Common Drug Review
Clinical Review Report

November 2015

Drug	ivermectin (Rosiver)
Indication	Treatment of inflammatory lesions (i.e., papules and pustules) of rosacea in adults 18 years of age or older.
Listing request	As per Health Canada indication
Manufacturer	Galderma Canada Inc

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
CMH	Cochran-Mantel-Haenszel test
DB	double-blind
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol 5-Dimensions Questionnaire
HRQoL	health-related quality of life
IGA	Investigator's Global Assessment
ITT	intention-to-treat
LOCF	last observation carried forward
MCID	minimal clinically important difference
PP	per protocol
QoL	quality of life
RCT	randomized controlled trial
RosaQoL	Rosacea Quality of Life Index
SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Rosacea is a common chronic dermatological condition that affects the cheeks, nose, eyes, chin, and forehead. Primary symptoms include recurrent episodes of facial flushing, erythema (redness), telangiectasia (chronic dilation of blood vessels), inflammatory papules and/or pustules, and watery or irritated eyes. Papulopustular rosacea is the second most common rosacea subtype and is characterized by persistent central facial erythema with transient papules and/or pustules in a central facial distribution.[1] In Canada, the overall prevalence of rosacea is estimated to be two million patients.[2]

Ivermectin is a macrocyclic lactone derivative of the avermectin class. Its mechanism of action in treating papulopustular lesions is unknown. It has been postulated that it may be linked to ivermectin's anti-inflammatory effect and its involvement in the death of *Demodex* mites. Ivermectin has received a Health Canada indication for the topical treatment of inflammatory lesions (papules and pustules) of rosacea in adults 18 years of age or older, and the manufacturer is seeking reimbursement in line with this indication (i.e., as first-line therapy for patients with rosacea).[3] Ivermectin is available in a topical formulation as a 1% (10 mg/g) cream applied once daily.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of ivermectin cream for the treatment of inflammatory lesions (papules and pustules) of rosacea in adults. Efficacy outcomes of interest included lesion count, Investigator's Global Assessment (IGA), patient global assessment, health-related quality of life (HRQoL), remission, and relapse. Harm outcomes of interest included serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and treatment-emergent adverse events (AEs).

Results and Interpretation

Included Studies

Three phase 3, multi-centre, randomized controlled trials (RCTs) (Studies 18170, 18171, and 40173) met the pre-specified inclusion criteria for this systematic review. All three studies had similar inclusion/exclusion criteria and recruited adults (≥ 18 years) with moderate to severe papulopustular rosacea (defined as an IGA score ≥ 3) and 15 to 70 inflammatory facial lesions. Patients presenting with other forms of rosacea (rosacea conglobata, rosacea fulminans, isolated pustulosis of the chin), facial dermatoses or other dermatological conditions (e.g., perioral dermatitis, facial keratosis pilaris, or seborrheic dermatitis, and acne vulgaris) were excluded. Patients in these studies were mostly Caucasian, and the population therefore did not represent the diversity of Canadian patients who may be candidates for treatment with ivermectin, according to the clinical expert consulted by CADTH Common Drug Review (CDR) for this review.

Studies 18170 (N = 683) and 18171 (N = 688) were identical in design: an initial 12-week, double-blind (DB), vehicle-controlled phase was used to evaluate the efficacy and safety of ivermectin 1% once daily. This was followed by a subsequent 40-week, investigator-blinded phase to evaluate the long-term safety of ivermectin, during which patients continued ivermectin treatment or switched to azelaic acid 15% gel twice daily if they had been treated with vehicle during the initial phase. Study 40173 (N = 962) was an investigator-blind, active-controlled study carried out to evaluate the comparative efficacy and safety of ivermectin 1% once daily against topical metronidazole 0.75% twice daily over 16 weeks. Patients who were treated successfully (IGA ≤ 1) were enrolled in a 36-week extension phase, during which treatment was discontinued until relapse (defined as an increase in IGA to ≥ 2).

The co-primary outcomes in Studies 18170 and 18171 were success rate (proportion of patients achieving an IGA ≤ 1) and absolute change in the number of inflammatory lesions from baseline to week 12. The co-primary outcomes in Study 40173 were per cent change in inflammatory lesion count from baseline to week 16 and time to onset of efficacy.

Efficacy

In both vehicle-controlled studies (18170 and 18171), ivermectin was associated with a statistically significantly greater reduction in the number of lesions after 12 weeks of treatment compared with vehicle. Specifically, the difference in the mean absolute change in the number of inflammatory lesions from baseline to week 12 was –8.13 (95% CI, –10.12 to –6.13) in Study 18170 and –8.22 (95% CI, –10.18 to –6.25) in Study 18171 ($P < 0.001$ for both). Therefore, ivermectin-treated patients had approximately eight fewer lesions compared with vehicle-treated patients at the end of treatment. This difference was also reflected in the per cent change in inflammatory lesion count from baseline to week 12, which was –64.9% versus –41.6% and –65.7% versus –43.4% for ivermectin versus vehicle in Studies 18170 and 18171, respectively ($P < 0.001$ for both). In addition to the differential effect of ivermectin on the number of lesions, ivermectin was also associated with a higher rate of success (defined as achievement of an IGA ≤ 1) compared with vehicle (38.4% of patients successful versus 11.6% and 40.1% versus 18.8% for ivermectin versus vehicle in Studies 18170 and 18171, respectively; $P < 0.001$ for both). The clinical significance of these differences between ivermectin and vehicle is not known, because the minimal clinically important difference (MCID) for the change in the number of lesions has not been established.

In the active-controlled study (40173), ivermectin was associated with a statistically significantly greater reduction in lesion count compared with metronidazole after 16 weeks of treatment. Specifically, the per cent change in inflammatory lesion count from baseline to week 16 was –83.0% versus –73.7% ($P < 0.001$) in ivermectin-treated versus metronidazole-treated patients, respectively. A statistically significant difference between treatments ($P < 0.05$) in the per cent change in inflammatory lesion count was observed as early as week 3 and was maintained until the end of treatment at week 16. Ivermectin was also associated with a higher rate of success (defined as achievement of an IGA ≤ 1) at week 16 compared with metronidazole (84.9% of patients successful versus 75.4% for the ivermectin and metronidazole treatment groups, respectively; $P < 0.001$). As noted earlier, the absence of an MCID for lesion count means that it is unclear whether these differences between ivermectin and metronidazole are clinically meaningful.

In both vehicle-controlled studies, a statistically significantly greater proportion of ivermectin-treated patients rated their improvement after 12 weeks of treatment as “excellent” (patient global assessment) compared with the vehicle treatment group (34.3% versus 9.5% and 32.0% versus 7.3% for ivermectin versus vehicle in Studies 18170 and 18171, respectively; $P < 0.001$ for both). Similarly, in Study 40173, the ratings for “excellent” on the patient global assessment significantly ($P < 0.002$) favoured ivermectin (52.3%) over metronidazole (37.0%). The clinical significance of these differences in patient ratings of treatments is not known.

In Studies 18170 and 18171, ivermectin treatment was associated with statistically significantly greater ($P < 0.001$) improvements in quality of life (QoL) compared with vehicle after 12 weeks of treatment. This was based on changes in the condition-specific Rosacea Quality of Life Index (RosaQoL) (mean absolute change from baseline to week 12 for ivermectin versus vehicle was –0.64 versus –0.35 and –0.60 versus –0.35 in Studies 18170 and 18171, respectively) and the Dermatology Life Quality Index (DLQI) (mean absolute change from baseline to week 12 for ivermectin versus vehicle was –3.5 versus

–2.2 and –3.2 versus –2.0 in Studies 18170 and 18171, respectively). In Study 40173, QoL scores measured using DLQI and EuroQol 5-Dimensions Questionnaire (EQ-5D) improved compared with baseline in both the ivermectin and metronidazole treatment groups following 16 weeks of treatment (mean absolute change from baseline to week 16 for DLQI was 6.9 and 6.2 for ivermectin and metronidazole, respectively), but there was no statistical analysis of these changes. A review of the literature revealed that the MCID for DLQI (based on patients with a variety of dermatological conditions, not only rosacea) is approximately a 3-point improvement. The ≤ 1.3-point difference in DLQI score improvement for ivermectin versus vehicle did not appear to exceed the MCID, which raises doubt as to the clinical relevance of the statistically significant difference. Similarly, the small difference in DLQI scores in Study 40173 (< 1 point) between the ivermectin-treated and metronidazole-treated patients was not clinically meaningful.

In the 36-week extension phase of Study 40173, the relapse rate in patients who had achieved treatment success after the initial 16 weeks of treatment was 62.7% in the ivermectin group and 68.4% in the metronidazole group. Subgroup analyses were performed for the primary efficacy outcomes of inflammatory lesion count and success rate for each of the three included studies after stratifying the population according to disease severity (mild versus severe). However, there was no clear difference in efficacy according to disease severity.

One limitation noted for Studies 18170 and 18171 was the large vehicle effect (improvement of ~40%) in vehicle-treated patients. According to the manufacturer, the vehicle is a hydrophilic, skin-neutral cream using Cetaphil moisturizing cream as the basis. The vehicle alone has been observed to have beneficial effects on rosacea (referred to herein as the "vehicle effect"). The improvement in vehicle-treated patients likely reflects the effects of behavioural factors, as the clinical expert consulted in this review noted that many external factors that are within a patient's control may impact rosacea severity and disease progression (e.g., exposure to sun, skin applications, alcohol consumption, heat, and emotional factors). The relatively large improvement in vehicle-treated patients suggests that other factors are a large confounder in determining the magnitude of the treatment effect of ivermectin, which makes it difficult to precisely determine the magnitude of improvement that is attributable to ivermectin exposure. A related issue is the difference in the magnitude of response to ivermectin observed in the vehicle-controlled studies compared with the active-controlled study, which creates further uncertainty as to the true magnitude of the effect size associated with ivermectin treatment. Specifically, the response to ivermectin in Study 40173 was greater than that in both Studies 18170 and 18171, whereas the response of the metronidazole-treated patients in Study 40173 was similar to ivermectin-treated patients in Studies 18170 and 18171. The greater response in ivermectin-treated patients in Study 40173 is not attributable to a difference in exposure (because the same dose of ivermectin was administered to patients in each of the three studies) or population (because inclusion and exclusion criteria, and the corresponding baseline characteristics, were similar across studies), but might be attributable to geographical variations in behaviour — i.e., behavioural variations that differentially affect the response to treatment in European (Study 40173) versus North American (Studies 18170 and 18171) settings.

Another limitation of the available evidence is that, although there was a statistically significant difference in the primary efficacy outcomes between ivermectin (Studies 18170 and 18171) and metronidazole (Study 40173), it is unclear whether these differences are clinically meaningful. The psychometric properties (e.g., validity and reliability) of all but one of the outcome measures that were used in the included studies have not been described. Moreover, it is not known what margin of difference might constitute an MCID for any of the outcomes in the included studies.

Study 40173 is the only trial in which ivermectin has been compared directly with an active comparator (metronidazole). To assess the relative efficacy of ivermectin compared with [redacted], the manufacturer conducted an indirect comparison (see Appendix 6) [redacted]

According to the patient input received by CADTH for this review (Appendix 1), a key issue of importance to patients is the symptomatic control of redness and bumps. Ivermectin appears to meet this expectation based on the results of each of the included studies. However, other than the statistically significantly greater improvement in ivermectin-treated patients compared with metronidazole observed in Study 40173 (the clinical relevance of which is unknown), there is no compelling evidence to suggest that the efficacy of ivermectin is greater than that of other topical therapies available for treating rosacea. Therefore, ivermectin appears to meet the needs of patients in the same manner as other available topical therapies. Nevertheless, the clinical expert consulted by CDR suggested that ivermectin could be considered a reasonable alternative treatment for patients who have either failed or choose not to use metronidazole or azelaic acid. However, considerable uncertainty remains on the efficacy of ivermectin in patients who have previously failed metronidazole.

Harms

The frequency of SAEs was low during the 12-week vehicle-controlled studies (0.7% versus 0.4% and 1.5% versus 1.7% for the ivermectin and vehicle groups in Studies 18170 and 18171, respectively) and in the 12-week active-controlled study (Study 40173, 1.7% versus 1.0% for the ivermectin and metronidazole groups, respectively). No SAEs were treatment-related.

The overall frequency of treatment-emergent AEs was similar between treatments. In Study 18170, the frequency of AEs was 40.5% versus 39.4% for the ivermectin and vehicle groups, respectively. In Study 18171, the frequency of AEs was 36.5% in both treatment groups. In Study 40173, the frequency of AEs was 32.4% versus 33.1% for the ivermectin and metronidazole groups, respectively. The most common AEs were nasopharyngitis, headache, and skin-burning sensation.

Across all three studies, WDAEs were infrequent (< 3%) and generally balanced between treatment groups. The most common reasons for withdrawal were related to skin and subcutaneous tissue disorders. There was no occurrence of treatment-related gastrointestinal or photosensitivity AEs related to the study drug. Reports of dermatological conditions related to the study drug included skin irritation, skin burning, dermatitis allergic, and pain of skin/pruritus, although the frequency of these events was low in both treatment groups (< 3%). Only one patient (0.2%) in the ivermectin group of Study 40173 reported two episodes of moderate drug hypersensitivity. No deaths occurred during the three studies.

Long-term safety outcomes (up to 52 weeks of continuous treatment) were available for patients from Studies 18170 and 18171, in which patients originally randomized to vehicle were switched to azelaic acid 15%, twice daily, while ivermectin-treated patients remained on ivermectin therapy. No new safety issues emerged from the long-term safety data (Appendix 4).

[redacted]

Conclusions

The results of two vehicle-controlled RCTs (Studies 18170 and 18171) suggest that treatment of adults with moderate to severe papulopustular rosacea with ivermectin (1% cream administered daily) for 12 weeks is associated with a statistically significantly greater reduction in the number of inflammatory lesions and a statistically significantly higher success rate than vehicle-treated patients. Similarly, 16 weeks of treatment with ivermectin (Study 40173) was associated with a statistically significantly greater percentage reduction in the number of inflammatory lesions and a statistically significantly higher success rate compared with metronidazole (0.75% cream applied twice daily), although it is not known whether the difference in the response to ivermectin versus metronidazole is clinically meaningful. [redacted]

TABLE 1: SUMMARY OF RESULTS

	18170		18171		40173	
	Ivermectin 1% N = 451	**Vehicle N = 232**	**Ivermectin 1% N = 459**	**Vehicle N = 229**	**Ivermectin 1% N = 478**	**Metronidazole 0.75% N = 484**
Inflammatory Lesion Count, ITT						
Mean inflammatory lesion count at baseline (SD)	31 (14.3)	30.5 (14.4)	33.3 (13.6)	32.2 (13.9)	32.9 (14.0)	32.1 (12.8)
Mean inflammatory lesion count at ET[a] (SD)	10.6 (13.1)	18.5 (16.8)	11.0 (11.7)	18.8 (17.5)	5.2 (8.4)	8.5 (13.2)
Mean absolute change from baseline to ET[a] (SD)	–20.5 (16.0)	–12.0 (13.6)	–22.2 (14.9)	–13.4 (14.5)	–27.7 (15.2)	–23.6 (15.5)
Difference vs. control (95% CI)	–8.13 (–10.12 to –6.13)		–8.22 (–10.18 to –6.25)		NR	
% change from baseline to ET[a] (SD)	–64.9 (39.9)	–41.6 (38.8)	–65.7 (33.2)	–43.4 (38.4)	–83.0 (26.0)	–73.7 (39.7)
% difference vs. control (95% CI)	NR		NR		NR (0.00 to 4.60)	
P value	< 0.001		< 0.001		< 0.001	
Investigator Global Assessment, ITT						
Success, IGA ≤ 1 at ET[a], N (%)	173 (38.4)	27 (11.6)	184 (40.1)	43 (18.8)	406 (84.9)	365 (75.4)
% difference vs. control	26.8		21.3		14.9[b]	
P value	< 0.001		< 0.001		< 0.001	
Relapse						
Relapse rates, n (%)	NA		NA		245 (68.4)	250 (62.7)
P value					0.10[b]	
Harms, n (%)						
Deaths	0	0	0	0	0	0
Patients with ≥ 1 SAE	3 (0.7)	1(0.4)	7 (1.5)	4 (1.7)	8 (1.7)	5 (1.0)
Patients with ≥ 1 AE	183 (40.5)	91 (39.4)	167 (36.5)	84 (36.5)	155 (32.4)	160 (33.1)
WDAE	7 (1.5)	6 (2.6)	6 (1.3)	4 (1.7)	6 (1.3)	13 (2.7)

AE = adverse event; CDR = CADTH Common Drug Review; CI = confidence interval; ET = end of treatment (Part A); IGA = Investigator's Global Assessment; ITT = intention-to-treat; NA = not applicable; NR = not reported; SD = standard deviation; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

[a] End of treatment is defined as week 12 in Studies 18170 and 18171, and as week 16 in Study 40173.

