Efficacy and safety of topical terbinafine 10% solution (MOB-015) in the treatment of mild to moderate distal subungual onychomycosis: A randomized, multicenter, double-blind, vehicle-controlled phase 3 study

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Background: Onychomycosis is a recalcitrant fungal nail infection. Topical antifungal agents may be preferred over systemic agents due to lack of systemic adverse effects.

Objective: To investigate the efficacy and safety of topical terbinafine 10% solution (MOB-015) for the treatment of distal and lateral subungual onychomycosis.

Methods: In a multicenter, double-blind, phase III, North American study, patients with mild to moderate distal and lateral subungual onychomycosis involving 20% to 60% of at least 1 great toenail were randomized to once daily application of MOB-015 or matching vehicle for 48 weeks. The primary efficacy variable was complete cure, while the secondary efficacy variables were mycological cure and treatment success. Safety evaluations were also performed.

Results: At week 52, the mycological cure (negative culture and potassium hydroxide microscopy) rate in the MOB-015 and vehicle groups was 69.9% and 27.7%, respectively ($P < .001$), and complete cure (0% clinical disease involvement and mycological cure) was achieved in 4.5% and 0% of patients, respectively ($P = .0195$). At least 1 adverse event leading to discontinuation of treatment occurred in 2.8% of patients in the MOB-015 group and in 4.2% in the vehicle group.

Limitation: The follow-up period after end of treatment may not be sufficient to accurately reflect cure in distal and lateral subungual onychomycosis.

Conclusions: MOB-015 is a treatment option for onychomycosis with an adverse event profile similar to vehicle. (J Am Acad Dermatol 2021;85:95-104.)

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Conflicts of interest: Dr Gupta is an advisor to Moberg Pharma, Bausch Health (Canada), and Ortho Dermatologics, and is an investigator for Bausch Health (Canada). Dr Rensfeldt is a consultant and was an employee of Moberg Pharma, Bromma, Sweden. Dr Tavakkol is an employee of Moberg Pharma. Drs Gupta, Surprenant, Kempers, and Pariser were investigators in the MOB-015 study. The authors are fully responsible for the content, editorial decisions, and opinions expressed in the current article. No author received an honorarium related to the development of this manuscript. Drs Surprenant, Kempers, and Pariser have no conflicts of interest to declare.

IRB approval status: This study received Institutional Review Board approval and was executed using Good Clinical Practices as per the FDA and International Conference on Harmonization guidelines.

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Oral terbinafine is the gold standard for treating onychomycosis, with mycological and complete cure rates of 70% and 38%, respectively.[1,2] Systemic agents can have potentially severe adverse effects and drug-drug interactions.[3-11] Treatment failure (20%-50%) and recurrence rates (10%-53%) are high and rising.[12-14] Topical treatments with their modest efficacy[15-21] have spurred the search for effective options.

CAPSULE SUMMARY

- MOB-015 is a topical formulation of fungicidal terbinafine for treatment of mild to moderate onychomycosis.
- The favorable benefit-to-risk ratio, with mycological cure of 69.9% and complete cure of 4.5% makes MOB-015 an option for managing onychomycosis.

A phase II study of MOB-015 demonstrated a mycological cure rate of 54.2% (n = 25 patients).[22] The pharmacokinetic profile was favorable compared with oral terbinafine, with higher concentrations of terbinafine in the nail plate (~1000×) and nail bed (~40×) and little or no systemic absorption.[22] In this phase III study, we evaluated the efficacy and safety of MOB-015 vs vehicle in patients 12 years and older with distal and lateral subungual onychomycosis (DSO).

METHODS

Patients and treatment

Male and female individuals aged 12 to 74 years with confirmed DSO involving 20% to 60% of at least 1 great toenail with positive culture for dermatophytes were eligible for inclusion in the study. Patients were excluded if they had other clinical types of onychomycosis, target toenail thickness >3 mm, DSO of the great toenail where involvement extended into the proximal region (unaffected proximal toenail was <3 mm), onychomycosis "spike" extending to eponychium of the target toenail, dermatophytoma, abnormal nail appearance due to conditions other than DSO, history of toenail surgery, known immunodeficiency, uncontrolled diabetes mellitus, peripheral circulatory insufficiency, and severe moccasin tinea pedis. Women with a positive pregnancy test or who were breastfeeding at screening were excluded. Patients who used systemic antifungal agents within 6 months or topical antifungal agents on toenails within 6 weeks of screening were also excluded.

