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CADTH COMMON DRUG REVIEW

Clinical Review Report

EFINACONAZOLE (JUBLIA)

(Valeant Canada LP)

Indication: For the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in immunocompetent adult patients.

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Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CMH	Cochran–Mantel–Haenszel
CrI	credible interval
DLSO	distal lateral subungual onychomycosis
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention-to-treat
KOH	potassium hydroxide
LOCF	last observation carried forward
MCID	minimal clinically important difference
mITT	modified intention-to-treat
NMA	network meta-analysis
OnyCOE-t	onychomycosis quality-of-life questionnaire
OR	odds ratio
PP	per-protocol
SAE	serious adverse event
SAP	statistical analysis plan

Drug	efinaconazole (Jublia)
Indication	For the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *T. mentagrophytes* in immunocompetent adult patients
Reimbursement Request	As per indication
Dosage Form(s)	Topical solution, 10% w/w
NOC Date	October 2, 2013
Manufacturer	Valeant Canada LP

Executive Summary

Introduction

Onychomycosis is a chronic and recurrent fungal infection that accounts for 50% to 60% of all nail abnormalities.[1] It predominantly affects older adult males and has a ratio of toenail to fingernail involvement of 19:1.[2] The global prevalence of onychomycosis is estimated to be 5.5%.[3] In Canada, a multi-centre survey reported the prevalence of onychomycosis to be 6.5%.[2] In adults aged 60 years and over, the prevalence of onychomycosis increases to between 14% and 48%, with higher rates attributed to diminished peripheral circulation, longer exposure to fungi, nail trauma, compromised immune systems, and slower nail growth.[4-6]

Onychomycosis is usually caused by dermatophytes (e.g., *Trichophyton rubrum* and *T. mentagrophytes*), yeasts (most commonly *Candida albicans*), and nondermatophyte molds.[1] Onychomycosis of the toenail typically appears as a yellow or brown thickening of the nail accompanied by crumbling or brittleness, and debris under the nail. It may lead to permanent toenail deformity that can significantly affect quality of life due to physical discomfort or pain, self-consciousness about toenail appearance, and interference with wearing shoes, walking, or participation in activities. Onychomycosis may also increase the risk of bacterial infections such as cellulitis in patients with diabetes or other immunocompromised states.[7,8] Accepted risk factors for onychomycosis include advanced age, swimming, occlusive footwear, tinea pedis, psoriasis, diabetes, immunodeficiency, genetic predisposition, obesity, smoking, and living with family members with onychomycosis.[1,3] The rate of recurrence of onychomycosis following successful treatment is reported to be 11.9% with terbinafine and 35.7% with itraconazole after a mean duration of 36 months.[9]

Currently available therapeutic options for onychomycosis in Canada include systemic antifungals such as terbinafine, itraconazole, and fluconazole (the latter used off-label), as well as topical agents such as ciclopirox and physical interventions such as debridement. Efinaconazole (Jublia) is a triazole antifungal agent that inhibits fungal lanosterol 14 alpha-demethylase, which is involved in ergosterol biosynthesis.[10] The Health Canada–approved indication for efinaconazole is for the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *T. rubrum* and *T. mentagrophytes* in immunocompetent adult patients.[10] Efinaconazole is available as a 10% w/w topical solution in a plastic squeeze bottle with a built-in flow-through brush applicator.

The recommended dosage is one drop applied to the affected toenail(s), with a second drop applied to the affected big toenail(s) once daily, preferably at bedtime.[10]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of efinaconazole for the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *T. rubrum* and *T. mentagrophytes* in immunocompetent adult patients.

Results and Interpretation

Included Studies

Two phase III, multi-centre, randomized (3:1), double-blind, parallel-group, vehicle-controlled superiority trials were included in the systematic review: Study P3-01 (N = 870) and Study P3-02 (N = 785). The trials, which were identical in design, evaluated the efficacy and safety of once-daily topical application of efinaconazole 10% solution compared with the vehicle alone, for the treatment of adult patients with mild-to-moderate distal lateral subungual onychomycosis (DLSO) over 52 weeks. DLSO was defined as 20% to 50% clinical involvement of the target toenail(s) without dermatophytomas or matrix (lunula) involvement. The primary efficacy outcome was a complete cure at week 52, defined as both 0% clinical involvement of the target toenail and mycologic cure (i.e., a negative potassium hydroxide [KOH] examination and a negative fungal culture of the target toenail sample). The eligibility criteria required that patients had at least one affected great toenail, and to qualify as the target toenail it must have had an uninfected length of at least 3 mm from the proximal nailfold, a thickness of no more than 3 mm, evidence of toenail growth, a positive microscopic examination with KOH for dermatophyte hyphae, and a positive dermatophyte culture or mixed dermatophyte/*Candida* culture no more than 42 days before the baseline visit. Secondary outcomes included treatment success or clinical efficacy (defined as < 10% affected toenail area involvement), mycologic cure, unaffected new toenail growth, and complete or almost-complete cure (defined as no more than 5% affected toenail area involvement and mycologic cure) at week 52. Safety outcomes included mortality, treatment-emergent adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events, and notable harms, such as application-site dermatitis, vesicles, and tinea pedis.

The mean age of enrolled patients ranged from 50 to 52 years across both trials, with a predominance of male and Caucasian patients. Both Study P3-01 and Study P3-02 enrolled patients from the US and Canada. However, because Study P3-01 also enrolled patients from Japan, the study population in Study P3-01 comprised 29.0% Asian patients compared with 2.2% Asian patients in Study P3-02. The mean area of target toenail involvement at baseline in both trials was approximately 36% and the mean number of affected non-target toenails was 2.8. The majority of patients had screening cultures of *T. rubrum* (> 89%) and *T. mentagrophytes* (> 4%).

A number of limitations were identified for the included trials. The first is that the study populations represent typically healthy, immunocompetent adult patients with mild-to-moderate disease who would primarily seek treatment for cosmetic reasons. This is in contrast to the population most in need of treatment (immunocompromised or diabetic patients at risk of secondary infection and patients with pain or functional impairment due to dystrophic nails). Data on the use of efinaconazole in elderly patients or those with more severe disease are limited. Although pre-specified subgroup analyses according to age and

disease severity at baseline were conducted, the results of these analyses are considered exploratory due to the lack of formal interaction tests or adjustment for multiple comparisons. Data to support an effect of efinaconazole on health-related quality of life (HRQoL) are also inconclusive as the onychomycosis quality-of-life questionnaire (OnyCOE-t) assessments were a supportive efficacy outcome in the trials, thereby precluding statistical comparisons between treatment groups. Moreover, because the OnyCOE-t was only administered to patients whose native tongue was English, a substantial amount of data from non-native English speakers is missing for this outcome. Other important limitations are the lack of comparative data with another active oral or topical antifungal treatment, lack of data on recurrence of onychomycosis following treatment, or any data on concomitant use of oral antifungal therapy with topical efinaconazole.

Efficacy

Efficacy outcomes identified in the CADTH Common Drug Review (CDR) review protocol were HRQoL, cure (clinical and/or mycological), pain, recurrence, nail parameters such as nail loss or unaffected new nail growth, and secondary complications (e.g., bacterial infection, ulceration, amputation). Of these, efficacy data were available for HRQoL, various definitions of clinical cure based on a percentage of toenail involvement, mycologic cure, and unaffected new nail growth.

The OnyCOE-t was used to assess HRQoL through the change in individual scale scores from baseline to week 24 and week 52. As it was considered a supportive efficacy outcome, results were reported descriptively, and no statistical comparisons were made between treatment groups. There is no overall score for the OnyCOE-t. However, based on the 33 items included within the seven scales of the instrument, the overall minimal clinically important difference across individual scales reportedly ranges from 7.3 (based on a 12.5% difference in nail clearing) to 16.6 points (based on new nail growth of at least 5 mm). Nonetheless, due to the lack of statistical comparisons between treatment groups, it is difficult to interpret the clinical relevance of any apparent between-group differences.

The primary outcome in both Study P3-01 and Study P3-02 was complete cure of the target toenail by week 52. The proportions of patients with complete cure were statistically significantly higher (17.8% and 15.2%) in the efinaconazole groups in both trials, respectively, compared with the vehicle control groups (3.3% and 5.5%) in each trial; $P < 0.001$ for both. Pre-specified subgroup analyses of complete cures at week 52 that are of relevance to this CDR review were age (< 54 years or ≥ 54 years in Study P3-01 and < 52 years or ≥ 52 years in Study P3-02) and disease severity measured as percentage of affected target toenail area at baseline (< 40% or ≥ 40% in both trials). Although the results of these analyses suggest that there were no differences in the treatment effect between subgroups, [redacted], the results are considered exploratory. In general, younger patients and patients with less-severe disease at baseline appeared to achieve higher rates of complete cure. However, these results are inconclusive in the absence of any statistical comparisons.

All secondary outcomes were tested according to a pre-specified statistical testing hierarchy to control for type I error. Two versions of the statistical analysis plan (SAP) were approved prior to database lock. As a result, the secondary outcomes differed, as did the order of testing, depending on which version of the SAP was applied. According to both the FDA and Health Canada, version 1 of the SAP was considered the main analysis for the secondary outcomes. However, because all secondary outcomes from either version of the

SAP had *P* values < 0.001, an analyses from either version would lead to the same conclusions of efficacy.

According to version 1 of the SAP, the key secondary outcome was treatment success or clinical efficacy (defined as < 10% affected toenail area involvement) at week 52. Results for this outcome were statistically significantly higher in the efinaconazole groups (35.7% and 31.0%) in both Study P3-01 and Study P3-02, respectively, compared with the vehicle control groups (11.7% and 11.9%); *P* < 0.001 for both. In version 2 of the SAP, treatment success or clinical efficacy was [redacted]. The results were [redacted] In version 2 of the SAP, complete or almost-complete cure (defined as at least 5% affected target toenail area and a mycologic cure) at week 52 was the key secondary outcome. Results were also statistically significant in favour of efinaconazole (26.4% and 23.4%) in Study P3-01 and Study P3-02, respectively, compared with the vehicle (7.0% and 7.5%); both *P* < 0.001.

Mycologic cure (defined as a negative KOH examination and a negative fungal culture of the target toenail sample) was a secondary outcome in both trials, regardless of the version of the SAP applied. Mycologic cure rates were statistically significantly higher in the efinaconazole groups (55.2% and 53.4%) in both Study P3-01 and Study P3-02, respectively, compared with the vehicle control groups (16.8% and 16.9%); *P* < 0.001 for both.

Unaffected new toenail growth was a secondary outcome in both trials, regardless of the SAP version. At week 52, unaffected new toenail growth was statistically significantly greater in the efinaconazole groups compared with the vehicle groups in both trials. In Study P3-01, the least squares mean (standard error) growth was 5.0 (0.2) mm with efinaconazole versus 1.6 (0.4) mm with the vehicle; *P* < 0.001. In Study P3-02, the least squares mean unaffected growth was 3.8 (0.2) mm with efinaconazole versus 0.9 (0.4) mm with vehicle; *P* < 0.001. The overall mean (standard deviation) target toenail growth at week 52 was [redacted]. The mean change from baseline in the number of affected non-target toenails at week 52 was 0.8 (1.5) in the efinaconazole groups of both trials compared with [redacted](Study P3-01) and [redacted] (Study P3-02) in the vehicle control groups.

An indirect treatment comparison (ITC) submitted by the manufacturer was reviewed. The ITC included a network meta-analysis that compared relative efficacy (based on mycologic cure) of efinaconazole with placebo, ciclopirox, terbinafine, itraconazole (continuous and pulse therapy), and fluconazole in addition to other topical treatments that are not approved in Canada. The network meta-analysis suggested that terbinafine 250 mg daily and itraconazole 200 mg daily were more effective than efinaconazole and that there was no statistically significant difference between efinaconazole and ciclopirox in inducing mycologic cure. These results appear to be consistent with the general perception reiterated by the clinical expert that oral antifungal therapy is more efficacious than topical therapy. Various limitations were identified, including reliance on only one outcome (mycologic cure), heterogeneity across the included trials, and other methodological issues. Furthermore, these results should be interpreted with caution, as mycologic cure may not be a relevant and clinically meaningful outcome due to the limitations associated with use.

Indeed, mycologic cure is influenced by its reliance on proper sampling technique (i.e., location and sampling of infected nails) and its association with false-negative results, which limit its clinical value.

Harms

The proportions of patients who experienced one or more AEs were generally similar across treatment groups in both trials (i.e., 66.0% and 64.5% of efinaconazole-treated patients and 61.0% and 58.5% of vehicle-treated patients, in Study P3-01 and Study P3-02, respectively). The most commonly reported AE in both trials was nasopharyngitis. The proportions of patients who experienced SAEs were 3.8% and 3.7% in the efinaconazole groups compared with 2.8% and 0.5% in the vehicle control groups. The most common SAEs were myocardial infarction, osteoarthritis, and intracranial aneurysm, all of which were judged unrelated to the study drug by the investigators. The proportions of patients who withdrew due to AEs were 3.2% and 1.9% in the efinaconazole groups and 0.5% and 0% in the vehicle control groups. The most common reasons for discontinuation were treatment-related application-site AEs (e.g., application-site dermatitis, erythema, pruritis, swelling, vesicles, and contact dermatitis). Two deaths were reported, one each in the efinaconazole group in each trial, but investigators considered both unrelated to the study drug.

Notable harms identified in the CDR review protocol were application-site dermatitis, vesicles, and tinea pedis. Application-site dermatitis occurred in 3.5% and 0.7% of efinaconazole-treated patients compared with 0% and 0.5% of vehicle-treated patients in Study P3-01 and Study P3-02, respectively. Similarly, application-site vesicles occurred infrequently (2.0% and 1.2% of efinaconazole-treated patients and no vehicle-treated patients) in both trials. Tinea pedis occurred in more vehicle-treated patients in both trials (2.8% and 3.0%) compared with efinaconazole-treated patients (1.1% and 0.7%). Despite the occurrence of application-site dermatitis and vesicles, analysis of localized skin reaction scores reported by patients indicated that, in general, application of efinaconazole did not result in redness, swelling, burning, itching, or vesiculation that differed from those caused by the vehicle.

Potential Place in Therapy[a]

Efinaconazole is an alternative for patients who prefer topical therapy to systemic treatment for mild-to-moderate onychomycosis. This is based on personal preference rather than a medical need. From a medical perspective, patients who have functional impairment, symptomatic disease, or underlying diseases (e.g., immunocompromised states, diabetes, or venous stasis) that predispose them to more serious infections should be treated with systemic antifungals rather than topical efinaconazole, which has a low efficacy and requires long-term treatment and good compliance. Three systemic options are available (terbinafine, itraconazole, and fluconazole) along with one topical option (ciclopirox). Patients who have significant medical contraindications to all three systemic agents are uncommon.

In real-world practice, topical antifungals, which are viewed as safe and benign, are often prescribed for dystrophic nails, usually without fungal cultures. It is estimated that more than 50% of dystrophic nails are not caused by dermatophytes. The etiology may be trauma, saprophytes, psoriasis, eczema, or other dermatologic diseases. Therefore, topical

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

antifungals are often misused. Efinaconazole should be prescribed only for patients with mild-to-moderate onychomycosis (caused by dermatophytes proven on culture) who understand the need for long-term adherence to the treatment.

Conclusions

Two phase III, double-blind, randomized, controlled, superiority trials in adult patients with mild-to-moderate DLSO confirm that, in comparison with vehicle alone, efinaconazole topical solution is associated with statistically significant higher complete cure rates, mycologic cure rates, and unaffected nail growth. The effect of efinaconazole on HRQoL, as measured by the OnyCOE-t instrument, is inconclusive due to various identified limitations and a lack of statistical comparisons between treatment groups. No data are available on improvement in functionality, reduction of pain or secondary complications, or recurrence of onychomycosis following efinaconazole treatment. A manufacturer-submitted ITC suggested that oral terbinafine 250 mg daily and itraconazole 200 mg daily were more effective than topical efinaconazole, and that there was no statistically significant difference between efinaconazole and ciclopirox at inducing mycologic cure. These results are consistent with the general perception that oral antifungal therapy is more efficacious than topical therapy for onychomycosis. However, confidence in the results of the ITC is limited due to reliance on mycologic cure as an outcome and other methodological limitations, such as the low number of studies included in the network and the lack of a direct comparison with efinaconazole. In the phase III trials, safety and tolerability of topical efinaconazole was similar to the vehicle. The most common treatment-related AEs were application-site dermatitis and vesicles, which generally did not result in localized skin reaction scores that differed between topical efinaconazole and the vehicle.