[b] Calculated by CDR reviewers.

Source: Clinical Study Reports.[4-6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Rosacea is a chronic dermatological condition that affects the cheeks, nose, eyes, chin, and forehead. Its characteristics include recurrent episodes of facial flushing and a spectrum of clinical signs including erythema (redness); telangiectasia (chronic dilation of blood vessels); inflammatory papules and/or pustules; and watery or irritated eyes. The disease usually manifests in persons aged 30 to 50 years.[7] Rosacea is estimated to affect approximately two million people in Canada.[2]

There is no standard clinical definition for rosacea. It can be classified into four subtypes (or stages) and one variant based on its presenting symptoms.[8] The four subtypes are: erythematotelangiectatic rosacea, characterized by flushing and persistent central facial erythema (subtype 1); papulopustular rosacea, characterized by persistent central facial erythema with transient papules and/or pustules in a central facial distribution (subtype 2); phymatous rosacea (rhinophyma), characterized by skin thickening, irregular surface nodularities, and enlargement most commonly of the cartilaginous portion (distal) of the nose (subtype 3); and ocular rosacea, characterized by hyperemia of conjunctivae with telangiectasia of the lids, blurred vision, and general irritation of the eyes (subtype 4). In addition, granulomatous rosacea is a rare variant. The subtypes of rosacea are not mutually exclusive and it is possible for an individual to present with overlapping symptoms that coincide with multiple subtypes. Papulopustular rosacea (subtype 2) is the second most common subtype.[1]

1.2 Standards of Therapy

As rosacea is a chronic condition that waxes and wanes, the goals of therapy reflect this in terms of reducing acute flares with rapid-acting therapies and maintaining remission.[9] In Canada, currently available treatment options for papulopustular rosacea include topical and/or systemic drugs. The most commonly used topical drugs are metronidazole and azelaic acid, while systemic therapies include antibiotics from the tetracycline class. According to the clinical expert consulted in this review, existing treatments have focused on reducing papules and pustules whereas other symptoms of rosacea, such as erythema and telangiectasia, have been harder to treat.

Typically, patients are initiated with metronidazole or another topical medication such as azelaic acid. Moderate to severe papulopustular rosacea may require systemic therapy and, in cases where no improvement is observed, combination therapy of topical and/or systematic therapies may be prescribed.[9] Because relapse is frequent within weeks of therapy cessation, maintenance therapy with either a topical or systemic drug is commonly given with a step-down approach to reduce drug dosage. There are currently no Canada-specific treatment guidelines for rosacea, although this is an area of focus for the Canadian Dermatology Association.[10]

1.3 Drug

Ivermectin is a macrocyclic lactone derivative belonging to the avermectin class. Its therapeutic effects are thought to be due to its anti-inflammatory properties in terms of inhibiting lipopolysaccharide-induced production of inflammatory cytokines while upregulating anti-inflammatory cytokine IL-10. Historically it has been used as a broad-spectrum antiparasitic drug.[11] Its mechanism of action in treating papulopustular skin lesions is presently unknown. It has been postulated to be linked to ivermectin's anti-inflammatory effect and its involvement in the death of *Demodex* mites.[11,12] Ivermectin has a Health Canada indication for the topical treatment of inflammatory lesions (papules and pustules) of rosacea in adults 18 years of age or older and is available as a 1% (i.e., 10 mg/g) cream, applied once daily, to treat

papulopustular rosacea.[3] The manufacturer is requesting that ivermectin be reimbursed in line with the Health Canada indication, i.e., as first-line therapy for patients with rosacea.[13]

Indication under review
Treatment of inflammatory lesions (i.e., papules and pustules) of rosacea in adults 18 years of age or older.
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF METRONIDAZOLE, TETRACYCLINE ANTIBIOTICS, AND AZELAIC ACID

	Metronidazole (MetroGel, MetroCream, MetroLotion, Rosasol[a])	Azelaic acid (FINACEA)	Tetracycline antibiotics[b]: doxycycline, tetracycline, minocycline	Ivermectin (ROSIVER)
Indication[c]	For the treatment of inflammatory lesions (papules and pustules), erythema, and telangiectasia associated with rosacea.	For the topical treatment of inflammatory papules and pustules and erythema of mild to moderate rosacea.	Doxycycline: For the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. No other tetracycline antibiotics are approved for treating rosacea.	For the treatment of inflammatory lesions (i.e., papules and pustules) of rosacea in adults 18 years of age or older.
Route of Administration	Topical		PO	Topical
Recommended Dose	MetroGel: 0.75% or 1% gel q.d. MetroCream: 0.75% cream b.i.d. MetroLotion: 0.75% lotion b.i.d. Rosasol: 1% cream b.i.d.	15% gel b.i.d.	40 mg q.d.	1% cream q.d.
Serious Side Effects/ Safety Issues	Dermatological disorders Eye disorders Gastrointestinal disorders	Dermatological disorders	Gastrointestinal disorders Headache Fungal infection	

b.i.d. = twice daily; PO = orally; q.d. = once daily.
[a] With sunscreen.
[b] The only drug within the tetracycline antibiotic class that has received approval for rosacea is doxycycline. Information summarized in this table refers specifically to doxycycline, unless otherwise specified.
[c] Health Canada indication.
Source: Health Canada product monographs.[3,14-17]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ivermectin 1% cream (Rosiver) for the treatment of inflammatory lesions (i.e., papules and pustules) of rosacea in adult patients 18 years of age or older.

2.2 Methods

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

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with inflammatory lesions of rosacea Subpopulations: • Disease severity (i.e., mild, moderate, severe) • Failure of metronidazole
Intervention	Ivermectin 1% cream q.d.
Comparators	Topical drugs: azelaic acid, MetroGel Oral antibiotics

Outcomes	**Key efficacy outcomes:**
	• Lesion counts
	• Investigator's Global Assessment
	• Patient global assessment
	• HRQoL
	• Remission
	• Relapse
	Harms outcomes:
	• SAEs
	• WDAEs
	• AEs, including but not limited to:
	  ○ Dermatological disorders
	  ○ Hypersensitivity reactions
	  ○ Gastrointestinal issues
	  ○ Photosensitivity

Study Design	Published and unpublished RCTs

AE = adverse event; HRQoL = health-related quality of life; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

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 (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via 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 ivermectin (Rosiver) and rosacea.

No methodological filters were applied. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The initial search was completed on June 1, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on October 21, 2015. 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 CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine):

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

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.

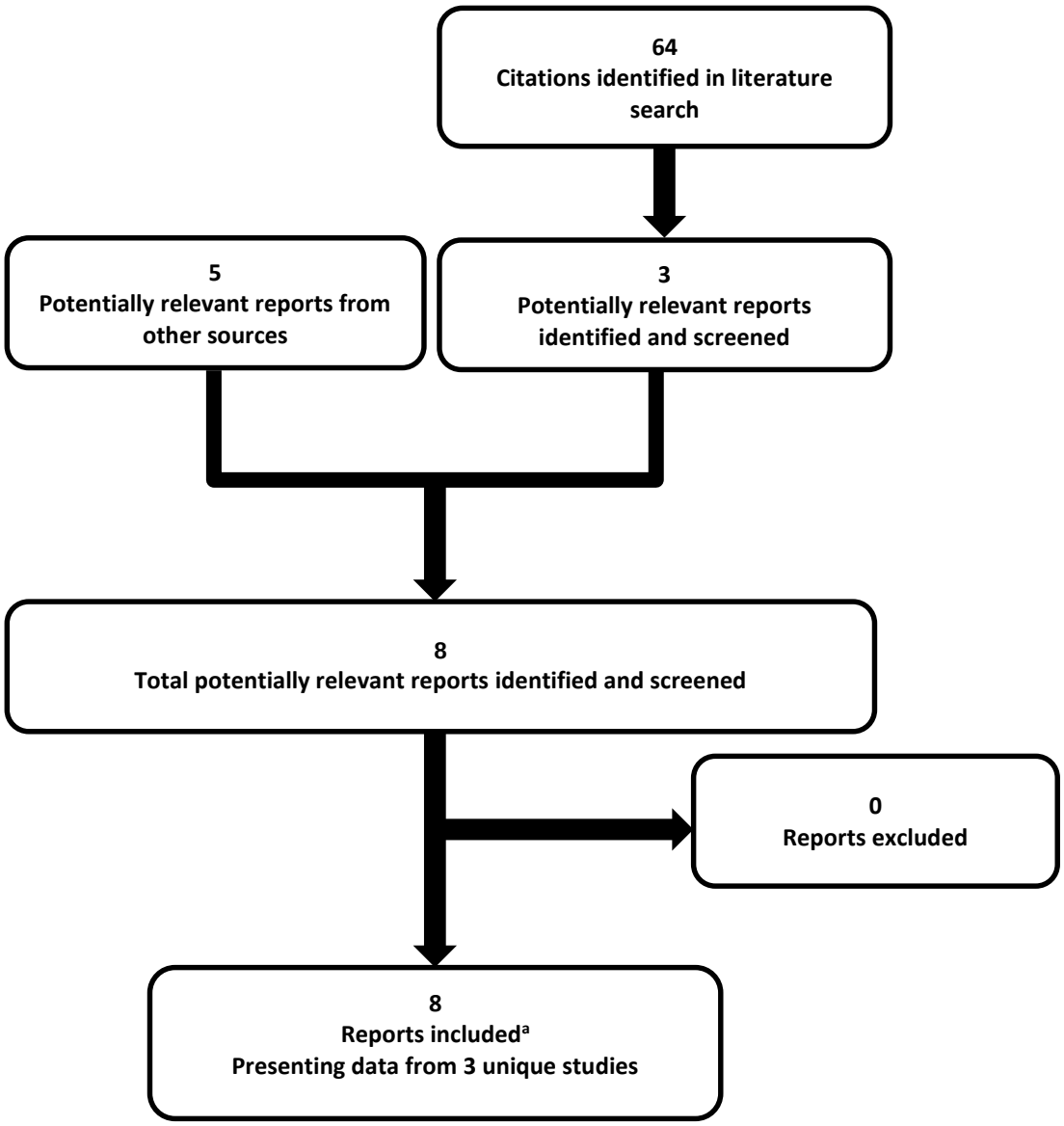
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers 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.

3. RESULTS

3.1 Findings From the Literature

A total of three unique studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



[a] Reports include published articles, Clinical Study Reports, Health Canada reviewer reports, and manufacturer's submission.

TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 18170	Study 18171	Study 40173
DESIGNS & POPULATIONS	**Study Design**	Part A: DB, vehicle-controlled, superiority RCT (efficacy and safety) Part B: investigator-blind, active-controlled RCT (safety)		Parts A and B: Investigator-blind, active-controlled, superiority RCT (efficacy and safety)
	Locations	US, Canada		Bulgaria, Czech Republic, France, Germany, Hungary, Poland, Romania, Russia, Ukraine, UK
	Randomized (N)	683	688	962
	Inclusion Criteria	• ≥ 18 years of age • Moderate or severe papulopustular rosacea based on IGA score ≥ 3 and 15 to 70 facial inflammatory lesions		PART A: • ≥ 18 years of age • Moderate or severe papulopustular rosacea based on IGA score of 3 or 4, and 15 to 70 facial inflammatory lesions PART B: • IGA score of 0 or 1 at week 16
	Exclusion Criteria	• Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated pustulosis of the chin), facial dermatoses, or other dermatological conditions that may be confounded with papulopustular rosacea, such as perioral dermatitis, facial keratosis pilaris, or seborrheic dermatitis and acne vulgaris • Rosacea with > 2 nodules on the face at screening or baseline visit • Topical or systemic treatment on face within 4 weeks of any facial procedure (e.g., laser or light treatment, electrocoagulation, dermabrasion, facial peel) within 6 weeks prior to baseline visit		
		• Known allergies or sensitivities to any components of the formulation of the study drugs (either ivermectin 1% cream or azelaic acid 15% gel)		• Known allergies or sensitivities to any components of the formulation of the study drugs (either ivermectin 1% cream or metronidazole 0.75 % cream) • Exposed to excessive UV radiation within 2 weeks prior to the baseline visit, or planning exposure during the study
DRUGS	**Intervention**	PARTS A and B: Ivermectin 1% cream, q.d.		PART A: Ivermectin 1% cream, q.d. PART B: No treatment
	Comparator(s)	PART A: Vehicle cream, q.d. PART B: Azelaic acid 15% gel, b.i.d.		PART A: Metronidazole 0.75% cream, b.i.d. PART B: No treatment
DURATION	**Phase**			
	Screening	2 weeks		2 weeks
	PART A	**Efficacy** 12 weeks		**Efficacy** 16 weeks
	PART B	**Long-term safety** 40 weeks		**Relapse** 36 weeks
	PART C:	**Treatment-free follow-up** 4 weeks		NA

		Study 18170	Study 18171	Study 40173
OUTCOMES	**Primary End Point**	PART A • Success rate based on IGA score[a] • Absolute change in inflammatory lesion counts[b]		PART A • Per cent change in inflammatory lesion counts[c] • Time to onset of efficacy
	Other End Points	PART A • Per cent change in inflammatory lesion counts[b] • Patient rosacea improvement assessment		PART A • Success rate based on IGA score[a] • IGA and change from baseline in IGA • Absolute change in inflammatory lesion counts • Patient's global improvement PART B • Relapse rate (IGA ≥ 2 after period free of study treatment) • Time to first relapse • Number of treatment-free days • Patient's global improvement
NOTES	**Publications**	Stein Gold et al. (2014a)[12] Stein Gold et al. (2014b)[11]		Taieb et al. (2015)[18]

b.i.d. = twice daily; DB = double-blind; IGA = Investigator's Global Assessment; NA = not applicable; q.d. = once daily; RCT = randomized controlled trial; UV = ultraviolet.

[a] Defined as percentage of patients who achieve "clear" or almost clear" ratings on the IGA scale (i.e., score of 0 or 1) at week 12.

[b] Defined at week 12.

[c] Defined at week 16.