Study treatments included MOB-015 and vehicle, which were indistinguishable in appearance and mode of administration. Patients were instructed to apply the treatment for 48 weeks to all affected fingernails and toenails, and under the free edge of the nail, once daily.

Study design

This study was a multicenter (28 study centers: 23 from the United States and 5 from Canada), randomized, 2-arm, parallel-group, vehicle-controlled, double-blind, phase III study conducted from September 2016 to September 2019 (NCT02859519). The study was performed in accordance with the Declaration of Helsinki and in compliance with the principles of the International Conference on Harmonization-Good Clinical Practice guidelines. The planning and conduct of this clinical study were in accordance with national laws and regulations of the country in which the clinical research was conducted, and all patients were required to provide written consent/assent to participate in the study. Regarding patients who were minor, permission from the parent or legal guardian was obtained.

The study design is presented in Figure 1. Screening of patients took place up to 8 weeks before randomization. Patients who met the inclusion criteria were assigned a computer-generated randomization number at week 0, which allocated them into 1 of 2 treatment arms, MOB-015 or matching vehicle, in a 2:1 ratio, respectively. The treatment period was 48 weeks, with visits every 12 weeks, followed by 4 weeks without treatment. The last study visit was performed at week 52.

Clinical disease involvement was assessed, and mycology sampling and nail trimming were performed at screening and at weeks 0, 12, 24, 36, 48, and 52. Photo documentation was performed at screening and at weeks 0, 12, 24, and 52. Patients were permitted to clip their toenails between visits but were instructed to not clip/trim the target toenail within 1 month of an upcoming visit. Nail samples from the great toenails were collected and sent to the central laboratory for direct potassium hydroxide (KOH) microscopy and fungal culture to identify dermatophyte species in a blinded manner.

Efficacy

The primary efficacy variable was complete cure of the target toenail, defined as mycological cure (negative direct KOH microscopy and negative

Abbreviations used:

AE:	adverse event
DSO:	distal and lateral subungual onychomycosis
FAS:	full analysis set
KOH:	potassium hydroxide
MOB-015:	topical terbinafine 10% solution

fungal culture of dermatophytes), and 0% clinical disease involvement at week 52. Key secondary efficacy variables of the target toenail included mycological cure at week 52 (negative direct KOH microscopy and negative fungal culture of dermatophytes of the target toenail) and treatment success at week 52 (negative direct KOH microscopy, negative fungal culture of dermatophytes, and ≤10% clinical disease involvement of the target toenail). Physicians were asked to assess the percentage of nail involvement in the target toenail.

At each visit, patients were asked to assess treatment response by answering the question "How do you perceive your response to treatment since last visit?" The 2 questions corresponding to almost cured or cured were "most symptoms have disappeared," or "completely cured without any symptoms left," respectively. The scoring system has been internally validated and used in other studies.[23] Patients' subjective scores of all their treated nails, except the little toenail, were recorded. Patients were also asked to report the ease of handling the study drug at each visit as very easy, easy, neither easy nor difficult, somewhat difficult, or very difficult.

Safety

Safety was assessed by recording all observed and patient-reported adverse events (AEs) throughout the study (weeks 0-52). AEs were coded using the terminology of the Medical Dictionary for Regulatory Activities, Version 21.0, and summarized by system organ class and preferred term.

AE severity was divided into those that caused no limitation to the patients or required any intervention (mild), caused some limitation or requiring minimal/local intervention (moderate), or was medically significant (severe). In addition, AEs were assigned causality of possible, probable, or definite by blinded investigators during the study with no knowledge of assigned study medication. A serious AE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening or required inpatient hospitalization or caused prolongation of hospitalization.

Determination of sample size

The minimum number of patients needed to show superiority of MOB-015 over vehicle was determined for complete cure rate at week 52, 4 weeks after the end of treatment. Based on a randomization ratio of 2:1 for MOB-015: vehicle, 80% power, and a 2-sided significance level of $\alpha = 0.05$, we determined 198 evaluable patients in the full analysis set (FAS) for MOB-015 and 99 for vehicle (297 patients in total) were required. With an estimated 20% dropouts, approximately 372 patients were planned to be randomized in the study.

