LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Terbinafin Moberg Pharma
(terbinafine hydrochloride)

SE/H/2249/001/DC

This module reflects the scientific discussion for the approval of Terbinafin Moberg Pharma. The procedure was finalised on 2023-06-28. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Terbinafin Moberg Pharma, 98 mg/ml, Cutaneous solution.

The active substance is terbinafine hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Terbinafin Moberg Pharma, 98 mg/ml, cutaneous solution, is submitted according to Article 8(3 of Directive 2001/83/EC. The applicant, Moberg Pharma AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CZ, DK, ES, FI, FR, HU, IE, IT, NL and NO as concerned member states (CMS).

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation
Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application includes an EMA Decision, P/0450/2021, on the agreement of a paediatric investigation plan (PIP). The applicant has obtained a partial PIP waiver for some subsets of the paediatric population.

At the time of submission of the application, the PIP EMEA-002984-PIP01-21 was not yet completed.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
The Applicant has provided a rather limited review of data found in the literature on primary and secondary pharmacodynamics, and safety pharmacology. No new studies were provided except for the cardiovascular recordings, included in the repeat-dose toxicity study in mini-pigs (818-034), where the ECG recordings revealed no treatment-related effects. Since the pharmacology of terbinafine is well-known and that the systematic exposure of MOB015B applied to the nails is low (approximately 2000-fold lower than following oral use of 250 mg Lamisil® tablets) the risk is considered low. Therefore, no additional non-clinical investigations are required and although limited, the pharmacology literature review is considered acceptable.

Pharmacokinetics
The applicant has provided a review of data found in the literature on pharmacokinetics of terbinafine. In addition, an exploratory absorption study was provided that indicates that terbinafine (10% solutions) has good penetration properties with those excipients chosen for the formulation. Since the pharmacokinetics of terbinafine is well-known and the systemic exposure to terbinafine following application of MOB015B onto the nails is negligible the risk is considered low. Therefore, no additional non-clinical pharmacokinetic investigations are required, and the pharmacokinetic literature review is considered acceptable.

Toxicology
The applicant has provided with a literature review on toxicology and a couple of performed toxicology studies with terbinafine or MOB015B.

The Applicant has conducted dermal repeat-dose toxicity studies in rat and mini-pig treated with terbinafine applied as a nail lacquer for up to 6 months and 9 months, respectively. The formulation used in these studies was not the same to that of MOB015B, but the systemic exposure was several-fold higher in these species compared to that in patients treated with MOB015B which indicates high local concentrations of terbinafine in the skin of the animals. The studies revealed treatment-related minimal to slight dermal toxicity consisting of epidermal hyperplasia, hyperkeratosis, and epidermal surface exudates that was only present in rats treated at 30 and 60 mg/kg for 28-days.
The applicant has not provided any literature regarding the cancerogenic potential of terbinafine or provided any cancer studies.

However, it is agreed with the applicant that there is no perceived systematic cancerogenic risk based on the low systematic exposure following maximum use conditions of MOB015B.
Furthermore, terbinafine for topical use is well-known and has not been associated with a carcinogenic risk and is not genotoxic or photoreactive. In addition, there were no pre-neoplastic changes or other cancerogenic signs in any of the repeat-toxicology studies conducted that indicates a cancerogenic potential of terbinafine when applied to dermis.

Terbinafine is not indicated to be teratogenic or have an embryotoxic potential according to the limited amount of available literature data on reproductive and developmental toxicity.

The applicant provided with a dermal irritation study in rabbits treated with terbinafine HCl nail lacquer for 28 days and a bovine corneal opacity and permeability (BCOP) test which were performed

both on the drug substance terbinafine and the drug product MOB015B. The dermal irritation study revealed that terbinafine HCl nail lacquer is slightly irritating at a concentration of 5 and 10%. The BCOP test showed that MOB015B is a severe/corrosive eye irritant, and it is recommended in SmPC 4.4 that exposure of eyes should be thoroughly avoided. Furthermore, MOB015B is not indicated to pose any phototoxic potential using the MTT test and the excipients used in MOB015B formulation are well-known. However, regarding phototoxic potential for topical applied products the 3T3 neutral red uptake phototoxicity test (3T3 NRU-PT) would have been considered according to ICH S10 guideline on Photosafety Evaluation of Pharmaceuticals.