Table 1: Summary of Results

Outcome	Study P3-01 (ITT)		Study P3-02 (mITT)	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
N	656	214	580	201
Complete cure at week 52[a]				
Success, n (%) **Failure, n (%)**	117 (17.8) 539 (82.2)	7 (3.3) 207 (96.7)	88 (15.2) 492 (84.8)	11 (5.5) 190 (94.5)
***P* value[b]**	< 0.001		< 0.001	
Treatment success or clinical efficacy at week 52[c]				
Success, n (%) **Failure, n (%)**	234 (35.7) 422 (64.3)	25 (11.7) 189 (88.3)	180 (31.0) 400 (69.0)	24 (11.9) 177 (88.1)
***P* value[b]**	< 0.001		< 0.001	
Mycologic cure at week 52[d]				
Success, n (%) **Failure, n (%)**	362 (55.2) 294 (44.8)	36 (16.8) 178 (83.2)	310 (53.4) 270 (46.6)	34 (16.9) 167 (83.1)
***P* value[b]**	< 0.001		< 0.001	
Unaffected new toenail growth at week 52, mm				
LSM (SE)	5.0 (0.2)	1.6 (0.4)	3.8 (0.2)	0.9 (0.4)
***P* value[e]**	< 0.001		< 0.001	
Complete or almost-complete cure at week 52[f]				
Success, n (%) **Failure, n (%)**	173 (26.4) 483 (73.6)	15 (7.0) 199 (93.0)	136 (23.4) 444 (76.6)	15 (7.5) 186 (92.5)

Outcome	Study P3-01 (ITT)		Study P3-02 (mITT)	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
***P* value**[b]	< 0.001		< 0.001	
Harms, n (%)				
AEs	431 (66.0)	130 (61.0)	370 (64.5)	117 (58.5)
SAEs	25 (3.8)	6 (2.8)	21 (3.7)	1 (0.5)
WDAEs	21 (3.2)	1 (0.5)	11 (1.9)	0 (0)
Deaths	1 (0.2)	0 (0)	1 (0.2)	0 (0)
Notable harms, n (%)				
Application-site dermatitis **Application-site vesicles** **Tinea pedis**	23 (3.5) 13 (2.0) 7 (1.1)	0 (0) 0 (0) 6 (2.8)	4 (0.7) 7 (1.2) 4 (0.7)	1 (0.5) 0 (0) 6 (3.0)

AE = adverse event; ITT= intention-to-treat population; KOH = potassium hydroxide; LSM = least squares mean; mITT = modified intention-to-treat population; SAE = serious adverse event; SE = standard error; SAP = statistical analysis plan; SE = standard error; WDAE = withdrawal due to adverse event.

Note: The last observation carried forward method was used to impute missing data. As per version 1 of the SAP, secondary outcomes and order of testing was treatment success or clinical efficacy > mycologic cure > unaffected new toenail growth, whereas in version 2 of the SAP secondary outcomes and order of testing was complete or almost-complete cure rate > unaffected new toenail growth > mycologic cure.

[a] A complete cure was defined as both 0% clinical involvement of the target toenail and mycologic cure (i.e., a negative KOH examination and a negative fungal culture of the target toenail sample).

[b] *P* value from a Cochran–Mantel–Haenszel test, stratified by analysis centre.

[c] Treatment success or clinical efficacy was defined as < 10% affected toenail area involvement and was a secondary outcome in SAP version 1.

[d] A mycologic cure was defined as a negative KOH examination and a negative fungal culture of the target toenail sample.

[e] LSM, SE and *P* value from an analysis of variance with treatment group and analysis centre as factors.

[f] A complete or almost-complete cure was defined as an affected target toenail area of no more than 5% and mycologic cure and was a secondary outcome in version 2 of the SAP.

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

Introduction

Disease Prevalence and Incidence

Onychomycosis is a chronic and recurrent fungal nail infection that accounts for 50% to 60% of all nail abnormalities.[1] It predominantly affects older adult males and the ratio of toenail to fingernail involvement is reported to be 19:1.[2] Onychomycosis is usually caused by dermatophytes (e.g., *Trichophyton rubrum, T. mentagrophytes*), yeasts (most commonly *Candida albicans*), and nondermatophyte molds.[1] There are three major subtypes of onychomycosis: distal lateral subungual onychomycosis (DLSO), which is the most common, followed by white superficial onychomycosis and proximal subungual onychomycosis.[1]

Onychomycosis of the toenail typically appears as a yellow or brown thickening of the nail accompanied by crumbling or brittleness and debris under the nail. It may lead to permanent toenail deformity that can significantly affect quality of life due to physical discomfort or pain, self-consciousness about toenail appearance, and interference with wearing shoes, walking, or participating in activities. Onychomycosis may also increase the risk of bacterial infections such as cellulitis in patients with diabetes or other immunocompromised states.[7,8] The global prevalence of onychomycosis is estimated to be 5.5%.[3] In Canada, a multi-centre survey of 15,000 patients reported the prevalence of onychomycosis to be 6.5%.[2] In older adults aged 60 years or more, the prevalence is estimated to range from 14% to 48%, with the increased risk in the elderly attributed to diminished peripheral circulation, longer exposure to fungi, nail trauma, immune compromise, and slower nail growth.[4-6]

Accepted risk factors for onychomycosis include advanced age, swimming, occlusive footwear, tinea pedis, psoriasis, diabetes, immunodeficiency, genetic predisposition, obesity, smoking, and living with family members with onychomycosis.[1,3] Following treatment, the rate of recurrence of onychomycosis is reported to be between 11.9% to 33.7%.[9]

Standards of Therapy

According to the clinical expert consulted for this review, a clinical diagnosis of onychomycosis is often made based on physical appearance of the nail, and treatment is prescribed empirically. Nonetheless, due to the broad differential diagnosis of nail dystrophy, it is recommended that laboratory evidence to confirm the presence of fungi be obtained to exclude other nail disorders that may resemble onychomycosis.[13] Ideally, patients should be evaluated with a potassium hydroxide (KOH) preparation and a fungal culture to identify the causative organism.[13] While a KOH preparation provides almost immediate results and has high specificity for onychomycosis, the accuracy of this test is highly dependent on accurate sampling. The clinical expert advised that the specimen should be obtained from the most proximal affected subungual area of the nail. Treatment of onychomycosis is not mandatory in all patients and it is suggested that treatment should be reserved for patients with a history of cellulitis of the lower extremities, diabetes with additional risk factors for cellulitis (e.g., previous cellulitis, venous insufficiency, edema), patients experiencing discomfort or pain associated with affected nails, immunocompromised patients, or those who desire treatment for cosmetic reasons.[13] Currently available therapeutic options for onychomycosis in Canada include oral

antifungals such as terbinafine, itraconazole, and fluconazole (the latter used off-label), and topical agents such as ciclopirox (Table 2).[3,13] In general, the duration of treatment with oral agents ranges from 6 to 12 weeks, although treatment of up to six months (terbinafine) or 12 months (fluconazole) may be required.[14-16] Treatment with topical ciclopirox typically lasts 48 weeks and also requires frequent nail debridement by patients (weekly) and health care professionals (monthly) in addition to weekly removal of residual nail lacquer.[13,17] Selection of topical versus systemic therapy may be driven by clinical subtype, causative organism, disease severity, adverse events (AEs) associated with treatment, drug-drug interactions, cost, and ultimately, patient preference.[13] An advantage of topical therapy is the negligible risk of serious AEs and drug-drug interactions compared with systemic therapy. However, topical therapy may be less effective and typically requires longer duration of treatment (and is therefore subject to poor patient adherence) compared with systemic therapy.[13] It has been suggested that systemic agents be used for moderate (20% to 60% nail-plate involvement) to severe (> 60% nail-plate involvement) onychomycosis and topical agents reserved for mild-to-moderate onychomycosis (≤ 60% nail-plate involvement) or patients for whom oral agents are contraindicated.[3]

Drug

Efinaconazole is a triazole antifungal agent that inhibits fungal lanosterol 14 alpha-demethylase, which is involved in ergosterol biosynthesis.[10] The accumulation of 14 alpha-methyl sterols and subsequent loss of ergosterol in the fungi cell wall may be responsible for the fungistatic and fungicidal activity of efinaconazole.[10] Efinaconazole has been shown in vitro to be substantially adsorbed to keratin, but keratin binding is weak, and low keratin affinity is expected to result in increased availability of efinaconazole to the nail infection site.[10]

Efinaconazole (Jublia) is indicated for the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *T. rubrum* and *T. mentagrophytes* in immunocompetent adult patients.[10] It is available as a 10% w/w topical solution in a plastic squeeze bottle with a built-in flow-through brush applicator. The recommended dosage is one drop applied to the affected toenail(s) with a second drop applied onto the affected big toenail(s) once daily (preferably at bedtime).[10]

Table 2: Key Characteristics of Antifungal Drugs Used for the Treatment of Onychomycosis

	Efinaconazole	Ciclopirox	Terbinafine	Itraconazole	Fluconazole[a]
Mechanism of action	Triazole antifungal; inhibits fungal lanosterol 14 alpha-demethylase involved in ergosterol biosynthesis	Suggested: Chelation of polyvalent cations (Fe^{+3} or Al^{+3}) resulting in inhibition of metal-dependent enzymes responsible for degradation of peroxides in fungal cell	Allylamine with broad antifungal activity; at low concentrations is fungicidal against dermatophytes, molds, and certain dimorphic fungi	Inhibitor of CYP450-dependent synthesis of ergosterol and fungitoxic to dermatophytes and yeast	Fungistatic, highly selective inhibitor of fungal CYP450 sterol C-14 alpha-demethylation
Indication[b]	Mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *T. mentagrophytes* in immunocompetent patients	Immunocompetent patients with mild-to-moderate onychomycosis (due to *T. rubrum*) of fingernails and toenails without lunula involvement	Onychomycosis caused by dermatophyte fungi	Onychomycosis in normal, predisposed, or immunocompromised patients	Oropharyngeal and esophageal candidiasis, serious systemic candidal infections, and cryptococcal meningitis; prophylaxis of candidiasis in patients undergoing bone marrow transplantation
Route of administration	Topical	Topical	Oral	Oral	Oral
Recommended dose and duration of treatment	One drop applied onto the affected toenail(s) once daily; a second drop should be applied to the affected big toenail(s) Duration: 48 weeks	Applied once daily to all affected nails as part of a comprehensive nail-management program Duration: 48 weeks[13]	250 mg once daily Duration: 6 weeks to 3 months, although some patients may require 6 months if poor nail growth	200 mg twice daily x 7 days. Toenail infections: 3 x 1-week courses; each course separated by 3-week drug-free interval Duration: 9 to 12 weeks	Toenail infections: 150 mg once weekly Duration: 6 to 12 months[15,16]
Serious side effects and safety Issues	Application-site irritation, flammable	Concomitant use with systemic antifungals not recommended	Contraindicated in hepatic disease, renal impairment; skin, ophthalmologic, immune, hematologic, and sensory disturbances	Contraindicated in ventricular dysfunction (CHF); rare cases of serious hepatic toxicity	Co-administration with drugs that prolong the QT interval or are metabolized via CYP3A4; use with caution in patients with liver or renal dysfunction
Other	Non-inhibitor and non- inducer of CYP450 isoenzymes		CYP2D6 inhibitor; topical terbinafine is not effective in onychomycosis	Potent CYP3A4 inhibitor	Moderate inhibitor of CYP2C9 and CYP3A4 and strong inhibitor of CYP2C19

Al = aluminum; CHF = congestive heart failure; Fe = iron.

[a] Fluconazole is not indicated for the treatment of onychomycosis in Canada but may be used off-label as an alternate treatment.[21]

[b] Health Canada–approved indication.

Sources: Jublia product monograph,[10] Ciclopirox product monograph,[17] Lamisil product monograph,[18] Sporanox product monograph,[19] and Diflucan product monograph.[20]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of efinaconazole 10% w/w topical solution for the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *T. rubrum* and *T. mentagrophytes* in immunocompetent adult patients.

Methods

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

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Immunocompetent adults with mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *T. mentagrophytes* Subgroups: • age • diabetic vs. non-diabetic • severity (e.g., percentage of clinical nail involvement at baseline, number of involved nails) • response to prior treatment
Intervention	Efinaconazole 10% w/w topical solution applied once daily (i.e., one drop should be applied to the affected toenail[s] and a second drop should be applied onto the affected big toenail[s])
Comparators	The following treatments with or without concomitant nail debridement: **Topical:** • Ciclopirox **Oral:** • Terbinafine • Itraconazole • Fluconazole **Other:** • Placebo • Vehicle • No treatment
Outcomes	**Efficacy outcomes:** • Health-related quality of life[a] • Cure (clinical and/or mycological) • Pain[a] • Recurrence • Nail parameters (e.g., nail loss, unaffected new nail growth)[a] • Secondary complications (e.g., bacterial infection, tinea pedis, ulceration, amputation)[a] **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms (e.g., application-site dermatitis, vesicles, tinea pedis)
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse event.

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

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

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) 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 Jublia/efinaconazole.

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

The initial search was completed on September 7, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on January 16, 2019. Regular search updates were performed on databases that do not provide alert services.

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

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

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two 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 and excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

Two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

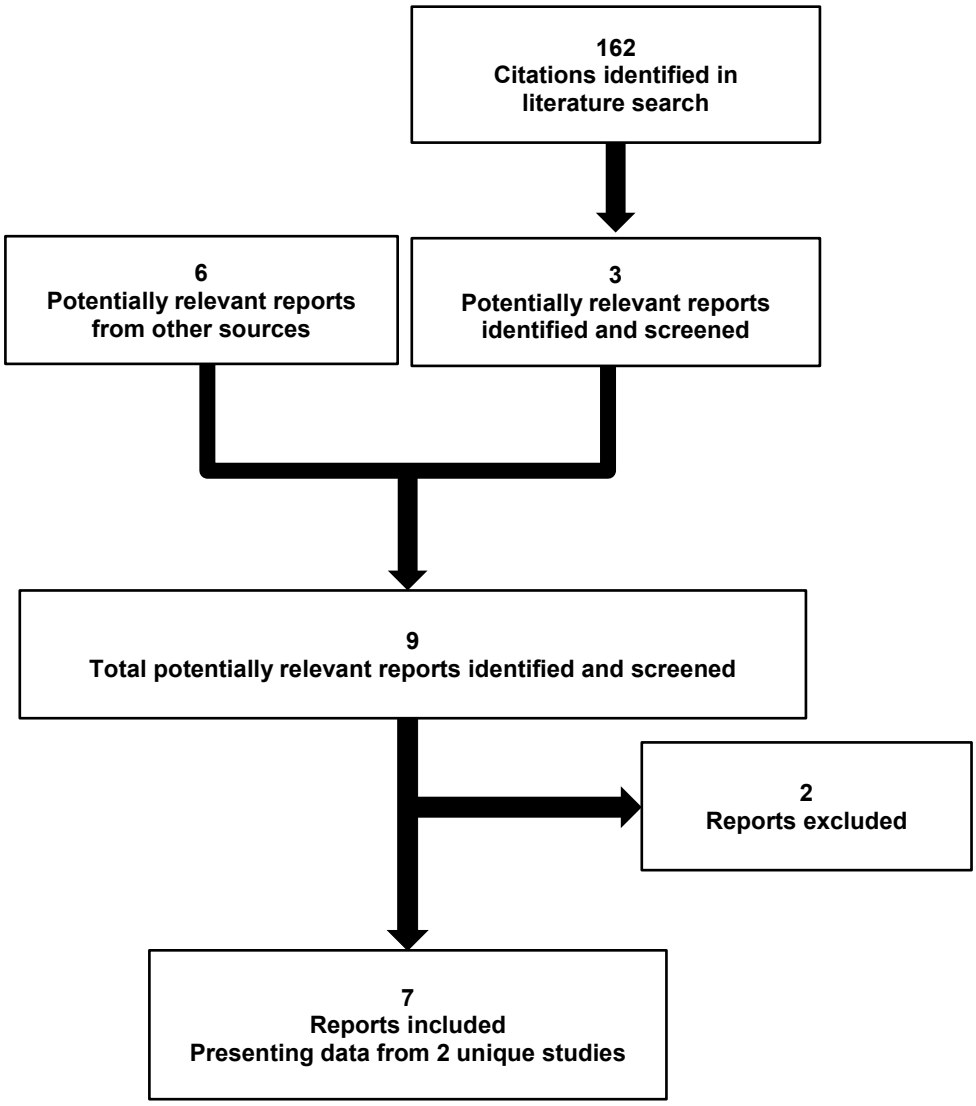


Table 4: Details of Included Studies

		Study P3-01	Study P3-02
Designs & Populations	**Study design**	DB, MC, PG, phase III, vehicle-controlled RCT	
	Locations	74 sites: Canada (7), US (34) and Japan (33)	44 sites: Canada (8); US (36)
	Randomized (N)	870	785
	Inclusion criteria	Adult patients with clinical diagnosis of mild-to-moderate DLSO affecting at least one great toenail. Mild-to-moderate DLSO was defined as 20% to 50% clinical involvement of the target toenail without dermatophytomas or matrix [lunula] involvement. The target toenail had to have an unaffected length ≥ 3 mm, thickness ≤ 3 mm, evidence of toenail growth, positive KOH examination and culture of dermatophyte or mixed dermatophyte/*Candida* ≤ 42 days before baseline.	
	Exclusion criteria	History of immunosuppression and/or clinical signs indicative of possible immunosuppression, HIV infection, uncontrolled DM, presence of toenail infection other than dermatophytes, severe moccasin tinea pedis or other disease/condition that could interfere with the evaluation, and previous target toenail surgery.	
Drugs	**Intervention**	Efinaconazole 10% w/w topical solution self-applied once daily without debridement; 1 to 2 drops per toenail for 48 weeks	
	Comparator(s)	Vehicle once daily without debridement; 1 to 2 drops per toenail for 48 weeks	
Duration	**Phase**		
	Run-in	NA	
	Double-blind	48 weeks	
	Follow-up	4 weeks	
Outcomes	**Primary end point**	Complete cure at week 52[a]	
	Other end points	• Treatment success or clinical efficacy at week 52[b] • Mycologic cure at week 52[c] • Unaffected new toenail growth from baseline at week 52 • Complete or almost-complete cure at week 52[d]	
Notes	**Publications**	Elewski et al. (2013)[22]	

DB = double-blind; DLSO = distal lateral subungual onychomycosis; DM = diabetes mellitus; KOH = potassium hydroxide; MC = multi-centre; NA = not applicable; PG = parallel-group; RCT = randomized controlled trial; SAP = statistical analysis plan.