Statistical analysis

The primary efficacy variable was evaluated in the intent-to-treat population or FAS, which included all patients who received the study medication and were randomized based on a single 2:1 randomization ratio. The FAS was analyzed according to the assigned treatment arm at the time of randomization, that is, according to the planned treatment.

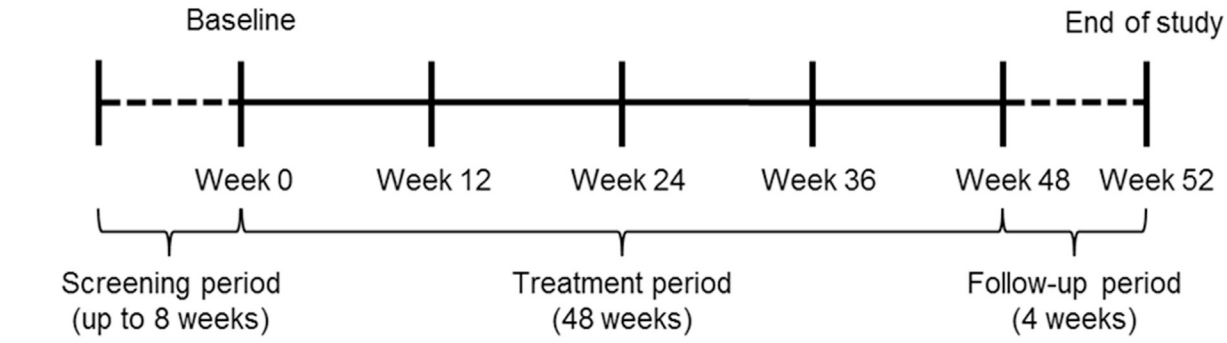
Comparisons between treatment arms for primary and key secondary efficacy end points were performed using a 2-sided Cochran-Mantel-Haenszel test stratified by country, at a 5% significance level. A last-observation-carried-forward approach was used to replace missing values. A number of sensitivity analyses were performed to support the analysis of the primary efficacy variable. All other secondary efficacy variables were exploratively compared between treatment groups.

RESULTS

Patients

There were 365 patients with DSO of at least 1 great toenail randomized to MOB-015 (n = 246) or vehicle (n = 119) in the FAS analysis (Fig 1). The average age in both the MOB-015 and vehicle groups at baseline was 55 years (range, 12-74 years) (Table I). The mean number of DSO affected toenails on the left and right foot was 2.3 and 2.4, respectively, in the MOB-015 group and was 2.5 and 2.7, respectively, in the vehicle group. Most patients had toenail involvement of ≥25% to ≤50% in both the MOB-015 (79.7%) and vehicle (79.0%) groups (Table I). There were no clinically meaningful differences between treatment groups for demographics or baseline characteristics.

Overall, 319 patients (87.4%) completed the 48-week treatment, and 287 (78.6%) completed the 4-week follow-up. There were 78 patients who prematurely discontinued the study because of withdrawal of consent (32/78 [41.0%]), lost to follow-up (26/78 [33.3%]), AEs (9/78 [11.5%]; 3 related AEs and 6 nonrelated AEs), other reasons