Source: Clinical Study Reports.[4-6]

3.2 Included Studies

3.2.1 Description of studies

Studies 18170, 18171, and 40173 were phase 3, multi-centre, two-group, randomized controlled trials (RCTs) that met the inclusion criteria for this systematic review. All three studies recruited a similar patient population consisting of adult patients with moderate to severe rosacea. Study design for each study is presented in Figure 2. Studies 18170 and 18171 evaluated the efficacy and safety of topical ivermectin 1% cream once daily compared with vehicle. The co-primary outcomes in Studies 18170 and 18171 were success rate and absolute change in inflammatory lesion count from baseline to week 12. Study 40173 assessed whether topical ivermectin 1% cream once daily was superior to topical metronidazole 0.75% cream twice daily in terms of per cent reduction in inflammatory lesions counts and time to onset of efficacy.

Studies 18170 and 18171 were identical in design: an initial 12-week, double-blind (DB), vehicle-controlled phase (i.e., Part A) followed by a 40-week, investigator-blind, active-controlled period (i.e., Part B) and a four-week safety follow-up without treatment. Patients were randomized in blocks of six to either ivermectin or vehicle. During the baseline visit, patients were observed to ensure proper application (i.e., amount and method of application) of the first dose of the study drug. Part A evaluated both safety and efficacy, measured at weeks 2, 4, 8, and 12. In Part B, the focus was on long-term safety with scheduled follow-up visits on weeks 16, 20, 28, 32, 40, and 44. During this 40-week extension, trial investigators discontinued treatment if a patient was considered "clear" (score of 0) on the

Investigator's Global Assessment (IGA) scale. Treatment was restarted only if a patient's IGA score increased to ≥ 1. The studies were identical to address replicability between trials.

Study 40173 was an investigator-blind, active-controlled RCT that consisted of an initial 16-week treatment period (i.e., Part A). Only patients with an IGA score ≤ 1 at the end of Part A continued in the second phase of the trial. At week 16, patients who had successfully responded to treatment stopped receiving treatment and were followed up over 36 weeks. The intent for Part B was to address relapse (defined as an IGA score ≥ 2), and similarly, only the investigators were blinded to a patient's original treatment allocation. Upon relapse, patients were provided their original study drug that they received in Part A. Treatment lasted until patients attained an IGA score ≤ 1 or up to a maximum duration of re-treatment (i.e., up to 28 weeks with a maximum of 16 consecutive weeks). Patients were randomized in a 1:1 ratio. During the baseline visit, patients were observed to ensure proper application (i.e., amount and method of application) of the first dose of the study drug. Patients were subsequently assessed at weeks 3, 6, 9, 12, and 16. In Part B, follow-up visits were scheduled monthly to assess outcomes of relapse.

3.2.2 Populations

a) Inclusion and exclusion criteria

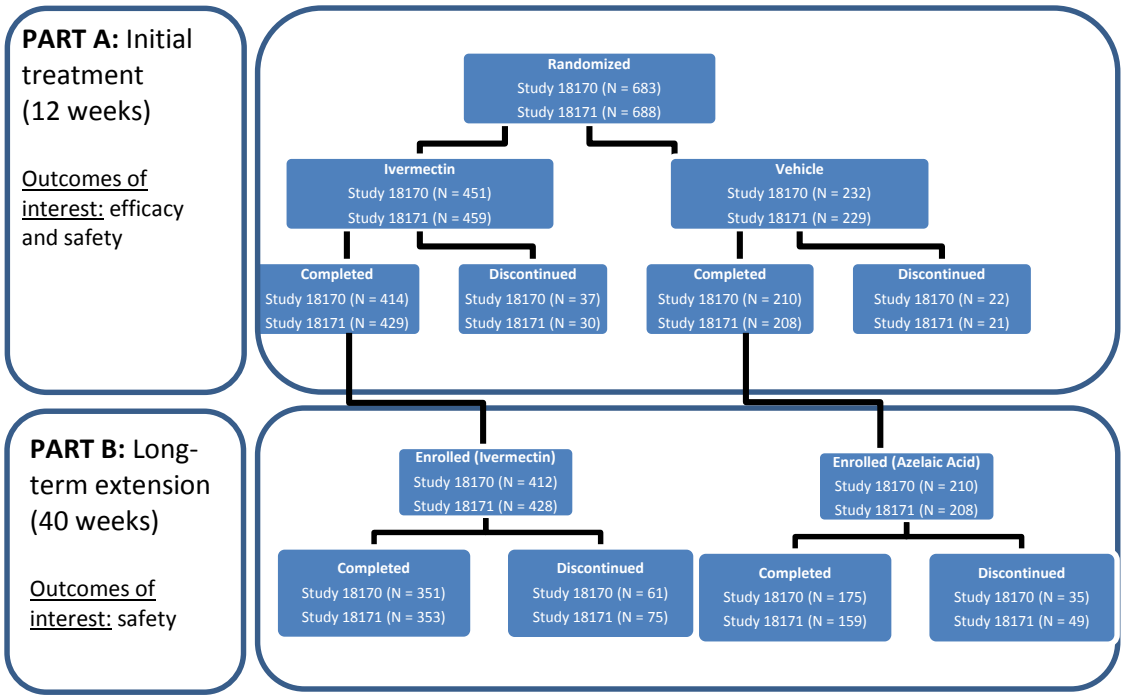
Enrolment in all three trials was similar in that it was limited to patients who met the following criteria: adults (≥ 18 years) with moderate to severe papulopustular rosacea (defined as an IGA score ≥ 3) and 15 to 70 facial inflammatory lesions. Patients were excluded if they met any of the following criteria: particular forms of rosacea (e.g., rosacea conglobata, rosacea fulminans, isolated pustulosis of the chin); facial dermatoses or other dermatological conditions (e.g., perioral dermatitis, facial keratosis pilaris, or seborrheic dermatitis and acne vulgaris); or rosacea with more than two nodules on the face. Patients were also excluded if they had known allergies or sensitivities to the study drugs. Patients who had received, applied, or taken topical or systemic treatments for rosacea were required to have undergone a washout of sufficient duration (ranging from two days to 12 weeks, depending on the treatment).

b) Baseline characteristics

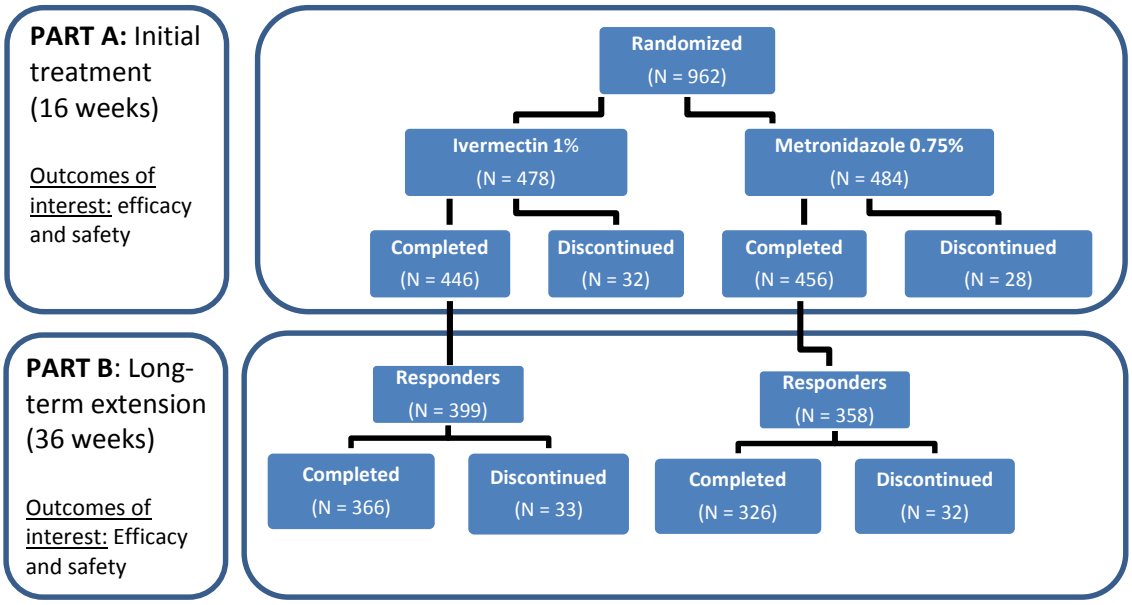
Key baseline characteristics of the study population are displayed in Table 5. Key baseline characteristics were similar between treatment groups in all three studies. The mean age of patients was approximately 50 years (50.4, 50.2, and 51.6 years in Studies 18170, 18171, and 40173, respectively). Across all three studies, the majority of patients were female (68.2%, 66.7%, and 65.2% in Studies 18170, 18171, and 40173, respectively) and Caucasian (96.2%, 95.3%, and 99.7% in Studies 18170, 18171, and 40173, respectively). The mean total lesion count ranged from 30.5 to 33.3 with the majority of patients classified as "moderate" on the IGA (82%, 75.9%, and 83.3% in Studies 18170, 18171, and 40173, respectively). In all three studies, the proportions of patients who had received at least one prior treatment for rosacea were similar and low between treatment groups (23.4%, 13.5%, and 17.3% in Studies 18170, 18171, and 40173, respectively), with the most common previous treatment being chemotherapeutics (such as metronidazole) or antibiotics from the tetracycline class.

FIGURE 2: FLOW DIAGRAM OF STUDY DESIGN AND PATIENT ENROLMENT/FOLLOW-UP

A. Studies 18170 and 18171



B. Study 40173



Source: Stein et al. (2014 a,b);[11,12] Taieb et al. (2014),[18] Clinical Study Reports.[4-6]

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS, INTENTION-TO-TREAT

	18170		18171		40173	
	Ivermectin 1% (n = 451)	**Vehicle (n = 232)**	**Ivermectin 1% (n = 459)**	**Vehicle (n = 229)**	**Ivermectin 1% (n = 478)**	**Metronidazole 0.75% (n = 484)**
Age in years, mean (SD)	49.9 (12.2)	51.6 (11.9)	50.5 (12.4)	49.5 (12.2)	51.2 (13.4)	51.9 (13.3)
Male, n (%)	137 (30.4)	80 (34.5)	145 (31.6)	84 (36.7)	167 (34.9)	168 (34.7)
Race, n (%)						
Caucasian	437 (96.9)	220 (94.8)	438 (95.4)	218 (95.2)	475 (99.4)	484 (100)
Asian	3 (0.7)	3 (1.3)	10 (2.2)	5 (2.2)	3 (0.6)	0
Black or African American	6 (1.3)	3 (1.3)	6 (1.3)	4 (1.7)	0	0
Other	5 (1.1)	6 (2.6)	5 (1.1)	2 (0.9)	0	0
Inflammatory lesion counts, mean (SD)	31.0 (14.3)	30.5 (14.4)	33.3 (13.6)	32.2 (13.9)	32.9 (14.0)	32.1 (12.8)
IGA, n (%)						
3 = moderate	369 (81.8)	191 (82.3)	346 (75.4)	176 (76.9)	398 (83.3)	403 (83.3)
4 = severe	82 (18.2)	41 (17.7)	113 (24.6)	53 (23.1)	80 (16.7)	81 (16.7)
Skin phototype, n (%)						
I	39 (8.6)	16 (6.9)	48 (10.5)	22 (9.6)	18 (3.8)	17 (3.5)
II	185 (41.0)	90 (38.8)	211 (46.0)	96 (41.9)	245 (51.3)	234 (48.3)
III	167 (37.0)	86 (37.1)	139 (30.3)	71 (31.0)	178 (37.2)	213 (44)
IV	51 (11.3)	26 (11.2)	50 (10.9)	31 (13.5)	36 (7.5)	19 (3.9)
V	8 (1.8)	11 (4.7)	11 (2.4)	7 (3.1)	1 (0.2)	1 (0.2)
VI	1 (0.2)	3 (1.3)	0	2 (0.9)	0	0
Papules, mean (SD)	25.8 (13.9)	25.4 (14.0)	27.6 (12.1)	27.6 (12.5)	25.7 (11.8)	24.3 (10.5)
Pustules, mean (SD)	5.2 (7.5)	5.1 (7.4)	5.6 (6.7)	4.6 (5.9)	7.2 (7.4)	7.73 (7.6)
Prior treatment, n (%)	109 (24.2)	51 (22.0)	58 (12.6)	35 (15.3)	92 (19.2)	74 (15.3)
Other chemotherapeutics (e.g., metronidazole)	38 (8.4)	12 (5.2)	24 (5.2)	11 (4.8)	46 (9.6)	31 (6.4)
Tetracycline antibiotic class	21 (4.7)	12 (5.2)	12 (2.6)	9 (3.9)	23 (4.8)	21 (4.3)

IGA = Investigator's Global Assessment; SD = standard deviation.
Source: Clinical Study Reports.[4-6]

3.2.3 Interventions

In Studies 18170 and 18171, patients were randomized to receive either once daily 1% topical ivermectin cream or vehicle cream over 12 weeks. Patients were instructed to apply a thin film of the cream on their entire face, approximately one small, pea-sized amount on each of the following facial regions: right and left cheeks, forehead, chin, and nose (even if those areas did not have rosacea). Both patients and study investigators were blinded. The study drug was packaged in the same type of tubes with no visible difference between creams. In Part B, patients on vehicle cream were switched to azelaic acid 15% gel, applied twice daily, as indicated in the product label. Patients were unblinded as the study materials differed in appearance, dosage form, and treatment regimen. Patients were instructed not to discuss the appearance of their treatment, dosing regimen, or calendar with the investigator to preserve investigator blinding. Part B of study drugs was dispensed to patients only after all week 12 (Part A) assessments were completed.

In Study 40173, patients were randomized to receive either 1% topical ivermectin cream once daily or metronidazole 0.75% twice daily for 16 weeks. Patients were unblinded. Patients receiving ivermectin were given the same instruction as those in Studies 18170 and 18171, whereas patients randomized to metronidazole were instructed to apply the cream to the entire face at morning and bedtime. To preserve investigator blinding, all study drug tubes had the same appearance and patients were instructed not to discuss the appearance and treatment regimen with the investigator. Patients who successfully responded to therapy (IGA ≤ 1) at the end of Part A continued on the second phase of the trial to assess time of first relapse, relapse rate, and number of days free of treatment during a 36-week extension period. Similarly, only the investigator was blinded in this phase, as patients remained unblinded to their original treatment group. Study treatment was stopped until a relapse occurred (IGA ≥ 2), whereby patients were provided their original study drug until IGA ≤ 1 or up to a maximum duration of re-treatment (i.e., up to 28 weeks with a maximum of 16 consecutive weeks).

a) Concomitant medications

Concomitant therapies were any new therapies or changes to existing therapies received by the patients. Table 6 summarizes the concomitant medications prohibited during the study period. Prohibited medication could be used at the investigator's discretion when necessary for safety or when in the best interest of the patient. Patients who received prohibited medication could continue to participate in the trial's safety assessment.

In all three studies, no other topical treatments other than the study drug, moisturizers, and sunscreens were permitted on the face during the conduct of the study. Cosmetics and make-up were permitted if applied after the administration of the study drug. In Studies 18170 and 18171, antibiotics were prohibited in Part A, although antibiotics for prophylaxis and anti-infective use were permitted in the subsequent study periods. In Study 40173, antibiotics were prohibited throughout the entire duration of the study.

The number of patients with protocol violations due to use of a prohibited medication was low in Part A of all three studies. In the vehicle-controlled trials, the rate of prohibited medication use was 3.5% versus 3.0% in Study 18170 and 4.8% versus 2.2% in Study 18171 for the ivermectin and vehicle groups. The reported rates were similarly low in Study 40173: 1.0% versus 2.5% for ivermectin and metronidazole groups, respectively.