Overall, the published studies regarding toxicity and the provided toxicity studies are regarded as sufficient for a known active substance application.

Environmental Risk Assessment (ERA)

Terbinafine has a molecular weight of 327.89 g/mol. It is lipophilic with reported experimentally derived log Kow values of 5.2 and 6, triggering a PBT assessment. As both reported log Kow values exceeds the trigger value of 3, a bioconcentration (BCF) study is requested and the Applicant has provided a post-authorisation commitment letter with a deadline for submission of such a study.

The Phase I PECSW was determined to be 0.16 µg/L using the default Fpen and an estimated daily dose of 31 mg. The PECSW exceeds the action limit of 0.01 µg/L and triggers an ERA Phase IIA assessment. The Fpen value used for calculating a refined Phase II PECsw is based on prevalence data, resulting in a refined PECsw of 0.853 µg/L.

According to the OECD TG106 study report for terbinafine the Koc values for the two sludges (3346 and 4694 L/Kg) did not exceed the action limit with regard to adsorption to sludge. [14C]Terbinafine shifted quicky from the water phase and partitioned into sediment at more than 10% (~72-83%) of applied radioactivity at day 14 and after. The DT50 values at a temperature of 20°C were <3 and 8 days in the water layer, and 16 and 31 days in the total water/sediment system for the two test systems, respectively. The mass balance (recovery) ranges were 98.8 - 109% and 88.5 - 102% in the two water/sediment systems. The significant partitioning of terbinafine to sediment triggers a Tier B sediment organism toxicity test. The Applicant has submitted a post-authorisation commitment letter to provide a Tier B sediment organism toxicity study no later than June 27, 2025.

For aquatic toxicity, freshwater algae growth rate and yield were the most sensitive endpoints reported, both with NOEC and LOEC values of 0.00053 and 0.0018 mg/L, respectively.
The risk ratios (PEC/PNEC) are calculated to be 16.08 (0.853/0.053) for surface water, 0.39 (0.213/0.55) for ground water and 0.0008 (0.853/1000) for sludge. As a sediment dwelling organism toxicity study is pending, the potential risk to the sediment compartment remains to be assessed.

Summary of main study results

Substance (INN/Invented Name): Terbinafine			
CAS-number (if available): 78628-80-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}	Cited value	log K_{ow} = 6.0	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	6.0	B
	BCF	Pending	Study pending

Persistence	DT50 or ready biodegradability	$DT_{50,\ water}$ = 6-17 days, 12°C $DT_{50,\ whole\ system}$ = 16 - 31d, 20°C			Not P
Toxicity	NA	NA			
PBT-statement:	Not PBT.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$ (refined based on prevalence)	0.853	µg/L			> 0.01 threshold Y
Other concerns (e.g., chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD TG106	K_{oc} sludge 1 = 3346 L/kg K_{oc} sludge 2 = 4694 L/kg K_{oc} soil 1 = 10 039 L/kg K_{oc} soil 2 = 11 365 L/kg K_{oc} soil 3 = 9 228 L/kg			K_{oc} sludge < 10 000 L/kg
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50,\ water}$ = 6-17 days, 12°C $DT_{50,\ whole\ system}$ = 16 - 31d, 20°C % shifting to sediment = ~72-83% AR after 14d.			%AR in sediment (14d) > 10, OECD TG218 test triggered.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG 201	NOEC Growth rate and yield	5.3	µg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD TG 211	NOEC	5.5	µg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG 210	NOEC	47	µg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG 209	EC50	> 100	mg/ L	Sludge from CH-4153 Reinach, Switzerland.
Phase IIb Studies					
Sediment dwelling organism	OECD TG 218				Study pending

NA = Not applicable

Conclusions on studies:

The potential of terbinafine for bioaccumulation is pending due to the lack of data from a bioconcentration study. The risk ratios (PEC/PNEC) for surface water exceeds the action limit thus triggering a Phase II tier B risk assessment. The Applicant has provided a post-authorisation commitment letter for the submission of a Phase II tier B risk assessment by the deadline 27/06/2025.