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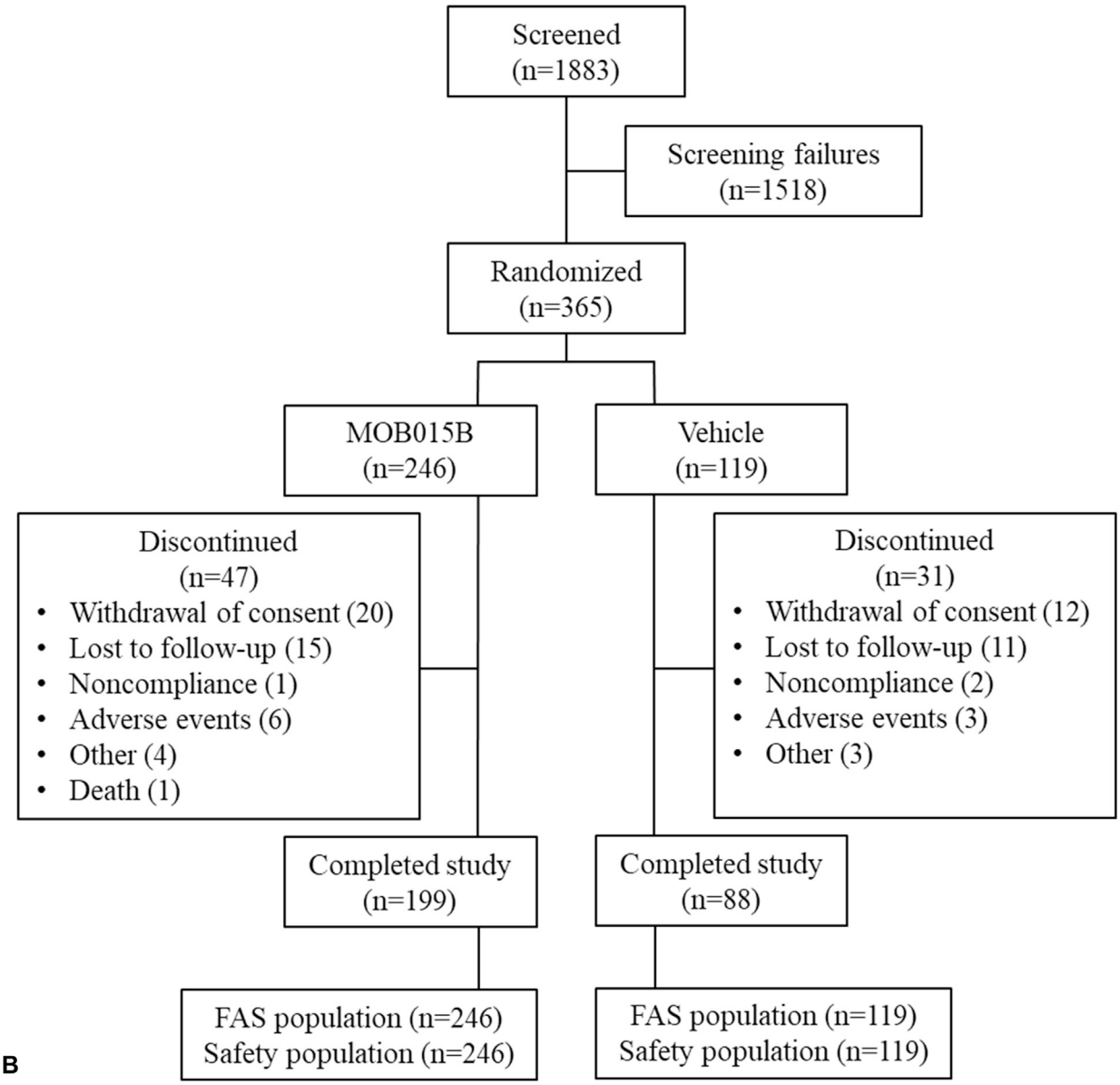

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Fig 1. Overview of the study. **A,** Study design. **B,** Study schematic and patient disposition. *FAS*, Full analysis set.

Table I. Demographics and baseline characteristics of the intent-to-treat population

Variable*	MOB-015 (n = 246)	Vehicle (n = 119)	Total (N = 365)
Age, y			
Mean (SD)	55.0 (11.1)	55.0 (13.4)	55.0 (11.9)
Range	21-74	12-74	12-74
Sex			
Male	207 (84.1)	98 (82.4)	305 (83.6)
Female	39 (15.9)	21 (17.6)	60 (16.4)
Race			
White	210 (85.4)	106 (89.1)	316 (86.6)
Black/African American	26 (10.6)	10 (8.4)	36 (9.9)
American Indian/Alaska Native	1 (0.4)	0 (0)	1 (0.3)
Asian	5 (2.0)	1 (0.8)	6 (1.6)
Native Hawaiian/Pacific Islander	1 (0.4)	0 (0)	1 (0.3)
Other	3 (1.2)	2 (1.7)	5 (1.4)
Ethnicity			
Hispanic or Latino	51 (20.7)	25 (21.0)	76 (20.8)
Not Hispanic or Latino	195 (79.3)	94 (79.0)	289 (79.2)
DSO affected toenails, No.			
Left, mean (median)	2.3 (1.6)	2.5 (1.7)	2.3 (1.6)
Right, mean (median)	2.4 (1.6)	2.7 (1.6)	2.5 (1.6)
Range, n	0-5	0-5	0-5
IGA of clinical disease involvement			
>10% to <25%	29 (11.8)	11 (9.2)	40 (11.0)
≥25% to ≤50%	196 (79.7)	94 (79.0)	290 (79.5)
>50% to ≤75%	21 (8.5)	14 (11.8)	35 (9.6)

DSO, Distal subungual onychomycosis; *IGA*, Investigator Global Assessment; *MOB-015*, topical terbinafine 10% solution.
*Data are presented as number (%) unless indicated otherwise.