TABLE 6: LIST OF PROHIBITED MEDICATION

3.2.4 Outcomes (see Appendix 5: Validity of Outcomes)

a) Lesion count

In all three studies, lesion counts were measured as the sum of inflammatory lesion counts (papules and pustules) on each of the five facial regions (forehead, chin, nose, and right and left cheeks). Lesion counts were conducted only in the initial treatment period (Part A) of all three studies. In Studies 18170 and 18171, one of the co-primary efficacy end points was the absolute change in total inflammatory lesion count from baseline to study end point. Study end point was defined at week 12 or at the last available post-baseline visit for each patient. In Study 40173, the primary end point was change in inflammatory lesion counts between baseline and week 16. A minimal clinically important difference (MCID) for inflammatory lesion count has not been established in patients with rosacea.

b) Investigator's Global Assessment

In all three studies, investigators completed the IGA during each trial visit. IGA is a 5-point Likert scale that provides a global clinical assessment of rosacea severity (ranging from 0 = clear to 4 = severe). The co-primary end point in Studies 18170 and 18171 was success rate, with the outcome of success defined by an IGA score ≤ 1 by week 12 or end of treatment. This would have represented a minimum 2-point reduction compared with baseline value for patients with at least moderate disease severity at the study's baseline. No information was found on the validity and reliability of the IGA scale.

TABLE 7: INVESTIGATOR'S GLOBAL ASSESSMENT SCALE

Score	Definition	Rating Guideline
0	Clear	No inflammatory lesions present; no erythema
1	Almost clear	Very few small papules/pustules; very mild erythema present
2	Mild	Few small papules/pustules; mild erythema
3	Moderate	Several small or large papules/pustules; moderate erythema
4	Severe	Numerous small and/or large papules/pustules; severe erythema

c) Patient assessment of rosacea improvement

Patients completed a 5-point Likert scale to evaluate improvement in rosacea symptoms compared with baseline (i.e., "worse", "no improvement", "moderate", "good", or "excellent"). This assessment was done at the end of Part A (week 12 in Studies 18170 and 18171; week 16 in Study 40173). Patients completed the patient assessment of rosacea improvement at the end of Part B of Study 40173. No information was found on the validity and reliability of this scale.

d) Quality of life

Health-related quality of life (HRQoL) was assessed by the Dermatology Life Quality Index (DLQI) in all three studies and by the condition-specific Rosacea Quality of Life Index (RosaQoL) in Studies 18170 and 18171, and by the generic EuroQol 5-Dimensions Questionnaire (EQ-5D) in Study 40173. These quality of life (QoL) assessments were conducted at baseline and at the end of Part A (week 12 in Studies 18170 and 18171; week 16 in Study 40173). During Part B of Study 40173, EQ-5D and DLQI were completed by patients at week 28 and week 52 or upon early termination.

e) Adverse events

Safety assessment included any adverse events (AEs) and an assessment of local tolerance parameters (e.g., stinging/burning, dryness, itching) by a 3-point Likert scale. The reporting period for AEs encapsulated the time a patient signed the informed consent form (i.e., typically two weeks prior to baseline visit) up to the end of the patient's participation in the study.

3.2.5 Statistical analysis

Safety was addressed over the entire duration of Studies 18170 and 18171, while efficacy was assessed only in Part A. For Study 40173, both efficacy and safety were examined in Parts A and B. The intention-to-treat (ITT) population was the primary population investigated in the efficacy analysis of Part A, with missing data handled by the last outcome carried forward (LOCF) approach. Analyses of the primary and secondary efficacy outcomes in Part A were repeated with the per protocol (PP) population to assess the robustness of the study findings.

Studies 18170 and 18171 specified two co-primary efficacy end points:

- Success rate, defined as the percentage of patients with IGA ≤ 1 at week 12 (ITT-LOCF)
- Absolute change in inflammatory lesion counts from baseline to week 12 (ITT-LOCF)

Time to the onset of efficacy, a nested hierarchical analysis of when both co-primary end points were satisfied, was also evaluated as a supplemental analysis. Secondary efficacy end points included per cent change in inflammatory lesions from baseline at week 12 (ITT-LOCF) and the patient's assessment of rosacea improvement. Other variables analyzed post-hoc included QoL (i.e., RosaQoL and DLQI). No pre-specified MCID was provided for any of these outcomes for this patient population.
Study 40173 similarly defined two co-primary end points, both specific to Part A:

- Per cent change in inflammatory lesions from baseline to week 16 (ITT-LOCF)
- Time to onset of efficacy, statistical significant difference between groups in per cent change in inflammatory lesion count by sequentially analyzing preceding time points

Secondary outcomes to Part A included success rate at each evaluation visit, IGA and change from baseline, absolute change in inflammatory lesion count, and patient's assessment of rosacea improvement. The secondary efficacy end points in Part B were related to the outcomes of relapse. This included relapse rates (IGA ≥ 2), time to relapse, number of days free of treatment, and patient's assessment of rosacea improvement at week 52. Similarly, QoL was conducted as a post-hoc analysis (using EQ-5D and DLQI).

The following statistical tests were performed as a two-sided analysis at a 0.05 significance level:

- Success rate — The percentage of patients considered treatment success was analyzed by the Cochran-Mantel-Haenszel (CMH) test, stratified by clinical centre.
- Per cent change in inflammatory lesion count — In Studies 18170 and 18171, per cent change in inflammatory lesion count was analyzed by the Mann-Whitney test using the CMH procedure, stratified by analysis centre. In Study 40173, this outcome was analyzed by analysis of covariance (ANCOVA) with baseline lesion count included as a model covariate, while treatment group and analysis centre was a factor within the model.
- Time to onset of efficacy — Efficacy was defined according to the (co-) primary efficacy end point(s). To determine the time to efficacy onset (i.e., the earliest time point when significance was reached for the primary end point[s]), a conditional backward stepwise analysis was conducted at a 5% two-sided significance test.
- QoL — QoL was summarized with standard descriptive statistics (e.g., mean, standard deviation [SD]).
- Relapse rate and time to relapse — Relapse, an outcome specific to Part B of Study 40173, was analyzed by the Kaplan–Meier method and log-rank test. In the primary analysis, patients who discontinued early from Part B without relapse were treated as censored. A sensitivity analysis was further performed to impute relapse, in which it was considered to occur four weeks later following early discontinuation.
- Treatment-free days — The number of treatment-free days was specific to Part B of Study 40173. Difference between treatment groups was compared by the CMH. Days in which treatment was temporarily stopped due to AE or missed applications were not considered treatment-free days. Patients who discontinued early from Period B were no longer considered treatment-free.

Across all three studies, no adjustment was performed for multiplicity of comparisons.

Determination of sample size

In Studies 18170 and 18171, a sample size of 681 patients was required to achieve 92% power for the co-primary outcome of success rate and 99% power for the other co-primary outcome of change in inflammatory lesion counts. This was based on the assumptions of a 15% treatment difference in success rates, an effect size for lesion count of 0.40 (delta of 6 lesions; SD: 15) and a two-sided alpha of 0.05, adjusting for an 85% evaluability rate for the PP analysis set.

In Study 40173, a sample size of 960 patients (480 patients per group) was required to achieve 93% power, assuming an 85% evaluability rate for the PP analysis set. This calculation assumed a 10%

difference in per cent change from baseline in lesion counts (SD: 45%) between treatments and a two-sided alpha of 0.05.

Subgroup analyses

Subgroup analyses were identified a priori and, in all three studies, were performed on the primary efficacy end points. The subgroups evaluated in Studies 18170 and 18171 included gender (female, male), race (Caucasian, non-Caucasian), age group (18 to 64 years old and ≥ 65 years old), baseline IGA (moderate or severe), and analysis centre. The subgroups evaluated in Study 40173 included gender, age group, and baseline IGA scores. Only the subgroup analysis pertaining to baseline disease severity is reported in this report.

Missing data

For the manufacturer's main analyses in all three trials, missing data were imputed by the LOCF approach. Sensitivity analyses were further conducted to evaluate the robustness of the findings by the method of handling missing data. In Studies 18170 and 18171, sensitivity analysis was carried forth by imputation of missing data by multiple imputations, assigning treatment failure or success to the missing data and mean/median substitution. Only Study 40173 conducted a separate sensitivity analysis in which missing data were handled by multiple imputations. These secondary analyses are not presented in this CDR report.

a) Analysis populations

In Part A of all three trials, the ITT analysis was defined as all patients who were randomized and to whom the study drug was dispensed. The ITT population served as the primary population for the efficacy analyses in Part A. The PP analysis set was defined as the ITT population excluding those patients deemed non-evaluable due to major protocol deviations during Part A (e.g., entrance criteria deviation, non-compliance, prohibited concomitant therapy use, and administrative errors).

The safety population was defined as the ITT population who applied the study drug at least once (in Part A) or all patients who entered Part B (in Part B).

In Part B of Study 40173, a full analysis set (FAS) was defined, which included all patients entering Period B with observable data. Similarly, a PP analysis set was defined that encompassed the FAS with the exclusion of patients with major protocol deviations.

3.3 Patient Disposition

Patient disposition is summarized in Table 8. A total of 683 and 688 patients were randomized into Studies 18170 and 18171, respectively. In both studies, more than 90% of patients completed Part A, with dropout rates balanced between treatment groups. The most common cause of study discontinuation was consent withdrawal (ranging from 2% to 4% across treatment groups). Following completion of Part A, patients either continued on ivermectin or, in the case of patients in the vehicle group, were switched to twice-daily treatment with azelaic acid for 40 weeks. Between 76.4% and 85.2% of the originally randomized patients in each treatment group completed the long-term extension (Part B) in both trials. In Study 18170, more than 75% of randomized patients in each treatment group completed all three parts of the trial, while the rate was nearly 70% in Study 18171.

A total of 962 patients were randomized in Study 40173, in which more than 90% completed the 16 weeks of Part A. Overall dropout rates were balanced between treatment groups. Part B of Study 40173 enrolled patients classified as treatment success (i.e., IGA ≤ 1) at the end of Part A and monitored these patients for 36 weeks, during which treatment was discontinued to evaluate relapse. Of the originally randomized patients, 399 (83.5%) and 358 (74.0%) patients in the ivermectin and metronidazole groups were considered treatment responders and enrolled in Part B. Discontinuation rates were low (< 10%) and balanced between treatment groups in Part B.

TABLE 8: PATIENT DISPOSITION

		18170		18171		40173	
		Ivermectin 1%	**Vehicle**	**Ivermectin 1%**	**Vehicle**	**Ivermectin 1%**	**Metronidazole 0.75%**
Screened, N		875		890		1,034	
PART A	**Randomized, N**	451	232	459	229	478	484
	Discontinued, N (%)	37 (8.2)	22 (9.5)	30 (6.5)	21 (9.2)	32 (6.7)	28 (5.8)
	Withdrew consent	18 (4)	7 (3)	9 (2)	8 (3.5)	21 (4.4)	9 (1.9)
	Lost to follow-up	7 (1.6)	8 (3.4)	8 (1.7)	8 (3.5)	3 (0.6)	2 (0.4)
	Adverse event	7 (1.6)	4 (1.7)	6 (1.3)	4 (1.7)	6 (1.3)	13 (2.7)
	Other	5 (1.0)	3 (1.2)	7 (1.5)	1 (0.4)	2 (0.4)	4 (0.8)
	ITT, N	451	232	459	229	478	484
	PP, N	402	204	398	198	432	433
	Safety, N	452[a]	231	458	230	478	484
PART B	**Enrolled, N**	412	210	428	208	399	358
	Completed, N (%)	351 (85.2)	175 (83.3)	353 (82.5)	159 (76.4)	366 (91.7)	326 (91.1)
	Discontinued, N (%)	61 (14.8)	35 (16.7)	75 (17.5)	49 (23.6)	33 (8.3)	32 (8.9)
	Withdrew consent	27 (6.6)	16 (7.6)	32 (7.5)	24 (11.5)	23 (5.8)	18 (5.0)
	Lost to follow-up	16 (3.9)	10 (4.8)	26 (6.1)	10 (4.8)	2 (0.5)	4 (1.1)
	Adverse event	5 (1.2)	4 (1.9)	3 (0.7)	5 (2.4)	2 (0.5)	4 (1.1)

		18170		18171		40173	
		Ivermectin 1%	**Vehicle**	**Ivermectin 1%**	**Vehicle**	**Ivermectin 1%**	**Metronidazole 0.75%**
	Other	13 (3.2)	5 (2.4)	14 (3.3)	10 (4.8)	6 (1.5)	6 (1.7)
	ITT/FAS[b], N	412	210	428	208	399	358
	PP, N	NA	NA	NA	NA	379	330
	Safety, N	412	210	428	208	399	359
PART C	**Enrolled, N**	350	175	353	159	NA[c]	
	Completed, N (%)	350	174	353	159		
	Discontinued, N (%)	0	1 (0.6)	0	0		
	Adverse event	0	1 (0.6)	0	0		
	Safety, N	350	175	353	159		

FAS = full analysis set; ITT = intention-to-treat; NA = not applicable; PP = per protocol.
[a] One patient had medication dispensed in error in Part A. That patient's planned treatment group was vehicle cream once daily (Part A) and azelaic acid 15% gel twice daily (Part B), although the patient received ivermectin 1% cream once daily (Part A) and azelaic acid 15% gel twice daily (Part B).
[b] In Studies 18170 and 18171, Part B analysis was based on the intention-to-treat population; in Study 40173, the analysis of Part B was based on the full analysis set.
[c] Study design of Study 40173 consisted of only two phases.
Source: Clinical Study Reports,[4-6] Stein et al. (2014 a,b),[11,12] Taieb et al. (2014).[18]

3.4 Exposure to Study Treatments

The number of applications was measured according to the actual number of days of treatment application recorded in the patient's dosing calendar. Treatment compliance in Part A of Studies 18170 and 18171 was calculated as the percentage of actual doses taken divided by the planned dose (i.e., 84 doses). The percentage of patients complying with treatment was high across both trials: more than 90% in both treatment groups (Table 9). In both studies, treatment exposure in Parts A and B for the safety population was similar between treatment groups in terms of mean treatment duration and daily drug use (Table 9).

Exposure to treatment in Study 40173 was calculated as the number of days of drug application (i.e., maximum treatment duration was 113 days). In Part A, the duration of treatment was similar between groups, with a mean of 108 days for ivermectin and 107 days for metronidazole in the efficacy population. A similar observation was made in Part A for the safety population. Patients eligible to continue in Part B were discontinued from treatment, which was restarted upon disease relapse. Measurement of treatment compliance in patients who were re-treated with their respective drugs was not assessed in Part B.

TABLE 9: SUMMARY OF TREATMENT DURATION

	18170		18171		40173	
	Ivermectin 1%	Comparator[a]	Ivermectin 1%	Comparator[a]	Ivermectin 1%	Metronidazole 0.75%
[redacted]						

NR = not reported; SD = standard deviation.
[a] Comparator in Part A was vehicle; comparator in Part B was azelaic acid 15% gel twice daily.
[b] Treatment compliance = percentage of actual doses in Part A divided by planned doses in Part A (i.e., 84 doses).
[c] Daily medication used = (total dispensed weight [g] minus the total returned weight [g] based on the same number of tubes)/treatment duration (days).
Source: Clinical Study Reports.[4-6]

Concomitant usage of antibiotics was prohibited in Part A of all three studies, although antibiotics for prophylaxis and anti-infective use were permitted in Parts B and C of Studies 18170 and 18171. A total of 13 patients (10 and three patients among the ivermectin and vehicle groups, respectively) in Study 18170, and 21 patients (16 and five patients among the ivermectin and vehicle groups, respectively) in Study 18171 were excluded in the PP population of Part A due to antibiotic usage that was classified as a major protocol deviation. In Study 40173, five and 12 patients in the ivermectin and metronidazole groups, respectively, were excluded from the PP population due to prohibited medication usage in Part A. In Part B of Study 40173, two patients, both in the metronidazole group, were considered to have a major protocol violated due to prohibited medication use.