In summary, the reported data do not allow to conclude on the potential risk of terbinafine to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
The plasma exposure following topical administration of Terbinafin Moberg Pharma (product ID code MOB015B) was evaluated in studies MOB015B-II and MOB015B-VIII.

Study MOB015B-II was an open, single-centre pilot study of efficacy and safety of topical MOB015B in the treatment of distal subungual onychomycosis (DSO). Patients were administered the investigational medicinal product, MoB015B, to affected nails once daily during 48 weeks. In a sub-set of 8 patients the concentration of terbinafine in plasma was measured after 4 weeks. In addition terbinafine concentration in nail and nail bed was measured at one occasion after 24 weeks.
Study MOB015B-II was a pilot study and the plasma results are considered as preliminary due to the few subjects and since there was only one plasma sample collected in each subject. The results in nail and nailbed are also considered as preliminary due to the few samples and high variability.

Study MOB015B-VIII was a repeated-dose study in 20 subjects with moderate to severe onychomycosis of the toenails. The primary objective was to measure the plasma exposure (Cmax, AUC0-t) of terbinafine after 1 day and 28 days of once daily applications of MOB015B under maximal use conditions. To maximize drug absorption, MOB015B was applied to all toenails once daily for 28 days. Blood samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after application on day 1. In addition, blood samples were collected prior to the day 14 topical application of study drug (pre-dose) and at 0.5, 1, 2, 4, 6, 8, 10, 24, 48, 72-hours following the day 28 dose. Pharmacokinetic variables were calculated using conventional non-compartmental methods.

Results: The results are presented in Table 1 and the mean plasma concentration-time profiles of terbinafine on days 1 and 28 are shown in Figure 1. Mean Cmax was 718 pg/mL on day 28 and mean AUC0-24 was 13645 h*pg/mL on Day 28. Steady-state appeared to be achieved after 28 days of once daily application of terfinabine. The plasma concentrations following 4 weeks of topical administration (718 pg/mL) were very low compared to mean plasma level (1.39 µg/mL) observed after oral administration of 250 mg terbinafine once daily for 28 days.

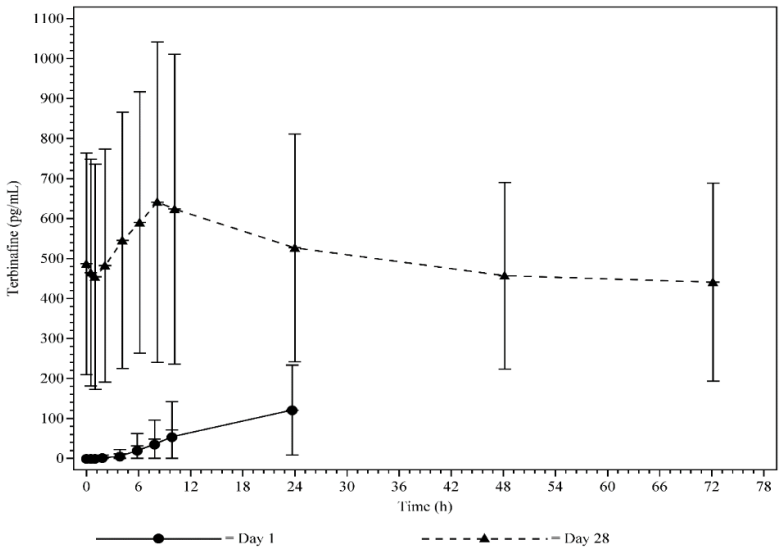


Figure 1. Mean (±SD) Plasma Concentration - Time Profiles of Terbinafine on a Linear Scale (Study MOB015B-VIII)