(7/78 [9.0%]), physician decision (3/78 [3.8%]), and death (1/78 [1.3%]).

Efficacy

Efficacy assessments were performed at the scheduled visits, with the primary and key secondary variables being evaluated at week 52.

Primary efficacy variables. At week 52, 4.5% of MOB-015 patients achieved complete cure compared with 0.0% of vehicle patients ($P = .0195$) (Figs 2 and 3).

Key secondary variables. At week 52, 69.9% of MOB-015 patients achieved mycological cure, compared with 27.7% of patients in the vehicle group ($P < .001$). More patients in the MOB-015 group also achieved treatment success (negative direct KOH microscopy, negative fungal culture of dermatophytes, and ≤10% clinical disease involvement of the target toenail) compared with the vehicle group, 15.4% and 4.2%, respectively ($P = .0018$) (Fig 3).

Other secondary variables. At week 52, 95.9% of MOB-015 patients had negative fungal cultures compared with 58.0% of vehicle patients. More MOB-015 patients had negative direct KOH microscopy results at follow-up compared with vehicle patients (69.9% and 34.5%, respectively). At week 52, the target toenail was completely clear or almost clear (ie, 0% to ≤10% clinical disease involvement) in 19.1% of MOB-015 patients, whereas 8.4% of vehicle patients had the same results (Fig 3).

In the MOB-015 group, complete cure was observed as early as week 24, while mycological cure was first seen at week 12 and increased through the end of treatment and follow-up. Negative fungal culture ranged from 93.5% at week 12 to 95.9% at week 52.

The subjective scores of the patients improved in both the MOB-015 and vehicle groups at week 52. At week 52, 26.8% of the patients in the MOB-015 group vs 13.4% in the vehicle group reported that their nails were cured or almost completely cured (Fig 3). The subjective assessment of the ease of handling of the drug was reported as "very easy" and "easy" in 89.4% in the MOB-015 group vs 86.6% in the vehicle group.

Subgroup analysis by age

The complete cure rate at week 52 in the age-group 18 to <65 years was 4.6% in the MOB-015 group and 0% in the vehicle group. In those ≥65 years, the corresponding values were 4.1%