Note: Six additional reports were included: Manufacturer's submission,[23] P3-01 Clinical Study Report,[11] P3-02 Clinical Study Report,[12] Health Canada Reviewer's Report,[24] FDA Medical Review,[25] and FDA Statistical Review.[26]

[a] A complete cure was defined as both 0% clinical involvement of the target toenail and mycologic cure (i.e., a negative KOH examination and a negative fungal culture of the target toenail sample).

[b] Treatment success or clinical efficacy was defined as < 10% affected toenail area involvement and was a secondary outcome in version 1 of the statistical analysis plan (SAP).

[c] A mycologic cure was defined as a negative KOH examination and a negative fungal culture of the target toenail sample.

[d] A complete or almost-complete cure was defined as an affected target toenail area no more than 5% and mycologic cure and was a secondary outcome in version 2 of the SAP.

Sources: Study P3-01 Clinical Study Report,[11] Study P3-02 Clinical Study Report,[12] and Elewski et al. (2013).[22]

Included Studies

Description of Studies

Two phase III, multi-centre, randomized, double-blind, parallel-group, vehicle-controlled superiority trials were included in the systematic review: Study P3-01 (N = 870) and Study P3-02 (N = 785). Both trials were identified as pivotal by the manufacturer. The trials were identical in design and evaluated the safety and efficacy of a once-daily topical application (one to two drops per toenail) of efinaconazole 10% topical solution, relative to vehicle alone, for the treatment of mild-to-moderate onychomycosis of the toenails (Table 4). Although both trials enrolled patients from Canada and the US, Study P3-01 also enrolled patients from Japan.

At the screening visit (up to day −42), patients underwent a visual examination of their feet to ascertain the presence of onychomycosis in at least one great toenail and rule out the presence of severe moccasin tinea pedis. The percentage involvement of the affected toenail(s) was recorded and a direct microscopic examination for hyphae associated with dermatophytes was performed using KOH on toenail scrapings collected from the affected great toenail(s). Those patients with KOH-positive toenail samples provided an additional sample from the affected great toenail(s) for mycological culture and KOH examination conducted at a central mycology laboratory for confirmation.

At the baseline visit (day 0), the target great toenail was identified and recorded for each subject, photographs were obtained, and a transverse notch was inscribed in the target toenail adjacent to the proximal toenail fold as a marker for measuring toenail growth at subsequent visits. Assessments of all non-target toenails on both feet were also conducted for the purpose of assessing the presence or absence of onychomycosis on each toenail. Patients whose native language was English also completed the onychomycosis quality-of-life questionnaire (OnyCOE-t) at the baseline visit.

Eligible patients (with both a positive KOH test result and a positive dermatophyte culture) were randomized (3:1) to either efinaconazole or the vehicle using an interactive Web/voice response system. Randomization was not stratified by any baseline factors. To maintain double-blinding, study drugs were provided for each patient in a kit containing identical masked bottles with a randomization number, which was assigned in sequential order by a computer-generated randomization schedule. Access to the randomization schedule was kept restricted until after the database was locked and the study was unblinded.

The trials consisted of a 48-week, double-blind, active-treatment period, followed by a four-week, treatment-free follow-up period (52 weeks total duration). Patients were assessed for efficacy and safety at baseline and at 12-week intervals post-baseline (i.e., 12, 24, 36, and 48 weeks), with a final follow-up visit at 52 weeks. Toenail growth was measured and repeat samples of the target toenail were collected at all study visits for KOH examination and mycological culture by the central mycology laboratory. Patients whose native language was English also completed the OnyCOE-t at weeks 24 and 52.

Populations

Inclusion and Exclusion Criteria

Eligible patients included adults (18 to 70 years of age inclusive) with a diagnosis of mild-to-moderate DLSO affecting at least one great toenail (i.e., the target toenail), with no more

than six toenails and no fingernails involved. DLSO was defined as 20% to 50% clinical involvement of the target toenail, without dermatophytomas or matrix (lunula) involvement. The target toenail must have had an uninfected length of at least 3 mm from the proximal nailfold, a thickness no more than 3 mm, evidence of toenail growth, a positive microscopic examination with KOH for dermatophyte hyphae and a positive dermatophyte culture or mixed dermatophyte/*Candida* culture no more than 42 days before the baseline visit. If both great toenails met the criteria, the great toenail with the highest percentage involvement at baseline was selected as the target toenail for all subsequent evaluations. Key exclusion criteria included history of immunosuppression and/or clinical signs of possible immunosuppression, known HIV infection, uncontrolled diabetes mellitus, presence of toenail infection other than dermatophytes, severe moccasin tinea pedis at screening or baseline, any disease or condition that might have caused toenail abnormalities or interfered with the evaluation, and previous toenail surgery. Patients receiving concomitant drugs that inhibit CYP3A4 were not excluded. Of note, three patients did not have positive fungal cultures (an inclusion criteria violation), but were randomized and dispensed study drug.

Baseline Characteristics

Baseline characteristics were generally balanced between treatment groups in both trials and were similar across the two trials (Table 5). Patients enrolled in Study P3-01 were slightly older, as the mean (standard deviation) age was 52.3 (11.1) years compared with 50.6 (11.6) years in Study P3-02. In both trials, patients were predominantly male (> 73%) and white (> 64% in Study P3-01 and > 81% in Study P3-02). In Study P3-01, due to the inclusion of 33 study sites from Japan, 29.0% of patients were Asian compared with 2.2% Asian patients in Study P3-02. The mean (standard deviation) area of target toenail involvement was 36.7 (10.4)% in Study P3-01 and 36.3 (10.7)% in Study P3-02. The mean number of affected non-target toenails was almost identical in the two trials: 2.8 (1.7) and 2.8 (1.6), respectively. The majority of patients had screening cultures of *T. rubrum* (> 89%) and *T. mentagrophytes* (> 4%).

Table 5: Summary of Baseline Characteristics

Baseline Characteristic	Study P3-01		Study P3-02	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
n	656	214	580	201
Age, years **Mean (SD)** **Median (min to max)**	 52.4 (10.9) 54.0 (20.0 to 71.0)	 51.9 (11.9) 54.0 (18.0 to 70.0)	 50.6 (11.9) 52.0 (18.0 to 71.0)	 50.7 (11.0) 51.0 (18.0 to 70.0)
Male, n (%)	489 (74.5)	158 (73.8)	464 (80.0)	164 (81.6)
Ethnicity, n (%) **Hispanic/Latino** **Not Hispanic/Latino**	 71 (10.8) 585 (89.2)	 31 (14.5) 183 (85.5)	 122 (21.1) 457 (78.9)	 46 (22.9) 155 (77.1)
Race, n (%) **White** **Black or African-American** **American-Indian/Alaskan Native** **Asian** **Native Hawaiian/Pacific Islander** **Other**	 425 (64.8) 36 (5.5) 1 (0.2) 189 (28.8) 1 (0.2) 4 (0.6)	 140 (65.4) 7 (3.3) 1 (0.5) 63 (29.4) 1 (0.5) 2 (0.9)	 522 (90.0) 34 (5.9) 2 (0.3) 11 (1.9) 1 (0.2) 10 (1.7)	 164 (81.6) 21 (10.4) 1 (0.5) 6 (3.0) 0 (0) 9 (4.5)
Patients with diabetes, n (%) **Type 1**	[redacted]	[redacted]	[redacted]	[redacted]

Baseline Characteristic	Study P3-01		Study P3-02	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
Type 2 Both types[a]	[redacted]	[redacted]	[redacted]	[redacted]
Per cent of affected target toenail				
Mean (SD)	36.7 (10.4)	36.8 (10.6)	36.2 (10.7)	36.7 (10.5)
Median (min to max)	40.0 (20.0 to 50.0)	40.0 (20.0 to 50.0)	35.0 (20.0 to 60.0)	40.0 (20.0 to 50.0)
Number of affected non-target toenails				
Mean (SD)	2.8 (1.7)	2.8 (1.7)	2.7 (1.6)	2.8 (1.7)
Median (min to max)	3.0 (0.0 to 5.0)	3.0 (0.0 to 5.0)	3.0 (0.0 to 5.0)	3.0 (0.0 to 5.0)
Screening culture, n (%)				
Trichophyton rubrum	604 (92)	191 (89)	540 (93)	193 (96)
T. mentagrophytes	47 (7)	22 (10)	33 (6)	8 (4)
Epidermophyton floccosum	5 (1)	0 (0)	4 (1)	0 (0)
T. tonsurans	0 (0)	0 (0)	1 (< 1)	0 (0)
No dermatophyte	0 (0)	1 (< 1)[b]	2 (< 1)[b]	0 (0)

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

Sources: Study P3-01 Clinical Study Report,[11] Study P3-02 Clinical Study Report,[12] Elewski et al., 2013,[22] and FDA statistical review.[26]

[redacted]

[b] Three patients did not have positive fungal cultures but were randomized and dispensed the study drug.

Interventions

Patients self-applied the first dose of their assigned study drug at the investigational centre under the supervision of designated study personnel. Patients were provided with verbal and written instructions for treatment application as well as diaries with instructions to complete a record of all applications and note any missed applications of the study treatments. Thereafter patients self-applied their assigned treatment (efinaconazole or matched vehicle) to the affected toenail(s) once daily at bedtime for 48 weeks without debridement. The treatment was applied to the clean, dry nail-plate surface, lateral and proximal nailfolds, hyponychium, and undersurface of the nail plate of the target toenails. Treatment was also to be applied to each of the other affected toenails in a similar manner using approximately one or two drops of study drug per nail. Patients were instructed to wait at least 10 minutes after showering or bathing to apply the study drug and to allow the solution to dry thoroughly before allowing the affected areas to come into contact with bed sheets, socks, or other clothing.

Patients were instructed to continue applying the study drug to the target toenail for the entire 48-week treatment period, even if the disease cleared and no affected area was observed on the target toenail. If new toenails became infected during the treatment period, the patient was instructed to start treating the additional affected toenail(s).

Patients were permitted to continue to use foot-care products (medicinal and non-medicinal) that had been used on or within 30 days prior to the screening visit that were not otherwise excluded. Concurrent use of the following medications or preparations were prohibited during the study: toenail polish; cosmetic toenail products or topical prescription or over-the-counter antifungal therapy for tinea pedis or onychomycosis; other topical prescription or over-the-counter medications to the feet or nails (with the exception of bland emollients); topical corticosteroids for the feet; systemic antifungal therapy; more than one two-week course of oral corticosteroid therapy or one intramuscular, intravenous, or intra-articular injection of corticosteroids (although nasal steroid sprays and steroid inhalers were permitted if use was stable and not expected to change during the study); and systemic

immunosuppressive agents. Although patients were generally prohibited from using concomitant therapies that could have affected the toenails or interfered with assessment of study outcomes, patients with inter-digital tinea pedis could apply an investigator-approved topical antifungal therapy.

New study bottles were dispensed as needed at every post-baseline visit through week 44. Used study drug bottles were collected and weighed and all new study bottles were weighed prior to dispensing. The study drug administration diary was also collected and/or dispensed at each post-baseline visit through week 48.

Outcomes

The primary efficacy outcome in both trials was the proportion of patients who achieved complete cure at week 52. Complete cure was defined as 0% clinical involvement of the target toenail and mycologic cure (negative KOH examination and negative fungal culture of the target toenail sample). Toenail specimens were obtained by clipping the toenail to the point of attachment and obtaining any crumbling subungual debris from under the distal edge of the target toenail using a disposable curette. All target toenail clippings and distal subungual debris were discarded. Only the soft toenail-bed keratin beneath the clipped toenail edge was used for both KOH examination and fungal culture. The collection of specimens in this manner was intended to minimize toenail specimen contamination and to maximize dermatophyte pathogen isolation. Where possible, the same investigator/evaluator performed the clinical assessments for each patient for the duration of the study and the clinical investigators received identical training within and across investigational centres.

The definitions of the secondary outcomes were:

- Treatment success or clinical efficacy was defined as an affected target toenail area of < 10% (when used as a secondary outcome in version 1 of the statistical analysis plan [SAP]) or as an affected target toenail area of ≤ 10% (when used as a supportive efficacy outcome in version 2 of the SAP).
- Complete or almost-complete cure was defined as an area of no more than 5% of the affected target toenail in addition to a negative KOH examination and a negative fungal culture of the target toenail sample.
- Mycologic cure was defined as a negative KOH examination and a negative fungal culture of the target toenail sample.
- Unaffected new toenail growth was defined as the change from baseline in the healthy (unaffected) target toenail measurement for the target toenail.

The involvement of the target toenail was estimated as the percentage of the toenail and toenail bed that was infected on the target toe (the distal margin of measurement was the distal groove after the toenail was trimmed). The target toenail growth was measured by inscribing a long transverse notch in the toenail adjacent to the proximal toenail fold at the baseline visit and subsequently measuring toenail growth between the notch and the proximal toenail fold from that time forward. If the toenail grew out completely or was clipped away during the study, the toenail was re-notched in the toenail adjacent to the proximal toenail fold. Where a new notch had been inscribed, the adjusted new toenail growth was calculated as the length of new toenail at visit plus the sum of all previous toenail growth measurements prior to the new inscribed notch. The length of the unaffected/healthy portion of the target toenail was defined as the distance between the

proximal toenail fold and a transverse line on the healthy part of the toenail immediately proximal to the infection (i.e., the onychomycotic border). It has been suggested that a 40% improvement in nail involvement is clinically meaningful as it represents a one-grade improvement in the condition of the diseased nail (i.e., from moderate to mild disease). However, it does not appear that this threshold value has been validated.[27]

Unaffected toenail growth was computed by subtracting the length of the unaffected part of the target toenail at baseline from the measurement of the unaffected toenail length obtained at any post-baseline visit (e.g., if the distance between the proximal toenail fold and onychomycotic border was 8 mm at baseline and 10 mm at day 84, then the unaffected target toenail growth on day 84 was 2 mm). In cases where the target toenail became clear of onychomycosis, unaffected toenail growth was computed by adding the unaffected toenail growth at the last measurement to the toenail growth (calculated with notch) that occurred since the last measurement. Growth after the toenail cleared was computed by subtracting the toenail growth prior to the toenail becoming clear from the toenail growth.

An assessment of both feet was performed for the purpose of assessing the presence or absence of onychomycosis in all non-target toenails at baseline, weeks 12, 24, 36, 48, and 52.

Supportive efficacy outcomes in both versions of the SAP included the target toenail growth at each study visit, the change from baseline in the number of affected non-target toenails, and the change from baseline at week 24 and week 52 in the OnyCOE-t assessments. The OnyCOE-t is a disease-specific health-related quality of life (HRQoL) measure comprising 33 items within seven individual scales (i.e., symptom frequency, symptom bothersomeness, physical activities problems, appearance problems, overall problem, stigma, and treatment satisfaction) as detailed in Appendix 5. All items in the OnyCOE-t are transformed to a 1-to-100 scale, with higher scores representing better function; scale scores are reported individually and there is no overall score. Estimation of the overall minimal clinically important difference (MCID) within individual scales has been based on various clinical assessments of nail clearing (i.e., 12.5% or 25% differences in nail clearing or at least 5 mm of new nail growth), resulting in overall MCID estimates across scales from 7.3 (based on 12.5% nail clearing) to 16.6 points (based on at least 5 mm of new nail growth).