Table 1. Summary of PK parameters (Study MOB015B-VIII)

PK Parameter	Overall (N=20)		
	Day 1	Day 13*	Day 28
C_{max} (pg/mL)			
N	19		19
Mean (SD)	127.83 (121.331)		718.05 (421.806)
GM	93.16		575.11
CV (%) of Mean	94.9		58.7
Median	76.80		733.00
Min, Max	22.0, 513.0		116.0, 1720.0
C_{24} (pg/mL)			
N	19	19	19
Mean (SD)	120.94 (112.614)	429.74 (268.486)	526.62 (284.926)
GM	90.71	342.78	444.23
CV (%) of Mean	93.1	62.5	54.1
Median	76.80	368.00	547.00
Min, Max	22.0, 513.0	53.0, 964.0	99.8, 1350.0
T_{max} (h)			
N	19		19
Mean (SD)	23.28 (3.217)		17.90 (20.767)
Median	24.00		8.00
Min, Max	10.0, 24.4		0.0, 72.0
AUC_{0-24} (h*pg/mL)			
N	17		19
Mean (SD)	1551.99 (1587.788)		13645.42 (7543.816)
GM	1105.09		11132.82
CV (%) of Mean	102.3		55.3
Median	852.00		13022.75
Min, Max	440.5, 5938.8		2568.1, 29176.6
AUC_{0-t} (h*pg/mL)			
N	19		19
Mean (SD)	1414.82 (1552.788)		36222.91 (18801.152)
GM	935.59		30432.24
CV (%) of Mean	109.8		51.9
Median	808.70		36641.00
Min, Max	153.1, 5938.8		6643.3, 77840.9

* Day 14 pre-dose concentration = Day 13 C_{24}

The systemic exposure to terbinafine following application of MOB015B onto the nails is very low, particularly when compared to approved oral terbinafine and therefore no dose-adjustments or warnings are necessary in elderly or patients with hepatic or renal impairment and the risk of pharmacokinetic drug interactions is negligible.

In conclusion, the systemic plasma exposure following topical application of MOB015B onto the nails are negligible compared to oral administration of terbinafine. The systemic pharmacokinetics of terbinafine are hence of limited relevance for this product.

Pharmacodynamics

Terbinafine is an allylamine antifungal compound that inhibits biosynthesis of ergosterol, an essential component of fungal cell membrane, via the inhibition of squalene epoxidase enzyme. Terbinafine can be formulated as tablets, but also in creams/gels/nail lacquer for topical administration.

The clinical experience with oral terbinafine is extensive, for systemic treatment of fungal infections of the skin and nails. There are disadvantages with systemic administration of terbinafine since hepatotoxic adverse events can occur and monitoring of liver function may be needed. Therefore, local treatment of onychomycosis is of advantage especially in less severe cases of the disease.

The product Terbinafin Moberg Pharma which is now proposed for marketing contains terbinafine hydrochloride formulated as a cutaneous solution, proposed to be indicated in the treatment of onychomycosis in adults.

Clinical efficacy

Design and conduct of clinical studies

The present application concerns a cutaneous solution of terbinafine hydrochloride 110 mg/g ml (test product MOB015B) as the active ingredient, equivalent to 98 mg/ml terbinafine an antifungal agent, for topical administration to nails in the treatment of onychomycosis caused by dermatophyte in adults.

The clinical efficacy is supported by one Phase 2 pharmacokinetic, safety and efficacy study (MOB015B-II) and two Phase 3 studies (MOB015B-III and MOB015B-IV) with similar design.