3.5 Critical Appraisal

3.5.1 Internal validity

a) Vehicle-controlled studies (Studies 18170 and 18171)

Selection, allocation, and disposition of patients

In both studies, patient characteristics were generally well balanced between treatment groups. The frequency of major protocol deviation (i.e., administrative error, entrance criteria deviation, prohibited medication, non-compliance) was balanced between groups (10.9% and 12.1% in Study 18170, and 13.3% and 13.5% in Study 18171 for the ivermectin and vehicle groups, respectively). Study 18170 conducted a reanalysis of the primary and secondary outcomes on the PP population (following the removal of 77 patients from the ITT population who had major protocol deviation). Results were similar between the PP and ITT analyses. This was also conducted in Study 18171, in which similar findings were observed between the ITT and PP analyses. Attrition rates were low (< 10%) and similar across treatment groups in Part A of both studies. In Study 18170, more than 75% of patients completed all three periods of the study, while this rate was nearly 70% of patients in Study 18171.

Adequate measures appear to have been implemented in both studies to conceal treatment allocation. Randomization appeared appropriate as it was conducted in blocks of six, in a 2:1 ratio, to ensure higher numbers of patients in the ivermectin group to detect safety issues. Blinding of both the patients and clinical investigators in Part A appears to have been conducted appropriately. As only the clinical investigator was blinded in Part B to evaluate the long-term safety of ivermectin, this may have introduced bias in the reporting of harm outcomes.

Statistical analyses and study design

In terms of the strength of these trials, as alluded to earlier, the primary approach to data analysis was on the ITT population. This is a conservative approach, given that the study was designed as a superiority trial. Sensitivity analyses were further performed on the methods of handling missing data and the population analysis set, with results remaining robust.

However, there was no adjustment made for multiple treatment comparisons in either study. Given that some of the outcomes are correlated (e.g., IGA-based success rate, inflammatory lesion count), this may have introduced multiple comparison errors in which type I error is inflated and may lead to a higher likelihood of false-positives. This concern is valid given that primary and secondary efficacy end points are linked and in some cases assessed at multiple time points. The only circumstance in which it may not have been necessary to correct for multiplicity is when outcomes were independent (e.g., QoL measures) or the assessment of time to onset of efficacy in which a conditional backward stepwise analysis was employed.

Sample size calculation revealed that both studies were adequately powered (> 90%) to detect differences for success rate and absolute change in inflammatory lesion count, but it is unclear whether other outcomes, such as per cent change in inflammatory lesion count and patient rosacea improvement, were adequately powered. The trials were most likely underpowered to detect differences in rare or serious adverse events (SAEs) despite the 2:1 allocation scheme. Furthermore, it is important to note that other outcomes were evaluated post-hoc, including erythema assessment and QoL measures. The findings from such analyses should be considered exploratory. Several subgroups were identified a priori, although interpretation of the findings may be limited, given that it unlikely had adequate power to detect differences.

A strong vehicle effect was observed in the two vehicle-controlled studies (e.g., > 42% reduction in inflammatory lesion count from baseline to week 12). Rosacea could have many alternative treatments, including natural treatments. As a chronic skin condition, it usually worsens over time if left untreated. Therefore, it is likely that during the 12-week initial treatment period, many patients may have applied some other alternatives. However, it is unknown what non-medicinal treatments the study patients had received. This compromised the interpretation of beneficial effects from ivermectin, particularly the reduction of absolute lesion counts or the success that could be attributable the treatment.

Study treatment compliance and treatment adherence were not well established, given that these were based on differences in the weights of dispensed and returned ivermectin (but waste was not counted). It remains unknown to what extent the study patients applied the cream on a daily basis. Although patients were given a dosing calendar to complete, this is a subjective method of measuring compliance and has its limits.

b) Active-comparator study (Study 40173)

Selection, allocation, and disposition of patients

Patient demographics were well balanced among treatment groups. Approximately 10% of patients in each group were classified as having a major protocol deviation in the ITT population. Nonetheless, PP analysis provided similar results to ITT analysis. Rates of discontinuation in Part A of Study 40173 were low overall (~7%) and, among those continuing on in Part B, rates of discontinuation remained low and balanced between treatment groups.

A concern in trials with selective follow-up, such as Study 40173, in which only responders were permitted to continue in Part B, is that randomization done prior to the first phase may no longer be applicable at the subsequent phase. For instance, patients responding to one treatment may have different baseline demographics and disease characteristics than patients responding to another treatment, especially if their mechanism of action differs. To address this concern, the baseline demographics and disease characteristics of only those patients who were included in Part B was provided. Overall, characteristics between the groups were similar. This suggests that, across measured baseline demographics and disease characteristics, the characteristics of ivermectin responders were similar to those of metronidazole responders. Despite the absence of preserving randomization in Part B, this is unlikely to be a major issue affecting the validity of the study findings regarding relapse.

Statistical analyses and study design

Despite all three trials administering the same dosage of ivermectin, having similar inclusion/exclusion criteria, and recruiting patients with similar baseline characteristics, Study 40173 reported better efficacy outcomes (higher per cent change in inflammatory lesion counts and success rates) in the ivermectin group than those reported by the DB, vehicle-controlled trials throughout the trial duration up to week 12. The clinical expert involved in this submission noted that many factors that may impact rosacea severity and disease progression are within control of the patient. For instance, exposure to sun, skin applications, alcohol consumption, heat, and emotional factors may all be aggravating factors for rosacea. Another potential reason for the differences, which was proposed by the clinical expert, was that the vehicle and active-comparator trials were conducted in different geographic locations: both Studies 18170 and 18171 recruited from North American sites, while Study 40173 recruited from European sites. Differences in the efficacy outcomes within the ivermectin group may have arisen due to differences in clinical management and practice between geographies. A third potential explanation for the observed differences in the efficacy response in the ivermectin group between trials was the fact that daily drug use was slightly higher in Study 40173. Within the safety population, daily ivermectin use

was 0.72 ± 0.3 g/day in Study 40173, whereas in the vehicle-controlled trial, daily ivermectin use was 0.65 ± 0.66 g/day and 0.64 ± 0.33 g/day in Studies 18170 and 18171, respectively.

The study was adequately powered to detect a 10% difference in per cent change in inflammatory lesion count. It is unclear whether this relative difference is indeed clinically meaningful to patients. A review of the literature (Appendix 5) on outcome validity found that no MCID has been established for inflammatory lesion counts in patients with rosacea. The clinical expert interviewed for this submission was similarly unable to provide an MCID, as in real world practice these outcome measures are rarely used. Rather, improvement from therapy is typically subjective and assessed in clinical practice.

Furthermore, as the sample size calculation was done on the primary efficacy end point, it remains uncertain whether other outcomes were adequately powered in this trial. Several subgroups were identified and evaluated a priori. However, interpretation of the findings may be compromised given the uncertainty of adequate power to detect meaningful differences and the lack of adjustment for multiplicity of co-primary outcomes.

3.5.2 External validity

a) Vehicle-controlled studies (Studies 18170 and 18171)

Although both vehicle-controlled RCTs were conducted in North America and included Canadian sites, a concern raised by the clinical expert involved in this review was that both studies included overwhelmingly Caucasian patients. The results of both studies may therefore not be generalizable to patients of other ethnicity groups. According to the clinical expert, patients with darker skin may have post-inflammatory pigmentation and skin discoloration in areas where papules and pustules have healed following topical treatment. Beyond this, the remaining patient characteristics were generally similar to those expected to be observed in clinical practice.

The inclusion and exclusion criteria appear to be reflective of Canadian papulopustular rosacea patients who would be considered candidates for treatment with ivermectin. However, it is important to note that both studies restricted enrolment to only patients with moderate to severe papulopustular rosacea, whereas ivermectin's Health Canada indication is broader and not limited by disease severity. The extent to which the findings observed in Studies 18170 and 18171 are applicable to patients with milder forms of rosacea is uncertain.

The trial protocol further excluded patients with other dermatosis, which is a reasonable exclusion criterion according to the clinical expert, as patients with other facial dermatoses may respond to ivermectin differently. However, the clinical expert did bring forth the fact that, although dermatosis would be fairly easily diagnosed by a dermatologist, this may be more difficult for general practitioners. Medical practitioners who misdiagnose their patients may inappropriately prescribe ivermectin.

The baseline patient demographics outlined in Table 5 highlight the fact that few patients had received previous therapy for rosacea. Across the vehicle-controlled trials, less than a quarter of patients reported using previous therapy. There is considerable uncertainty how patients who have previously failed metronidazole may respond to ivermectin.

b) Active-comparator study (Study 40173)

According to the clinical expert, the results of the active-comparator study are likely generalizable to Canadian papulopustular rosacea patients. Patient characteristics were generally similar to those expected in clinical practice, with one notable exception. Similar to the vehicle-controlled studies, Study

40173 was nearly exclusive in enrolling Caucasian patients (99.4% to 100%). Therefore, the findings from Study 40173 may not be representative of Canadian patients with rosacea with different skin pigmentation, and there is uncertainty as to whether these patients may respond differently to treatment. As Study 40173 shared nearly identical inclusion and exclusion criteria to Studies 18170 and 18171, the same discussion presented earlier applies to this study. Although the patient population is reflective of Canadian patients with moderate to severe papulopustular rosacea, the results may not apply to patients with milder forms of this disease or to patients who have previously failed metronidazole.

As mentioned earlier, differences in efficacy outcomes were observed in the ivermectin groups between Study 40173 and the two vehicle-controlled studies. If the differences arose due to geographic differences in clinical practice, it is likely that the efficacy of ivermectin in the Canadian setting would be more similar to what was observed in the vehicle-controlled studies than what was observed in Study 40173. It is unclear, however, whether such a difference would apply only to the ivermectin treatment or to other treatments also, such as metronidazole.

The design of Study 40173 involved a 16-week treatment period followed by discontinuation of therapy for 36 weeks until relapse. The clinical expert consulted noted that this may be unrealistic, as patients are likely to continue on treatment indefinitely with the dose tapered down. As such, the long-term comparative efficacy of ivermectin compared with metronidazole remains unknown.

3.6 Efficacy

Only those efficacy outcomes identified in the review's protocol are reported below, with the main statistical analysis (ITT-LOCF) presented unless otherwise specified (Section 2.2, Table 3). See Appendix 4 for detailed efficacy data.

3.6.1 Inflammatory lesion count

The mean absolute change in inflammatory lesion count from baseline to week 12 was –20.5 and –12.0 in Study 18170 and –22.2 and –13.4 in Study 18171 for the ivermectin and vehicle groups, respectively. The per cent change in inflammatory lesion count from baseline to week 12 was –64.9% and –41.6% in Study 18170, and –65.7% and –43.4% in Study 18171 among the ivermectin and vehicle groups, respectively. In both studies, the mean absolute and per cent change in lesion count was statistically greater in ivermectin than vehicle within the ITT population ($P < 0.001$) (Table 10).

In Study 40173, the ITT population reported a per cent change in inflammatory lesions count at week 16 of –83.0% for ivermectin and –73.7% for metronidazole (Table 10). This difference between ivermectin and metronidazole was statistically significant as early as week 3 and persisted up to week 16 of treatment ($P < 0.05$) (Appendix 4). In terms of the mean absolute change in inflammatory lesion count from baseline to week 16, this reduced by 27.7 and 23.6 in the ivermectin and metronidazole groups ($P < 0.001$).

a) Subgroups: disease severity

Among the vehicle-control group, mean absolute change in inflammatory lesions count from baseline to week 12 in the ITT population was similar regardless of baseline disease severity. In the ivermectin group, patients with severe rosacea had a greater mean absolute change in inflammatory lesion counts from baseline to week 12 (–31.9 and –27.5 in Studies 18170 and 18171, respectively) than patients with moderate rosacea (–17.9 and –20.5 in Studies 18170 and 18171, respectively) (Table 14). This was expected, as patients with more severe forms of rosacea would present with more lesions at baseline

than patients with moderate rosacea. Similar observations were reached with per cent change in inflammatory lesion count. The difference in inflammatory lesion counts, both as a mean absolute or as a percentage, when compared with vehicle, was greater in patients with severe rosacea than in patients with moderate rosacea.

Study 40173 found that both mean absolute and per cent change in inflammatory lesion counts from baseline to week 16 were greater in patients with severe rosacea than in patients with moderate rosacea in both the ivermectin and metronidazole groups. As such, differences in the mean absolute and per cent change in inflammatory lesions count from baseline to week 16 were similar between patients with different disease severity (Table 14).

3.6.2 Investigator Global Assessment

Success rate, defined as ≤ 1 on the IGA score, was greater in the ivermectin group compared with vehicle group at week 12: 38.4% versus 11.6% in Study 18170, and 40.1% versus 18.8% in Study 18171 for ivermectin and vehicle groups, respectively (Table 10). Difference between treatment groups was statistically significant in both studies ($P < 0.001$).

By the end of Part A (i.e., week 16) of Study 40173, success rate in the ivermectin group was 84.9% compared with 75.4% in the metronidazole group ($P < 0.001$). Success rate in Study 40173 was notably higher than the rates observed in both vehicle-controlled trials at comparable time periods. At week 12, 64.9% of patients in the ivermectin group were considered successful in Study 40173, whereas the success rates in the ivermectin group were 38.4% and 40.1% in Studies 18170 and 18171, respectively (Table 10).

a) Subgroup: disease severity

In Studies 18170 and 18171, the success rate at week 12 for patients with moderate rosacea was higher than for patients with severe rosacea in both the treatment and control groups. Difference in success rate between treatment groups was similar across disease severity (i.e., 26.8% and 26.9% in Study 18170 and 21.2% and 22.6% in Study 18171 among patients with moderate and severe rosacea, respectively) (Table 14).

A similar finding was observed in the active-comparator trial. Difference in success rate versus metronidazole was similar across subgroups (Table 14).

3.6.3 Patient's assessment of rosacea improvement

The proportion of patients rating their improvement after treatment as "excellent" was statistically significantly higher in the ivermectin group compared with the vehicle group at week 12: 34.3% versus 9.5% in Study 18170, and 32.0% versus 7.3% in Study 18171 ($P < 0.001$) (Table 10). At week 16 of Study 40173, the rating of "excellent" was 52.3% for the ivermectin group compared with 37.0% for the metronidazole group. This difference was also statistically significant ($P < 0.002$).