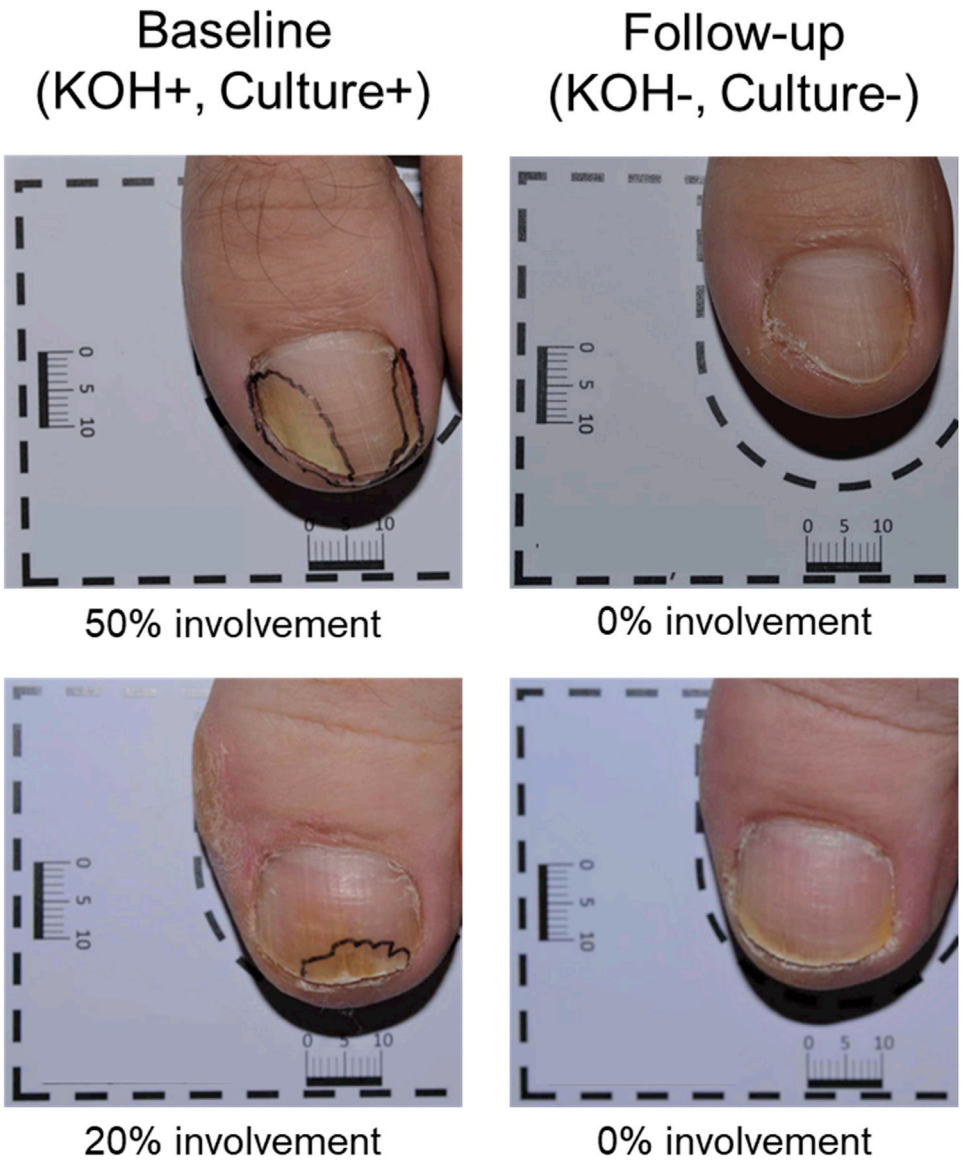

Fig 2. Dermatophyte toenail onychomycosis. Illustrative cases of complete cure. **Left,** Before treatment at baseline. **Right**, After treatment (follow-up) at week 52. *KOH*, Potassium hydroxide microscopy result; +, positive; −, negative.

and 0%, respectively. For mycological cure rate, in the age-group 18 to <65 years, the rates for MOB-015 and vehicle were 69.5% and 26.7%, respectively, and for the group ≥65 years, the rates were 71.4% and 29.0%, respectively.

Subgroup analysis by baseline severity of the target toenail and sex

The complete cure and mycological cure rates were numerically higher in the MOB-015 group when the baseline severity of the target nail plate was 20% to 50% compared with when the baseline severity of the target toenail was >50%, and higher in female patients compared with male patients.

Safety

Overall, AEs were reported in 47.2% of patients in the MOB-015 group and in 51.3% in the vehicle group (Table II). There were no clinically meaningful changes in vital sign measurements or laboratory changes.

The percentage of patients with at least 1 AE related to the study medication was 12.2% in the MOB-015 group and 16.0% in the vehicle group. Most AEs were mild to moderate in severity for both