Phase 2 pilot study of efficacy and safety MOB015B-II

Study MOB015B-II was an open, single-centre Phase 2 pilot study of efficacy and safety of topical MOB015B in the treatment of distal subungual onychomycosis (DSO).

All subjects were treated with MOB015B solution, containing 10% terbinafine, once daily for 48 weeks after which a follow-up period of 12 weeks without treatment ensued. The absence of a vehicle arm is considered a deficiency of the study.

The objectives of the study were to assess the safety, efficacy, and PK of concentrations of the test product in patients with DSO.

Eligible were adult patients, aged 18-70 years, with DSO of at least one great toe nail involving 25 to 75% of the target nail and positive culture for dermatophytes. Although the inclusion criteria for this study allowed for target nails with 25 to 75% of the nail to be affected, from target nail photos it is noted that many subjects had more than 50% disease involvement at inclusion.

Efficacy assessments included the proportion of subjects with mycological cure of the target nail, defined as negative fungal culture and negative direct microscopy at 60 weeks. In addition, several secondary efficacy variables were assessed, such as the proportion of subjects with mycological cure of the target nail defined as negative fungal culture and negative direct potassium hydroxide (KOH) microscopy at 12, 24 and 36 weeks and the proportion of subjects with complete cure. Safety was assessed by recording all directly observed and spontaneously reported adverse events (AEs) during the study.

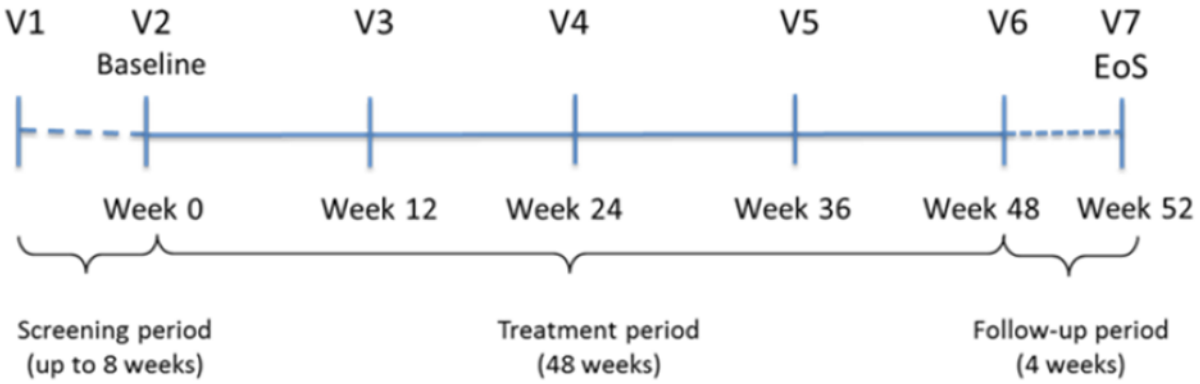
Phase 3 studies MOB015B-III and MOB015B-IV

Study MOB015B-III was a multi-center, randomized, two-arm, parallel group, and evaluator-blinded phase III study to evaluate efficacy and safety of topical product MOB015B.

Study MOB015B-IV was a multicenter, randomized, two-arm, parallel group, vehicle-controlled and double-blinded phase III study to evaluate efficacy and safety of topical product MOB015B.

The design of the studies is similar including study schedule (see figure below) and the two studies are therefore described together. Differences in study design are highlighted where relevant.

Figure 2. Study Schedule of Pivotal Phase III Studies (from 2.5, Clinical Overview)



All products used in the two pivotal studies, the test product MOB015B, the active comparator ciclopirox 80 mg/g and the vehicle to the test product, were administered once daily in the evening to all affected toenails and fingernails. The subjects treated themselves with the test products at home, which is reasonable considering the disease to be treated, and the nature of the product (topical cutaneous solution). The first application took place on study site under supervision of the site staff.

Treatment compliance was documented in an electronic case report form. In addition, for each subject it was recorded how many of the dispensed containers (tubes/bottles) had been used (completely or partially) since last visit.

