[redacted]	[redacted]
Open-angle glaucoma	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]
Conjunctival hemorrhage	[redacted]	[redacted]
Secondary cataract	5 (5.9)	2 (2.0)
Vitreous detachment	[redacted]	[redacted]
Vitreous hemorrhage	[redacted]	[redacted]
Anterior chamber inflammation	[redacted]	[redacted]
Detachment of retinal pigment epithelium	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]
Device dislocation	[redacted]	[redacted]
Optic nerve cupping	[redacted]	[redacted]
Endophthalmitis	[redacted]	[redacted]
Eye infection	[redacted]	[redacted]
Defects in visual acuity and visual field	[redacted]	[redacted]
Necrotizing retinitis	[redacted]	[redacted]

AE = adverse event; DEX = dexamethasone; IOP = intraocular pressure; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] The incidence of cataract were identified as secondary cataract (posterior capsule opacification), a common complication of cataract surgery.

Ocular harms were evaluated in the safety population.

Source: MEAD-010 CSR[23], MEAD-011 CSR[24]

Discussion

Summary of Available Evidence

No trials were identified that exclusively enrolled the patient population of interest for this review (i.e., adults with DME who are pseudophakic). Rather, the evidence for this review as it pertains to the use of dexamethasone 700 mcg intravitreal injection was derived from subgroups of adult patients with DME who were pseudophakic drawn from two similarly designed masked phase III multi-centre, multinational, and sham-controlled pivotal RCTs. MEAD-010 (N = 494) and MEAD-011 (N = 554) randomized general DME patients to a 1:1:1 ratio of dexamethasone 700 mcg, dexamethasone 350 mcg (not of interest to this review) or sham. Overall, only a small subset of the enrolled population (a pre-specified subgroup of adult patients with DME who are pseudophakic [MEAD-010 n = 94; MEAD-011 n = 93] derived from the ITT and the safety populations) met the Health Canada–approved indication.

While the risk of type I error remains given that subgroups were not adjusted for multiple statistical tests, the validity of the results for the subgroup of patients with DME who are pseudophakic are strengthened by its pre-specified nature and the biological plausibility of the treatment effect.[51] Furthermore, although the subgroup was pre-specified, it should be noted that the initial submission to the regulator was based on the full DME population. Only after a notice of non-compliance was an analysis subsequently conducted in the pre-specified subgroup of adult patients with DME who are pseudophakic. Both MEAD trials were initially designed to assess the efficacy and safety of dexamethasone in the general DME population over three years. The FDA criticized the study duration of MEAD trials, suggesting that 36 months of follow-up was considered short term. The FDA recommends that the treatment effect be demonstrated at a time point of at least 36 months or later for the indication of DME given that earlier treatment success is not necessarily an appropriate indicator of a later success.[52] Therefore, it is unclear if the results of the MEAD trials would be representative of the long-term treatment effect. The MEAD trials used accepted methods to conceal allocation and randomize patients (Interactive Voice/Web Response System). In addition, the use of the ANCOVA method of analysis would have ensured that the results were adjusted for variables including baseline BCVA and CRT as measured by OCT. The primary efficacy outcome was the average BCVA mean change from baseline based on ETDRS charts using an area-under-the-curve (AUC) approach. Secondary outcomes included other BCVA end points, retinal thickness, health-related quality of life and vision-related quality of life.

Key limitations associated with the interpretation of the subgroup of adult patients who are pseudophakic drawn from the MEAD trials include concerns with randomization; lack of adjustments for multiple statistical testing across end points, subgroups, and sensitivity analyses; variability of treatment effect at different time points, unexplained variation in relative treatment effect between the two MEAD trials; imbalances in patient disposition and patient characteristics; and differences in clinical practice between the study centres included in the MEAD trials and what would be seen in a Canadian setting.

As there were no studies identified that compared dexamethasone against other active treatments for DME, CADTH also considered the results of the manufacturer's indirect comparison (IDC) for the treatment of adult patients with DME (Appendix 6).

Interpretation of Results

Efficacy

The adjusted least squares mean differences in average BCVA mean change from baseline as measured by ETDRS and using the AUC approach (the primary outcome) were 5.9 letters (95% CI[redacted]), $P < 0.001$ and 3.6 letters (95% CI[redacted]), $P = 0.018$ in MEAD-010 and MEAD-011, respectively. Sensitivity analyses using a PP population instead of the ITT population in both MEAD-010 and MEAD-011 were consistent with the primary analysis. For macular edema, the FDA recommends a mean change of 15 letters or more based on an ETDRS chart as clinically relevant outcome measures in clinical trials.[52] According to the clinical expert CDR consulted for this review, the degree of improvement reported in the MEAD trials may be considered clinically relevant, especially for patients with poor visual acuity; however, only one of the two trials (MEAD-010) exceeded a five-letter difference in change score between dexamethasone and sham. 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 less.[54] Therefore it is unclear if the improvements as measured by ETDRS are sensitive to small changes such as those reported in the MEAD trials. Although the MEAD trials were similarly designed studies, the modest improvements in BCVA as measured by ETDRS were relatively different in magnitude. Overall, the effect associated with dexamethasone in MEAD-010 is approximately twice that observed in MEAD-011. The underlying reasons for the variability between the two trials remains unclear; however it may be due to the imbalances in baseline patient characteristics given that randomization was not stratified for the subgroup of adult patients who were pseudophakic or if the differences are due to the sensitivity of the ETDRS charts. Furthermore, 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.[55] Given that the inclusion criteria of the MEAD trials was restricted to patients with visual acuities between 20/200 Snellen equivalent and 20/50 Snellen equivalent, the 90% probability of a real change can be expected to be greater than five letters. Furthermore, based on the sample size calculations, the MEAD studies were designed as superiority trials, with the expectation to show a clinical difference of at least four letters. However, MEAD-011 failed to meet the expected difference of four letters.[51]

The MEAD trials were not initially designed to assess the average BCVA mean change from baseline as the primary end point. Rather, the original end point was the proportion of patients who achieved at least a 15 letter improvement by end of study. Only subsequent to a protocol amendment was the primary end point changed to include the average BCVA mean change from baseline. Furthermore, the FDA did not accept the amendment to the primary end point and a separate statistical analysis plan was submitted including the ≥ 15 letter improvement from baseline at the last study visit as the primary end point. Overall, the difference in the proportion of patients achieving a ≥ 15 letter improvement versus sham was 18.1% (95% CI, 0.8 to 35.4; $P = 0.043$) and 6.0% (95% CI, –5.7 to 17.8; $P = 0.461$) in MEAD-010 and MEAD-011, respectively.

Although there was a statistically significant difference in the primary end point (end of study mean change in baseline BCVA), the primary end point was evaluated using an AUC approach, which, while statistically efficient, can mask the variability of treatment

effect at different time points. The change from baseline in BCVA was measured throughout the MEAD trials including month 3, 6, 9, 12, 18, 24, 30, 36 and 39. Assessments of BCVA at these time points (95% CI) ranged between [redacted], and the differences between dexamethasone and sham treatment groups were not statistically significant at each study visit. A similar concern was raised in the Health Canada Reviewer Report.[51] The FDA also commented on the robustness of the AUC approach, noting that the average BCVA mean change from baseline does not differentiate the short-term treatment effect from the long-term treatment effect.[52] The reason for the variability in treatment effect at each study visit is uncertain, and suggests some uncertainty in the magnitude of improvement in visual acuity attributable to dexamethasone.

Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes in DME but is modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient reported outcomes.[56-58] One study demonstrated that for every 100 µm decrease in center-point thickness, visual acuity increased by 4.4 letters (95% CI, 3.5 to 5.3).[56] The adjusted least squares mean differences in average CRT as measured by OCT using the AUC approach were [redacted] $P < 0.001$ and [redacted] $P = 0.007$ in MEAD-010 and MEAD-011, respectively. The changes from baseline in CRT as measured by OCT were also evaluated at the last study visit and in a sensitivity analysis using the PP population and were consistent with the AUC method. The clinical meaningfulness of the changes in CRT as measured by OCT is uncertain.

The National Eye Institute Visual Functioning Questionnaire 25 was developed to measure vision-targeted quality of life and is believed to be valid and reliable measure of health-related quality of life among patients with a wide range of eye conditions including DME; however, recent studies have suggested that it may be more appropriately identified as a measure of visual functioning. [59,60] The MEAD trials evaluated vision-related outcomes using the NEI-VFQ-25. Overall, no differences were observed between treatment groups with adjusted average least squares mean differences for the overall composite score of [redacted] in MEAD-010 and MEAD-011, respectively. Minimal clinically important differences for the NEI-VFQ-25 (among the general DME population) between 3.3 and 6.13 points in the overall composite score have been reported.[20] No post-baseline data associated to health-related quality of life measures using the SF-36 or the EQ-5D were provided for the subgroup of patients who are pseudophakic in the MEAD trials.

No trials were identified that directly compared dexamethasone against other active treatments for DME while satisfying the criteria outlined in the review protocol (Table 3). Therefore, the manufacturer submitted an unpublished IDC investigating the comparative efficacy and safety of dexamethasone for use in the treatment of DME. The manufacturer–submitted IDC was originally prepared for the National Institute for Health and Care Excellence (NICE) in 2014. [redacted]

[redacted]There is, however, considerable clinical and methodological heterogeneity across the various studies included in the manufacturer's analyses, thus increasing the uncertainty of the results. Of note, MEAD-010 and MEAD-011 (trials included in this CDR review) did not meet the eligibility criteria for inclusion in the systematic review, as they did not report 10-letter analyses. [redacted]Given the differing treatment effects between the overall DME population and the pseudophakic population in the MEAD trials, the assumption that the results from the overall DME population can be used to inform the comparative efficacy of dexamethasone to other therapies in the pseudophakic population may not be appropriate.