In version 2 of the SAP, two additional supportive efficacy outcomes were added (clear-nail rate and almost-clear-nail rate) and treatment success or clinical efficacy was changed from a secondary efficacy outcome to a supportive efficacy outcome with a change in definition. According to version 2 of the SAP, the additional supportive efficacy outcomes defined treatment success or clinical efficacy as ≤ 10% target toenail involvement, clear nail as an affected target toenail area of 0%, and almost-clear nail as an affected target toenail area of no more than 5%.

Safety outcomes were derived from ongoing monitoring and recording of AEs at baseline and each study visit to week 52, scores for localized skin reactions, clinical laboratory assessments, vital sign measurements, and electrocardiogram readings (for patients in Canada and the US only). Localized skin reactions (redness, swelling, burning, itching, and vesiculation) were reviewed with patients at each post-baseline visit to week 48. The presence or absence of burning, itching, and vesiculation was reported as “yes” or “no.” The worst instances of redness and swelling since the previous study visit were reported using a four-point scale for which 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Statistical Analysis

Sample Size Calculations

For both included trials, sample size calculations were based on power calculations computed from the results of complete cure obtained in a phase II study (DPSI-IDP-108-P2-01). In this study, at the 30-day follow-up visit after 36 weeks of treatment, the complete cure rate was 25.6% (efinaconazole) and 9.1% (vehicle) using the intention-to-treat (ITT) analysis set. Using a two-sided test at alpha = 0.05, a total of 300 and 100 patients in the efinaconazole and vehicle groups, respectively, was expected to provide 95% power for detecting a similar statistically significant difference between groups. It was expected that the estimates for complete cure after 48 weeks of treatment would show an even larger difference, and the power calculation was therefore considered conservative. To ensure a sufficient number of patients were exposed to the active drug for safety purposes, it was proposed that 600 and 200 patients be included in the efinaconazole and vehicle groups, respectively, in each trial.

Statistical Analysis Plans

Two versions of the SAP that were applicable to both trials were approved prior to database lock. The primary outcome was the same in both versions, although the secondary and supportive efficacy outcomes and multiplicity adjustment differed depending on the version of the SAP applied. In version 2, a new secondary outcome of complete or almost-complete cure was added and was tested prior to unaffected toenail growth, which was tested prior to mycologic cure. Additional supportive efficacy outcomes were also added: clear-nail rate, almost-clear-nail rate, and treatment success or clinical efficacy, the latter being a secondary outcome in version 1 of the SAP, although the definition was modified to include an unaffected target toenail area of ≤ 10%, rather than an area < 10%.

According to the clinical study reports,[11,12] the reason for version 2 of the SAP was [redacted]

According to both the FDA statistical review[26] and the Health Canada Reviewer's report,[24] version 1 of the SAP was considered the main analysis for the secondary outcomes and version 2 of the SAP was considered supportive only. In the FDA statistical review it was noted that, because all proposed secondary end points from either version of the SAP had *P* values of < 0.001, analyses from either version of the SAP would lead to the same conclusions of efficacy.[26] In the Health Canada Reviewer's report, it was stated that a consultation with the Biostatistics Division was requested and that subsequent to this, the

Division had no statistical concerns about the two versions of the SAP as the change did not result in any difference, as far as decision-making is concerned.[24]

Primary Outcome

For the primary outcome, differences between treatment groups at week 52 were analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by analysis centre in the ITT data set in Study P3-01 or the modified intention-to-treat (mITT) data set in Study P3-02. An analysis centre differs from an investigational centre and was identified as such primarily for the purpose of pooling the data from the two trials. The trials were intended to be conducted so that each investigational centre enrolled a minimum of nine patients into the efinaconazole group and a minimum of three patients into the vehicle group. In the event that the minimum was not enrolled in either group at an investigational centre, data from the lowest enrolling investigational centre were combined with data from the highest enrolling investigational centre to reach the desired minimum sample size per treatment group. If there was a need to further combine data, then data from the investigational centre with the second-lowest enrolment were combined with data from the centre with the second-highest enrolment, and so on. The process of combining data resulted in redefining groups of investigators for statistical analyses and these combined groups were referred to as analysis centres in all statistical analyses where a factor of investigator or investigational centre was involved. The consistency of treatment response was investigated across the analysis centres subsequent to combining the data using the Breslow–Day test for homogeneity. If the Breslow–Day test was significant at 0.10, sensitivity analyses were conducted to assess the impact of extreme centres. The *P* values from the Breslow–Day test for homogeneity were 0.935 (Study P3-01) and 0.774 (Study P3-02); neither test identified significant heterogeneity.[26] The results of the pooled analyses of the data are reported in Table 16.

Secondary Outcomes

Secondary outcomes were all assessed at week 52 and differences between groups in treatment success/clinical efficacy rate, complete or almost-complete cure rate, and mycologic cure were analyzed using a CMH test stratified by analysis centre. Unaffected new toenail growth was analyzed using a two-way analysis of variance with factors of treatment group and analysis centre.

Exploratory Outcomes

Supportive efficacy end points, which included target toenail growth at each study visit, change from baseline in number of affected non-target toenails, and change from baseline to weeks 24 and 52 in the OnyCOE-t assessments, as well as clear-nail rate, almost-clear-nail rate, and treatment success or clinical efficacy rate (as per SAP version 2) were summarized using only descriptive statistics. No statistical comparisons were conducted between treatment groups.

Multiplicity Adjustment

To adjust for multiplicity and control for type I error, statistical testing for the secondary outcomes was conducted in a sequential manner. However, as previously described, the secondary outcomes and order of testing differed according to the version of the SAP. According to the statistical hierarchy, the subsequent secondary outcome was only

considered statistically significant if the preceding secondary outcome was statistically significant at $P < 0.05$. The order of testing by version of the SAP was as follows:

SAP version 1:

1. Treatment success or clinical efficacy rate
2. Mycologic cure
3. Unaffected toenail growth

SAP version 2:

1. Complete or almost-complete cure
2. Unaffected toenail growth
3. Mycologic cure

Imputation

Missing efficacy data were imputed using the last observation carried forward (LOCF) method. No imputations for safety data were performed.

Sensitivity Analyses

Two sensitivity analyses of the primary outcome were performed to evaluate the potential bias due to the handling of dropouts and/or missing data as the LOCF method was used to impute missing efficacy data in the primary efficacy analysis. In these analyses, patients with missing week-52 evaluations had their data imputed as “failures” and in the second case as “successes.” The outcomes of the two sensitivity analyses were reviewed and compared qualitatively with the outcomes of the primary efficacy analysis.

Subgroup Analyses

Pre-specified subgroup analyses of the complete-cure rate at week 52 were conducted by gender, age, ethnicity, race, and the percentage involvement of the target toenail at baseline. The analyses were performed using the ITT analysis set. Within the subgroups, age was dichotomized to less than the median age and greater than or equal to the median age, while the involvement of the target toenail was dichotomized to less than the median percentage and greater than or equal to the median percentage. All subgroup analyses were reported using descriptive statistics by treatment group and subgroup and no formal interaction tests or adjustment for multiple comparisons was conducted.

Post Hoc Analyses

Various post hoc analyses of the included trials were available in the published literature. Post hoc analyses of relevance to this CDR review are reported in Table 16 (e.g., overall pooled analysis, subgroup analyses of pooled data by severity [≤ 33% involvement and > 33% involvement], and age [< 65 years and ≥ 65 years]). In general, analyses were conducted in the ITT population with missing data imputed using the LOCF technique and statistical comparisons using CMH tests stratified by analysis centre and trial. As these were post hoc analyses and not adjusted for multiple comparisons, the results should be considered exploratory.

Analysis Populations

Three analysis sets were defined in the included trials: ITT, per-protocol (PP), and safety analysis sets. Efficacy analyses were performed primarily with the ITT (or mITT) analysis set and secondarily with the PP analysis set, whereas all safety analyses were conducted with the safety analysis set.

In Study P3-01, the ITT analysis set included all randomized patients who were dispensed the study drug. In Study P3-02, four patients were randomized in error and were not dispensed the study drug. As these patients were excluded from the data set, it is considered to be a mITT analysis set.

The PP analysis set included all subjects in the safety population who completed week 52 without noteworthy study protocol violations. A total of 164 patients (Study P3-01) and 166 patients (Study P3-02) were excluded from the PP analysis set due to important protocol deviations, with the most common in both trials being missing the week 52 visit.

The safety analysis set included all patients who were randomized to the study drug, received at least one confirmed application of the study drug, and had at least one post-baseline assessment. In Study P3-01, four patients were excluded from the safety analysis set due to having no post-baseline assessment, and in Study P3-02, 11 patients were excluded, seven of whom had no post-baseline assessments and four who had no documented use of study drug (i.e., the same four patients who were randomized in error and did not receive any study drug) (Table 6).

Patient Disposition

In Study P3-01, a similar proportion of patients in the efinaconazole (12.3%) and vehicle (12.6%) groups prematurely discontinued the trial, whereas in Study P3-02, a slightly higher proportion of patients discontinued in the vehicle group (20.8%) compared with the efinaconazole group (14.6%) (Table 6). The most frequent reasons for discontinuation were patient request and loss-to-follow-up, with rates numerically higher in the vehicle groups compared with the efinaconazole groups in both trials. Discontinuations due to AEs were higher in the efinaconazole groups (3.2% and 1.9%) compared with the vehicle groups (0.5% and 0%) in each trial and were primarily due to application-site AEs associated with efinaconazole.

Table 6: Patient Disposition

Baseline Characteristic	Study P3-01		Study P3-02	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
Screened, N	NR		NR	
Randomized, N (%)	656	214	583	202
Discontinued, N (%)	81 (12.3)	27 (12.6)	85 (14.6)	42 (20.8)
Adverse event	21 (3.2)	1 (0.5)	11 (1.9)	0 (0)
Patient request	31 (4.7)	12 (5.6)	36 (6.2)	19 (9.4)
Protocol violation	0 (0)	1 (0.5)	3 (0.5)	3 (1.5)
Lost to follow-up	20 (3.0)	11 (5.1)	29 (5.0)	18 (8.9)
Pregnancy	0 (0)	0 (0)	0 (0)	1 (0.5)
Worsening condition	0 (0)	0 (0)	1 (0.2)	0 (0)
Other	9 (1.4)	2 (0.9)	5 (0.9)	1 (0.5)
ITT or mITT, N[a]	656	214	580[d]	201[d]

Baseline Characteristic	Study P3-01		Study P3-02	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
PP, N[b]	533	173	473	146
Safety, N[c]	653	213	574	200

ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol.

[a] Study P3-01 is an ITT analysis set and Study P3-02 is a mITT analysis set.

[b] In Study P3-01 (n = 164) and in Study P3-02 (n = 166) patients were excluded from the PP analysis set mainly due to having missed the week 52 visit (41.5% and 57.2% of excluded patients, respectively).

[c] In Study P3-01 (n = 4) patients were excluded from the safety analysis due to no post-baseline assessments and in Study P3-02 (n = 11) patients were excluded from the safety analysis due to no post-baseline assessment in seven patients (63.6%) and no documented use of study drug in four patients (36.4%) who were the same four who were randomized in error.

[d] In Study P3-02 (n = 4) patients were randomized in error and were never dispensed study drug.

Sources: Study P3-01 Clinical Study Report,[11] Study P3-02 Clinical Study Report,[12] and Elewski et al. (2013).[22]

Exposure to Study Treatments

The planned number of study drug applications was 336 and in both trials the mean number of applications was similar (i.e., 315 and 318 for the efinaconazole groups and 317 and 310 for the vehicle groups) (Table 7). The mean amount of study drug used was also similar, approximately 49 g in the efinaconazole groups and 49 g to 53 g in the vehicle groups.

Patients were considered non-compliant if they missed more than [redacted]. Using this definition, more than [redacted] of patients were considered compliant in the efinaconazole groups and more than [redacted] of patients were compliant in the vehicle control groups for patients with available data.

Table 7: Exposure to Study Drugs (Safety Population)

Baseline Characteristic	Study P3-01		Study P3-02	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
n	653	213	574	200
Number of applications **n** **Mean (SD)** **Median (min to max)**	 633 314.5 (51.2) [redacted](2.0 to 357.0)	 204 317.1 (52.0) [redacted](1.0 to 378.0)	 547 317.7 (54.6) [redacted](1.0 to 365.0)	 182 310.0 (68.4) [redacted](1.0 to 351.0)
Amount of study drug used, g **n** **Mean (SD)** **Median (min to max)**	 576 49.3 (24.1) [redacted](0.5 to 150.5)	 189 53.2 (24.0) [redacted](6.2 to 119.6)	 493 49.4 (23.5) [redacted](0.4 to 104.5)	 164 49.0 (23.2) [redacted](0.3 to 121.5)
Compliant, n (%)[a,b] **Yes** **No** **Unknown**	[redacted]	[redacted]	[redacted]	[redacted]

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

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

[a] [redacted]

[b] [redacted]

Critical Appraisal

Internal Validity

- Baseline demographic and disease characteristics appeared to be balanced between treatment groups in both included trials. In Study P3-02, four patients were excluded from the efficacy analyses due to randomization error and did not receive any study drug. As a result, the study population comprises an mITT rather than a true ITT analysis set. Given that only four patients were excluded, it is unlikely to have affected the study results.
- Methods for random allocation (interactive voice/Web response) and allocation concealment (i.e., identical masked bottles with a unique randomization number) were appropriate. Blinding appeared to be successful as adherence rates for both the efinaconazole and vehicle groups were relatively high by study end, suggesting that vehicle-treated patients were unaware they were receiving the control treatment. Three patients without positive fungal culture were randomized and received study drug, which was an inclusion criteria violation.
- Both included trials used a statistical testing hierarchy to examine secondary outcomes in order to control for type I error. According to the statistical hierarchy, a secondary outcome was considered statistically significant only if the preceding secondary outcome was statistically significant at $P < 0.05$. The secondary outcomes and order of testing differed according to the version of the SAP that was used. According to the manufacturer, two versions of the SAP were approved prior to database lock. In the FDA statistical review, it was noted that the second version of the SAP was proposed after the trials were completed. The manufacturer maintained that the trials were still blinded at the time the second SAP was written. However, changing end points after the trials were completed raises concern that the type I error rate could be inflated.[26] Nonetheless, because all of the secondary outcomes had *P* values < 0.001 regardless of the version of SAP applied, both would result in the same conclusions of efficacy. As a result, neither Health Canada nor the FDA had a concern regarding the two versions of the SAP.[24,26]
- Pre-specified subgroup analyses of complete cure at week 52 that are of relevance to this CDR review were age (< 54 years or ≥ 54 years in Study P3-01 and < 52 years or ≥ 52 years in Study P3-02) and disease severity measured as percentage of affected target toenail area at baseline (< 40% or ≥ 40% in both trials). No formal interaction tests or adjustment for multiple comparisons were made for these analyses. Because subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was not the case for the included trials) and are often underpowered, these analyses should be considered exploratory. Various post hoc subgroup analyses of the included studies have been published and those that were considered relevant to this review were age (< 65 years or ≥ 65 years), severity (≤ 33% involvement or > 33% involvement) and diabetic patients versus non-diabetic patients as reported in Table 17 and Table 18. As these are all post hoc analyses and uncontrolled for multiple comparisons, the results should be considered exploratory.
- The LOCF method was used for imputation of missing data in both trials. The FDA statistical review noted that 84 (13%) and 90 (16%) efinaconazole-treated patients and 29 (14%) and 43 (21%) vehicle-treated patients in Study P3-01 and Study P3-02, respectively, did not have complete efficacy assessments at week 52 and so had at least one component of the complete cure outcome imputed for the primary analysis.[26] As detailed in Table 13, the manufacturer conducted sensitivity analyses to evaluate

potential bias due to the handling of dropouts and/or missing data such that patients with missing data had their data imputed as “failures” and, in the second case, as “successes.” The FDA reviewer commented that both sensitivity analyses treated all missing data in both treatment groups the same — either as failures or successes — instead of varying the estimated treatment effect.[26] As an additional post hoc sensitivity analysis, the FDA reviewer imputed 15% of the vehicle-treated patients with missing data as responders (approximately three times the rate observed in patients with complete data) and the statistical significance was maintained in both trials.[26] Still, as the true outcome distribution across patients with missing data is not known, the impact of missing data on the study results is difficult to determine.

- HRQoL was a key efficacy outcome identified in the CDR review protocol and was measured as the change from baseline to week 24 and week 52 by the OnyCOE-t. As detailed in Appendix 5, although there is some evidence of the validity and internal consistency reliability of the OnyCOE-t, it may be overly sensitive and show a response when no clinical change has occurred.[28,29] Furthermore, the overall MCID estimates across individual scales, which range from 7.3 to 16.6 points, are based on several measures of nail clearance (i.e., 12.5% or 25% difference in nail clearing and at least 5 mm of new clear nail growth) and it is not known if these differences would be perceived as meaningful changes by patients. There is also no overall aggregate score for the OnyCOE-t, which renders the overall MCID estimates reported by Potter et al.[28] confusing and difficult to apply to the study results. Furthermore, the OnyCOE-t was [redacted]. Lastly, the change from baseline in the OnyCOE-t assessments was a supportive efficacy outcome in the included trials, precluding any between-group statistical comparisons. Due to these limitations, no meaningful conclusions could be made regarding the impact of efinaconazole on HRQoL as measured by the OnyCOE-t.
- Dosing compliance was defined broadly in the included trials (i.e., patients were considered non-compliant if they missed [redacted] This broad definition could have resulted in an underestimate of the potential efficacy of efinaconazole.