The objectives of the studies were the assessment of efficacy and safety of MOB015B.

Eligible were patients, aged 12-75 years (based on inclusion criteria), with a diagnosis of DSO, the most common form of onychomycosis which can affect both toe- and fingernails, however more often the toenails. Patients with proximal subungual onychomycosis, and DSO of both great toenails where involvement has extended into the proximal portion of the target nail, were excluded from the studies. The inclusion and exclusion criteria are overall considered adequate to reflect the proposed therapeutic indication.

The primary efficacy endpoint was the proportion of subjects with complete cure (negative fungal culture of dermatophytes, negative direct KOH microscopy and 0% clinical disease involvement) of the target toenail at Week 52 (end of study).

The key secondary endpoints were 1) the proportion of subjects with mycological cure (defined as negative KOH and negative dermatophyte culture) of the target toenail at week 52 and 2) the proportion of subjects with treatment success (clinical disease involvement rated as “completely clear” [0%] or “almost clear” [less than or equal to 10%] and negative mycology) of the target toenail at Week 52. Both the primary efficacy and the key secondary endpoints have a clinical relevance if met. Moreover, several other secondary endpoints were investigated.

The study objectives and outcomes are considered adequate for clinical studies evaluating a new product with the proposed therapeutic indication onychomycosis caused by dermatophyte. The number of subjects included in the pivotal Phase 3 studies and the duration of treatment are considered relevant. Study MOB015B-III has a non-inferiority design of MOB015B versus ciclopirox, while study MOB015B-IV has a superiority design compared with vehicle. Ciclopirox (Onytec®) in Sweden, was approved in 2012. The product is a medical nail lacquer with antimycotic effect against a broad range of dermatophytes.

The study design of the two pivotal clinical studies have overall been agreed upon by national competent authorities. However, a three-arm trial with a vehicle group in the active comparator trial MOB015B-III would have been of advantage but is not requested.

Statistical aspects
The sample size calculations in the two studies were based on assumptions of a Complete Cure Rate of 15%, 8% and 4.5% for MOB015B, active comparator and vehicle respectively. Also, a non-inferiority margin of -3% was used for comparison against the active comparator. Of note is that this margin has not been clinically or statistically justified.

Although the active comparator and the vehicle are not used in the same study, these assumptions implies that the NI margin represents a large proportion of the active comparator's (assumed) effect over vehicle. Those assumptions turned out to be far from the observed rates. In particular, the Complete Cure Rate of the active comparator in the study MOB015B-III was 1.6%, making the -3% NI margin obsolete. The minimal requirement for a non-inferiority trial to successfully lead to a non-inferiority claim is that efficacy over a (putative) placebo is established. To reach this, the comparator needs to perform in line with previous placebo-controlled trials (constancy assumption) and the NI margin be such that a reasonable proportion of the comparators effect over placebo is maintained. This is not fulfilled here.

The Non-Inferiority margin defined for the primary endpoint was also used for the secondary endpoints. No justification has been given, however since the absolute rates of responders are much larger in the secondary endpoints this is acceptable.

Although it is not agreed that non-inferiority is shown in the primary endpoint, no alpha is considered to have been spent in the primary testing and secondary endpoints can still be evaluated in the formal testing sequence.

If data on the primary endpoint was missing at the week 52 visit, LOCF were used for handling of missing data based on pre-defined criteria. This might not be a conservative way to handle missing data. In the responses to questions the applicant presented the number of missing data at week 52 and the number of those imputed as success using the LOCF for primary and key secondary endpoints for both pivotal studies. The number of "imputed successes" are low and similar between treatment groups. Hence, the method used is considered acceptable. It is not acceptable to exclude outliers from analysis, as this could introduce a bias in the treatment comparison. The Applicant has clarified that no data was classified as outlier and excluded from analysis.