TABLE 10: KEY EFFICACY OUTCOMES — PART A

		18170		18171		40173	
		Ivermectin 1% **(N = 451)**	**Vehicle** **(N = 232)**	**Ivermectin 1%** **(N = 459)**	**Vehicle** **(N = 229)**	**Ivermectin 1%** **(N = 478)**	**Metronidazole 0.75%** **(N = 484)**
Inflammatory Lesion Count, ITT							
Baseline	Mean (SD)	31 (14.3)	30.5 (14.4)	33.3 (13.6)	32.2 (13.9)	32.9 (14.0)	32.1 (12.8)
Week 12	Mean (SD)	10.6 (13.1)	18.5 (16.8)	11.0 (11.7)	18.8 (17.5)	7.7 (8.8)	10.6 (12.1)
	Mean absolute change from baseline (SD)	–20.5 (16.0)	–12.0 (13.6)	–22.2 (14.9)	–13.4 (14.5)	–25.2 (14.3)	–21.5 (13.8)
	Difference vs. control (95% CI)	–8.13 (–10.12 to –6.13)		–8.22 (–10.18 to –6.25)		NR	
	P value	**< 0.001**		**< 0.001**		**< 0.001**	
	Per cent change from baseline (SD)	–64.9 (39.9)	–41.6 (38.8)	–65.7 (33.2)	–43.4 (38.4)	–75.7 (26.1)	–67.1 (37.0)
	% difference vs. control (95% CI)	NR		NR		NR (2.40 to 7.70)	
	P value	**< 0.001**		**< 0.001**		**< 0.001**	
Week 16	Mean (SD)	NA		NA		5.2 (8.4)	8.5 (13.2)
	Mean absolute change from baseline (SD)					–27.7 (15.2)	–23.6 (15.5)
	Difference vs. control (95% CI)					NR	
	P value					**< 0.001**	
	Per cent change from baseline (SD)					–83.0 (26.0)	–73.7 (39.7)
	% difference vs. control (95% CI)					NR (0.00 to 4.60)	
	P value					**< 0.001**	
Investigator's Global Assessment, ITT							
Week 12	Success IGA ≤ 1, N (%)	173 (38.4)	27 (11.6)	184 (40.1)	43 (18.8)	310 (64.9)	242 (50.0)
	% difference vs. control	26.8		21.3		14.9[b]	
	P value	**< 0.001**		**< 0.001**		**< 0.001**	
Week 16	Success IGA ≤ 1, N (%)	NA		NA		406 (84.9)	365 (75.4)
	% difference vs. control					9.5[b]	
	P value					**< 0.001**	
Patient's Assessment of Rosacea Improvement							
End of	N	NR	NR	447	221	470	473

		18170		18171		40173	
		Ivermectin 1% (N = 451)	Vehicle (N = 232)	Ivermectin 1% (N = 459)	Vehicle (N = 229)	Ivermectin 1% (N = 478)	Metronidazole 0.75% (N = 484)
Part A[a]	N (%) rated as "excellent"	149 (34.3)	21 (9.5)	143 (32.0)	16 (7.3)	246 (52.3)	175 (37.0)
	P value	**< 0.001**		**< 0.001**		**< 0.002**[b]	

CDR = CADTH Common Drug Review; CI = confidence interval; IGA = Investigator's Global Assessment; ITT = intention-to-treat; NA = not applicable; NR = not reported; SD = standard deviation; vs. = versus.
[a] End of Part A is defined as week 12 in Studies 18170 and 18171 and as week 16 in Study 40173.
[b] Calculated by CDR reviewers.
Source: Clinical Study Reports.[4-6]

3.6.4 Quality of life

All three studies performed post-hoc analysis on QoL (Table 11). In Studies 18170 and 18171, patients receiving ivermectin had statistically greater improvement than those receiving vehicle ($P < 0.001$) in both RosaQoL and DLQI. By the end of Part A in Study 18170, the mean score (SD) on DLQI had decreased to 2.3 (3.1) and 3.3 (3.5), representing an absolute change from baseline to week 12 of –3.5 (4.0) and –2.2 (3.7) in the ivermectin and vehicle groups, respectively ($P < 0.001$). A similar observation was reached with Study 18171: patients receiving ivermectin had statistically greater improvement in QoL measures than those receiving vehicle ($P < 0.001$).

In Study 40173, QoL scores improved following treatment in both study groups. Mean absolute change from baseline to week 16 on DLQI was 5.2 in the ivermectin group and 3.9 in the metronidazole group. It is unclear whether the difference was statistically and clinically significant between treatments. The mean EQ-5D scores (SD) at baseline were 77.5 (16.9) and 75.8 (18.9), respectively. By the end of Part A, the mean score (SD) reported in 464 patients who completed the questionnaire increased to 84.4 (13.6) in the ivermectin group and 82.0 (15.2) for the 471 patients who completed the questionnaire in the metronidazole group. Mean absolute change from baseline to week 16 was similar across both treatment groups, with an improvement of 6.9 and 6.2 reported for the ivermectin and metronidazole groups, respectively. Similarly, it is unclear whether this difference between treatment groups is statistically or clinically significant (Table 15).

TABLE 11: QUALITY OF LIFE OUTCOMES — PART A

		18170		18171		40173	
		Ivermectin 1%	**Vehicle**	**Ivermectin 1%**	**Vehicle**	**Ivermectin 1%**	**Metronidazole 0.75%**
RosaQoL							
Baseline	N	NR	NR	456	228	NA	
	Mean (SD)	NR	NR	3.53 (0.67)	3.48 (0.70)		
End of Part A[a]	N	NR	NR	447	218		
	Mean (SD)	NR	NR	2.93 (0.75)	3.11 (0.76)		
	Mean absolute change from baseline (SD)	–0.64 (0.7)	–0.35 (0.5)	–0.60 (0.64)	–0.35 (0.47)		
	P value	**< 0.001**		**< 0.001**			
DLQI							
Baseline	N	451	232	457	228	476	482
	Mean (SD)	5.8 (4.5)	5.6 (4.5)	5.6 (4.2)	5.3 (4.14)	6.9 (5.6)	6.1 (5.0)
End of Part A[a]	N	436	221	445	218	464	469
	Mean (SD)	2.3 (3.1)	3.3 (3.5)	2.4 (3.0)	3.2 (3.3)	1.8 (3.4)	2.1 (3.5)
	Mean absolute change from baseline (SD)	–3.5 (4.0)	–2.2 (3.7)	–3.2 (3.8)	–2.0 (3.1)	5.2 (6.6[b])	3.9 (6.1[b])
	P value	**< 0.001**		**< 0.001**		NR	

CDR = CADTH Common Drug Review; DLQI = Dermatology Life Quality Index; NA = not applicable; NR = not reported; RosaQoL = Rosacea Quality of Life Index; SD = standard deviation.

[a] End of Part A is defined as week 12 in Studies 18170 and 18171 and as week 16 in Study 40173.

[b] Calculated by CDR reviewers.

Source: Clinical Study Reports.[4-6]

3.6.5 Remission and relapse

Relapse was addressed specifically in Part B of Study 40173. Patients classified as treatment success (IGA ≤ 1) after 16 weeks of treatment were subsequently enrolled in a 36-week extension (Part B) in which study treatment was stopped. Relapse was defined as IGA > 1 in which the same treatment was re-administered until the patient achieved IGA ≤ 1. Among 399 patients in the ivermectin group, the relapse rate was 62.7%, while the relapse rate in 358 patients in the metronidazole group was 68.4% (*P* = 0.10). Mean time to first relapse was significantly longer in the ivermectin group (114 days; 95% confidence interval [CI], 113 to 147) than the metronidazole group (85 days; 95% CI, 84 to 112) (Table 12).

TABLE 12: KEY EFFICACY OUTCOMES — PART B (RELAPSE)

	40173		
	Ivermectin 1% (N = 399)	**Metronidazole 0.75% (N = 358)**	***P* value**
Time to first relapse,[a] median days (95% CI)	115 (113 to 165)	85 (85 to 113)	0.037
Relapse rates, n (%)	250 (62.7)	245 (68.4)	0.10[b]
Treatment-free days,[c] mean (SD)	183.4 (69.2)	170.4 (74)	0.026
Patient's Assessment of Rosacea Improvement			
N	384	349	
N (%) rated as "excellent" at end of Part B	222 (57.8)	140 (40.1)	< 0.002[b]

CDR = CADTH Common Drug Review; CI = confidence interval; IGA = Investigator's Global Assessment; SD = standard deviation.
[a] Relapse defined as IGA > 1.
[b] Calculated by CDR reviewers.
[c] Treatment-free days defined as the time interval between visit where IGA ≤ 1 and the next visit, summed over all visits meeting this criterion.
Source: Manufacturer's submission.[13]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1 Protocol). The focus of this section is on Part A of each study, although Appendix 4 contains details on the long-term safety of ivermectin obtained from Part B of Studies 18170 and 18171.

3.7.1 Serious adverse events

Over the course of 12 weeks of treatment, the overall frequency of SAEs was 0.7% and 0.4% in Study 18170 and 1.5% and 1.7% in Study 18171 for the ivermectin and vehicle groups, respectively (Table 13). When compared with metronidazole, the incidence of SAEs over the course of 16 weeks was 1.7% for the ivermectin group compared with 1.0% for the metronidazole group. As highlighted in Table 13, the reasons for SAEs were rare (< 1%). SAEs were considered non-treatment-related.

3.7.2 Withdrawals due to adverse events

Study withdrawals due to adverse events (WDAEs) were low (< 3%) in all three studies, and were generally balanced between treatment groups (Table 13). The most common reason for withdrawal was related to skin and subcutaneous tissue disorders.

3.7.3 Adverse events

The overall frequency of treatment-emergent AEs was 40.5% and 39.4% in Study 18170 for the ivermectin and vehicle groups, respectively, and 36.5% in both treatment groups of Study 18171 (Table 13). A similar frequency of treatment-emergent AEs was observed in Study 40173 (32.4% versus 33.1% in the ivermectin and metronidazole groups, respectively). Overall, the most common reasons for AEs were nasopharyngitis, headache, and skin-burning sensation. With the exception of nasopharyngitis, which occurred in 6.7% and 6.0% of patients in the ivermectin and metronidazole groups, respectively, in Study 40173 the frequency of each type of treatment-emergent AE within each treatment group in each trial was less than 5%.

3.7.4 Notable harms

No deaths occurred over the duration of the three trials. Furthermore, no accounts of treatment-related gastrointestinal or photosensitivity AEs were reported in Part A. Reports of dermatological AEs related to the study drug, such as skin irritation, skin burning, dermatitis, and pain of skin/pruritus were low in frequency and balanced between treatment groups (< 3%) (Table 13). Worsening of rosacea was noted in one patient in the control group (0.4%) of Study 18170, and in five patients in Study 40173: two (0.4%) and three patients (0.6%) in the ivermectin and metronidazole groups, respectively. Only one patient (0.2%) in the ivermectin group of Study 40173 reported two episodes of moderate drug hypersensitivity. The incidence of notable harm was lower in the ivermectin group than the vehicle group within both trials, although it is unlikely the difference between treatment groups is statistically significant.

TABLE 13: HARMS — PART A (SAFETY POPULATION)

	18170		18171		40173	
Treatment-Emergent AEs	**Ivermectin 1% (N = 452)**	**Vehicle (N = 231)**	**Ivermectin 1% (N = 458)**	**Vehicle (N = 230)**	**Ivermectin 1% (N = 478)**	**Metronidazole 0.75% (N = 484)**
Patients with > 0 AEs, N (%)	183 (40.5)	91 (39.4)	167 (36.5)	84 (36.5)	155 (32.4)	160 (33.1)
Events, N	309	148	280	164	260	267
Most common AEs[a]						
Nasopharyngitis	12 (2.7)	6 (2.6)	10 (2.2)	6 (2.6)	32 (6.7)	29 (6)
Influenza	NR	NR	NR	NR	9 (1.9)	10 (2.1)
Headache	13 (2.9)	4 (1.7)	9 (2.0)	3 (1.3)	15 (3.1)	11 (2.3)
Skin-burning sensation	8 (1.8)	6 (2.6)	1 (0.2)	4 (1.7)	1 (0.2)	1 (0.2)
Upper respiratory tract infection	6 (1.3)	2 (0.9)	12 (2.6)	8 (3.5)	6 (1.3)	4 (0.8)
Sinusitis	5 (1.1)	1 (0.4)	9 (2.0)	6 (2.6)	2 (0.4)	1 (0.2)
Skin irritation	5 (1.1)	4 (1.7)	3 (0.7)	7 (3.0)	4 (0.8)	4 (0.8)
SAEs						
Patients with > 0 SAEs, N (%)[b]	3 (0.7)	1(0.4)	7 (1.5)	4 (1.7)	8 (1.7)	5 (1.0)
WDAEs						
WDAEs, N (%)	7 (1.5)	6 (2.6)	6 (1.3)	6 (2.6)	6 (1.3)	13 (2.7)
Events, N	9	8	7	6	7	14
Most common reasons						

	18170		18171		40173	
Treatment-Emergent AEs	**Ivermectin 1% (N = 452)**	**Vehicle (N = 231)**	**Ivermectin 1% (N = 458)**	**Vehicle (N = 230)**	**Ivermectin 1% (N = 478)**	**Metronidazole 0.75% (N = 484)**
Skin and subcutaneous tissue disorders	6 (1.3)	5 (2.2)	1 (0.2)	3 (1.3)	3 (0.6)	10 (2.1)
Deaths, N (%)	0	0	0	0	0	0
Notable harms related to study drug, N (%)						
Skin irritation	3 (0.7)	2 (0.9)	1 (0.2)	6 (2.6)	3 (0.6)	4 (0.8)
Skin burning	2 (0.4)	1 (0.4)	1 (0.2)	4 (1.7)	1 (0.2)	0
Dry skin	1 (0.2)	1 (0.4)	3 (0.7)	2 (0.9)	0	0
Dermatitis	1 (0.2)	0	1 (0.2)	0	0	3 (0.6)
Pain of skin/pruritus	1 (0.2)	1 (0.4)	3 (0.7)	1 (0.4)	1 (0.2)	2 (0.4)
Rosacea	0	1 (0.4)	0	0	2 (0.4)	3 (0.6)
Neutropenia	1 (0.2)	0	0	0	1 (0.2)	0
Flushing/erythema	1 (0.2)	0	1 (0.2)	0	2 (0.4)	1 (0.2)
Eye irritation	0	1 (0.4)	2 (0.4)	1 (0.4)	0	1 (0.2)
Hypersensitivity	0	0	0	0	1 (0.2)	0

AE = adverse event; SAE = serious adverse event; NR = not reported; WDAE = withdrawal due to adverse event.
[a] Frequency > 2%.
[b] None of the SAEs were considered by the investigator to be treatment-related, and frequency by specific class was < 2% in frequency.
Note: AEs are defined as events that occurred on the date of first use of medication or after, with exception of those reported from day 1 laboratory data, because blood sample was to be drawn before the time of first application.
Source: Clinical Study Reports.[4-6]

4. DISCUSSION

4.1 Summary of Available Evidence

Three published, manufacturer-sponsored, investigator-blind RCTs were included in this systematic review: namely, Studies 18170, 18171, and 40173. Studies 18170 and 18171 were vehicle-controlled with identical designs: patients received either ivermectin 1% or vehicle, once daily, for 12 weeks, followed by a 40-week follow-up phase. Study 40173 was an active-controlled superior trial designed to assess whether ivermectin 1% once daily was superior to metronidazole 0.75% cream twice daily for treating moderate to severe rosacea in adults.

4.2 Interpretation of Results

4.2.1 Efficacy

According to the clinical expert involved in this review, all three trial populations were generally reflective of patients with moderate to severe rosacea treated in Canadian practices. However, concerns were raised about the poor representation of patients with different ethnicities. Given that all three trials were predominantly of a Caucasian population, it is unclear how patients of different skin colours may respond to ivermectin. The trial was further restricted, through the application of its inclusion/exclusion criteria, to enrol patients with moderate to severe rosacea, whereas ivermectin's Health Canada indication and listing request is broader, covering the full spectrum of rosacea severities. It is uncertain how patients with milder rosacea will respond to ivermectin. The clinical expert involved in this review further noted that, although it is easy for a dermatologist to diagnose papulopustular rosacea and differentiate it from other cutaneous disorders, this may not be the case for general practitioners who may not have the necessary training and may prescribe ivermectin incorrectly.