Three phase II studies (RAN study, BEVORDEX and the COMB Study) which evaluated the effects of dexamethasone compared with anti-VEGF therapies (ranibizumab, bevacizumab) for the treatment of adult patients with DME were also summarized in Appendix 7. The study findings suggested a similar change from baseline in the BCVA letters between treatment with dexamethasone and anti-VEGF therapy. However, these studies were designed to evaluate the effects of dexamethasone in the general DME population, not the pseudophakic subgroup of patients which is of interest for this review. Approximately 24% to 50% of overall enrolled patients were pseudophakic. Some pseudophakic subgroup results were reported, however the lack of stratification at randomization based on this factor, as well as the absence of reporting on baseline characteristics for the pseudophakic population make it difficult to assess the comparative efficacy and harms between dexamethasone and anti-VEGF drugs (i.e., bevacizumab and ranibizumab). These studies were also likely underpowered to detect differences between treatments in the pseudophakic subgroup, there was no control for

multiple statistical testing, study durations were short, and no Canadian sites were included.

Harms

Frequencies of AEs, SAEs, WDAEs, and notable harms were provided for the individual MEAD trials; however, the most common AEs, SAEs, WDAEs and notable harms were only reported based on a pooled analysis. Given the differences in frequency of harms for the individual trials (MEAD-010 and MEAD-011) in the subgroup of patients with DME who were pseudophakic, it is uncertain if the pooled harms analysis is generalizable to the patients included in both trials.

A greater proportion of patients in the dexamethasone group experienced AEs compared with the sham group. AEs that occurred more frequently in the dexamethasone treatment groups compared with the sham groups were elevated IOP and secondary cataracts, which is consistent with the AEs profile of intravitreal steroid therapies.[12,19] These results may suggest the requirement for more frequent use of IOP-lowering therapies to mitigate complications as a result of these elevations. Further, although dexamethasone is indicated for adults with DME who are pseudophakic, the increased frequency of cataracts were identified as secondary cataract (posterior capsule opacification), which is a common complication of cataract surgery. Contrarily, the frequency of blepharitis in the dexamethasone groups was smaller than those observed in the sham groups. Similar frequencies of SAEs were reported in the dexamethasone groups compared with the sham groups. No data were provided regarding the most common reasons for ocular SAEs in the subgroup of patients who are pseudophakic. The overall WDAEs were similar between treatment groups; however, no data regarding the withdrawals due to ocular AEs was provided for the subgroup of adult patients with DME who are pseudophakic in the MEAD trials.

Occurrence of the remaining notable harms — specifically, eye inflammation, retinal detachment, ATE, dislocated implants, glaucoma, damage to optic nerve, conjunctival hemorrhage, and vitreous hemorrhage — was approximately equal in both treatment groups across the MEAD trials. Endophthalmitis, eye infection, defects in visual acuity and visual field and necrotizing retinitis were not reported in the MEAD trials.

Other Considerations

A key expectation with new therapies highlighted by the patient groups was the requirement for more or similarly efficacious treatments with fewer injections. The dexamethasone retreatment regimen could not occur more frequently than every six months in both MEAD trials. Given the modest treatment effect observed in the MEAD trials, and the treatment being indicated for use on an as-needed basis, more frequent injections may be utilized in clinical practice. The clinical expert consulted for this CDR review suggested that the effects of intravitreal dexamethasone injections wane over time and are rarely sustained six months post injection; therefore, dexamethasone may be used more frequently than every six months in clinical practice. The same expert suggested a retreatment regimen closer to every four months rather than the regimen included in the trials. The effects of using a more frequent injection regimen of dexamethasone were not evaluated in the MEAD trials and therefore remain unclear.

If both eyes were eligible for the studies, the eye with shorter duration of macular edema was to be selected. The study eye was identified at the qualification/baseline visit and

remained the same throughout the entire study duration in both MEAD trials. Only the study eye was treated in the MEAD trials. The clinical expert consulted for this CDR review highlighted that fellow eye involvement due to presence of DME or its treatment in the accompanying eye is not likely. According to the same expert, in the presence of DME, both eyes would likely be treated with dexamethasone in clinical practice; however, injections would not occur at the same time. Rather, the expert indicated that treatments in both eyes would likely be offset requiring separate medical visits to administer intravitreal dexamethasone injections. Contrarily, a non-comparative retrospective study conducted by Kapoor and Colchao. evaluating the safety and tolerance of consecutive bilateral intravitreal dexamethasone injections during a single visit for the treatment of cystoid macular edema secondary to retinal vein occlusion, DME, or noninfectious posterior uveitis in may suggest that consecutive same-day bilateral treatment is safe and well tolerated, and that same-day treatment may optimize efficiency and decrease patient visits and ultimate treatment burden without compromising patient safety or clinical efficacy.[61]

In consideration of the potential place in therapy for dexamethasone 700 mcg intravitreal injection (first or second-line), the protocol for the CDR review included examination of a subgroup of patients with DME who are pseudophakic and who are either unsuitable for anti-VEGF therapy or have had inadequate response to prior anti-VEGF therapy. However, only between [redacted] and [redacted] of patients included in the MEAD trials had prior experience with anti-VEGF therapy therefore, it is unclear if the results of the MEAD trials can be generalized to patients with prior experience or prior inadequate response to anti-VEGF therapy. Studies by Pacella et al. and Gonzalez et al., as well as a systematic review and meta-analysis conducted by Khan et al. evaluated the effects of dexamethasone in the general DME population who were refractory to anti-VEGF therapy; however results in patients with DME who are pseudophakic were not reported.[9,21,22] Furthermore, the criteria for unsuitability for anti-VEGF mostly remain unclear. The clinical expert consulted for this CDR review noted that there are different circumstances that may define unsuitability such as history of glaucoma, allergies to anti-VEGF drugs and its components, pregnancy, phakic lens status with or without recent myocardial infarction, ischemic heart disease or stroke. Similarly, patients may be considered unsuitable if they are unable to return for their regular monthly or bimonthly intraocular injection of anti-VEGF therapy either due to transportation difficulties or work demands, which are especially common among younger patients who are actively employed.

Potential Place in Therapy[2]

The current standard of care for patients requiring treatment of center-involved DME is intraocular injection of anti-VEGF drugs. While the beneficial effects of anti-VEGF drugs typically only last between four and six weeks at the most, some patients may not adequately respond to treatment. Furthermore, treating DME with anti-VEGF drugs usually requires monthly or bimonthly injections, which creates barriers to adherence and therefore optimized treatment. In these cases, further improvement in BCVA is still possible; however, a switch to another anti-VEGF may not be effective or appropriate. According to the clinical expert consulted for this CDR review, all clinical studies associated to the treatment of DME with anti-VEGF therapy or intravitreal steroid therapy compared favourably to laser treatment. Therefore, currently preferred clinical practice for

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

center-involved DME is either anti-VEGF or intravitreal steroid injections, with laser therapy being reserved for those with non–center-involved DME.

For some patients, switching to treatment with an intravitreal steroid such as dexamethasone may be a reasonable alternative; however, the use of this medication class for many patients is currently limited due to elevated IOPs and the development and progression of cataracts. The clinical expert consulted for this CDR review highlighted potential issues in the prescribing of dexamethasone given that treatment is typically associated with increased frequency of elevated intraocular pressure likely requiring IOP-lowering drugs, which may add to the treatment burden (number of concomitant treatments) and the overall cost of treatment. However, the expert noted that IOP-lowering treatments would mostly entail the use of topical medications which should not be too bothersome. Furthermore, the development and progression of secondary cataracts as a result of intravitreal steroid injections would likely require further treatment to address the issue. For patients who have had complete removal of their natural lens, secondary cataract will not form on the artificial lens. Generally, treatment regimens with intravitreal steroids injections are less frequent than those of associated with anti-VEGF drugs (quarterly or biannual injections).

The clinical expert consulted for this CDR review noted that there are different circumstances when alternate therapy such as dexamethasone implant should be considered, such as in patients who are allergic to anti-VEGF drugs and its components or in women during pregnancy given the teratogenicity of anti-VEGF drugs. In clinical practice, patients with DME who are pseudophakic without any history of glaucoma would be the best candidates to receive treatment with dexamethasone. The same clinical expert noted that intravitreal steroid injections should be particularly considered in those who are pseudophakic with or without recent myocardial infarction, ischemic heart disease or stroke. Similarly, dexamethasone may also be considered in patients who are unable to return for their regular monthly or bimonthly intraocular injection of anti-VEGF either due to transportation difficulties or work demands, which are especially common among younger patients who are actively employed. Patients who do not respond to the anti-VEGF treatment after three consecutive monthly intraocular injections or who have an inadequate response to anti-VEGF therapy would also be considered for treatment with dexamethasone.

The clinical expert also highlighted that, overall, the effects of dexamethasone on BCVA reported in the MEAD trials (especially in MEAD-011) were found to be modest when compared with the change in BCVA that has been reported for anti-VEGF therapies. The same clinical expert noted that no specialized diagnostic test would be needed to identify patients in whom dexamethasone may be appropriate, and that clinicians would likely base their decision on BCVA as well as OCT CRT, which would be routinely requested in this patient population.

Conclusions

The CDR systematic review included two masked, Phase III, sham-controlled randomized controlled trials (RCTs) designed to assess the benefits and harms of dexamethasone in adult patients with DME. Given the Health Canada–approved indication for dexamethasone, the CDR review focused on the results of a subgroup of patients from the MEAD trials (i.e., adult patients with DME who are pseudophakic [MEAD-010, n = 94; MEAD-011, n = 93]).

Overall, dexamethasone was associated with a statistically significant improvement when compared with sham for the primary outcome (average BCVA mean change from baseline as measured by ETDRS based on the AUC approach) for patients with DME who are pseudophakic in both MEAD trials, while the proportion of patients achieving a ≥ 15 letter improvement was reported to be statistically significantly greater in the dexamethasone group in MEAD-010 only. However, between-group differences did not exceed a 10-letter improvement in either MEAD-010 or MEAD-011 (differences of 5.9 and 3.6 letters respectively) and were considered modest by the clinical expert consulted for this review. Further, the magnitude of improvement in visual acuity with dexamethasone compared with sham is uncertain, given the results are for a subgroup that was not subject to stratification at randomization and for which there was no adjustment for multiple testing. More patients in the dexamethasone group experienced AEs compared with the sham group in the MEAD trials. The most commonly reported AEs that occurred more frequently in the dexamethasone treatment groups compared with the sham groups were elevated IOP, which is consistent with the adverse event risk profile of intravitreal steroid injection therapies.