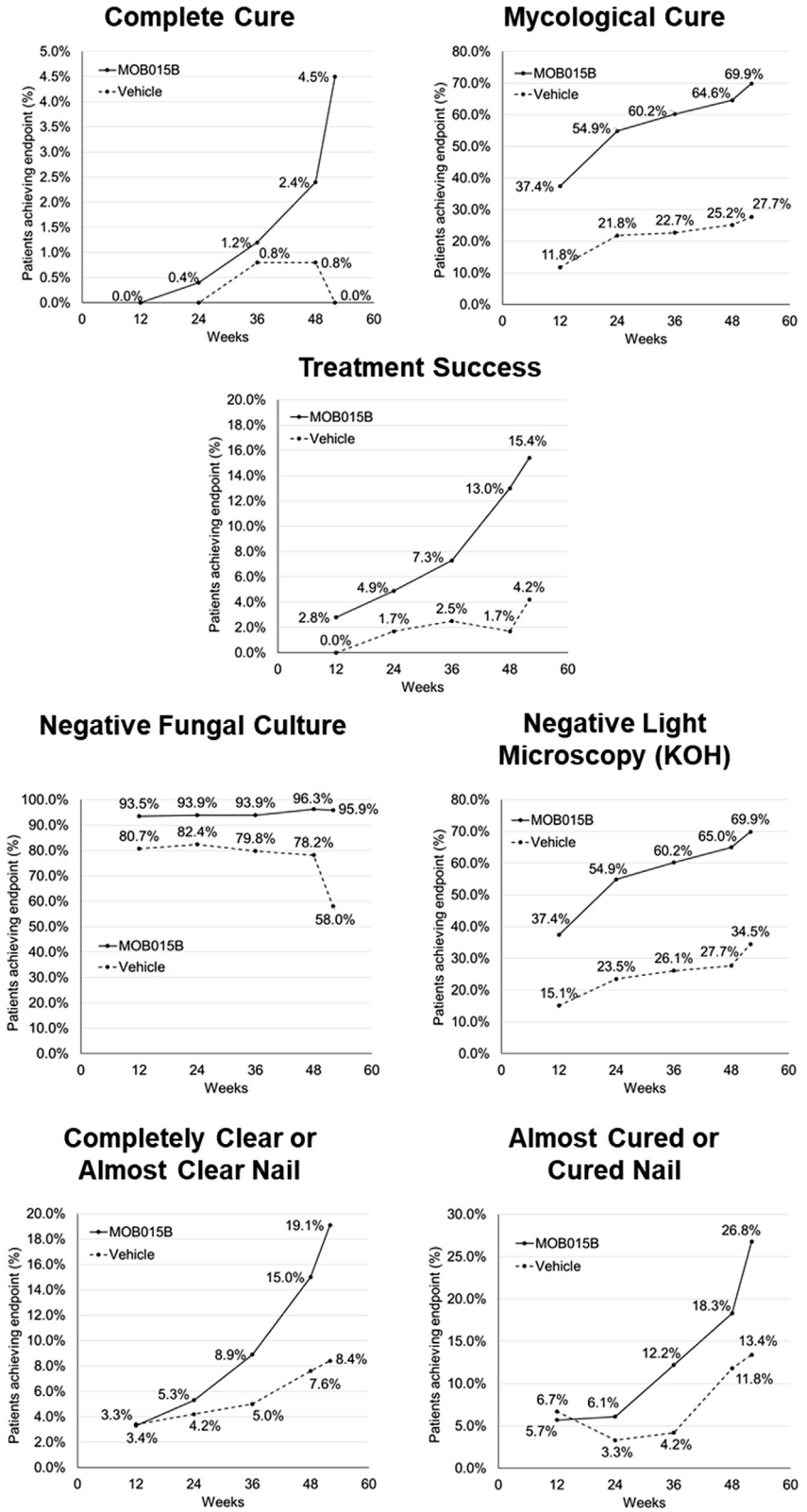

Fig 3. MOB-015 efficacy in dermatophyte toenail onychomycosis. Percentage of patients achieving the end point at week 52. Complete cure: negative direct potassium hydroxide (*KOH*) microscopy, negative fungal culture of dermatophytes, and 0% clinical disease involvement of target toenail. Mycological cure: negative direct KOH microscopy and negative fungal culture of dermatophytes of target toenail. Treatment success: negative direct KOH microscopy, negative fungal culture of dermatophytes, and ≤10% clinical disease involvement of target toenail. Completely clear or almost clear nail: 0% to ≤10% clinical disease involvement of target toenail. Almost cured or cured nail: patient subjective score.

Table II. Summary of adverse events

Adverse event	MOB-015 (n = 246), No. (%)	Vehicle (n = 119), No. (%)	Total (N = 365), No. (%)
No. of patients who reported ≥1 TEAE	116 (47.2)	61 (51.3)	177 (48.5)
Individual TEAEs reported by >2 patients			
Actinic keratosis	4 (1.6)	1 (0.8)	5 (1.4)
Acute sinusitis	2 (0.8)	1 (0.8)	3 (0.8)
Bronchitis	4 (1.6)	3 (2.5)	7 (1.9)
Gastrointestinal disorders	10 (4.1)	2 (1.7)	12 (3.3)
Influenza	3 (1.2)	3 (2.5)	6 (1.6)
Injury, poisoning, and procedural complications	16 (6.5)	8 (6.7)	24 (6.6)
Nasopharyngitis	15 (6.1)	6 (5.0)	21 (5.8)
Neoplasms (benign, malignant, and unspecified)	3 (1.2)	4 (3.4)	7 (1.9)
Nervous system disorders	11 (4.5)	3 (2.5)	14 (3.8)
Onychomadesis	9 (3.7)	6 (5.0)	15 (4.1)
Onychomycosis	3 (1.2)	1 (0.8)	4 (1.1)
Tinea pedis	27 (11.0)	23 (19.3)	50 (13.7)
Vascular disorders	9 (3.7)	0	9 (2.5)
Most common application site TEAEs			
Blister	2 (0.8)	2 (1.7)	4 (1.1)
Dermatitis	3 (1.2)	0	3 (0.8)
Dermatitis contact	7 (2.8)	0	7 (1.9)
Erythema	1 (0.4)	2 (1.7)	3 (0.8)
Nail bed bleeding	2 (0.8)	1 (0.8)	3 (0.8)
Onycholysis	2 (0.8)	4 (3.4)	6 (1.6)