Overall, the patients recruited were treatment-naive, and it may be hard to generalize existing findings to understand how patients may respond to ivermectin if they had a previous treatment failure. Although the review protocol pre-specified prior metronidazole failure as one of the subgroups of interest, the existing trials recruited too few patients who have been previously treated with metronidazole to explore this subgroup.

a) Efficacy of ivermectin compared with vehicle

One of the outcomes of importance identified from the patient input received is the symptomatic control of redness and bumps, which were addressed by the outcome measures used in these trials. Studies 18170 and 18171 consistently found statistically significant results for mean absolute and per cent change in inflammatory lesion count and for success rate, defined by the IGA scale. At week 12, ivermectin was statistically better than vehicle in reducing the number of inflammatory lesions (mean adjusted difference –8.13 [95% CI,–10.12 to –6.13] in Study 18170 and –8.22 [95% CI, –10.18 to –6.25] in Study 18171; both $P < 0.001$) and had higher success rates (difference in proportion 26.8% in Study 18170 and 21.3% in Study 18171, both $P < 0.001$). Findings were consistent between the ITT and PP populations. However, the majority of the outcome measures that were used in these trials have not been validated despite their widespread use in clinical research. Whether the difference in efficacy between the ivermectin and vehicle groups was clinically meaningful in patients with rosacea remains unknown.

The pre-specified subgroup analysis on baseline disease severity found no clear difference between patients with severe or moderate rosacea in terms of their response to treatment.

Although QoL data were collected, the analysis was conducted post-hoc and should be considered exploratory. Both studies consistently found that patients on ivermectin had a statistically significantly greater improvement than patients on vehicle in terms of QoL measures ($P < 0.0001$). As this analysis was not corrected for multiplicity and it remains uncertain whether studies were adequately powered to detect meaningful differences, further caution is warranted in drawing conclusions from this data.

Rosacea is a chronic condition and its long-term efficacy remains unknown, as both trials' efficacy assessments were limited to 12 weeks as Part B of both vehicle-controlled studies focused solely on safety outcomes.

b) Efficacy of ivermectin compared with metronidazole

Evidence on the comparative efficacy of ivermectin to metronidazole is available directly from Study 40173 [redacted]. Similar to the vehicle-controlled trials, Study 40173 was able to demonstrate that ivermectin was statistically significantly better than metronidazole 0.75% twice daily in reducing the number of inflammatory lesions at week 16 (absolute change from baseline in inflammatory lesions with ivermectin: 83% versus metronidazole: –73.7%, $P < 0.05$). Success rate at week 16 in the ivermectin group was 84.9% compared with 75.4% in the metronidazole group in the ITT population ($P < 0.001$). As identified from the patient input summary that was received by CADTH, a key issue of importance for patient is the symptomatic control of "redness and bumps". Although inflammatory lesion count (mean absolute change and per cent change) and success rate improved following treatment and were statistically in favour of ivermectin compared with metronidazole, it remains uncertain whether differences in the efficacy outcomes between treatment groups were clinically significant to patients, as no MCID has been established. The pre-specified subgroup analysis did not reveal any differences in treatment efficacy in patients with different baseline rosacea severities.

The manufacturer submitted an indirect treatment comparison, described in Appendix 6. [redacted]

QoL data were collected and analyzed post-hoc. Although QoL improved from baseline following treatment, no differences emerged in the improvement attained between treatment groups. This analysis is, however, considered exploratory.

One potential limitation of Study 40173 was that patients were not blinded. Knowledge of group assignment may have affected patients' behaviour during the trial and their responses to the outcome measures. Yet these data were not collected during the conduct of the trial. Indeed, differences were observed in the efficacy outcomes in the ivermectin group when comparing the results attained in the DB, vehicle-controlled trials (i.e., Studies 18170 and 18171) with the results observed in Study 40173 at identical time points. For instance, the success rate for the ivermectin group at week 12 was reported to be 84.9% in Study 40173, whereas in the vehicle-controlled trials, the success rates were 38.4% and 40.1% at week 12 in Studies 18170 and 18171, respectively (Figure 4). It is not clear precisely how knowledge of treatment assignment could have produced a greater-than-expected response in the ivermectin treatment group in Study 40173, but the clinical expert noted that differential behaviour

related to several confounding factors within a patient's control — such as exposure to sun, skin applications, alcohol consumption, heat, and emotional factors — could have affected their symptoms of rosacea. Other potential explanations for the differences that were observed across trials in the ivermectin group include the fact that the vehicle-controlled and active-comparator trials were conducted in different geographic regions, and the fact that differences were recorded in treatment exposure.

Upon stopping treatment in the treatment responders, relapse rate (IGA ≥ 2) was 62.7% in the ivermectin group compared with 68.4% in the metronidazole group (*P* = 0.10). The time to first relapse was statistically significantly longer in patients receiving ivermectin than in patients receiving metronidazole (114 days [95% CI, 113 to 147] versus 85 days [95% CI, 84 to 112]; *P* = 0.026). However, as rosacea is a chronic condition, the clinical expert noted that it is unrealistic to discontinue treatment among patients responding to treatment in clinical practice. The long-term comparative efficacy of ivermectin to metronidazole is unknown beyond 16 weeks of treatment.

c) Efficacy of ivermectin compared with other therapies

The relative efficacy of ivermectin to therapies for rosacea, other than metronidazole, has not been studied directly. Although patients in Studies 18170 and 18171 were treated with vehicle during the initial phase and subsequently switched to azelaic acid from weeks 13 to 52, these studies were not designed to assess the comparative efficacy of ivermectin versus azelaic acid. [redacted]

There is no evidence on the comparative efficacy of ivermectin to systemic therapies for rosacea such as oral tetracyclines. However, according to the clinical expert consulted by CDR, systemic antibiotics are not first-line therapies in rosacea patients and are therefore not directly relevant comparators for ivermectin and the other available topical treatments.

4.2.2 Harms

Across all three trials, the frequency of SAEs was low and similar between treatment groups by the end of 12 to 16 weeks of therapy. None of the SAEs were related to the study drug. The frequencies of WDAEs were low and balanced between treatment groups within trials, with dermatological conditions being the most common reason for study discontinuation (< 3% across study groups). The frequency of any treatment-emergent AEs was similar between treatment groups and between studies (ranging between ~32.4% to ~40.5% across studies). The most common reasons included nasopharyngitis, influenza, headache, and skin-burning sensation. Potentially notable harms such as dermatological disorders, hypersensitivity reactions, gastrointestinal issues, and photosensitivity were generally rare (< 3%). Long-term safety data, up to 52 weeks of therapy, was reported from Studies 18170 and 18171 with the findings reported in Appendix 4 (Table 16). Similar observations to the acute treatment period were noted: the incidence and types of AEs were balanced between treatment groups.

[redacted]

4.3 Potential Place in Therapy

Oral tetracyclines (e.g., minocycline and doxycycline) have been the cornerstones of systemic therapy for papulopustular rosacea (type 2). However, in recent years, the need for an antibiotic effect has been questioned and topical therapy is preferable to systemic medication, especially since rosacea, by definition, is a chronic, relapsing, cosmetically embarrassing condition.[19] Azelaic acid and metronidazole are the most commonly used topical drugs in Canada for the treatment of papulopustular rosacea (type 2). However, azelaic acid frequently irritates the skin and is commonly associated with adverse cutaneous effects such as burning, stinging, and redness, which exaggerate the underlying signs and symptoms of rosacea. Therefore, from a practical point of view, topical metronidazole is the preferred first-line topical treatment option. An alternative, effective, and safe form of topical therapy, at an acceptable cost, it is reasonable to pursue. Rosiver represents an alternative to metronidazole and azelaic acid that is appropriate for those patients who have tried or choose not to use topical metronidazole. Clinical diagnosis is relatively straightforward for dermatologists and not likely to be confused with other cutaneous problems, although a definitive diagnosis may not be as easily achieved by family physicians. No diagnostic test, such as biopsy, is commonly utilized in the diagnosis.

5. CONCLUSIONS

The results of two vehicle-controlled RCTs (Studies 18170 and 18171) suggest that treatment of adults with moderate to severe papulopustular rosacea with ivermectin (1% cream administered daily) for 12 weeks is associated with a statistically significantly greater reduction in the number of inflammatory lesions and a statistically significantly higher success rate than vehicle-treated patients. Similarly, 16 weeks of treatment with ivermectin (Study 40173) was associated with a statistically significantly greater percentage reduction in the number of inflammatory lesions and a statistically significantly higher success rate compared with metronidazole (0.75% cream applied twice daily), although it is not known whether the difference in the response to ivermectin versus metronidazole is clinically meaningful. [redacted]

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

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

The Canadian Skin Patient Alliance is a non-profit patient organization that serves individuals living with dermatological conditions in Canada. It focuses on education, support, and advocacy for patients and 21 affiliate disease-specific organizations, including the Acne and Rosacea Society of Canada.

As part of its conflict of interest declaration, the group has reported that it is currently receiving funding from Galderma, the manufacturer of Rosiver, for projects related to rosacea. In addition, it has received funding over the past 12 months from the following pharmaceutical companies: AbbVie, Amgen, Celgene, GSK, Leo Pharma, Janssen, Merck, Roche, and Valeant.

2. Condition-Related Information

The main source of patient information for this submission was gathered from a one-week Facebook campaign inviting individuals living with rosacea to take a questionnaire that resulted in 184 respondents. In addition, some dermatologists were approached to help distribute the questionnaire to patients who were involved in ivermectin clinical trials. This approach resulted in 20 submitted questionnaires. Out of the total 204 respondents, 45% have been living with rosacea for well over 10 years.

Rosacea varies in severity and presents with many symptoms, including: central facial skin redness; dry and scaly skin; pimples; red lines; knobby bumps and an enlarged nose; eye inflammation; and vascular dysfunction. The majority of questionnaire respondents stated that the “redness and the bumps” were the most important symptoms to control.

Since rosacea causes noticeable skin changes on the face, it can have profound long-term effects on a person’s quality of life (QoL). Low self-esteem, embarrassment, frustration, sadness, shame, depression, and inability to participate in day-to-day activities are all part of the reported consequences of rosacea.

Especially embarrassing are the unpredicted and severe flushing, and the permanent reddening of the face. Patients with these symptoms worry that they are perceived as heavy drinkers. Of the questionnaire respondents, when their rosacea is not under control, more than 70% felt embarrassed or felt the need to hide their skin. More than 50% felt depressed and ashamed and had a drop in their self-confidence, while 38% expressed that their skin condition affected their ability to sleep and perform daily activities, and more than 20% admitted it affected their level of sexual intimacy.

> *“It has gotten worse over the last year and people seem to think that it is from drinking. I have no alcohol not even wine so it is embarrassing.”*

The questionnaire did not specifically ask about the impact of rosacea on caregivers. However, according to the Canadian Skin Patient Alliance, skin conditions that affect a patient’s appearance and self-esteem can have a significant impact on close family members. Not wanting to participate in family activities is the most common concern expressed by caregivers, followed by a loss of self-esteem and depression, and an impact on intimacy.

3. Current Therapy-Related Information

According to the questionnaire administered by the Canadian Skin Patient Alliance, the most common therapies patients were using included 1% MetroGel, Finacea, a variety of prescription creams, and over-the-counter acne medication. Many responders also reported not using anything. One of the survey respondents noted that he/she would get a red sore reaction to anything. Some respondents tried laser therapy with limited results. As mentioned in one quote, treatment "made me red and itchy, extremely sensitive."

Others expressed concerns over the high expenses associated with the treatment, and with trying different therapies to find relief of their rosacea symptoms.

Specifically, when asked, "How well other treatments have helped them control their symptoms?" more than 50% responded that the treatment either "didn't work at all" or worked "somewhat" in controlling redness, pimples, dry thick scales, and red lines. More than 40% responded that the treatment either "didn't work at all" or worked "somewhat" in controlling knobby bumps on nose, eye inflammation, or vascular dysfunction, and nearly 20% said they had never treated their rosacea in the past.

4. Expectations About the Drug Being Reviewed

In patients who completed the questionnaire and had tried ivermectin, overwhelming positive feedback was received. Patients expressed views of how ivermectin was life-changing, emphasizing being less embarrassed, much more confident, and overall feeling physically and emotionally better. One patient wrote:

> *"This is a miracle drug...not only did it work while I was using it but I have had much less flare ups since I stopped. Prior to this study, I had concluded that I would just have to live with it and it was embarrassing to go out in public…"*

When asked to rate any previous treatment compared with ivermectin, the responses were as follows:

- In reducing redness: 80% reported "very good" with ivermectin versus 22% using an existing treatment.
- In treating pimples: 73% reported "good" or "very good" results with ivermectin versus 24% using an existing treatment.
- In treating dry scaly skin: 66% reported "good" or "very good" results with ivermectin versus 11% using an existing treatment.
- In treating red lines: 60% reported "good" or "very good" results with ivermectin versus 11% using an existing treatment.
- In treating knobby bumps on nose: 47% reported "good" or "very good" results with ivermectin versus 10% using an existing treatment.

Of patients who took ivermectin, 93% had no side effects. Of those who had negative side effects, they still felt that the benefits outweighed the side effects and that ivermectin should be made available to patients with rosacea.

More than 90% reported in the questionnaire that they would like to see ivermectin available via a public or private drug plan as soon as possible.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 1, 2015
Alerts:	Bi-weekly search updates until October 21, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
Fs	Floating subheading
Exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
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
.pt .po	Publication type Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY			
#	**Searches**	**Results**	**Search Type**
1	(Rosiver* or Soolantra or Stromectol or MK-933 or MK933or MK 933 or 70288-86-7).ti,ab,ot,sh,hw,rn,nm.	13052	Advanced
2	Ivermectin/ or Ivermectin*.ti,ab.	15233	Advanced
3	1 or 2	15233	Advanced
4	Rosacea/ or (rosacea* or rozacea*).ti,ab,sh.	11390	Advanced
5	3 and 4	89	Advanced
6	(Rosiver* or Soolantra or Stromectol or MK-933 or MK933or MK 933 or 70288-86-7).ti,ab,ot,hw,rn,nm.	13052	Advanced
7	Ivermectin/ or Ivermectin*or ivermectol.ti,ab.	13495	Advanced
8	6 or 7	13496	Advanced
9	Rosacea/ or (rosacea* or rozacea*).ti,ab.	9777	Advanced
10	8 and 9	72	Advanced
11	5 or 10	89	Advanced
12	exp animals/	38340224	Advanced
13	exp animal experimentation/ or exp animal experiment/	1861101	Advanced
14	exp models animal/	1272987	Advanced
15	nonhuman/	4520615	Advanced
16	exp vertebrate/ or exp vertebrates/	37269579	Advanced
17	animal.po.	0	Advanced
18	or/12-17	39673871	Advanced
19	exp humans/	29939595	Advanced
20	exp human experimentation/ or exp human experiment/	349195	Advanced
21	human.po.	0	Advanced
22	or/19-21	29941688	Advanced
23	18 not 22	9733781	Advanced
24	5 not 23	85	Advanced
25	10 not 23	68	Advanced
26	24 or 25	85	Advanced
27	26 use pmez	27	Advanced
28	26 use oemezd	58	Advanced

OTHER DATABASES	
PubMed	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:	Open ended
Keywords:	Rosiver (ivermectin) for Rosacea
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 evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

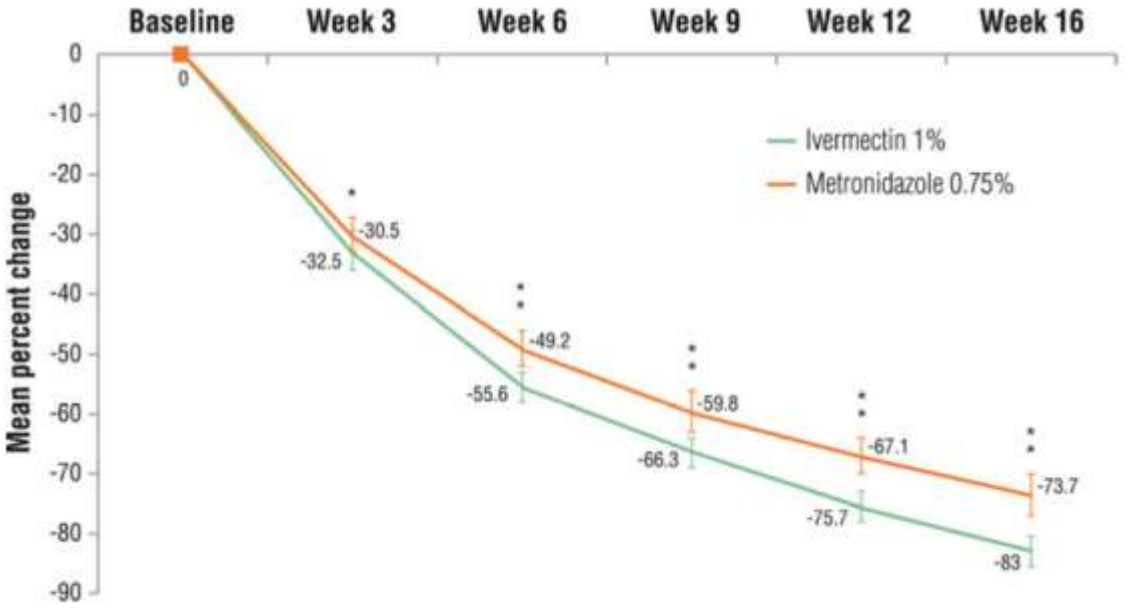
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

No studies were excluded.