No data from the MEAD trials were available to assess the efficacy and safety of dexamethasone 700 mcg in adults with DME who are pseudophakic and who are either unsuitable for anti-VEGF therapy or have had an inadequate response to prior anti-VEGF therapy.

Due to the lack of direct evidence of dexamethasone versus other drugs in the MEAD trials, and the limitations with the supportive evidence including the manufacturer–submitted IDC, no definitive conclusions could be made regarding the comparative efficacy and safety of dexamethasone versus other drugs (including anti-VEGFs) for the treatment of patients with DME who are pseudophakic.

Appendix 1: Patient Input Summary

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

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

Three patient groups, the Canadian Council of the Blind (CCB), the Canadian National Institute for the Blind (CNIB) and the Foundation Fighting Blindness (FFB), submitted patient input for this summary. All three groups are not-for-profit charities and are co-signatories on the Canadian Patient Charter for Vision Care, which illustrates their commitment to ensuring that patients have access to the highest standard of vision care across Canada.

The CCB is dedicated to improve the quality of life for Canadians with vision loss. It has more than 70 chapters across Canada and more than 1,500 members. All officers and directors are blind or visually impaired, which gives 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.

The CNIB is committed to create an inclusive, accessible, barrier-free society which provides the tools blind or partially sighted Canadians require to live safe, fulfilling and independent lives. It provides post vision-loss rehabilitation therapy through safety and mobility training, assistance with remaining gainful employment or gaining access to alternative formats of published works. It is funded almost entirely by charitable donations received from the public.

The mission of the FFB is to lead the fight against blindness by advancing retinal disease research, education and public awareness. The FFB has contributed more than $32 million to sight-saving research during the past four decades. Members include various stakeholders, such as donors, educational event participants or researchers.

The patient groups declared receiving help to design, deploy and analyze the survey data (by Environics Research), and consultation with members of Diabetes Action Canada in the preparation of this submission. The groups also declared a financial payment from Allergan in excess of $50,000 within the last two years: the amount was paid to the FFB. The FFB specified that funding from Allergan is part of a broader network of support, financial and otherwise, from pharmaceutical companies as well as patients, donors, and other corporate sponsors, and that the source of funding never influences research outcomes. The FFB indicated that it does not receive direct funding from government; however uses support from pharmaceutical companies and elsewhere to support its research activities, and to produce high-quality evidence that can help illuminate the needs of patients. According to the FFB, rigorous, patient-centred analysis, including the study the submission is based on, is impossible without leveraging funding from a wide array of sources.

2. Condition Related Information

The FFB collected information for this submission from a 10-minute online survey which was completed by 64 patients with diabetic macular edema (DME), from March 24 to June 13, 2017. The average age of the respondents was 49 years old, 56% of them lived in Ontario, 59% were male, and 84% were from urban and suburban areas.

According to the collected survey data, DME has a significant impact on the daily lives of the respondents – nearly half of them reported that their lives were affected in some way by the condition, particularly on their ability to participate in work and school activities. In addition to living with DME, six out of 10 patients reported that they had at least one other eye problem diagnosed as a result of their DR, such as cataracts, glaucoma or dry eyes. The respondents also indicated that DME impacts them as much as other chronic and costly conditions such as chronic obstructive pulmonary disease, cancer and depression. Due to the many comorbidities that occur concomitantly with diabetes, respondents were also seeing a variety of different health care professionals (e.g., family doctor, endocrinologist, and ophthalmologist). An average of 38 different appointments was needed by these respondents each year. Among respondents that were receiving injections for DME and also working, four in 10 take half a day off while more than one-third take the full day off to receive the injection. The respondents indicated that the disease presents a significant psychological burden as well – 69% of the group considered the disease “very serious” (36%) or “fairly serious” (33%). Nearly 40% of the group reported that they think about their DME at least once a day. The patient groups indicated that the psychological burden of the disease increases in parallel with the disease’s seriousness.

The family members and friends of the respondents also shared the disease burden. They often accompany the respondents to the hospital and other health centres, wait with them and provide care after the injection. Forty-four per cent of the surveyed patients required help with everyday tasks after the injection and 39% required emotional support.

3. Current Therapy Related Information

The current approaches to treating DME include laser treatment and injections of anti-VEGF drugs. Overall, the patient groups indicated that older patients, those in an urban setting, or individuals with higher income have better access to injections and that those receiving laser treatments are also more likely to be covered by public insurance. Among the surveyed patients, the most commonly used injections were Lucentis and Eylea (32% in both cases), followed by Avastin (18%) and Ozurdex (5%). Fourteen per cent of the respondents were not sure which injection drug they received. Generally, doctors had different recommendations on the frequency of drug treatment. Some respondents were told that the injections were needed at least every 2 to 4 months, while some were told once a month. The majority of the patients were compliant with the recommended injection frequency, but one in 10 of those who were recommended a monthly treatment regimen were noncompliant. Approximately 27% of the sample indicated that they missed appointments in the past, for the reasons of weather conditions (33% out of those who missed appointments, in particular for those living in the rural area), length of travel time, anxiety about the injection, unable to get time off work or school, cost of transportation, or illness. Among the patients who were not compliant, the reasons for missing appointments were unaffordable drug (50%) and long wait time to see a specialist (50%).

Overall, cost, frequency and accessibility of treatment were most important to patients. Half of the respondents receiving injections were covered by private insurance, with 41% being completely covered and 23% partially covered. On average, the cost for a patient to travel back and forth from injection appointments was $136 in the past year; among those who were working, patients had to take an average of 24 hours off work in a year.

The treatment effect and adverse effect of the currently available injections among the respondents are not reported in the submission.

4. Expectations About the Drug Being Reviewed

According to the patient groups, when evaluating any potential new treatments, patient's quality of life (both during and after treatment) is imperative.

Based on the survey data, a decreased frequency of injections was considered a key factor in leading to improved compliance and overall better quality of life for patients with DME: 27% of the respondents rated having fewer injections to get the same results as the most important factor, 23% rated this as the second most important factor and 14% rated it as the third.

Among the respondents who were not compliant to treatment, half of them indicated that the drug was not affordable. Therefore it is reasonable to assume that lower drug cost can be related to improved patient experience, and subsequently may have a beneficial effect on their health outcomes. The patient groups also state that "Accessibility factors are also important… and its availability should be equitable and barrier-free within the context of Canada's regulatory and policy frameworks – that is, it should be accessible to Canadians regardless of geography, employment, culture, and so forth."

As the incidence of diabetes grows, DME grows as well. The disease significantly impacts the patients' life (both physically and psychologically) and their caregivers, especially for those living outside of Canada's urban centres. Thus, more patients in rural communities will need options that are effective, that help them comply with treatment programs, and that reduce the psychological toll of the disease.

Appendix 2: 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:	October 27, 2017
Alerts:	By-weekly search updates until February 21, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were applied Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
Exp	Explode a subject heading
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
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 dexamethasone/
2	(7S5I7G3JQL or 50-02-2 or 1050677-47-8 or 137098-19-2 or 8054-59-9 or 906362-70-7 or 906422-84-2).rn,nm.
3	(ozurdex* or dexamethason* or dexametason* or hexadecadrol* or decameth or decaspray* or dexason* or dexpak* or maxidex* or millicorten* or oradexon* or decaject* or hexadrol* or aeroseb-D or aeroseb-dex* or anaflogistico* or aphtasolon* or auxiron* or azium* or bisu DS or calonat* or corsone* or cortisumman* or decacortin* or decaderm* or decadron* or decagel* or decalix* or decasone* or dectancyl* or dekacort* or deltafluoren* or dergramin* or desadrene* or desametasone* or desamethasone* or desameton* or deseronil* or dex-ide or dexa mamallet* or dexa-cortidelt* or dexa-cortisyl* or dexa-scheroson* or dexa-sine* or dexacort* or dexacortal* or dexacortin* or dexadeltone* or dexafarma* or dexalona* or dexameth* or dexapolcort* or dexapos* or dexaprol* or dexinolon* or dexinoral* or dexone* or dextelan* or dezone* or dinormon* or fluormethylprednisolon* or fluormone* or fluorocort* or fortecortin* or gammacorten* or HL-dex* or isopto-dex* or lokalison F or loverine* or luxazone* or mediamethasone* or methylfluorprednisolone* or mexidex* or mymethasone* or ocu-trol or pet derm III or policort* or prednisolon F or prednisolone F or spoloven* or sunia Sol D or superprednol* or turbinaire* or visumetazone* or adrecort* or adrenocot* or aeroseb dex* or aflucoson* or aflucosone* or alfalyl* or arcodexan* or artrosone* or bidexol* or calonat* or cebedex* or colofoam* or corsona* or cortastat* or cortidex*or cortidrona* or cortidrone* or dacortina fuerte* or dacortine fuerte* or dalalone* or danasone* or de-sone la or decadeltosona* or decadeltosone* or decadion* or decadran* or decaesadril* or decamethasone* or decasterolone* or decdan* or decilone* or decofluor* or delladec* or deronil* or desacort* or desalark* or desigdron* or dexa cortisyl* or dexa dabrosan* or dexa korti* or dexa scherosan* or dexa scherozon* or dexa-p or dexacen 4 or dexachel* or dexacorten* or dexacortisyl* or dexadabroson* or dexadecadrol* or dexadrol* or dexagel* or dexagel* or dexagen* or dexahelvacort* or dexakorti* or dexalien* or dexalocal* or dexame* or dexamecortin* or dexameson* or dexamethazon* or dexamethonium* or dexamonozon* or dexan* or dexapot* or dexascheroson* or dexascherozon* or dexionil* or dexmethsone* or dexona* or dextrasone* or dezone* or dibasona* or dexamethasone* or esacortene* or exadion* or firmalone* or fluormethyl prednisolone* or fluorodelta* or fluoromethylprednisolone* or grosodexon* or hexadecadiol* or hexadiol* or isnacort* or isopto dex* or isopto maxidex* or isoptodex* or isoptomaxidex* or marvidione* or megacortin* or mephameson* or metasolon* or methazon ion* or methazone ion* or methazonion* or metisone lafi* or mexasone* or millicortenol* or neoforderx* or neofordex* or nisomethasona* or novocort* or oftan-dexa* or opticorten* or opticortinol* or oradexan* or orgadrone* or pidexon* or posurdex* or predni f tablinen* or predni-f or prednisolone f or prodexon* or sanamethasone* or santenson* or santeson* or sawasone* or solurex* or sterasone* or thilodexine* or triamcimetil* or vexamet* or visumethazone* or tobradex* or maxitrol* or AI3-50934 or CCRIS 7067 or DXMS or EINECS 200-003-9 or HSDB 3053 or MK 125 or MK125 or NSC 34521 or NSC34521).ti,ab,kf,ot,hw,rn,nm.
4	or/1-3
5	Diabetic retinopathy/
6	(DME or DMO).ti,ab,kf.
7	(exp diabetes mellitus/ or diabet*.ti,ab,kf.) and macular edema/
8	(exp diabetes mellitus/ or diabet*.ti,ab,kf.) and ((macula* adj3 edema) or (macula* adj3 oedema)).ti,ab,kf.
9	(exp diabetes mellitus/ or diabet*.ti,ab,kf.) and (retinopath* or retina*).ti,ab,kf.
10	(exp diabetes mellitus/ or diabet*.ti,ab,kf.) and Intravitreal injections/
11	(exp diabetes mellitus/ or diabet*.ti,ab,kf.) and ((intravitreal or eye or eyes) and implant*).ti,ab,kf.
12	or/5-11
13	4 and 12
14	13 use medall
15	*Dexamethasone/
16	(ozurdex* or dexamethason* or dexametason* or hexadecadrol* or decameth or decaspray* or dexason* or dexpak* or maxidex* or millicorten* or oradexon* or decaject* or hexadrol* or aeroseb-D or aeroseb-dex* or anaflogistico* or aphtasolon* or auxiron* or azium* or bisu DS or calonat* or corsone* or cortisumman* or decacortin* or decaderm* or decadron* or decagel* or decalix* or decasone* or dectancyl* or dekacort* or deltafluoren* or dergramin* or desadrene* or desametasone* or desamethasone* or desameton* or deseronil* or dex-ide or dexa mamallet* or dexa-cortidelt* or dexa-cortisyl* or dexa-scheroson* or dexa-sine* or dexacort* or dexacortal* or dexacortin* or dexadeltone* or dexafarma* or dexalona* or dexameth* or dexapolcort* or dexapos* or dexaprol* or dexinolon* or dexinoral* or dexone* or dextelan* or dezone* or dinormon* or fluormethylprednisolon* or fluormone* or fluorocort* or fortecortin* or gammacorten* or HL-dex*