External Validity

- Patients in the included trials represent typically healthy, immunocompetent adult patients with mild-to-moderate disease who would primarily seek treatment for cosmetic reasons. This is in contrast to the population most in need of treatment (e.g., immunocompromised or diabetic patients at risk of secondary infection, patients with pain or functional impairment due to dystrophic nails). In fact, patients with uncontrolled diabetes or who were immunocompromised were specifically excluded from the trials. In addition, as noted by the clinical expert consulted on this review, patients are not typically identified for treatment through the use of a positive KOH test and fungal culture in Canadian clinical practice as required by the inclusion criteria. As a result, the generalizability of the results of the included trials to patient populations in most need of treatment is potentially limited.
- The OnyCOE-t was [redacted]

[redacted].

- The high compliance rate [redacted] for a year-long therapy is not representative of typical clinical practice, according to the clinical expert. As a result, the efficacy results may have been exaggerated as they appear to be much higher than what would be expected with real-world use.
- Mycologic cure was a secondary outcome in the included trials. However, according to the clinical expert consulted on this review and others,[3] it may not be a reliable outcome due to its association with false-negative results and a high rate of sampling error. The clinical expert advised that clinicians are often unfamiliar with proper nail-sampling techniques or do not have the time to accurately obtain and prepare a nail sample — rarely is a nail sample taken at the end of treatment to confirm treatment success. The clinical expert also explained that in a clinical trial, mycologic cure alone is a misleading outcome because, while a positive fungal culture is typically necessary for inclusion into a trial, at the end of treatment, re-sampling to confirm treatment success is rarely performed. Rather, the clinical expert advised that the most robust outcome is a composite of both clinical and mycologic outcomes, as was the primary outcome in the included trials (clinical cure).
- According to the clinical expert, the duration of the trials (48-week treatment and follow-up to 52 weeks) should be sufficient to reliably assess the treatment effect. Nonetheless, it has been suggested that the primary outcome of complete cure rate (which is a regulatory standard) may have underestimated the clinical value of efinaconazole as toenails require up to 78 weeks to grow cleanly.[22] Furthermore, given the proportion of patients with treatment success or clinical efficacy (defined as ≤ 10% toenail involvement, which was a supportive efficacy outcome according to version 2 of the SAP), which was 40% to 45%, a substantial number of patients may have been heading toward a complete cure.[22] Whether continued improvement would have occurred with longer treatment or follow-up is unknown.
- Important data are lacking and not addressed by the included trials. There are no comparative data available for efinaconazole with another active antifungal treatment (topical or oral therapy). There are also no data to inform the possible combination use of efinaconazole with oral antifungal therapy. Of key importance is that there are no data available for the recurrence of onychomycosis following successful treatment with efinaconazole. Onychomycosis is a chronic, recurring fungal infection and recurrence rates of 11.9% (after terbinafine treatment) and 35.7% (after itraconazole) have been reported after a mean of 36 months following successful treatment.[9] As oral therapies are generally considered more effective than topical therapies, onychomycosis recurrence rates could be even higher with efinaconazole.

Efficacy

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

Health-Related Quality of Life

The OnyCOE-t disease-specific quality-of-life questionnaire was administered [redacted] at baseline, week 24, and week 52. The OnyCOE-t comprises a total of 33 items within seven scales transformed to a 1-to-100

scale (Table 8). Higher scores represent better function and there is no overall aggregate score. Overall MCID estimates — across individual scales based on three different definitions of nail clearing (i.e., 12.5% and 25% difference in nail clearing and ≥ 5 mm new nail growth) — range from 7.3 to 16.6 points, as detailed in Appendix 5.

Table 8: Change from Baseline in OnyCOE-t Domains at Weeks 24 and 52

Domain	Study P3-01 (ITT)				Study P3-02 (mITT)			
	Efinaconazole		Vehicle		Efinaconazole		Vehicle	
N	[redacted]		[redacted]		[redacted]		[redacted]	
Symptom frequency								
	Baseline		Baseline		Baseline		Baseline	
n Mean (SD) Median (min to max)	[redacted]		[redacted]		[redacted]		[redacted]	
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
n Mean (SD) Median (min to max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom bothersomeness								
	Baseline		Baseline		Baseline		Baseline	
n Mean (SD) Median (min to max)	[redacted]		[redacted]		[redacted]		[redacted]	
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
n Mean (SD) Median (min to max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical activities problems								
	Baseline		Baseline		Baseline		Baseline	
n Mean (SD) Median (min to max)	[redacted]		[redacted]		[redacted]		[redacted]	
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
n Mean (SD) Median (min to max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appearance problems								
	Baseline		Baseline		Baseline		Baseline	
n Mean (SD) Median (min to max)	[redacted]		[redacted]		[redacted]		[redacted]	

Domain	Study P3-01 (ITT)				Study P3-02 (mITT)			
	Efinaconazole		Vehicle		Efinaconazole		Vehicle	
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
n Mean (SD) Median (min to max)	[redacted]							
Overall problem								
	Baseline		Baseline		Baseline		Baseline	
n Mean (SD) Median (min to max)	[redacted]							
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
n Mean (SD) Median (min to max)	[redacted]							
Stigma								
	Baseline		Baseline		Baseline		Baseline	
n Mean (SD) Median (min to max)	[redacted]							
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
n Mean (SD) Median (min to max)	[redacted]							
Treatment satisfaction[a]								
n Mean (SD) Median (min to max)	[redacted]							

ITT = intention-to-treat population; max = maximum; min = minimum; mITT = modified intention-to-treat population; SD = standard deviation.

[redacted]

[a] [redacted]

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12] Additional data requested from manufacturer.[30]

The change from baseline in the OnyCOE-t assessments at week 24 and week 52 was a supportive efficacy outcome; only descriptive statistics were reported, and no statistical comparisons were made between treatment groups. As a result, it is not possible to interpret the clinical relevance of any apparent between-group differences in the individual scales of the OnyCOE-t as reported in Table 8.

Clinical and Mycologic Cures

The results for various outcomes that constitute either a clinical or mycologic cure are reported in Table 9. All secondary outcomes reported in Table 9 were tested according to a pre-specified statistical hierarchy to control for type I error.

The primary outcome of complete cure (defined as both 0% clinical involvement of the target toenail and mycologic cure) at week 52 was statistically significantly higher (17.8% and 15.2%) in the efinaconazole groups compared with the vehicle groups (3.3% and 5.5%), in both Study P3-01 and Study P3-02, respectively; $P < 0.001$ for both using the LOCF method to impute missing data (Table 9). Sensitivity analyses of complete cure at week 52 where missing values were imputed as failures and as successes yielded similar results supporting the superiority of efinaconazole compared with the vehicle, with the exception of imputing missing data as successes in Study P3-02 (Table 13).

Results of pre-specified subgroup analyses of complete cure at week 52 by age [redacted] or percentage of affected target toenail area at baseline (< 40% or ≥ 40% in both trials) are depicted in Table 15. In the efinaconazole groups, the proportions of patients with complete cure were [redacted]. The corresponding vehicle-treated patients with complete cure were [redacted]. The proportions of efinaconazole-treated patients who achieved complete cure and who had < 40% affected toenail area at baseline were [redacted] in the two trials respectively, compared with [redacted] of patients who had ≥ 40% toenail involvement. The corresponding proportions of vehicle-treated patients were [redacted] in those with < 40% toenail involvement and [redacted] in those with ≥ 40% toenail involvement, in the two trials, respectively.

No pre-specified subgroup analyses by diabetes status of included patients in the trials were conducted. However, a post hoc analysis of pooled data from both trials in patients with diabetes was identified in the literature as detailed in Table 18.[31] No statistically significant differences were reported for the primary or any secondary outcomes or the supportive outcomes of clear nail or almost-clear nail between patients with or without diabetes.

According to version 1 of the SAP, the key secondary outcome was treatment success or clinical efficacy (defined as < 10% affected toenail area involvement) at week 52. Results for treatment success or clinical efficacy were statistically significantly higher in both trials in the efinaconazole groups (35.7% and 31.0%) compared with the vehicle groups (11.7% and 11.9%), respectively; $P < 0.001$ for both (Table 9). [redacted] (Table 14).

Mycologic cure (defined as a negative KOH examination and a negative fungal culture of the target toenail sample) was a secondary outcome in both Study P3-01 and Study P3-02, regardless of the SAP version applied. In both trials, the mycologic cure rate (55.2% and 53.4%) was statistically significantly higher in patients who received efinaconazole

compared with those who received just the vehicle (16.8% and 16.9%), in Study P3-01 and Study P3-02, respectively; $P < 0.001$ for both (Table 9).

Complete or almost-complete cure (no more than 5% affected target toenail area and a mycologic cure) at week 52 was the key secondary outcome according to version 2 of the SAP. Results were also statistically significant in favour of efinaconazole (26.4% and 23.4%) compared with the vehicle (7.0% and 7.5%), in Study P3-01 and Study P3-02, respectively; both $P < 0.001$ (Table 9).

Table 9: Key Efficacy Outcomes

	Study P3-01 (ITT)		Study P3-02 (mITT)	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
N	656	214	580	201
Complete cure at week 52[a]				
Success, n (%) **Failure, n (%)**	117 (17.8) 539 (82.2)	7 (3.3) 207 (96.7)	88 (15.2) 492 (84.8)	11 (5.5) 190 (94.5)
***P* value[b]**	< 0.001		< 0.001	
Treatment success or clinical efficacy at week 52[c]				
Success, n (%) **Failure, n (%)**	234 (35.7) 422 (64.3)	25 (11.7) 189 (88.3)	180 (31.0) 400 (69.0)	24 (11.9) 177 (88.1)
***P* value[b]**	< 0.001		< 0.001	
Mycologic cure at week 52[d]				
Success, n (%) **Failure, n (%)**	362 (55.2) 294 (44.8)	36 (16.8) 178 (83.2)	310 (53.4) 270 (46.6)	34 (16.9) 167 (83.1)
***P* value[b]**	< 0.001		< 0.001	
Unaffected new toenail growth at week 52, mm				
LSM (SE)	5.0 (0.2)	1.6 (0.4)	3.8 (0.2)	0.9 (0.4)
***P* value[e]**	< 0.001		< 0.001	
Complete or almost-complete cure at week 52[f]				
Success, n (%) **Failure, n (%)**	173 (26.4) 483 (73.6)	15 (7.0) 199 (93.0)	136 (23.4) 444 (76.6)	15 (7.5) 186 (92.5)
***P* value[b]**	< 0.001		< 0.001	

ITT = intention-to-treat population; LSM = least squares mean; mITT = modified intention-to-treat population; SAP = statistical analysis plan; SE = standard error.

Note: The last observation carried forward method was used to impute missing data prior to the analysis. As per version 1 of the SAP secondary outcomes and order of testing was treatment success or clinical efficacy > mycologic cure > unaffected new toenail growth, whereas in version 2 of the SAP secondary outcomes and order of testing was complete or almost-complete cure rate > unaffected new toenail growth > mycologic cure.

[a] A complete cure was defined as both 0% clinical involvement of the target toenail and mycologic cure (i.e., a negative potassium hydroxide examination and a negative fungal culture of the target toenail sample).

[b] *P* value from a Cochran–Mantel–Haenszel test, stratified by analysis centre.

[c] Treatment success or clinical efficacy rate was defined as < 10% affected toenail area involvement and was a secondary outcome in version 1 of the SAP

[d] A mycologic cure was defined as a negative potassium hydroxide examination and a negative fungal culture of the target toenail sample.

[e] LSM, SE, and *P* values from an analysis of variance with treatment group and analysis centre as factors.

[f] A complete or almost-complete cure was defined as an affected target toenail area ≤ 5% and a mycologic cure and was a secondary outcome in version 2 of the SAP.

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

[redacted]

[redacted]

Unaffected New Nail Growth

The least squares mean (standard error) unaffected new growth in the target toenail at week 52 was statistically significantly greater in the efinaconazole groups compared with the vehicle groups in both trials (i.e., 5.0 [0.2] versus 1.6 [0.4] mm in Study P3-01 and 3.8 [0.2] versus 0.9 [0.4] mm in Study P3-02); both $P < 0.001$ (Table 9). [redacted]

[redacted]

No data were available for the outcomes of pain, recurrence, nail parameters such as nail loss, and secondary complications (e.g., bacterial infection, ulceration, amputation) as defined in the CDR review protocol. [redacted]

Harms

Only those harms identified in the review protocol are reported below (see Table 3, Protocol). Refer to Table 10 and Table 11 for detailed harms data.

Adverse Events

The proportions of patients in each treatment group who experienced one or more AEs were generally similar in both trials (i.e., 66.0% and 64.5% of efinaconazole-treated patients and 61.0% and 58.5% of vehicle-treated patients) as per Table 10. The majority (> 96%) of AEs reported were generally mild-to-moderate in severity. The most commonly reported AE in both trials was nasopharyngitis and the most common treatment-related AEs, regardless of seriousness or severity, were application-site dermatitis (3.5% and 0.7% with efinaconazole versus 0.7% and 0.5% with the vehicle in Study P3-01 and Study P3-02, respectively) and application-site vesicles (2.0% and 1.2% with efinaconazole versus 0% [both studies], respectively).

Serious Adverse Events

The proportions of patients who experienced serious adverse events (SAEs) were 3.8% and 3.7% in the efinaconazole groups compared with 2.8% and 0.5% in the vehicle control groups in Study P3-01 and Study P3-02, respectively, as per Table 11. The most common SAEs were myocardial infarction, osteoarthritis, and intracranial aneurysm, all of which were considered unrelated to study drug by the investigators.

Withdrawals Due to Adverse Events

The proportions of patients who withdrew due to AEs were 3.2% and 1.9% in the efinaconazole groups and 0.5% and 0% in the vehicle control groups in the two trials, respectively, as per Table 11. The most common reasons that led to discontinuation were AEs associated with the application site (e.g., application-site dermatitis, erythema, pruritis, swelling, vesicles, and contact dermatitis).

Mortality

Two deaths were reported, one in each of the efinaconazole groups. Both were considered unrelated to the study drug (Table 11). The cause of death in Study P3-01 was due to [redacted], whereas in Study P3-02 the death was due to lung squamous cell carcinoma [redacted].

Notable Harms

Notable harms identified in the review protocol were application-site dermatitis, vesicles, and tinea pedis. As detailed in Table 10 and Table 11, application-site dermatitis occurred in 3.5% and 0.7% of efinaconazole-treated patients compared with 0% and 0.5% of vehicle-treated patients in Study P3-01 and Study P3-02, respectively. Similarly, application-site vesicles occurred infrequently (i.e., 2.0% and 1.2% of efinaconazole-treated patients and no vehicle-treated patients) (Table 10). Tinea pedis occurred in more vehicle-treated patients in both trials (2.8% and 3.0%) compared with efinaconazole-treated patients (1.1% and 0.7%) in both trials (Table 10).