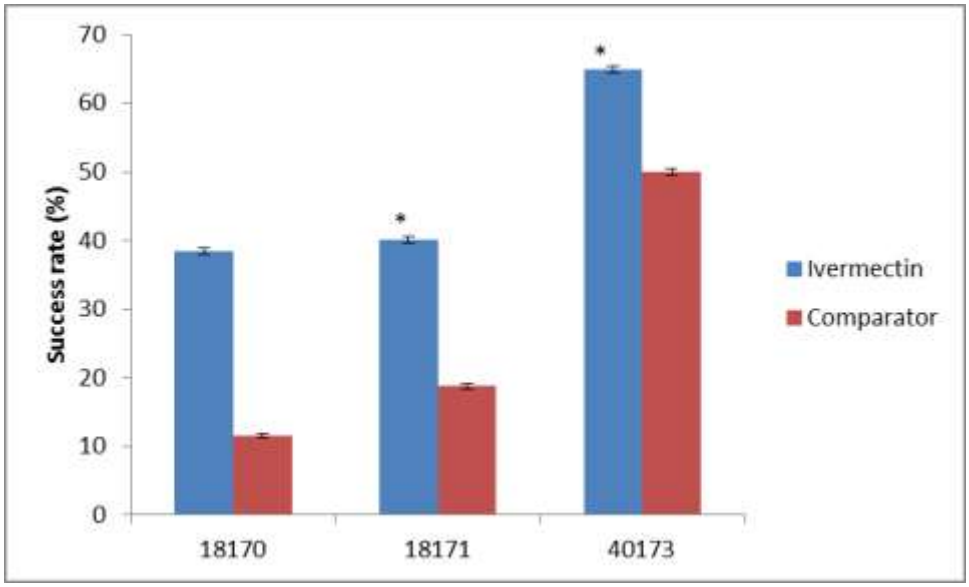
APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 3: MEAN PER CENT CHANGE FROM BASELINE IN INFLAMMATORY LESION COUNTS AND 95% CONFIDENCE INTERVAL (INTENTION-TO-TREAT) IN STUDY 40173



Source: Taieb.[18]

FIGURE 4: SUCCESS RATE (MEAN ± STANDARD DEVIATION), DEFINED AS AN INVESTIGATOR'S GLOBAL ASSESSMENT ≤ 1, AT WEEK 12 (INTENTION-TO-TREAT) ACROSS THE THREE STUDIES



The comparator in Studies 18170 and 18171 was vehicle, while the comparator in Study 40173 was metronidazole 0.75% cream.
*P < 0.01.
Source: Clinical Study Reports.[4-6]

TABLE 14: EFFICACY OUTCOMES IN PART A (BY BASELINE DISEASE SEVERITY)

Baseline Disease Severity		18170		18171		40173	
		Ivermectin 1%	Vehicle	Ivermectin 1%	Vehicle	Ivermectin 1%	Metronidazole 0.75%
Inflammatory Lesion Counts							
IGA = Moderate	N	369	191	346	176	398	403
	Mean inflammatory lesion count at ET[a] (SD)	10 (12.8)	15.7 (14.3)	9.6 (9.5)	14.3 (11.4)	4.9 (7.6)	8.0 (13.1)
	Mean absolute change from baseline to ET[a] (SD)	–17.9 (14.3)	–11.9 (12.9)	–20.5 (13.1)	–13.8 (11.9)	–25.3 (14.4[b])	–21.5 (16.7[b])
	% change from baseline to ET[a] (SD)	–63.6 (41.9)	–43.9 (38.8)	–66.6 (31.8)	–48.0 (35.8)	–82.5 (26.6)	–73.4 (41.7)
IGA = Severe	N	82	41	113	53	80	81
	Mean inflammatory lesion count at ET[a] (SD)	12.9 (14.1)	31.3 (21.2)	15.4 (15.9)	34 (24.5)	6.6 (11.4)	11.3 (13.6)
	Mean absolute change from baseline to ET[a] (SD)	–31.9 (17.8)	–12.7 (16.5)	–27.5 (18.4)	–12.2 (20.9)	–39.7 (18.5[b])	–33.7 (20.4[b])
	% change from baseline to ET[a] (SD)	–70.9 (28.7)	–31.0 (37.9)	–63.1 (37.2)	–28.1 (43.0)	–85.1 (22.5)	–75.2 (28.1)
Investigator Global Assessment, ITT							
IGA = Moderate	N	369	191	346	176	398	403
	Success, IGA ≤ 1 at ET[a], N (%)	149 (40.4)	26 (13.6)	150 (43.4)	39 (22.2)	340 (85.4)	314 (77.9)
IGA = Severe	N	82	41	113	53	80	81
	Success, IGA ≤ 1 at ET[a], N (%)	24 (29.3)	1 (2.4)	34 (30.1)	4 (7.5)	66 (82.5)	51 (37.0)

CDR = CADTH Common Drug Review; ET = end of treatment; IGA = Investigator's Global Assessment; ITT = intention-to-treat; SD = standard deviation.

[a] End of treatment was defined as 12 weeks in Studies 18170 and 18171 and 16 weeks in Study 40173.

[b] Calculated by CDR reviewers.

Source: Clinical Study Reports.[4-6]

TABLE 15: EUROQOL 5-DIMENSIONS QUESTIONNAIRE FROM STUDY 40173

		40173	
		Ivermectin 1%	**Metronidazole 0.75%**
Baseline	N	477	481
	Mean EQ-5D VAS (SD)	77.5 (16.9)	75.8 (18.9)
Week 16 (end of Part A)	N	464	471
	Mean EQ-5D VAS (SD)	84.4 (13.6)	82.0 (15.2)
Week 52 (end of Part B)	N	384	347
	Mean EQ-5D VAS (SD)	86.1 (12.9)	84.5 (13.3)

EQ-5D = EuroQol 5-Dimensions Questionnaire; SD = standard deviation; VAS = visual analogue scale.
Source: Clinical Study Reports.[6]

TABLE 16: LONG-TERM HARMS — PART B OF STUDIES 18170 AND 18171 (SAFETY POPULATION)

	18170		18171	
Treatment-emergent AEs	**Ivermectin 1% (N = 412)**	**Azelaic acid 15% (N = 210)**	**Ivermectin 1% (N = 428)**	**Azelaic acid 15% (N = 208)**
Patients with > 0 AEs, N (%)	249 (60.4)	127 (60.5)	254 (59.3)	122 (58.7)
Events, N	610	346	658	307
Most common AEs[a]				
Nasopharyngitis	54 (35.2)	31 (14.8)	43 (10)	18 (8.7)
Upper respiratory tract infection	31 (7.5)	14 (6.7)	40 (9.3)	17 (8.2)
SAEs				
Patients with > 0 SAEs, N (%)[b]	7 (1.7)	8 (3.8)	13 (3.0)	4 (1.9)
WDAEs				
WDAEs, N (%)	5 (1.2)	2 (1.0)	3 (0.7)	3 (1.4)
Events, N	5	9	3	4
Deaths, N (%)	0	0	0	0
Notable harms related to study drug, N (%)				
Skin-burning sensation	1 (0.3)	1 (0.5)	2 (0.5)	3 (1.4)
Skin irritation	2 (0.5)	3 (1.4)	1 (0.2)	4 (1.9)
Dry skin	2 (0.5)	4 (2.0)	0	2 (1.0)
Pruritus	0	1 (0.5)	1 (0.2)	4 (1.9)
Pain of skin	0	5 (2.6)	1 (0.2)	0
Eyelids pruritus	1 (0.3)	0	0	0
Nausea	0	1 (0.5)	0	0

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Frequency > 5%.
[b] None of the SAEs were considered by the investigator to be treatment-related, and frequency by specific class was < 2%.
Note: AEs are defined as events that occurred on the date of first use of medication or after, with the exception of those reported from day 1 laboratory data, because the blood sample was to be drawn before the time of first application.
Source: Clinical Study Reports.[4-6]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the measurement properties (e.g., reliability, validity, minimal clinically important difference [MCID]) of the following outcome measures:

- Investigator's Global Assessment (IGA)
- Patient global assessment
- Inflammatory lesion count
- Dermatology Life Quality Index (DLQI)
- Rosacea Quality of Life Index (RosaQoL)

These measures were used in the manufacturer's pivotal studies of ivermectin 1% once daily for the treatment of inflammatory lesions in rosacea.

Findings

Table 17 provides a summary of the findings.

a) Investigator Global Assessment

IGA is a 5-point Likert scale that provides a global clinical assessment of rosacea severity (ranging from 0 = clear to 4 = severe) based on erythema and the number of papules/pustules. A decrease in score relates to an improvement in signs and symptoms. However, the clinical expert consulted for this review explained that, in practice, a physician would assess a patient's rosacea more subjectively (evaluating inflammatory lesions or erythema) without using the IGA scale.

A review of the literature found no information on the validity and reliability of the IGA scale. Similarly, no information was found on what would constitute an MCID in patients with rosacea.

b) Patient Global Assessment

Patients were asked to assess their improvement, as compared to the baseline, on a 5-point global scale (worse, no improvement, moderate, good, or excellent).

No information was found on the validity, reliability, and MCID of the patient's global assessment scale.

c) Inflammatory Lesion Count

Inflammatory lesion count is the sum of all papules and pustules that patients present with, which was counted separately on each of five facial regions (i.e., forehead, chin, nose, right cheek, left cheek). Inflammatory lesion count is an objective outcome and, in the trials, inflammatory lesions were defined as follows:

- papule: a small, solid elevation less than one centimetre in diameter
- pustule: a small, circumscribed elevation of the skin, which contains yellow-white exudates.

No information was found on the validity and reliability of inflammatory lesion count. Similarly, what constitutes MCID is unknown.

d) Dermatology Life Quality Index

The DLQI is a generic quality of life (QoL) measure broadly applied to all dermatologic conditions. It consists of 10 questions concerning the impact of a dermatological disease on a patient's QoL over a one-week period. Items include questions concerning the impact of a dermatological disease (e.g., symptoms) and the impact of treatment on feelings, daily activities, work, school, leisure, and personal relationships. Patients answer each question with one of four possible scored choices: 0 = not at all; 1 = a little; 2 = a lot; and 3 = very much. A summed score of 30 represents maximum impairment and 0 refers to no impairment.[20] In general, DLQI is a validated tool,[21] with a recent study determining the MCID to be 3.3 in a population of patients with variety of dermatological conditions.[22] It is uncertain, though, whether this MCID would translate to patients with rosacea.

With respect to rosacea, no information was found supporting the validity and reliability of DLQI in this disease condition.

e) Rosacea Quality of Life

RosaQoL is a disease-specific QoL measure. It was developed in 2007 based on a study in which six patients provided in-depth interviews on how rosacea affected their lives, and subsequent item reduction based on the response of 62 patients.[23] Twenty-one rosacea-specific items were developed based on three constructs: seven items based on symptoms, three on functioning, and 11 on emotions. Response categories include: 1 = never; 2 = rarely; 3 = sometime; 4 = often; and 5 = all the time, with higher scores indicative of a greater impact of rosacea on the patient's QoL.

Construct validity with this measure has been demonstrated, as the scores within the three constructs correlate with a patient's self-reported severity of rosacea. The study was found to have high reliability (internal consistency, Cronbach's alpha: 0.82 to 0.97; test–re-test reliability, intraclass correlation coefficient: 0.70 to 0.95). In a cohort of participants who completed RosaQoL at baseline and four to six months, the rosacea-specific QoL instrument showed statistically significant preliminary responsiveness for patients with improved disease, although the change in QoL scores was not statistically different in patients with worsening rosacea. Compared to Skindex-29 (a dermatological QoL scale), RosaQoL had statistically better responsiveness in detecting disease improvement.[23] A review of the literature did not find an MCID for RosaQoL.

TABLE 17: SUMMARY OF FINDINGS

Instrument	Description	Validated	MCID	References
IGA	A physician's global clinical assessment of rosacea severity	UNKNOWN	UNKNOWN	None found
Patient global assessment	Patient's subjective assessment of rosacea improvements compared to baseline	UNKNOWN	UNKNOWN	None found
Inflammatory lesion count	Sum of all papules and pustules with which patients present	UNKNOWN	UNKNOWN	None found
DLQI	Patient assessment of the impact of their dermatological disease on their QoL in the past week	UNKNOWN	UNKNOWN	None found
RosaQoL	Disease-specific measure on the impact of a rosacea on patient's QoL	YES	UNKNOWN	Nicholson et al. (2007)[23]

DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; MCID = minimal clinically important difference; QoL = quality of life; RosaQoL = Rosacea Quality of Life Index.

Conclusion

In a literature search, only one article was found that evaluated the measurement properties of one of outcomes in a rosacea population. The study was the original pilot study in which the RosaQoL questionnaire was developed. The study demonstrated the validity and reliability of this outcome measure, though no MCID was investigated.

No information was found regarding the validity and MCID of IGA, patient global assessment, inflammatory lesion count, and DLQI.

APPENDIX 6: SUMMARY AND CRITICAL APPRAISAL OF NETWORK META-ANALYSIS

1. Introduction

1.1 Background

[redacted]

[redacted]

1.2 Methods

[redacted]

2. Description of Indirect Comparisons Identified

[redacted]

3. Review and Appraisal of Indirect Comparisons

3.1 Review of Manufacturer's Indirect Comparison

3.1.1 Objectives and rationale for manufacturer's indirect comparison

[redacted]

3.1.2 Methods for manufacturer's indirect comparison

a) Study eligibility and selection process

[redacted]

[redacted]

[redacted]

[redacted]

b) Data extraction

[redacted]

c) Comparators

[redacted]

[redacted]

d) Outcomes

[redacted]

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e) Quality assessment of included studies

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f) Evidence network

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3.1.3 Indirect comparison methods

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3.1.4 Results

a) Study characteristics

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3.1.5 Critical appraisal

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4. Discussion

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5. Conclusion

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