MULTI-DATABASE STRATEGY	
	or isopto-dex* or lokalison F or loverine* or luxazone* or mediamethasone* or methylfluorprednisolone* or mexidex* or mymethasone* or ocu-trol or pet derm III or policort* or prednisolon F or prednisolone F or spoloven* or sunia Sol D or superprednol* or turbinaire* or visumetazone* or adrecort* or adrenocot* or aeroseb dex* or aflucoson* or aflucosone* or alfalyl* or arcodexan* or artrosone* or bidexol* or calonat* or cebedex* or colofoam* or corsona* or cortastat* or cortidex*or cortidrona* or cortidrone* or dacortina fuerte* or dacortine fuerte* or dalalone* or danasone* or de-sone la or decadeltosona* or decadeltosone* or decadion* or decadran* or decaesadril* or decamethasone* or decasterolone* or decdan* or decilone* or decofluor* or delladec* or deronil* or desacort* or desalark* or desigdron* or dexa cortisyl* or dexa dabrosan* or dexa korti* or dexa scherosan* or dexa scherozon* or dexa-p or dexacen 4 or dexachel* or dexacorten* or dexacortisyl* or dexadabroson* or dexadecadrol* or dexadrol* or dexagel* or dexagel* or dexagen* or dexahelvacort* or dexakorti* or dexalien* or dexalocal* or dexame* or dexamecortin* or dexameson* or dexamethazon* or dexamethonium* or dexamonozon* or dexan* or dexapot* or dexascheroson* or dexascherozon* or dexionil* or dexmethsone* or dexona* or dextrasone* or dezone* or dibasona* or dexamethasone* or esacortene* or exadion* or firmalone* or fluormethyl prednisolone* or fluorodelta* or fluoromethylprednisolone* or grosodexon* or hexadecadiol* or hexadiol* or isnacort* or isopto dex* or isopto maxidex* or isoptodex* or isoptomaxidex* or marvidione* or megacortin* or mephameson* or metasolon* or methazonion* or methazone ion* or methazonion* or metisone lafi* or mexasone* or millicortenol* or neoforderx* or neofordex* or nisomethasona* or novocort* or oftan-dexa* or opticorten* or opticortinol* or oradexan* or orgadrone* or pidexon* or posurdex* or predni f tablinen* or predni-f or prednisolone f or prodexon* or sanamethasone* or santenson* or santeson* or sawasone* or solurex* or sterasone*or thilodexine* or triamcimetil* or vexamet* or visumethazone* or tobradex* or maxitrol* or AI3-50934 or CCRIS 7067 or DXMS or EINECS 200-003-9 or HSDB 3053 or MK 125 or MK125 or NSC 34521 or NSC34521).ti,ab,kw.
17	or/15-16
18	Diabetic macular edema/ or exp diabetic retinopathy/
19	(DME or DMO).ti,ab,kw.
20	((exp diabetes mellitus/ or diabet*.ti,ab,kw.) and macular edema/) or retina macula cystoid edema/
21	(exp diabetes mellitus/ or diabet*.ti,ab,kw.) and ((macula* adj3 edema) or (macula* adj3 oedema)).ti,ab,kw.
22	(exp diabetes mellitus/ or diabet*.ti,ab,kw.) and Retinopathy/
23	(exp diabetes mellitus/ or diabet*.ti,ab,kw.) and (retinopath* or retina*).ti,ab,kw.
24	(exp diabetes mellitus/ or diabet*.ti,ab,kw.) and Intravitreal implant/
25	(exp diabetes mellitus/ or diabet*.ti,ab,kw.) and ((intravitreal or eye or eyes) and implant*).ti,ab,kw.
26	or/18-25
27	17 and 26
28	27 use oemezd
29	28 not conference abstract.pt.
30	14 or 29
31	exp animals/
32	exp animal experimentation/ or exp animal experiment/
33	exp models animal/
34	nonhuman/
35	exp vertebrate/ or exp vertebrates/
36	or/31-35
37	exp humans/
38	exp human experimentation/ or exp human experiment/
39	or/37-38
40	36 not 39
41	30 not 40
42	remove duplicates from 41

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	October 2017
Keywords:	Ozurdex (dexamethasone), diabetic macular edema
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
HALLER et al., 2010[62]	Study population - irrelevant
HENG et al., 2016[63]	Intervention - irrelevant
MATURI et al., 2015[64]	Study population - irrelevant
SHAH et al., 2016[65]	Study population - irrelevant

Appendix 4: Detailed Outcome Data

Table 12: Number of Patients Receiving Injections (Pseudophakic Subgroup)

Number of treatments, N (%)	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
≥ 1	[redacted]	[redacted]	[redacted]	[redacted]
≥ 2	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]	[redacted]	[redacted]
≥ 5	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]

DEX = dexamethasone.
Note: Exposure was based on the safety population.
Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Table 13: Exposure to IOP-Lowering Medication in the Study Eye (Pseudophakic Subgroup)

	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 N = 85	Sham N = 100
Baseline[a], n/N (%)	[redacted]	[redacted]
Year 3 final visit[b], n/N (%)	[redacted]	[redacted]
Any time during the study, n/N (%)	[redacted]	[redacted]

DEX = dexamethasone; IOP = intraocular pressure.
[a] Baseline refers to medications used prior to the first injection.
[b] Year 3 final visit includes only those medications marked as ongoing at year three.
Note: Exposure to IOP-lowering medication was evaluated in the safety population.
Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Table 14: Patients with Glaucoma procedure in the Study Eye (Pseudophakic Subgroup)

	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 N = 85	Sham N = 100
Number of patients with glaucoma procedure during the study	[redacted]	[redacted]

DEX = dexamethasone.
Notes: Glaucoma procedure includes: trabeculoplasty, Iridotomy, trabeculectomy, iridectomy, and phacotrabeculectomy.
Exposure to glaucoma procedure was evaluated in the safety population.
Source: MEAD-010 CSR,[23] MEAD-011 CSR.[24]

Table 15: Visual Acuity Efficacy Outcomes (Pseudophakic Subgroup; ITT Analysis)

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
BCVA change from baseline				
At month 3				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 6				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 9				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 12				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 18				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 24				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 30				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At month 36				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
At last visit				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	51 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
BCVA change from baseline by category at last visit				
≥ 5 and < 15 letter improvement				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
No change (includes a 5-letter improvement or worsening)				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
≥ 5 and < 15 letter worsening				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
≥ 15 worsening				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
≥ 10 letter improvement	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
< 10 letter change (includes improvement or worsening)				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
≥ 10 letter worsening				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
BCVA change from baseline by category at month 12				
≥ 10 letter improvement				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
< 10 letter change (includes improvement or worsening)				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
≥ 10 letter worsening				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
BCVA ≥ 15 letter worsening from baseline at any time during the study				
Proportion of patients, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
Per cent of visits with BCVA 15 letter improvement during the study				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean, % (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
CRT as measured by OCT change from baseline[a]				
At last visit				
Baseline, n (%)	44 (100)	50 (100)	42 (100)	[redacted]
Adjusted LS mean change from baseline, microns (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; ITT = intention to treat; LS = least squares; MD = mean difference; OCT = optical coherence tomography; SD = standard deviation.
[a] Based on AUC approach and observed data, missing data were not imputed.