The worst instances of localized skin reactions (redness, swelling, burning, itching, and vesiculation) were recorded by patients using a four-point scale (where 0 = none and 3 = severe or presence or absence, indicated as “yes” or “no”) and reviewed at each study visit. In Study P3-01, at least 95.8% (efinaconazole) and 97.2% (vehicle) of patients had no redness at any study visit.[11] Similarly, at least 97.9% and 99.0% of patients had no swelling and at least 97.8% and 99.1% of patients had no burning, itching, or vesiculation, respectively, at any study visit.[11] Similar results were reported in Study P3-02, in which at least 97.1% (efinaconazole) and 97.4% (vehicle) of patients had no redness at any study visit.[12] Overall, at least 97.9% and 99.4% of patients had no swelling and at least 98.6% and 98.9% of patients had no burning, itching, or vesiculation, respectively, at any study visit.[12]

Table 10: Harms (Safety Population)

	Study 1		Study 2	
N (%)	Efinaconazole (N = 653)	Vehicle (N = 213)	Efinaconazole (N = 574)	Vehicle (N = 200)
No. of patients who reported at least 1 TEAE	431 (66.0%)	130 (61.0%)	370 (64.5%)	117 (58.5%)
Individual TEAEs reported by >2% of patients in at least 1 study				
Application site dermatitis	23 (3.5%)	0 (0.0%)	-	-
Application site vesicles	13 (2.0%)	0 (0.0%)	7 (1.2%)	0 (0.0%)
Arthralgia	13 (2.0%)	7 (3.3%)	18 (3.1%)	2 (1.0%)
Back pain	16 (2.5%)	6 (2.8%)	19 (3.3%)	7 (3.5%)
Blood creatinine phosphokinase increased	-	-	11 (1.9%)	5 (2.5%)
Bronchitis	8 (1.2%)	4 (1.9%)	14 (2.4%)	3 (1.5%)
Contact dermatitis	19 (2.9%)	4 (1.9%)	8 (1.4%)	2 (1.0%)
Eczema	22 (3.4%)	7 (3.3%)	-	-
Folliculitis	5 (0.8%)	5 (2.3%)	-	-
Headache	15 (2.3%)	5 (2.3%)	25 (4.4%)	7 (3.5%)
Hypertension	17 (2.6%)	10 (4.7%)	11 (1.9%)	5 (2.5%)
Influenza	16 (2.5%)	8 (3.8%)	10 (1.7%)	1 (0.5%)
Ingrowing nail	17 (2.6%)	1 (0.5%)	11 (1.9%)	2 (1.0%)
Nasopharyngitis	78 (11.9%)	25 (11.7%)	63 (11.0%)	15 (7.5%)
Procedural pain	10 (1.5%)	7 (3.3%)	6 (1.0%)	0 (0.0%)
Sinusitis	30 (4.6%)	4 (1.9%)	17 (3.0%)	5 (2.5%)
Tinea pedis	7 (1.1%)	6 (2.8%)	4 (0.7%)	6 (3.0%)
Upper respiratory tract infection	38 (5.8%)	13 (6.1%)	35 (6.1%)	11 (5.5%)
Urinary tract infection	12 (1.8%)	8 (3.8%)	12 (2.1%)	2 (1.0%)

TEAE = treatment-emergent adverse event.

Note: Study 1 = Study P3-01 and Study 2 = Study P3-02. Notable harms identified in the CADTH Common Drug Review protocol are application-site dermatitis, application-site vesicles, and tinea pedis.

Source: Reprinted from J Am Acad Dermatol, 68(4), Elewski BE, Rich P, Pollak R, Pariser DM, Watanabe S, Senda H, et al., Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. [Erratum appears in J Am Acad Dermatol. 2014 Feb;70(2):399], 600-608, Copyright (2013), with permission from Elsevier.

Table 11: Additional Harms (Safety Population)

	Study P3-01		Study P3-02	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
N	653	213	574	200
AEs				
Patients with ≥ 1 AE, n (%)	431 (66.0)	130 (61.0)	370 (64.5)	117 (58.5)
Most common AEs[a] **Application-site dermatitis[b]** **Blood CPK increased** **Eczema** **Folliculitis**	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
Patients with ≥ 1 SAE, n (%)	25 (3.8)	6 (2.8)	21 (3.7)	1 (0.5)
Most common SAEs[c] **Myocardial infarction** **Osteoarthritis** **Intracranial aneurysm**	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
Patients with ≥ 1 WDAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common reason for WDAEs[c] **Application-site dermatitis** **Application-site erythema** **Application-site pruritis** **Application-site swelling** **Application-site vesicles** **Dermatitis contact**	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
n (%)	1 (0.2)[d]	0 (0)	1 (0.2)[e]	0 (0)

AE = adverse event; CPK = creatine phosphokinase; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 2% of patients in either Study P3-01 or Study P3-02.

[b] Identified as notable harms in the review protocol.

[c] Frequency > 1 patient in either Study P3-01 or Study P3-02.

[d] One death due to [redacted] was reported in the efinaconazole group. It was judged by investigators to be unrelated to study drug.

[e] One death due to lung squamous cell carcinoma [redacted] was reported in the efinaconazole group. It was judged by investigators to be unrelated to study drug.

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

Discussion

Summary of Available Evidence

Two phase III, multi-centre, randomized, double-blind, parallel-group, vehicle-controlled superiority trials were included in the systematic review: Study P3-01 (N = 870)[11,22] and Study P3-02 (N = 785).[12,22] The trials were identical in design and evaluated the efficacy and safety of once-daily topical application of efinaconazole 10% solution compared with vehicle alone, for the treatment of adult patients with mild-to-moderate DLSO, defined as 20% to 50% clinical involvement of the target toenail(s) without dermatophytomas or matrix (lunula) involvement. The primary efficacy outcome was complete cure at week 52, which was defined as both 0% clinical involvement of the target toenail and mycologic cure (i.e., a negative KOH examination and a negative fungal culture of the target toenail sample). Key secondary end points were treatment success or clinical efficacy, mycologic cure, unaffected new toenail growth, and complete or almost-complete cure at week 52.

The mean age of enrolled patients ranged between 50 and 52 years, with a predominance of male and Caucasian patients. Both Study P3-01 and Study P3-02 enrolled patients from the US and Canada. Study P3-01 also enrolled patients from Japan, thus the study population in Study P3-01 comprised 29.0% Asian patients compared with 2.2% Asian patients in Study P3-02. The mean area of toenail involvement at baseline in both trials was approximately 36% and the mean number of affected non-target toenails was 2.8. The majority of patients had screening cultures of *T. rubrum* (> 89%) and *T. mentagrophytes* (> 4%).

A number of limitations were identified for the included trials. The first is that the study populations represent typically healthy, immunocompetent adult patients with mild-to-moderate disease who would primarily seek treatment for cosmetic reasons. This is in contrast to the population most in need of treatment (e.g., immunocompromised or diabetic patients at risk of secondary infection and patients with pain or functional impairment due to dystrophic nails). Few data are available on the use of efinaconazole in elderly patients or in patients with more severe disease. Although pre-specified subgroup analyses according to age and disease severity at baseline were conducted, the results of these analyses are considered exploratory due to the lack of formal interaction tests or adjustment for multiple comparisons. The LOCF method was used for imputation of missing data in both trials and a proportion of patients (> 13% across treatment groups) did not have complete efficacy assessments at week 52. The manufacturer conducted sensitivity analyses to evaluate potential bias by imputing all missing values as successes and failures, but this did not appear to affect the study results. Nonetheless, as the true outcome distribution across patients with missing data is not known, the true impact of missing data on the study results is difficult to determine. Data to support an effect of efinaconazole on HRQoL are also inconclusive as the OnyCOE-t quality of life questionnaire was [redacted] and it being a supportive efficacy outcome precluded statistical comparisons between treatment groups. Other important limitations are the lack of comparative data with another active oral or topical antifungal treatment, lack of data on recurrence of onychomycosis following treatment, or any data on concomitant use of oral antifungal therapy with topical efinaconazole.

Interpretation of Results

Efficacy

Onychomycosis is a chronic and recurring fungal infection that predominantly affects toenails. It can lead to physical discomfort or pain and can cause serious sequelae such as dystrophic nails, impaired function, and increased risk of bacterial infections such as cellulitis in patients with diabetes, venous insufficiency, or other immunocompromised states.[7,8] Patients most in need of treatment are those in whom these factors are either present or in whom either ineffective treatment or no treatment would lead to serious consequences. The patient populations enrolled in Study P3-01 and Study P3-02 largely represent middle-aged adult patients with mild-to-moderate onychomycosis who would primarily be seeking treatment for cosmetic reasons. Therefore, it is unknown if the findings from the included trials can be generalized to patients with more severe disease or dysfunction, the elderly with comorbidities, or diabetic and immunocompromised patients. Post hoc analyses of the included trials, as reported in Table 17, suggest that the treatment effect with efinaconazole compared with the vehicle is maintained in patients 65 years of age and older, those with disease severity defined as more than 33% toenail involvement at baseline, and diabetic patients compared with non-diabetic patients. However, these findings are considered exploratory.

Onychomycosis can negatively affect quality of life, thus HRQoL was a key efficacy outcome identified in the CDR review protocol and was identified as being important in patient input received for this review. In the included trials, HRQoL was measured using the OnyCOE-t instrument. However, the change from baseline in the OnyCOE-t assessments at week 24 and week 52 was a supportive efficacy outcome. As a result, no between-group differences were reported and no statistical comparisons between groups were made. Furthermore, while there is some evidence of the validity and internal consistency reliability of the OnyCOE-t, it has been criticized as being overly sensitive and showing a response when no clinical change has occurred.[28,29] Whether the differences upon which the MCID was based (i.e., clinical assessment of nail clearing) would be perceived as meaningful changes by patients is also not known. Given these limitations, along with [redacted], it is difficult to interpret the clinical relevance of any apparent between-group differences observed for the individual scales of the OnyCOE-t.

The primary outcome in the included trials was complete cure, which was a composite of clinical and mycologic cure. According to the clinical expert, both clinical cure and mycologic cures are necessary to evaluate the success of an antifungal treatment. In clinical practice, antifungal therapy is frequently initiated without confirmation of a positive diagnosis of onychomycosis by KOH examination or a fungal culture. Rather, a clinical diagnosis of onychomycosis is based on the appearance of the nail, and oral treatment is most often initiated as it is considered to be the most effective and generally safe, and the potential for drug-drug interactions and serious liver toxicity is rare. There is also a high rate of sampling error as clinicians are often unfamiliar with proper nail-sampling techniques or do not have the time to accurately obtain and prepare a nail sample, which in turn predisposes clinicians to empiric treatment.[3] In addition, the patient may not return until the course of treatment is completed (which may range from three months to one year) and rarely is a nail sample taken at the end of treatment to confirm treatment success. The clinical expert also advised that, in a clinical trial, mycologic cure alone is misleading because, while a positive fungal culture is typically necessary for inclusion into a trial,

sampling at the end of treatment may either not be done or be done inaccurately, which may lead to false-negatives and an overestimate of treatment efficacy.

The proportions of efinaconazole-treated patients with complete cure (a composite of clinical and mycologic cure) in the included trials were 17.8% and 15.2% after 52 weeks, both statistically significantly superior to vehicle. Effective treatment with oral agents such as terbinafine or itraconazole (both pulsed and continuous therapy) are reported to be higher.[18,32] In contrast, complete cure rates for ciclopirox are reported to be lower over the same treatment duration (48 weeks).[17] When only mycologic cure is considered, the proportions of efinaconazole-treated patients in the included trials who achieved this outcome were 55.2% and 53.4%, which is also statistically significantly superior to vehicle. As noted previously, mycologic cure rate alone may overestimate treatment effect, although mycologic cure rates with oral agents such as terbinafine and itraconazole (pulsed and continuous therapy) are reported to be higher.[18,32] Similar to complete cure, mycologic cure rates with ciclopirox are reported to be lower after 48 weeks of treatment.[17] Although the clinical outcomes differ somewhat, based on these findings, the clinical and mycologic outcomes appear to confirm that oral antifungal therapy is more effective over a shorter duration of treatment compared with topical efinaconazole therapy.

An indirect treatment comparison (ITC) submitted by the manufacturer included a network meta-analysis that compared the relative efficacy (based on mycologic cure) of efinaconazole with placebo, ciclopirox, terbinafine, itraconazole (continuous and pulse therapy), and fluconazole as well as other topical treatments that are not approved in Canada (Appendix 6).[33,34] Various limitations of the ITC were identified, including reliance on only one outcome (mycologic cure), considerable heterogeneity across the included trials, and other methodological issues as detailed in Appendix 6. The network meta-analysis suggested that terbinafine 250 mg daily and itraconazole 200 mg daily were more effective than efinaconazole at inducing mycologic cure and that there was no statistically significant difference between efinaconazole and ciclopirox. Some comparisons demonstrated considerable uncertainty with wide credible intervals, although the results are consistent with the general perception echoed by the clinical expert that oral antifungal therapy is more efficacious than topical therapy. The results should be interpreted with caution, especially in light of limitations associated with mycologic cure as a relevant and meaningful outcome due to its reliance on proper sampling technique and association with false-negative results.[3]

In the included trials, adherence with daily treatment over the 48-week treatment period was high ([redacted]) although the definition of non-compliance was liberal. According to the clinical expert, these results are not in line with what is typically experienced in clinical practice, but can be attributed to the controlled conditions and ongoing monitoring within the clinical trial setting. Given the length of treatment, which can span one year or more, it is expected that patient compliance with and adherence to a daily topical therapy would be considerably less than what was observed in the included trials, and the overall benefits observed may be somewhat reduced with real-world use.

The primary outcome of complete cure in the included trials was also evaluated within various pre-specified subgroups (Table 15). Of the pre-specified subgroups, those of relevance to this review were age and disease severity at baseline. As no formal interaction tests or adjustment for multiple comparisons were made for these analyses, they are considered exploratory. In general, the results suggest that younger patients and patients

with less-severe disease at baseline appeared to achieve higher rates of complete cure. However, these results are inconclusive in the absence of any statistical comparisons. Numerous post hoc analyses of the included trials have also been published and those of relevance are reported in Table 17 and Table 18. The results of the overall pooled analysis of the primary and secondary outcomes of the included trials were consistent with the primary analyses in the individual trials (Table 16). With regard to the post hoc analyses that are relevant to this review, numerically higher proportions of patients with disease severity defined as ≤ 33% involvement at baseline and patients less than 65 years of age achieved complete cure, as compared with those with > 33% involvement and 65 years of age and older, respectively (Table 17). In addition, a post hoc analysis of trial outcomes by diabetic versus non-diabetic patients reported no differences between the two groups (Table 18). As these were all post hoc analyses and not adjusted for multiple comparisons, the findings should be considered exploratory.

It is not known if continued improvement with efinaconazole would have occurred over a longer treatment duration or longer follow-up period. It has been speculated that the complete cure rate could have underestimated the clinical value of efinaconazole because it may take up to 78 weeks for toenails to grow cleanly and that the observed treatment success or clinical efficacy rates (defined as ≤ 10% toenail involvement) of between 40% to 45% could imply that patients were heading toward complete cure.[22] While it is unknown if better outcomes would have been obtained with longer treatment or follow-up, the clinical expert advised that the 48-week treatment period and 52-week follow-up period is sufficient to evaluate the efficacy and safety of a topical antifungal therapy such as efinaconazole. Perhaps more importantly, there is no information available on the rate of recurrence of onychomycosis following efinaconazole therapy. Recurrence rates of 35.7% and 11.9% have been reported following use of oral therapies such as itraconazole and terbinafine, respectively.[9] As oral therapies are generally considered more effective than topical therapies, it is uncertain if this also leads to reduced recurrence compared with topical therapies such as efinaconazole.

Harms

Overall, the safety and tolerability of efinaconazole appeared to be similar to the vehicle as the proportions of patients in each treatment group who experienced AEs were generally similar. The majority of AEs were mild or moderate in severity and after nasopharyngitis (which was the most common AE in all treatment groups), the most commonly reported treatment-related AEs were related to application-site dermatitis and application-site vesicles. The application-site AEs were experienced primarily by efinaconazole-treated patients. The proportions of patients with SAEs were low and no SAEs were judged by the investigators to be treatment-related. Neither of the two deaths reported during the trials were deemed by the investigators to be related to treatment. More patients in the efinaconazole treatment groups withdrew due to AEs and the most common reasons for discontinuation were application-site AEs. Notable harms identified in the CDR review protocol were application-site dermatitis, vesicles, and tinea pedis. As noted previously, application-site dermatitis and vesicles occurred infrequently and were experienced primarily by efinaconazole-treated patients, whereas tinea pedis occurred more frequently in vehicle-treated patients in both trials. The analysis of localized skin reaction scores reported by patients indicated that, in general, application of efinaconazole or vehicle did not result in redness, swelling, burning, itching, or vesiculation as > 97% of patients in either treatment group did not experience local skin irritation.

Potential Place in Therapy[b]

Efinaconazole is an alternative for patients who prefer topical therapy to systemic treatment for mild-to-moderate onychomycosis. This is based on personal preference rather than a medical need. From a medical perspective, patients who have functional impairment, symptomatic disease, or an underlying disease (e.g., immunocompromised states, diabetes, or venous stasis) that predisposes them to more serious infections should be treated with systemic antifungals rather than topical efinaconazole, which has a low efficacy and requires long-term treatment and good compliance. Three systemic options are available (terbinafine, itraconazole and fluconazole) along with one topical option (ciclopirox). Patients with significant medical contraindications to all three systemic agents are uncommon.

In real-world practice, topical antifungals, which are viewed as safe and benign, are often prescribed for dystrophic nails, usually without the benefit of fungal cultures. It is estimated that more than 50% of dystrophic nails are not caused by dermatophytes. The etiology may be trauma, saprophytes, psoriasis, eczema, or other dermatologic diseases. As a result, topical antifungals are often misused. Efinaconazole should only be prescribed for patients with mild-to-moderate onychomycosis caused by dermatophytes proven on culture and who understand the need for long-term adherence to the treatment.