MOB-015, Topical terbinafine 10% solution; *TEAE*, treatment emergent adverse event.

the MOB-015 and vehicle groups (95.4% and 94.7%, respectively). The percentage of patients who discontinued treatment due to at least 1 AE was 2.8% for the MOB-015 group and 4.2% for the vehicle group. Two patients in each group withdrew from the study due to an AE related to the study medication.

Serious AEs were reported in 9 patients (3.7%) receiving MOB-015 and in 5 (4.2%) using the vehicle control. All were of moderate or severe intensity, and none were related to the study medication. There was 1 death during the study in the MOB-015 group. The cause of death was reported as secondary to chronic obstructive pulmonary disease and was not related to the study medication.

DISCUSSION

MOB-015 was significantly more effective in treating dermatophyte toe onychomycosis than vehicle, demonstrating a mycological cure rate of 69.9% without systemic adverse reactions or drug interactions that are associated with the oral formulation.[1,2] In comparison, the mycological cure rate of oral terbinafine is 70% with a complete cure rate of 38%. The mycological and complete cure rates of MOB-015 both continued to improve after treatment was discontinued at week 48, suggesting these rates would continue to increase over time (Fig 3).

The fungicidal nature of terbinafine and the high concentrations in the nail bed and nail plate after topical application of MOB-015 result in terbinafine levels that are several thousand times greater than the minimum inhibitory concentration for common dermatophytes causing onychomycosis (eg, minimum inhibitory concentration 0.002-0.03 μg/g for *Trichophyton rubrum*).[22,24] This would explain the early onset and persistent fungal cure with MOB-015.

Mycological cure rate is an objective way to measure efficacy of an antifungal agent. The clinical cure rate is more subjective.[25] That being said, despite the mycological cure rate of 69.9%, the complete cure rate of MOB-015 was 4.5%. Analysis has shown that the vehicle (urea, lactic acid, propylene glycol), while enhancing the ability of terbinafine to penetrate the dorsal nail plate and improving fungal clearance, resulted in aesthetic color changes in the nail. These changes manifested as nail plate opaqueness that interfered with the assessment of clinical cure, thereby giving the nail the false appearance of failed clinical cure (data on file, Moberg Pharma). The upward slope of complete cure at week 52, 4 weeks after therapy was discontinued, suggests that the complete cure rate would likely continue to increase over time, especially as the fungus is eradicated and healthy toenail grows out (Fig 3). The negative culture rates of 80% to 90% achieved within 12 weeks of therapy and

maintained until the end of study at week 52 suggest that less frequent dosing might reduce the vehicle effect, minimize the color changes, and increase the complete cure rates of MOB-015.

Patients often associate mycological cure with clearance of the diseased nail plate; however, in this study, the vehicle-induced opaqueness delayed the appearance of normal-appearing nail plate until the nail plate was able to grow out. Therefore, patients would need to be counseled about this slow normalization of nail plate appearance.

The number and nature of AEs observed with MOB-015 and vehicle were similar. Most AEs were not related, as judged by the investigator, to treatment with MOB-015 or vehicle. This is in keeping with what would be expected of a topical antifungal preparation for managing onychomycosis.

CONCLUSION

Oral terbinafine is effective and safe in the treatment of onychomycosis in the geriatric population.[26,27] MOB-015 was effective in treating onychomycosis in patients 12 to 74 years of age. The lack of systemic absorption of MOB-015 reduces the potential for systemic AEs seen in oral terbinafine. MOB-015 has a favorable benefit-to-risk ratio, with a mycological and complete cure rate of 69.9% and 4.5%, respectively, making it a consideration for the treatment of dermatophyte onychomycosis.

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