Notes: Last visit refers to either month 39 or month 36 which ever was the final visit.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic.

LOCF was used to impute missing data unless otherwise specified. Patients without post-baseline BCVA were set to value 0 in the analysis.

Means and mean differences were analyzed using an ANCOVA model stratified by treatment as fixed effects and baseline BCVA as the covariate, with the exception of CRT as measure by OCT outcomes which utilized baseline CRT as measured by OCT as the covariate.

Source: MEAD-010 CSR[23], MEAD-011 CSR.[24]

Table 16: Visual Acuity Efficacy Outcomes (Pseudophakic Subgroup; PP analysis)

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
BCVA average change from baseline[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	
Per cent of visits with BCVA 15 letter improvement during the study[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean, % (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus sham	[redacted]		[redacted]	
CRT as measured by OCT average change from baseline[a]				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline, microns (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]		[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; LS = least squares; MD = mean difference; OCT = optical coherence tomography; PP = per-protocol; SD = standard deviation.
[a] Based on AUC approach and observed data, missing data were not imputed.

Notes: Last visit refers to either month 39 or month 36 which ever was the final visit.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic.

LOCF was used to impute missing data unless otherwise specified. Patients without post-baseline BCVA were set to value 0 in the analysis.

Means and mean differences were analyzed using an ANCOVA model stratified by treatment as fixed effects and baseline BCVA as the covariate, with the exception of CRT as measure by OCT outcomes which utilized baseline CRT as measured by OCT as the covariate.

Source: MEAD-010 CSR,[23] MEAD-011 CSR.[24]

Table 17: Pooled Visual Acuity Efficacy Outcomes (Pseudophakic Subgroup)

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 N = 86	Sham N = 101
Baseline BCVA		
Baseline, n (%)	86 (100)	101 (100)
Mean letters (SD)	[redacted]	[redacted]
BCVA average change from baseline (ITT)[a]		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	6.5 [redacted]	1.7 [redacted]
Adjusted LS MD versus sham (95% CI)	NR $P < 0.001$	
BCVA change from baseline (ITT)		
At month 3		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 6		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 9		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 12		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 18		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 24		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 30		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At month 36		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At last visit		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 N = 86	Sham N = 101
BCVA change from baseline by category at last visit (ITT)		
≥ 15 letter improvement		
Proportion of patients, n/N (%)	20/86 (23.3)	11/101 (10.9)
Difference versus sham	12.4% (1.6 to 23.2) *P* = 0.024	
CRT as measured by OCT change from baseline (ITT)		
Average[a]		
Baseline, n (%)	86 (100)	101 (100)
Adjusted LS mean change from baseline, microns (SD)	–131.8 [redacted]	–50.8 [redacted]
Adjusted LS MD versus sham (95% CI)	NR *P* < 0.001	
Time to ≥ 15-letter improvement in BCVA from baseline,[b] %	57.4	26.3

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; ITT = intention to treat; LS = least squares; MD = mean difference; OCT = optical coherence tomography; PP = per protocol; SD = standard deviation.

[a] Based on AUC approach and observed data, missing data were not imputed.

[b] Cumulative response rate at study end.

Last visit refers to either month 39 or month 36 which ever was the final visit.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic

LOCF was used to impute missing data unless otherwise specified. Patients without post-baseline BCVA were set to value 0 in the analysis

Means and mean differences were analyzed using an ANCOVA model stratified by treatment and study as fixed effects and baseline BCVA as the covariate, with the exception of OCT retinal outcomes which utilized baseline CRT as measured by OCT as the covariate.

Source: Boyer 2014[49], MEAD-010 CSR[23], MEAD-011 CSR[24]

Table 18: Pooled Visual Acuity Efficacy Outcomes (Pseudophakic with DME ≤ 3 Years Subgroup)

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 [redacted]	Sham [redacted]
Baseline BCVA		
Baseline, n (%)	[redacted]	[redacted]
Mean letters (SD)	[redacted]	[redacted]
BCVA average change from baseline (ITT)[a,b]		
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
BCVA change from baseline (ITT)		
At last visit		
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
BCVA change from baseline by category at last visit (ITT)		
≥ 15 letter improvement		
Proportion of patients, n/N (%)	[redacted]	[redacted]
Difference versus sham	[redacted]	
CRT as measured by OCT change from baseline (ITT)		
Average[a,b]		
Baseline, n (%)	[redacted]	[redacted]

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 [redacted]	Sham [redacted]
Adjusted LS mean change from baseline, microns (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At last visit		
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, microns (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; LS = least squares; MD = mean difference; OCT = optical coherence tomography; PP = per-protocol; SD = standard deviation.
[a] Based on AUC approach and observed data, missing data were not imputed.

Notes: Last visit refers to either month 39 or month 36 which ever was the final visit.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic.

LOCF was used to impute missing data unless otherwise specified. Patients without post-baseline BCVA were set to value 0 in the analysis.

Means and mean differences were analyzed using an ANCOVA model stratified by treatment as fixed effects and baseline BCVA as the covariate, with the exception of CRT as measure by OCT outcomes which utilized baseline CRT as measured by OCT as the covariate.

Source: MEAD-010 CSR[23], MEAD-011 CSR[24]

Table 19: Pooled Visual Acuity Efficacy Outcomes (Pseudophakic with DME > 3 Years Subgroup)

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 [redacted]	Sham [redacted]
Baseline BCVA		
Baseline, n (%)	[redacted]	[redacted]
Mean letters (SD)	[redacted]	[redacted]
BCVA average change from baseline (ITT)[ab]		
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
BCVA change from baseline (ITT)		
At last visit		
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, letters (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
BCVA change from baseline by category at last visit (ITT)		
≥ 15 letter improvement		
Proportion of patients, n/N (%)	[redacted]	[redacted]
Difference versus sham	[redacted]	
CRT as measured by OCT change from baseline (ITT)		
Average[a,b]		
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, microns (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	
At last visit		

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 [redacted]	Sham [redacted]
Baseline, n (%)	[redacted]	[redacted]
Adjusted LS mean change from baseline, microns (SD)	[redacted]	[redacted]
Adjusted LS MD versus sham (95% CI)	[redacted]	

BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; LS = least squares; MD = mean difference; OCT = optical coherence tomography; PP = per-protocol; SD = standard deviation.

[a] Based on AUC approach and observed data, missing data were not imputed.

Last visit refers to either month 39 or month 36 which ever was the final visit.

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic.

LOCF was used to impute missing data unless otherwise specified. Patients without post-baseline BCVA were set to value 0 in the analysis.

Means and mean differences were analyzed using an ANCOVA model stratified by treatment as fixed effects and baseline BCVA as the covariate, with the exception of CRT as measure by OCT outcomes which utilized baseline CRT as measured by OCT as the covariate.

Source: MEAD-010 CSR[23], MEAD-011 CSR[24]

Table 20: Harms (Pseudophakic Subgroup)

Outcome	MEAD-010		MEAD-011	
	DEX 700 N = 44	Sham N = 50	DEX 700 N = 42	Sham N = 51
AEs, n (%)				
Subjects with > 0 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Most common reason[a]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)				
Subjects with > 0 SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Most common reason[a]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)				
Subjects with > 0 SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Most common reason[a]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms, n (%)				
Most common reason	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; DEX = dexamethasone; NA = not available; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

Source: MEAD-010 CSR[23], MEAD-011 CSR[24]

Table 21: Pooled Non-Ocular Harms (Pseudophakic Subgroup)

Outcome	Pooled Data (MEAD-010 and MEAD-011)	
	DEX 700 N = 85	Sham N = 100
AEs		
Subjects with > 0 AEs, n (%)	[redacted]	[redacted]
Most common AEs[a]		
Hypertension	[redacted]	[redacted]
Anemia	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypercholesterolemia	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Gastroesophageal reflux	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
SAEs		
Subjects with > 0 SAEs, n (%)	[redacted]	[redacted]
Treatment related	[redacted]	[redacted]
WDAEs		
WDAEs, n (%)	[redacted]	[redacted]
Most common reasons	[redacted]	[redacted]
Notable Harms		
Deep vein thrombosis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]

AE = adverse event; DEX = dexamethasone; NA = not available; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

Non-ocular harms were evaluated in the safety population.

Source: MEAD-010 CSR,[23] MEAD-011 CSR.[24]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Best-corrected visual acuity (BCVA) measurement with the Early Treatment Diabetic Retinopathy Study (ETDRS) letters score
- Central retinal thickness (CRT) assessed by optical coherence tomography (OCT)
- National Eye Institute Visual Function Questionnaire-25 items (NEI-VFQ-25).

Findings

Table 22: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
ETDRS charts	Developed to measure visual acuity. Patients are present a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows; a total of 14 lines (70 letters).	Yes	10 to 15 letters	Kniestedt and Stamper 2003,[66] FDA Statistical Review,[52] Lucentis medical review,[67] Rosser 2003[54]
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[43]
NEI-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 (½ SD-based method) for the composite score	Mangione 1998,[68] Mangione 2001,[69] Dougherty 2010,[70] Lloyd 2013[20]

ETDRS = Early Treatment Diabetic Retinopathy Study; MCID = minimal clinically important difference; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire (25 items); OCT = optical coherence tomography; SD = standard deviation; SEM = standard error of measurement.