Conclusions

Two phase III, double-blind, randomized, controlled superiority trials in adult patients with mild-to-moderate DLSO confirm that, in comparison with the vehicle alone, efinaconazole topical solution is associated with statistically significant higher complete cure rates, mycologic cure rates, and unaffected nail growth. The effect of efinaconazole on HRQoL, as measured by the OnyCOE-t instrument, is inconclusive due to various identified limitations and a lack of statistical comparisons between treatment groups. No data are available on improvement in functionality, reduction of pain or secondary complications, or recurrence of onychomycosis following efinaconazole treatment. A manufacturer-submitted ITC suggested that oral terbinafine 250 mg daily and itraconazole 200 mg daily were more effective than topical efinaconazole and that there was no statistically significant difference between efinaconazole and ciclopirox at inducing mycologic cure. These results are consistent with the general perception that oral antifungal therapy is more efficacious than topical therapy for onychomycosis. However, confidence in the results of the ITC is limited due to reliance on mycologic cure as an outcome and other methodological shortcomings, such as the limited number of studies included in the network and lack of a direct comparison with efinaconazole. In the phase III trials, safety and tolerability of topical efinaconazole were similar to the vehicle. The most common treatment-related AEs were application-site dermatitis and vesicles, which generally did not result in localized skin reaction scores that differed between topical efinaconazole and the vehicle.

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

Appendix 1: Patient Input Summary

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

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

A submission was received from the Canadian Skin Patient Alliance (CSPA) in collaboration with Wounds Canada.

According to its website (www.canadianskin.ca), CSPA is a national non-profit organization dedicated to advocating, educating, and supporting Canadians living with skin diseases, conditions, and traumas. Its mission is to promote skin health and improve the quality of life of Canadians living with skin conditions, diseases, and traumas. The CSPA advocates for best treatment options, educates on issues affecting these patients; and supports the members of affiliate organizations who work in specific disease areas.

Wounds Canada (Canadian Association of Wound Care) is a non-profit organization dedicated to the advancement of wound prevention and management by being the leading knowledge mobilization organization relating to wounds in Canada. According to its website (www.woundscanada.ca), Wounds Canada provides educational programs to health professionals, patients, and their caregivers; collaborates with universities, health ministries, agencies, and industry to conduct research; and advocates on behalf of patients living with wounds or at risk for wounds.

On their conflict of interest declarations, CSPA and Wounds Canada responded that they had received no help from outside their groups to complete the submission or to collect or analyze data used in the submission. CSPA stated that in the last two years they had received up to $5,000 from Valeant. Wounds Canada had received no financial support from organizations relevant to this review.

2. Condition-Related Information

CSPA hosted an online survey in July and August 2018, which was advertised on the CSPA and Wounds Canada social media platforms and shared with personal contacts. Responses were received from nine people (85% female), with ages ranging from 26 to 65 years, and most were from Ontario. Additional data were gathered from online disease-discussion boards.

Onychomycosis is a fungal infection of the nails that is estimated to account for 50% of all nail problems. The survey respondents reported experiencing nail discoloration or yellowing, thickening, crumbling, or brittleness of nails, as well as debris under the nail. One person reported pain and pressure when wearing certain shoes. Others reported feeling self-conscious or embarrassed about the appearance of their nails and were reluctant to wear open-toe shoes. Some reported stopping activities such as swimming or yoga due to the appearance of their nails and were worried that the fungus may spread to family members.

Wounds Canada stated that onychomycosis is a risk factor for ulceration and subsequent amputation in patients with diabetic food disease. If left untreated it may spread to other toenails, skin or fingernails.

3. Current Therapy-Related Information

Common treatments for onychomycosis include topical, oral, and physical treatments. Topical treatments, such as ciclopirox, may cause redness in the skin around the toenail. Oral treatments, which are usually prescribed for severe fungal infections, may be toxic to the liver, or cause adverse effects such as headache, skin rash, or digestive issues. Physical treatments, including laser therapy and removal of the infected nail, are often used in conjunction with antifungal treatments, and can be expensive. Of the survey respondents, three had tried topical treatments other than efinaconazole, three had tried natural health products, and three patients had tried laser treatment. All respondents stated that the treatments were not effective.

Patients indicated that they are looking for a permanent cure that has quick results, so they may have healthy, normal looking nails.

4. Expectations About the Drug Being Reviewed

Eight of the nine patients had used efinaconazole previously, one of whom reported experiencing redness around the nail. The others reported no adverse effects with treatment. The respondents indicated some success, with two patients reporting the fungus infection was resolved with efinaconazole alone or in combination with laser treatments. Another reported that the nail was clearing. Respondents indicated that efinaconazole was easy to use, or as easy as other treatments.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE All **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 7, 2018
Alerts:	Bi-weekly search updates until (date of CDEC meeting)
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
*	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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE All
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
1	(Julia* or Clenafin* or efinaconazole or HSDB 8341 or HSDB8341 or KP103 or KP 103 or IDP 108 or IDP108 or J82SB7FXWB).ti,ab,kf,ot,hw,rn,nm.	372
2	1 use medall	140
3	*efinaconazole/	87
4	(Julia* or Clenafin* or efinaconazole or HSDB 8341 or HSDB8341 or KP103 or KP 103 or IDP 108 or IDP108).ti,ab,kw,dq.	295
5	3 or 4	296
6	5 use oemezd	166
7	6 not conference abstract.pt.	133
8	2 or 7	273
9	remove duplicates from 8	162

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

Grey Literature

Dates for Search:	September 5, 2018
Keywords:	Drug name, Indication
Limits:	Publication years 1996 to present

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

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

Appendix 3: Excluded Studies

Table 12: Excluded Studies

Reference	Reason for Exclusion
Gupta et al. (2014)[35]	Incorrect study design
Noguchi et al. (2018)[36]	Incorrect study design

Appendix 4: Detailed Outcome Data

Table 13: Sensitivity Analysis of the Primary Outcome at Week 52

	Study P3-01 (ITT)		Study P3-02 (mITT)	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
N	656	214	580	201
Complete cure at week 52[a]				
Missing values imputed as failures				
Success, n (%) **Failure, n (%)**	115 (17.5) 541 (82.5)	7 (3.3) 207 (96.7)	81 (14.0) 499 (86.0)	9 (4.5) 192 (95.5)
***P* value[b]**	< 0.001		< 0.001	
Missing values imputed as successes				
Success, n (%) **Failure, n (%)**	199 (30.3) 457 (69.7)	36 (16.8) 178 (83.2)	171 (29.5) 409 (70.5)	52 (25.9) 149 (74.1)
***P* value[b]**	< 0.001		< 0.319	

ITT = intention-to-treat population; mITT = modified intention-to-treat population.

[a] Complete cure defined as 0% clinical involvement of the target toenail (totally clear) and mycologic cure (negative potassium hydroxide examination and negative fungal culture of the target toenail sample).

[b] *P* value from a Cochran–Mantel-Haenszel test stratified by analysis centre.

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

Table 14: Supportive Efficacy Outcomes at Week 52

	Study P3-01 (ITT)		Study P3-02 (mITT)	
	Efinaconazole	Vehicle	Efinaconazole	Vehicle
N	[redacted]	[redacted]	[redacted]	[redacted]
Clear nail at week 52[a]				
Success, n (%) Failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Almost-clear nail at week 52[b]				
Success, n (%) Failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment success or clinical efficacy at week 52[c]				
Success, n (%) Failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in the number of affected non-target toenails at week 52, mm[d]				
Baseline Mean (SD) Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 Mean (SD) Median	[redacted]	[redacted]	[redacted]	[redacted]
Target toenail growth at week 52, mm				
Mean (SD) Median	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intention-to-treat population; mITT = modified intention-to-treat population; SD = standard deviation.

Note: the [redacted] was used to impute missing data prior to analysis. [redacted].

[a] Clear nail was defined as [redacted].

[b] Almost-clear nail was defined as [redacted].

[c] Treatment success or clinical efficacy was defined as [redacted].

[d] Change from baseline was computed as [redacted].

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

Table 15: Pre-Specified Subgroup Analyses of Complete Cure at Week 52

Subgroup	Study P3-01 (ITT)				Study P3-02 (mITT)			
	Efina-conazole	Vehicle	Efina-conazole	Vehicle	Efina-conazole	Vehicle	Efina-conazole	Vehicle
Complete cure at week 52								
Age[a]	[redacted]							
n **Success, n (%)** **Failure, n (%)**	[redacted]							
Per cent affected target nail area[a]	[redacted]							
n **Success, n (%)** **Failure, n (%)**	[redacted]							

ITT = intention-to-treat population; mITT = modified intention-to-treat.

Note: All subgroup analyses were reported [redacted].

[a] Within the subgroups, age was dichotomized to [redacted]

Sources: Study P3-01 Clinical Study Report[11] and Study P3-02 Clinical Study Report.[12]

Table 16: Post Hoc Pooled Analyses of Study P3-01 and Study P3-02

Efficacy Outcomes at End Point (Last Observation Carried Forward) and at Week 52 (Observed Case)						
Outcome Measure	End Point LOCF Success (N,%)			Week 52 Observed CaseSuccess (N,%)		
	Efinaconazole	Vehicle	*P* Value	Efinaconazole	Vehicle	*P* Value
Clear Nail	244/1236 (19.7%)	26/415 (6.3%)	<0.001	237/1072 (22.1%)	25/346 (7.2%)	<0.001
Almost Clear Nail	398/1236 (32.2%)	45/415 (10.8%)	<0.001	386/1072 (36.0%)	42/346 (12.1%)	<0.001
Clinical Efficacy	527/1236 (42.6%)	67/415 (16.1%)	<0.001	506/1072 (47.2%)	63/346 (18.2%)	<0.001
Mycological Cure	672/1236 (54.4%)	70/415 (16.9%)	<0.001	599/1064 (56.3%)	57/343 (16.6%)	<0.001
Complete or Almost Complete Cure	309/1236 (25.0%)	30/415 (7.2%)	<0.001	294/1062 (27.7%)	27/343 (7.9%)	<0.001
Complete Cure	205/1236 (16.6%)	18/415 (4.3%)	<0.001	196/1062 (18.5%)	16/343 (4.7%)	<0.001

A clear nail success is defined as 0% affected target nail area.
An almost clear nail success is defined as < 5% affected target nail area
A clinical efficacy success is defined as <10% affected target nail area.
A mycological cure success is defined as negative KOH (potassium hydroxide) examination and negative fungal culture of the target nail specimen.
A complete or almost complete cure success is defined as < 5% affected target nail area in addition to mycological cure.
A complete cure success is defined as zero percent clinical involvement of the target nail (nail is totally clear) in addition to mycological cure.

Source: J Drugs Dermatol. 2014;13(7):815-820.

Table 17: Post Hoc Pooled Subgroup Analysis by Gender, Severity, Age and Weight

Subgroup Analysis Complete Cure at Week 52						
Prognostic Factor	End Point LOCF Success (N,%)			Week 52 Observed Case Success (N,%)		
	Efinaconazole	Vehicle	*P* Value	Efinaconazole	Vehicle	*P* Value
Gender						
Male	134/953 (14.1%)	12/322 (3.7%)	<0.001	129/815 (15.8%)	11/263 (4.2%)	<0.001
Female	71/283 (25.1%)	6/93 (6.5%)	<0.001	67/247 (27.1%)	5/80 (6.3%)	<0.001
Severity						
≤33% involvement	108/499 (21.6%)	15/166 (9.0%)	0.001	105/434 (24.2%)	13/131 (9.9%)	0.002
>33% involvement	97/737 (13.2%)	3/249 (1.2%)	<0.001	91/628 (14.5%)	3/212 (1.4%)	<0.001
Age						
<65 years	183/1074 (17.0%)	16/359 (4.5%)	<0.001	174/922 (18.9%)	14/294 (4.8%)	<0.001
≥65 years	22/162 (13.6%)	2/56 (3.6%)	0.014	22/140 (15.7%)	2/49 (4.1%)	0.016
Weight						
<84.4kg	120/622 (19.3%)	10/197 (5.1%)	<0.001	114/543 (21.0%)	9 /165 (5.5%)	<0.001
≥84.4kg	85/612 (13.9%)	8/216 (3.7%)	<0.001	82/517 (15.9%)	7/176 (4.0%)	<0.001

Source: J Drugs Dermatol. 2014;13(7):815-820.

Table 18: Post Hoc Analyses in Patients With Diabetes at Week 52

Comparison of Primary and Secondary Efficacy Endpoints
(Week 52, OC diabetic and non-Diabetic ITT population)

Endpoint	Diabetic Patients	Non-Diabetic Patients	*P*-value
Complete Cure	9/69 (13.0%)	187/993 (18.8%)	0.606
Clear Nail	11/71 (15.5%)	226/1001 (22.6%)	0.409
Almost Clear Nail	20/71 (28.2%)	366/1001 (36.6%)	0.640
Complete or Almost Complete Cure	17/69 (24.6%)	277/993 (27.9%)	0.770
Mycologic Cure	39/69 (56.5%)	560/995 (56.3%)	0.970
Treatment Success	29/71 (40.8%)	477/1001 (47.7%)	0.649

A clear nail success is defined as 0% affected target nail area. An almost clear nail success is defined as <=5% affected target nail area. A treatment success is defined as <=10% affected target nail area. A mycological cure success is defined as negative KOH (potassium hydroxide) examination and negative fungal culture of the target nail specimen. A complete or almost complete cure success is defined as <=5% affected target nail area in addition to mycologic cure. A complete cure success is defined as zero percent clinical involvement of the target nail (nail is totally clear) in addition to mycologic cure.

Source: J Drugs Dermatol. 2014;13(10):1186-1190.

Appendix 5: Validity of Outcome Measures

Aim

To provide a description and critical appraisal of the onychomycosis quality-of-life questionnaire (OnyCOE-t).

Findings

The OnyCOE-t is a disease-specific health-related quality-of-life measure for patients with onychomycosis of the toenails. It has a total of 33 items, including:

- Toenail symptom assessment (seven items), including symptom frequency (five response categories: 1 = never, 5 = very often) and symptom bothersomeness scales (five response categories: 1 = not at all bothered, 5 = extremely bothered)
- Appearance problems scale (eight items) with four response categories: 1 = very much a problem, 4 = not a problem
- Physical activities problems scale (seven items) with four response categories: 1 = very much a problem, 4 = not a problem
- Overall problem scale (one item) with four response categories; 1 = very much a problem, 4 = not a problem
- Stigma scale (seven items) with five response categories: 0 = does not describe me at all, 4 = describes me very well
- Treatment satisfaction scale (three items) with five response categories: 1 = very satisfied, 5 = very dissatisfied.[28]

All items are transformed to a 1-to-100 scale, with higher scores representing better function. Scale scores are the average of the non-missing items, provided at least half of the items for each scale were reported.[28] Scale scores are reported individually, and no methods were reported in the literature for the calculation of an overall score. The recall period is four weeks.

Potter et al.[28] evaluated the psychometric properties of the OnyCOE-t questionnaire using data from a 48-week open-label randomized controlled trial of 504 patients who received terbinafine 250 mg daily, with or without debridement. All multi-item scales showed good internal consistency reliability with Cronbach's alpha coefficients, which were ≥ 0.7 (range: 0.84 to 0.91). Items that were thought to measure the same construct, such as stigma and embarrassment about appearance, were highly correlated. Moderate-to-high correlation was reported for the physical activity problems, physical appearance problems and overall problem scales and items. Symptom frequency and bothersomeness items were highly correlated. Known-group validity was assessed by comparing change scores for patients who were cured versus not cured. Although three definitions of cure were reported to have been tested (complete cure, clinical cure [≥ 87.5% clearing of the nail], and mycological cure), the authors reported that statistically significant differences were detected for mycological cure only.