Early Treatment Diabetic Retinopathy Study Charts

The ETDRS charts are based on a design by Bailey and Lovie, and are commonly used in clinical research.[66,71-74] 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 letters 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 less 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 read correctly at 1.0 metre in the first six lines. Therefore, the ETDRS letter score could result in a maximum score of 100.[75,76]

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.[66,77] 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. For example a person with 20/100 vision can read letters at 20 feet that a person with 20/20 vision could read at 100 feet.[66,78] 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 (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 less.[54] 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.[55] A loss or gain of three lines (15 letters) is considered a moderate degree of change and is commonly used as a outcome in clinical trials.[79] 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 greater than or equal to 15-letter change in visual acuity, as clinically relevant outcome measures in trials of interventions.[52]

With regards 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.[80] 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,[79] and difficulties with reading is a common complaint among persons with eye disease.[68] Rather, contrast sensitivity is a more important contributor to reading performance.[79,81]

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.[43] 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.[43,82] 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.[83]

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 ration of OCT were 0.81, 0.85, 5.4 and 0.22, respectively.[84] 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.[43] 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.[85] Another study which 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.[83] 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 of 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.[86]

In patients with DME, the association between OCT measured retinal thickness and BCVA has been evaluated. A moderate correlation between visual acuity and OCT center-point thickness has been observed (r = 0.52).[56] For every 100 µm decrease in center-point thickness, visual acuity increased by 4.4 letters (95% CI, 3.5 to 5.3).[56] Other studies have shown similarly modest correlations between visual acuity and CRT determined by OCT.[57,58] In eyes with DME treated by laser photocoagulation, changes in center-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.[56] Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes in DME but is modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient reported outcomes.

National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)

The NEI-VFQ was developed as a means to measure vision-targeted quality of life. The original 51-item questionnaire was developed based on focus groups comprised of persons with a number of common eye conditions (e.g., age-related cataracts, age-related macular degeneration, and diabetic retinopathy), and thus may be used to assess quality of life in a broad range of eye conditions.[68] The original 51-item questionnaire is comprised of 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.[87]

A shorter version of the original instrument, the NEI-VFQ-25, was subsequently developed, which retained the multidimensional nature of the original, and is more practical and efficient to administer.[69] With the exception of the expectations for future vision, all the constructs listed above were retained in the shortened version, with a reduced number of items within each subscale. Thus, the NEI-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 NEI-VFQ-25 have been proposed.[70] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring to Rasch analysis and an algorithm to approximate Rasch scores, all methods were highly correlated.[70] 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.[70]

Determination of what constitutes a clinically meaningful change in the NEI-VFQ-25 appears to be linked to its correlation with visual acuity. A three-line (15 letters) change in visual acuity has been used as the outcome of interest in clinical trials, and corresponding changes in the NEI-VFQ-25 are suggested as clinically meaningful end points. For patients with neovascular age-related macular degeneration (AMD) and specifically for the study eye, which is typically the worse seeing eye, a 15-letter change in visual acuity corresponds to a four-point change in overall NEI-VFQ-25 score.[88] For the better-seeing eye, the clinically relevant difference for NEI-VFQ-25 scores based on a three-line change is seven to eight for overall score. Other studies in patients with subfoveal choroidal neovascularization have shown similar estimated clinically relevant differences.[89] The instrument showed weaker correlation or was not responsive to changes in the visual acuity of the worse eye in patients with AMD.[90,91] This may have implications when evaluating patients with unilateral disease. A psychometric validation study of the NEI-VFQ-25 specifically in patients with DME has more recently been conducted, and two distribution-based methods were employed to determine a minimal clinically important difference (MCID) from baseline to week 54.[20] Using a ½ standard deviation-based approach, the MCID for each NEI-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 (SEM) 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.

Both versions of the NEI-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[20,69,87,90] 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.[90,91] However, some assessments of the psychometric validity of the NEI-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.[59,60,91] 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.[59,60] Re-engineering the NEI-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.[59,60] Considering the evidence of multidimensionality, the validity of the single composite score of the NEI-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 for DME population.[20] The near vision and distance vision subscales are 3-item domains on the NEI-VFQ-25; their internal reliability as represented by Cronbach's alpha was reported as 0.73 and 0.58, respectively. Convergent validity analysis to examine the relationship between NEI-VFQ-25 scores and other disease-related variables provided mixed results, and the NEI-VFQ-25 domains collectively showed low to moderate correlations with ETDRS visual acuity score for both the study 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 NEI-VFQ-25 and the EQ-5D Visual Analogue Scale (VAS), and the EQ-5D VAS along with ETDRS was a significant predictor of near and distance vision subscale scores, suggesting that general health-related quality of life was captured by the NEI-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 NEI-VFQ-25 composite. Overall, the authors concluded that despite its documented limitations and the need for an improved instrument, the NEI-VFQ-25 demonstrated a degree of validity to measure health-related quality of life in patients with DME.[20]

Conclusion

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 scores are based on the number of letters correctly read by a patient. A loss or gain of 2 to 3 lines (10 to15 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 is modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient reported outcomes.

The NEI-VFQ-25 was developed to measure vision-targeted quality of life. The NEI-VFQ was reported to be 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 more appropriately identified as a measure of visual functioning. The NEI-VFQ has a reported MCID between 3.3 and 6.13 points for the overall composite score.

Appendix 6: Summary of Indirect Comparisons

Background

[redacted]

Methods

[redacted]

Description of IDCs Identified

[redacted]

[redacted]

Review of the Manufacturer–Submitted IDC

Objectives and Rationale

[redacted]

Methods

Study Eligibility and Selection Process

[redacted]

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Data Extraction

[redacted]

Comparators

[redacted]

Outcomes

[redacted]

[redacted]

Quality Assessment of Included Studies

[redacted]

Evidence Network

[redacted]

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Source: The manufacturer–submitted IDC[92]

Indirect Comparison Methods

[redacted]

[redacted]

[redacted]

Results

[redacted]

Study and Patient Characteristics

[redacted]

[redacted]

Table 23: [redacted]

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Table 24: [redacted]

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Comparators

[redacted]

Risk of Bias

[redacted]

Evidence Network

[redacted]

Efficacy

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[redacted]

[redacted]

[redacted]

Table 25: [redacted]

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Critical Appraisal

[redacted] [93,94]

Systematic Review Methods

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Reporting of the IDCs

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IDC Methods

Analytical Methods

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[redacted]

Evidence Network

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Risk of Bias

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Patient Characteristics

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Study Characteristics

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Dosage of Comparators

[redacted]

Summary and Conclusion

[redacted]

[redacted]

Appendix 7: Summary of Phase II Studies

Objective

To summarize the results from three phase II studies that evaluated the effects of dexamethasone compared with anti-VEGF therapies (ranibizumab, bevacizumab) for the treatment of adult patients with diabetic macular edema (DME) who are pseudophakic.

Findings

Study Design

A total of three phase II trials studied the effects of dexamethasone compared with anti-VEGF drugs in adult patients with diabetic macular edema (DME) who are pseudophakic**.** All trials were multi-centre; however, only two were multinational and none recruited patients from Canada. One study was a noninferiority study that compared 700 mcg dexamethasone injections to 0.5 mg ranibizumab injections (RAN study), and another superiority study compared 700 mcg dexamethasone injections to 1.25 mg bevacizumab injections (BEVORDEX). In addition to 0.3 mg ranibizumab, the other superiority study compared 700 mcg dexamethasone injections to sham (COMB Study). Detailed study characteristics are provided in Table 26.

Patients in the RAN study were randomized to a 1:1 ratio using IVRS/IWRS and stratified by BCVA score at baseline (≥ 34 to ≤ 49 or ≥ 50 to ≤ 70). Both the study personnel who measured BCVA and evaluators at the reading center were masked to the study treatment assignment. Patients who experienced a decrease of ≥ 10 BCVA letters from baseline or > 300 µm CRT (> 320 µm on Spectralis OCT) as measured by Cirrus OCT could also receive deferred laser therapy. A sample size of 149 patients in each group was determined to provide 80% power to detect a two-letter difference between treatments groups from baseline in BCVA using a standard deviation of 9.21 based on the RESOLVE trial. A noninferiority margin of five letters was used based on half the historical maximum treatment effect of ranibizumab. A 2-sided alpha of 0.05 and 95% CI for the least squares mean difference between treatments were used to establish statistical significance of efficacy outcomes using the ITT population and based on an ANOVA model with treatment group and baseline BCVA as the main effects. Safety analyses were based on the safety population.

Patients in BEVORDEX Study were randomized to a 1:1 ratio using computer-generated pseudorandom numbers in permuted block of variable size. Only the study personnel who measured BCVA were masked to the study treatment assignment. Patients with two eligible eyes had one treated with the randomly generated treatment assignment, while the fellow eye received the other treatment. A sample size of 35 eyes per group and a difference of at least 30% between treatment groups were required to provide 80% using a two-sided alpha of 0.05. Logistic regression with BCVA as a covariate and generalized correlation equation methods were used to model the primary outcome given that a correlation was possible between the same eyes of a patient using the ITT population and LOCF approach.

Initially, only pseudophakic eyes were eligible for enrolment in the COMB Study; however, due to recruitment difficulties, the eligibility criteria were broadened to include phakic eyes. During a 12-week run-in phase, patients were required to receive three additional anti-VEGF injections of ranibizumab (at enrolment week 4 and week 8) in addition to the

minimum of three prior injection required for enrolment. Patients were randomized to a 1:1 ratio using a permuted block design and stratified improvement in BCVA and CRT during the run-in phase. A sample size of 150 eyes was determined to provide 90% power to detect a five-letter difference between treatments groups from baseline in BCVA using a standard deviation of nine. Patients with two eligible eye for enrolment had one eye randomly assigned to each group. In COMB, patients and investigators assessing AEs were masked to treatment. Refractionists, visual acuity testers, and OCT technicians were masked at the 24-week primary end point. Investigators and study coordinators were not masked. Between-group differences (95% CI and 0.05 of the two-sided alpha) were performed using a linear mixed model with visual acuity at randomization and randomization stratification as fixed effects using the ITT population and multiple imputation to account for missing data. For patients that had both eyes involved in the study, a random effect was included to account for any fellow eye correlation.

Table 26: Details of the Phase II Studies

		RAN Study	BEVORDEX Study	COMB Study
Designs and Populations	**Study design**	Active-control, multi-centre, phase II, RCT		
		Multinational, single -masked, noninferiority trial	Single-masked, superiority trial	Masked (patient and investigator), superiority trial
	Locations	60 sites in 12 countries Israel. South Africa, US, Western Europe	4 sites in Australia	40 sites in the US
	Patients (N)	363 (one eye per patient)	88 eyes from 61 patients	236 eyes from 203 patients
	Eligibility	Adult patients with DME involving the center of the macula with mean CRT as measured by OCT ≥ 300 µm with Spectralis (Heidelberg) or ≥ 275 µm with Cirrus (Zeiss) at screening. Patients with BCVA > 34 and < 70 ETDRS letters (Snellen equivalent between 20/200 and 20/40). Patients with glycated hemoglobin > 12 %, IOP > 22 mm Hg at, glaucoma, a history of laser treatment within 3 months prior to screening, use of anti-VEGF treatment within 3 months prior to screening, use of intravitreal triamcinolone acetonide within 6 months prior to screening, and a history of vitrectomy were excluded.	Adult patients with DME involving the central fovea at least 3 months following at least 1 session of laser treatment. Patients for whom the investigator believed that laser treatment would be unhelpful, with Snellen equivalent between 20/400 and 20/40. Patients with uncontrolled glaucoma or glaucoma controlled with more than 1 medication, loss of vision because of other causes, intercurrent severe systemic disease, or any condition affecting follow-up or documentation were excluded.	Adult patients with DME with CRT as measured by OCT ≥ 290 in women, ≥ 305 in men with Cirrus (Zeiss) or ≥ 305 in women, ≥ 320 in men with Spectralis (Heidelberg). Patients with BCVA score of 78 to 24 (Snellen equivalent between 20/320 and 20/32). Patient received treatment with at least 3 anti-VEGF injections for DME (aflibercept, bevacizumab, or ranibizumab) within the previous 20 weeks. Patients with glaucoma loss of vision because of other causes, or any condition affecting follow-up or documentation were excluded.

		RAN Study	BEVORDEX Study	COMB Study
Drugs	**Intervention**	Dexamethasone 700 mcg intravitreal injection at baseline month 5 and month 10.	Dexamethasone 700 mcg intravitreal injection at baseline. Patients were eligible for retreatment if retinal thickness as measured by OCT was ≥ 300 µm or visual acuity was 79 letters or better (Snellen equivalent 20/25). Study treatment procedure was not to be performed more often than every 16 weeks.	Dexamethasone 700 mcg intravitreal injection was to be administered no more than 8 days following background ranibizumab 0.3 mg administered at baseline. At weeks 4 and 8 only ranibizumab injections were permitted. At weeks 12 through 20, patients were eligible for retreatment with dexamethasone in combination with ranibizumab if the visual acuity letter score was less than 84 (Snellen equivalent of 20/25 or worse) or if the CRT as measured by OCT was at or above ≥ 290 in women, ≥ 305 in men with Cirrus (Zeiss) or ≥ 305 in women, ≥ 320 in men with Spectralis (Heidelberg) A maximum of 2 injections of dexamethasone were given in each eye.
	Comparators	Ranibizumab 0.5 mg administered at baseline and monthly thereafter until the patients' visual acuity was stable for three consecutive monthly assessments. If no improvements in visual acuity were observed, monthly injections could be suspended until a decrease in visual acuity was observed (i.e., reinitiation of monthly injections after decrease in visual acuity). No treatment could be administered at month 12 (i.e., last dose was at month 11).	Bevacizumab 1.25 mg injection at baseline. Patients were eligible for retreatment if retinal thickness as measured by OCT was ≥ 300 µm or visual acuity was 79 letters or better (Snellen equivalent 20/25) Study treatment procedure was not to be performed more often than every 4 weeks	Sham procedure using a needleless applicator pressed against the conjunctiva was to be administered no more than 8 days following background ranibizumab 0.3 mg administered at baseline. At weeks 4 and 8 only ranibizumab injections were permitted. At weeks 12 through 20, patients were eligible for retreatment with sham in combination with ranibizumab if the visual acuity letter score was less than 84 (Snellen equivalent of 20/25 or worse) or if the CRT as measured by OCT was at or above ≥ 290 in women, ≥ 305 in men with Cirrus (Zeiss) or ≥ 305 in women, ≥ 320 in men with Spectralis (Heidelberg). A maximum of 2 injections of sham treatment were given in each eye.
Duration	**Phase**			
	Pre-treatment	2 week screening phase	None	12 week run-in phase
	Treatment	12 months	Every 4 weeks for up to 50 weeks	Every 4 weeks for 24 weeks
Outcomes	**Primary end point**	Change from randomization at each visit over 12 months in the mean average BCVA as measured by ETDRS.	Proportion of eyes with BCVA improvement of 10 or more letters as measured by ETDRS at week 48	Change from randomization to week 24 in the mean visual acuity letter score as measured by ETDRS

		RAN Study	BEVORDEX Study	COMB Study
	Other end points	• Change from baseline in retinal thickness of the central subfield • Safety	• Change in BCVA • Change from baseline in retinal thickness of the central subfield • Impact for vision impairment questionnaire • Safety	• Change from baseline in retinal thickness of the central subfield • Safety
NOTES	**Publications**	Callanan et al. 2016[95]	Gillies et al. 2014[96] Fraser-Bell et al. 2016[97]	Maturi et al. 2018[98]

BCVA = best-corrected visual acuity; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; OCT = optical coherence tomography; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

Source: Callanan et al. 2016,[95] Gillies et al. 2014,[96] Fraser-Bell et al. 2016,[97] Maturi et al. 2017.[98]

Methods

Patient Disposition

Disposition data were only available for the full DME populations included in the trials. No disposition data were available for the subgroup of patients that were pseudophakic. Most patients in all trials (between 90% and 100%) completed the studies. Reasons for discontinuations were not transparently reported. Of those that were reported, the most common reasons were loss to follow-up (between 7% and 10%), personal reasons (3%), and non-ocular AEs (3%). Detailed disposition is provided in Table 27.

Table 27: Patient Disposition (Full DME population)

	RAN Study[a]		BEVORDEX[c]		COMB Study[c]	
	DEX	RAN	DEX	BEV	DEX+RAN	SHAM+RAN
Full trial population[b]						
Randomized, N (%)	181	182	46	42	65	64
Discontinued study, N (%)	16 (88)	16 (88)	3 (7)	4 (10)	2 (3)	0
Completed study, N (%)	165 (91)	166 (91)	43 (93)	38 (90)	63 (97)	64 (100)
Reasons for discontinuation, N (%)						
Ocular AEs	4 (2)	0	NA	NA	NA	NA
Non-ocular AEs	6 (3)	5 (3)	NA	NA	NA	NA
Lack of efficacy	1 (<1)	1 (<1)	NA	NA	NA	NA
Pregnancy	0	1 (<1)	NA	NA	NA	NA
Lost to follow-up	3 (2)	1 (<1)	3 (7)	4 (10)	NA	NA
Personal reasons	0	5 (3)	NA	NA	NA	NA
Protocol violations	0	0	NA	NA	NA	NA
Other	2 (1)	3 (2)	NA	NA	NA	NA
Pseudophakic subgroup	**54 (30)**	**62 (34)**	**16 (35)**	**10 (24)**	**26 (40)**	**32 (50)**

AE = adverse event; BEV = bevacizumab; DEX = dexamethasone; NA = not available; RAN = ranibizumab.

[a] N represents the number of patients.

[b] Patients screened in the overall DME population.

[c] N represents the number of eyes.

Source: Callanan et al. 2016,[95] Gillies et al. 2014,[96] Fraser-Bell et al. 2016,[97] Maturi et al. 2017.[98]

Baseline Characteristics

Baseline characteristics were only available for the full DME populations included in the trials. No baseline characteristics were available for the subgroup of patients that were pseudophakic. Overall, patients were between 61.4 and 66 years of age (SD 9.0 to 10.5) and were mostly male (52% to 65%) with the exception of the SHAM+RAN group in the COMB Study (44% male). Mean DME duration was only available for the RAN study in which patients had DME for approximately 30 months. The majority of patients in the RAN study had diabetes for more than five years (87%). Overall, the minority of patients included in the trials were pseudophakic, 24% in BEVORDEX, and up to 50% in one arm of the COMB Study. The minority of patients were previously treated with laser therapy (between 25% and 48%) in the COMB STUDY and the RAN study, whereas all patients were previously treated with laser therapy in BEVORDEX. The minority of patients were previously treated with anti-VEGF drugs in the RAN study (22%), whereas all patients were treated with prior anti-VEGF drugs in the COMB Study. BEVORDEX did not report on prior use of anti-VEGF drugs. In general, A1C was similar between all trials (between 7.1% and 7.8%) as was IOP (between 14.5 and 16 mm Hg). Both BCVA and CRT varied across trials ranging between 55.5 letters to 63 letters and 375 µm to 503 µm, respectively. Detailed baseline characteristics are provided in Table 28.