Responsiveness was evaluated by comparing the change from baseline in OnyCOE-t scores among patients who showed a clinical improvement (defined as a positive change in nail clearing from baseline to the end of the study) or no improvement. The "improved" group of patients reported a mean change from baseline scores that ranged from 15.4

points (stigma) to 46.1 points (treatment satisfaction), with *P* values < 0.0001 for all scales. Statistically significant differences were also detected in the "not improved" group for five of the seven scales (symptom frequency and bothersomeness scales, physical activity problems, appearance problems and overall problems), with mean differences ranging from 1.7 points (treatment satisfaction) to 24.5 points (overall problem) for the change from baseline scores. Based on the Guyatt's statistic comparing patients who improved (n = 400) with those who were stable (n = 37), the authors concluded that treatment satisfaction, symptom frequency, overall problems, and appearance problem were highly responsive to clinical change.[28] However, others have suggested that the instrument may be overly sensitive and can show a response when no clinical change has occurred.[29]

Estimates of the minimal clinically important difference (MCID) were calculated using clinical assessments of nail clearing as the anchor.[28] Patients were categorized based on 12.5% differences in percentage of the nail cleared of infection (i.e., 12.5%, 25%, 37.5 %, etc.). Average distances in scale scores between adjacent groups were used to estimate the minimum clinically important difference (MCID). The authors also calculated the MCID based on groups showing 12.5% and 25% differences in nail clearing and at least 5 mm of new clear nail growth (versus less than 5 mm). The estimates of MCID ranged from 5.4 points for stigmas to 11.2 points for overall problems, based on 12.5% differences in nail clearing (overall estimate 7.3 points) (Table 19). The MCID estimates were generally higher if 25% differences in nail clearing (overall 8.5; range 5.2 to 11.8 points) or at least 5 mm of new clear nail growth (overall 16.6; range 9.4 to 25.3 points) were used to estimate the MCID.[28]

Table 19: Estimates of the MCID for the OnyCOE-t Instrument

	Average Difference Between Adjacent PRO Scores		
Scale	**12.5% Difference in nail clearing***	**25% Difference in nail clearing***	**≥ 5 mm new nail growth†**
Symptom Frequency	6.48	9.12	17.28
Symptom Bothersomeness	5.95	5.84	11.83
Physical Activities Problems	7.54	8.32	17.69
Appearance Problems	8.04	8.69	18.51
Overall Problem	11.19	11.77	25.32
Stigma	5.44	5.21	9.41
Treatment Satisfaction	7.42	9.11	16.37
Overall	**7.30**	**8.45**	**16.63**

* Based on comparisons that are significant at the .05 level
†Based on comparisons that are significant at the .0001 level

MCID = minimum clinically important difference; OnyCOE-t = onychomycosis quality-of-life questionnaire; PRO = patient-reported outcome.

Source: Potter LP, Mathias SD, Raut M, Kianifard F, Tavakkol A. The OnyCOE-t questionnaire: responsiveness and clinical meaningfulness of a patient-reported outcomes questionnaire for toenail onychomycosis. Health Qual Life Outcomes. 2006;4:50. http://creativecommons.org/licenses/by/2.0 No changes were made.

The evaluation of the psychometric properties of the OnyCOE-t by Potter et al.[28] was based on an open-label clinical trial, in which all patients received active treatment. The patients' knowledge of the treatment received may have influenced their responses to questionnaires and potentially inflated the scores. In addition, the MCID estimates were based on clinical assessments of nail clearing, and it is unclear if the thresholds used (i.e., 12.5% or 25% difference) would be perceived by patients as clinically important changes. No data were found that evaluated variability or test re-test reliability for the OnyCOE-t.[29]

Conclusion

The OnyCOE-t is a disease-specific health-related quality-of-life measure for patients with onychomycosis of the toenails. It has a total of 33 items within seven scales including toenail symptom and bothersomeness, appearance problems, physical activity problems, overall problems, stigma, and treatment satisfaction. Although there is some evidence of the validity and internal consistency reliability of the questionnaire, the instrument may be overly sensitive and show a response when no clinical change has occurred.[28,29] The overall MCID estimates, which range from 7.3 to 16.6 points, are based on several measures of nail clearance (i.e., 12.5% or 25% difference in nail clearing and at least 5 mm of new clear nail growth). However, these values were based on clinical assessments of the percentage of nail cleared and it is not known if these differences would be perceived as meaningful changes by patients.

Appendix 6: Summary of Indirect Comparison

Background

As there were no head-to-head studies identified in the systematic review, the aim of this appendix is to summarize and appraise any indirect treatment comparisons (ITCs) that evaluated the comparative efficacy and safety of efinaconazole topical solution for the treatment of onychomycosis.

Methods

A literature search was conducted for ITCs that included the patients, treatments, and outcomes specified in this CADTH Common Drug Review protocol. The manufacturer supplied one published ITC (Gupta, Daigle, and Foley)[33] which was an update to a prior systematic review and ITC conducted by the same primary author (Gupta, Daigle, and Paquet).[34] No other ITCs were identified from the literature search.

Description of Indirect Treatment Comparison

The objective of the report by Gupta, Daigle and Foley[33] was to conduct a network meta-analysis (NMA) to compare the relative efficacy of onychomycosis treatments for the outcome of mycologic cure.

Review of Manufacturer-Supplied Indirect Treatment Comparison

Systematic Review Methods

The authors conducted a literature search of Scopus, PubMed, MEDLINE, OLDMEDLINE, Healthstar, Embase, Embase Classic, and International Pharmaceutical Abstracts databases via Ovid up to March 25, 2013. The search was updated to include results as of October 31, 2014. The search terms included onychomycosis and treatment, and was limited to clinical trials. The clinicaltrials.gov website was also searched for relevant trials.

English-language studies that examined oral or topical treatments (as monotherapy) for toenail onychomycosis caused by dermatophytes and that reported mycological cure rates (defined as negative potassium hydroxide mount and culture) were eligible for inclusion. The studies had to be phase III or IV randomized controlled trials with a parallel-group design and a minimum of 48 weeks in duration. Dosages of fluconazole of 150 mg, 300 mg or 450 mg administered weekly for six or nine months were combined into one treatment group based on data from a prior study that found these dosages were equivalent. For all other treatments, different dosages were analyzed separately. For multi-arm trials, only treatment groups that reported standard dosages were included. Terbinafine groups with treatment duration of more than 12 weeks were therefore excluded. The authors excluded phase II data due to their narrow inclusion criteria.

Two reviewers screened the titles, abstracts and full-text articles to determine if they met the inclusion criteria. Two reviewers also rated the methodological quality of each trial using a study-quality assessment tool based on the Consolidated Standards of Reporting Trials statement. This instrument included 12 items on the reporting of randomization, blinding, patient characteristics, and statistical analysis in clinical trials. A score of 11 points or higher out of a maximum of 20 was deemed to be a study of high quality.[37] The data extraction

was performed by one reviewer and verified by a second reviewer. Mycological cure, defined as negative potassium hydroxide and the absence of dermatophytes in culture, was the only outcome assessed.

A kappa statistic was used to assess the degree of inter-rater agreement on study quality. Between-trial heterogeneity was evaluated narratively based on the study design and patients' baseline characteristics, and quantitatively based on the I^2 values from Mantel–Haenszel random-effects pairwise meta-analysis (Review Manager 5.3).

Analysis Methods

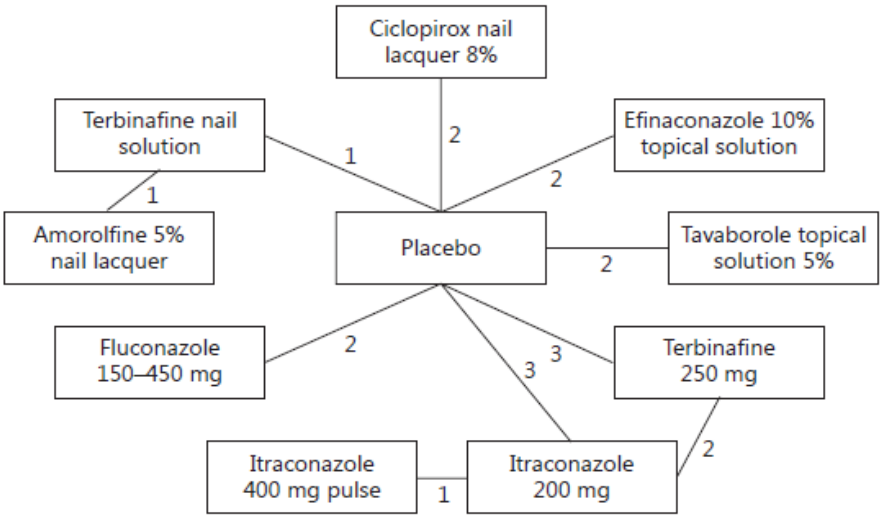
The network meta-analysis was conducted using a Bayesian random-effects consistency model, using Aggregate Data Drug Information System software version 1.16.3. The model used minimally informative priors (not specified) and arbitrary values for the Markov chain that were assigned by ADDIS and updated with each iteration. A burn-in of 20,000 iterations was used with 100,000 iterations for parameter estimation. Convergence was assessed using the Brooks–Gelman diagnostic. A node-splitting analysis was conducted to evaluate the consistency between direct and indirect evidence using significance level of 0.05. Treatment effects were reported as odds ratios (ORs) and 95% credible intervals (CrIs). Treatment comparisons with a 95% CrI that excluded the null were interpreted as statistically significant. There was no mention of any assessment of model fit.

Evidence Network

The ITC included 19 randomized controlled trials that evaluated efinaconazole 10% topical solution (two trials, N on active treatment = 1,239), ciclopirox 8% nail lacquer (two trials, N = 231), and the following oral therapies: terbinafine 250 mg (five trials, N = 499), itraconazole 200 mg (six trials, N = 445), itraconazole 400 mg pulse therapy (one trial, N = 64), and fluconazole 150 mg to 450 mg (two trials, N = 461) (Figure 2). Three other topical treatments that have not been approved for use in Canada were also included: terbinafine nail solution (two trials, N = 778), amorolfine 5% nail lacquer (one trial, N = 522), and tavaborole 5% topical solution (two trials, N = 795). Four of the trials were active-controlled; the other 15 trials compared an oral or topical treatment with placebo. The trials for oral treatments were published between 1992 and 1998 and generally had smaller sample sizes (range: 31 to 372) than the trials evaluating topical treatments, which were reported between the years 2000 and 2013 and enrolled between 223 and 1,018 patients. All trials were double-blind except for one comparing terbinafine nail solution with amorolfine lacquer. The authors rated all studies as high quality.

The mean age per treatment group ranged from 41 years to 55.5 years, except for one trial that reported an age range from 18 to 70 years, and another that did not report age. The patients enrolled in most trials had distal and lateral subungual onychomycosis due to dermatophytes; four trials also enrolled patients with proximal subungual onychomycosis or total dystrophic nail bed disease. Although severity was difficult to compare across trials as the measurements of nail involvement differed, the review authors stated that more patients with milder disease were enrolled in the trials for topical therapies. Statistical heterogeneity was low for comparisons where pairwise meta-analysis was possible, with I^2 values ranging from 0% to 29%. Mycological cure assessments were performed at 48 to 60 weeks.

Figure 2: Evidence Network



Source: Gupta AK, Daigle D, Foley KA. Network Meta-Analysis of Onychomycosis Treatments. Skin Appendage Disorders. 2015;1(2):74-81. Copyright © 2015 Karger Publishers, Basel, Switzerland.

Indirect Comparison Methods

Results

The authors stated that convergence was reached after a 20,000-iteration burn-in and 100,000 iterations for parameter estimation for the consistency model.

The ORs of mycological cure were statistically significantly higher for efinaconazole versus placebo (OR 5.95; 95% CrI, 3.67 to 9.67) but statistically significantly lower than terbinafine 250 mg daily oral therapy (OR 0.13; 95% CrI, 0.05 to 0.28) and itraconazole 200 mg daily oral (OR 0.36; 95% CrI, 0.14 to 0.76) (Table 20). The direction and magnitude of differences between itraconazole pulse therapy and efinaconazole were similar to those reported for the comparison with itraconazole daily therapy, although the 95% CrI did not exclude the null (OR 0.32; 95% CrI, 0.08 to 1.06). No statistically significant differences were found between efinaconazole and ciclopirox 5% nail lacquer (OR 1.41; 95% CrI, 0.63 to 3.08) (Table 20).

The authors conducted a node-splitting analysis to explore a possible inconsistency in the one closed loop available (placebo, terbinafine 250 mg, and itraconazole 200 mg). The analysis suggested the direct and indirect evidence were in agreement with each other and with the consistency model (inconsistency *P* values were 0.32 to 0.40).

Table 20: Indirect Evidence of Mycologic Cure

Control	Mycologic Cure Efinaconazole vs. Control OR (95% CrI)[a]
Placebo	**5.95 (3.67 to 9.67)**
Terbinafine 250 mg	**0.13 (0.05 to 0.28)**
Itraconazole 400 mg pulse therapy[b]	0.32 (0.08 to 1.06)
Itraconazole 200 mg	**0.36 (0.14 to 0.76)**
Fluconazole 150 mg to 450 mg[c]	0.65 (0.29 to 1.43)
Ciclopirox 5% nail lacquer	1.41 (0.63 to 3.08)

CrI = credible interval; OR = odds ratio.

[a] Efinaconazole was associated with higher odds of mycological cure for comparisons with OR > 1. Any 95% CrI that excluded the null (i.e., 1) were interpreted as statistically significant and are shown in bold.

[b] Pulse therapy includes a three-month cycle of itraconazole 400 mg daily for one week then no treatment for three weeks.[21]

[c] Fluconazole is not approved for onychomycosis in Canada.

Source: Gupta, Daigle, Foley.[33]

Critical Appraisal

The authors conducted a systematic review to identify relevant studies for inclusion in the ITC. This included a literature search of multiple databases, with screening and quality assessment conducted by two researchers. Data extraction was conducted by one researcher and verified by another. The literature search was limited to English-language reports, and other than clinicaltrials.gov, there was no search of grey literature. The review is also dated, having included studies published up to 2013 in the analysis. There was no assessment of publication bias. Although the review included all treatments for onychomycosis that have been approved in Canada, the scope was limited to trials reporting on mycological cure, and no other efficacy or safety outcomes were evaluated. Mycological cure is less relevant to patients, who desire normal looking nails. In addition, mycological cure may not be a reliable outcome measure as it has been reported to yield false-negatives.[3] The authors justified the narrow scope by stating that it was necessary to minimize between-study heterogeneity, and that other relevant outcomes, such as clinical cure, are subjective and not reported consistently across trials. It is possible that trials that report on other potentially relevant outcomes may have been excluded.

The authors used an instrument developed by Gupta et al.[37] to assess the quality of the included studies. This instrument focused on the quality of the reporting rather than the risk of bias of the trials, and used the number of citations as a metric to define high-quality trials. Although the authors rated all studies as high quality, considering the differences in the trials' publication dates (1990s for oral therapies, 2000 for ciclopirox, and 2013 to 2014 for other topicals) some variation in the quality of the conduct of the trials would be expected. One trial was open-label and thus the assessment of subjective outcomes may by biased by knowledge of the treatment received. However, this study compared two active topical treatments, making the impact of any potential bias unclear.

Key to the validity of any ITC is whether the transitivity assumption has been met, i.e., whether it was equally likely that any patient in the network could have been given any of the treatments in the network. For this ITC, it is unclear if this assumption was met as there were differences in the severity of the onychomycosis across trials. The patients who

received topical therapies generally had a lower percentage of nail involvement than those enrolled in trials for oral therapies. The placebo response rate also suggests that differences may exist between the groups. In the topical treatment trials the median percentage of patients with mycological cure in the placebo groups was 11.5% (range 5.5% to 16.8%) whereas the oral studies median percentage was 6.2% (range 0% to 13%). The review did not assess treatment adherence, which may be another source of heterogeneity, considering that topical treatment requires daily administration for one year versus oral therapies, which are generally limited to three months.

The authors used a Bayesian random-effects consistency model to evaluate treatment effects. The authors provided limited justification for the model selected, and other than the node-splitting analysis, and did not explore any alternative models or sensitivity analyses. The priors used in the random-effects model were not specified other than stating that they were minimally informative. Moreover, data from the direct pairwise meta-analyses were not reported, and it was not possible to compare the direct and indirect treatment estimates. Given the heterogeneity between studies, a random-effects model may be most appropriate, but this cannot be confirmed with the data available. Some comparisons showed wide CrIs, suggesting there is considerable uncertainty in the estimates. In general, the data were sparse, especially for oral treatments, with some treatment comparisons limited to data from one randomized controlled trial. There was only one closed loop for which consistency between direct and indirect evidence could be evaluated.

The authors disclosed their relationship to the pharmaceutical industry, which included conducting clinical trials or serving as a speaker for Valeant Canada and other pharmaceutical companies.

The external validity of the analysis is limited due to the selection of mycological cure as the outcome of interest. This outcome is less relevant to patients and has a high likelihood of false-negative results. Moreover, the duration of the included trials (48 to 60 weeks) precluded the assessment of relapse. Based on the data available from the report, it is unclear if patients most in need of treatment, for example, those with functional impairment or with a higher risk of secondary infections, were included in the trials. In addition, some of the dosing regimens used in the trials were not consistent with those recommended in Canadian product monographs.

Conclusion

The manufacturer supplied an ITC published in 2015 that evaluated the efficacy of efinaconazole 10% topical solution relative to oral and topical treatments for onychomycosis.[33] The ITC included data from one open-label and 18 double-blind randomized controlled trials that were 48 to 60 weeks in duration. The authors conducted a random-effects Bayesian network meta-analysis that suggested terbinafine 250 mg daily and itraconazole 200 mg daily were more effective than efinaconazole at inducing mycological cure. No statistically significant differences were found between efinaconazole and ciclopirox 5% nail lacquer. However, these data should be interpreted with caution due to differences in disease severity among the patients enrolled in trials for oral versus topical treatments. Data were sparse for some treatment comparisons, which may have contributed to the wide CrIs observed. Moreover, the clinical relevance of mycological cure has been questioned as it is associated with false-negative results.

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