Table 28: Summary of Baseline Characteristics (Full DME population)

Characteristics	RAN Study[a]		BEVORDEX[c]		COMB Study[c]	
	DEX N = 181	RAN N = 182	DEX N = 46	BEV N =42	DEX+RAN N = 65	SHAM+RAN N = 64
Age						
Mean years (SD)	63.4 (9.39)	63.7 (10.05)	61.4 (9.0)	62.2 (10.5)	NR	NR
Median years (IQR)	NR	NR	NR	NR	64 (59 to 69)	66 (59 to 71)
Gender, n (%)						
Male	112 (61.9)	116 (63.7)	30 (65)	26 (62)	34 (52)	28 (44)
Female	69 (38.1)	66 (36.3)	16 (35)	16 (38)	31 (48)	36 (56)
DME duration						
Mean months (SD)	36.3 (58.1)	29.7 (33.3)	NR	NR	NR	NR
Diabetes duration, years						
Mean (SD)	NR	NR	16.7 (10.3)	16.7 (10.7)	NR	NR
Median (IQR)	NR	NR	NR	NR	15 (10 to 21)	19 (10 to 26)
≤ 6 months	1 (0.6)	1 (0.5)	NR	NR	NR	NR
> 6 months to1 year	5 (2.8)	7 (3.8)	NR	NR	NR	NR
>1 to5 years	14 (7.7)	15 (8.2)	NR	NR	NR	NR
> 5 years	160 (88.4)	158 (86.8)	NR	NR	NR	NR
Lens status of the study eye, pseudophakic, n (%)	54 (29.8)	62 (34.1)	16 (35)	10 (24)	26 (40)	32 (50)
Prior treatment, n (%)						
Laser	53 (29.3)	47 (25.8)	46 (100)	42 (100)	31 (48)	31 (48)
Anti-VEGF	40 (22.1)	39 (21.4)	NR	NR	65 (100)	64 (100)
Intravitreal steroid injection	NR	NR	NR	NR	9 (14)	10 (16)
A1C						
Mean, % (SD)	7.7 (1.4)	7.5 (1.3)	7.7 (2.5)	7.8 (2.1)	NR	NR
Median (IQR)	NR	NR	NR	NR	7.1 (6.4 to 8.3)	7.4 (6.6 to 8.2)

Characteristics	RAN Study[a]		BEVORDEX[c]		COMB Study[c]	
	DEX N = 181	RAN N = 182	DEX N = 46	BEV N =42	DEX+RAN N = 65	SHAM+RAN N = 64
BCVA in the study eye at baseline						
Mean (SD)	60.2 (9.74)	60.4 (9.34)	55.5 (12.5)	56.3 (11.9)	63 (12)	63 (13)
IOP in the study eye, mm Hg						
Mean (SD)	14.9 (2.9)	14.9 (2.7)	14.8 (3.0)	14.5 (2.4)	NR	NR
Median (IQR)	NR	NR	NR	NR	15 (13 to 17)	16 (14 to 18)
OCT retinal thickness at center subfield, microns						
Mean (SD)	465 (136)	471 (140)	474.3 (95.9)	503 (140.9)	375 (97)	396 (122)

A1C = glycated hemoglobin; BCVA = best-corrected visual acuity; BEV = bevacizumab; DEX = dexamethasone; DME = diabetic macular edema; IOP = intraocular pressure; IQR = interquartile range; OCT = optical coherence tomography; RAN = ranibizumab; SD = standard deviation; VEGF = vascular endothelial growth factor.

[a] N represents the number of patients.

[b] Patients screened in the overall DME population.

[c] N represents the number of eyes.

Source: Callanan et al. 2016,[95] Gillies et al. 2014,[96] Fraser-Bell et al. 2016,[97] Maturi et al. 2017.[98]

Results

Efficacy

The adjusted the least squares (LS) mean difference for the BCVA average change from baseline was not provided for the pseudophakic group in BEVORDEX or the RAN study. The adjusted LS mean change from baseline in the average BCVA was 4.6 letters in the DEX group and 6.6 letters in the RAN group in the RAN study, whereas it was 10.4.etters in the DEX group and 7.7 letters in the BEV group at year 1 and 8.9 letters (95% CI, 2.0 to 13.4) in the DEX group and 7.7 letters (95% CI, 3.03 to 14.8) in the BEV group at year 2 in BEVORDEX.

The adjusted LS mean difference for the BCVA average change from baseline between treatment groups was 3.1 letters (95% CI,
–2.1 to 8.3) in the COMB Study. The adjusted LS mean difference between treatment groups for the CRT as measured by OCT average change from baseline was –78 µm (95% CI, –131 to –25).

Table 29: Visual Acuity Efficacy Outcomes (Pseudophakic Subgroup)

Outcome	RAN Study[a]		BEVORDEX[c]				COMB Study[c]	
			Year 1		Year 2			
	DEX N = 54	RAN N = 62	DEX N = 16	BEV N =10	DEX N = 16	BEV N =10	DEX+RAN N = 26	SHAM+RAN N = 32
BCVA average change from baseline[a]								
Baseline, n (%)	NR	NR	NR	NR	NR	NR	NR	NR
Adjusted LS mean change from baseline, letters (SD)	4.6 (NR)	6.6 (NR)	10.4 (NR)	7.7 (NR)	8.9 (95% CI, 2.0, 13.4)	7.7 (95% CI, 3.03, 14.8)	5.1 (9.7)	2.0 (7.6)
Adjusted LS MD versus comparator (95% CI)	NR		NR *P* = 0.47		NR *P* = 0.77		3.1 (–2.1 to 8.3) *P* = NR	
CRT as measured by OCT average change from baseline[a]								
Baseline, n (%)	NR	NR	NR	NR	NR	NR	NR	NR
Adjusted LS mean change from baseline, microns (SD)	NR	NR	NR	NR	NR	NR	–111 (86)	–49 (96)
Adjusted LS MD versus sham (95% CI)	NR		NR		NR		–78 (–131 to –25) *P* = NR	

BCVA = best-corrected visual acuity; BEV = bevacizumab; CI = confidence interval; CRT = central retinal thickness; DEX = dexamethasone; LS = least squares; MD = mean difference; OCT = optical coherence tomography; RAN = ranibizumab; SD = standard deviation.

[a] N represents the number of patients

[b] Patients screened in the overall DME population

[c] N represents the number of eyes

No adjustments for multiple statistical tests were made for any outcomes in the subgroup of adult patients with DME who were pseudophakic

Source: Callanan et al. 2016[95] Gillies et al. 2014[96] Fraser-Bell et al. 2016[97] Maturi et al. 2017[98]

Safety

No safety data were provided for the pseudophakic subgroups in any of the phase II trials.

Limitations

There are several limitations to the phase II trials included in this section (RAN Study, BEVORDEX Study, and COMB Study). The phase II trials were active-controlled RCTs that used appropriate methods to randomize patients. However, these trials were originally designed to evaluate the effects of dexamethasone in the general DME population. This CDR report is based on the results of a subgroup (i.e., adults with DME who are pseudophakic) which only consisted of approximately 24% to 50% of overall enrolled patients. Subgroup analyses were performed in the pseudophakic populations; however, randomization was not stratified for this subgroup. Inadequate randomization introduces biases through the presence of confounders (known and unknown). Given that no baseline characteristics or disposition data were provided in any of the trials for the pseudophakic subgroup, it is difficult to assess adequacy of randomization and therefore appropriately interpret the validity of the results.

All phase II trials included in this section based their sample size calculations on the general DME population and not the subgroup. Given that the subgroup of patients who are pseudophakic would consist of a smaller subset of this population (24% to 50%) the subgroups are also likely underpowered to detect a statistically significant difference.

Therefore, the results of these phase II trials are susceptible to false negatives (i.e., finding no difference between treatments when a difference truly exists).

Although, patients and investigators assessing AEs were masked to treatment, as well as refractionists, visual acuity testers, and OCT technicians, some investigators and study coordinators were not masked. Both the RAN study and BEVORDEX were single-masked trials in which patients were not blinded to treatment allocation. Furthermore, the adverse event profile associated with intravitreal steroids (i.e., IOP) is well known, therefore some accidental unblinding may have occurred.[12,19] Given that prior intravitreal steroid experience was not an exclusion criterion in any of the trials, some patients with prior experience may have surmised that the allocated treatment was dexamethasone. However, considering that the primary end point of the MEAD trials is relatively objective, the potential for bias is of lesser concern.

The Health Canada–approved indication is for the treatment of patients with DME who are pseudophakic. Therefore, the focus of this CDR review is based on a subset of the overall DME population. In addition, subgroups of interest included pseudophakic patients with DME who are either unsuitable for anti-VEGF therapy or have had inadequate response to prior anti-VEGF therapy. However, only approximately 20% of patients in the general DME population included in the trial in the RAN study were previously treated with anti-VEGF drugs; whereas, all patients in the general DME population included in the trial were previously treated with anti-VEGF drugs in the COMB Study. Prior use of anti-VEGF drugs were not provided in BEVORDEX. It is important to note that prior use of anti-VEGF drugs in the pseudophakic subgroups were not reported in any of the trials. Furthermore, it remains unclear if these patients responded to these treatments and were truly anti-VEGF refractory. It is also unclear if there were any patients included in the phase II trials that were considered unsuitable for anti-VEGF therapy. According to the clinical expert consulted for this review, the date of conduct of the trials (between February 2005 to June 2012) was prior to the adoption of anti-VEGF therapies and may therefore have influenced the number of patients having access to anti-VEGF therapy. It is therefore unclear if the results of the phase II trials can be generalized to patients who are unsuitable for anti-VEGF therapy or have had an inadequate response to anti-VEGF therapy.

All phase II trials were multi-centre; however they did not include any sites from Canada. Based on the characteristics of the MEAD studies, the phase II trials appear to have recruited patients with characteristics similar to those of the overall DME population in Canada, however, given that the baseline characteristics of the pseudophakic subgroup, it remains unclear whether the patient population included in these trials is truly representative of patients with DME who are pseudophakic in Canadian clinical practice.

With respect to the study duration, the FDA suggested that 36 months is considered short term. The FDA recommends that the treatment effect be demonstrated at a time point of at least 36 month or later for the indication of DME given that earlier treatment success is not necessarily a good indicator of a later success.[52] Therefore, it is unclear if the results of the phase II trials would be representative of the long-term treatment effect given that they are considerably shorter in duration (i.e., between approximately six months and one year in duration).

Summary

The three phase II studies (RAN study, BEVORDEX and the COMB Study) summarized here were designed to evaluate the effects of dexamethasone in the general DME population, not the pseudophakic subgroup of patients which is of interest for this review. Some pseudophakic subgroup results were reported, however the lack of stratification at randomization based on this factor, as well as the absence of reporting on baseline characteristics for the pseudophakic population make it difficult to truly assess the comparative efficacy and harms between dexamethasone and anti-VEGF drugs (i.e., bevacizumab and ranibizumab). These studies were also likely underpowered to detect differences between treatments in the pseudophakic subgroup, there was no control for multiple statistical testing, study durations were short, and no Canadian sites were included. These limitations make it difficult to appropriately interpret the comparative efficacy and safety of dexamethasone versus other drugs used for the treatment of patients with DME who are pseudophakic.

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