Efficacy data and additional analyses

Phase 2 pilot study of efficacy and safety MOB015B-II

This study is an open, single-center study performed in adult individuals with DSO in Sweden. A total of 25 patients were included in the study, 24 patients completed the study.

All study patients were male and Caucasian. The average age of subjects at baseline was 59 (range 38-68) years. The subjects included in the study all had DSO, with the number of DSO-affected nails varied between 1 and 10. Although the inclusion criteria for this study allowed for target nails with 25 to 75% of the nail to be affected, from target nail photos it is noted that many subjects had more than 50% disease involvement at inclusion.

Efficacy results – Phase 2 study MOB015B-II

The primary efficacy variable, the proportion of subjects with mycological cure of the target nail, defined as negative fungal culture and negative direct microscopy evaluated at week 60 (following 48 weeks of treatment) showed that 52% (13/25) met the primary endpoint mycological cure. However, none of the subjects were assessed as clinically cured (i.e., in this study meaning 100% clearance of clinical signs of disease, physician GES = 5) and consequently, no subject reached complete cure during the study.

Overall, the submitted Phase 2 study MOB015B-II is assessed as supportive from a clinical efficacy perspective.

The systemic plasma exposure following topical application of MOB015B onto nails are negligible compared to oral administration of terbinafine. The systemic pharmacokinetics of terbinafine are hence of limited relevance for this product.

Phase 3 studies MOB015B-III and MOB015B-IV

The Phase 3 study MOB015B-III was performed at 48 study centres in EU, while the study MOB015B-IV was performed at 32 study centres in US and Canada.

The Full Analysis Set of (FAS) population of study MOB015B-III comprised 452 subjects and the Per Protocol Set Phase (PPS) population comprised 351 subjects. 296 were randomized to receive MOB015B and 153 to receive ciclopirox (80 mg/g). Study completion was medium high (84% in total). 51 subjects treated with MOB015B discontinued, 17 subjects due to withdrawal of consent, adverse events (n=17), lost to follow-up (n=12), or other reasons (n=3) / protocol deviations (n=2). Of subjects treated with the active comparator ciclopirox 80 mg/g 21 discontinued, 7 patients due to withdrawal of consent, adverse events (n=3), lost to follow-up (n=16) or other reasons (n=2) / protocol deviations (n=3).

The study MOB015B-IV comprised 365 subjects in the FAS population and 253 in the PPS population. 246 were randomized to receive MOB015B and 119 to receive Vehicle. Study completion was slightly less 79% in study MOB015B-IV. 47 subjects treated with MOB015B discontinued, 20 patients due to withdrawal of consent, lost to follow-up (n=15), adverse events (n=6), other reasons (n=4), noncompliance and death (n=1 for each). Of subjects who received vehicle 31 discontinued, 12 subjects due to withdrawal of consent, lost to follow-up (n=11), adverse events (n=3), or other reasons (n=3) / noncompliance (n=2).

In study MOB015B-III, important protocol deviations were reported in the category of ‘No data for primary efficacy variable’, ‘Compliance less than 80% (completed subjects / dropout subjects)’. In study MOB015B-IV the most frequent protocol deviation was ‘IMP compliance less than 80%’. None of the protocol deviations are thought to seriously affect the evaluation of efficacy or safety results of the study.

The demographic and baseline characteristics of study MOB015B-III showed a majority (69.2%) of male, white individuals (99.3%) with mean age of 56 years (range 19-76). All subjects had abnormal toenails, the mean number of DSO-affected toenails were 2.2 (1.5) on the left foot and 2.2 (1.6) on the right foot. The investigators global assessment (IGA) of clinical disease involvement was estimated to be ≥25% to ≤50% in 76.4% of included subjects, ≥50% to ≤75% in 10.3% of included subjects and ≥10% to ≤25% in 13.4%.

In study MOB015B-IV, the average age of subjects in both treatment groups at baseline was 55 (range 21-74) years and subjects were predominantly male (83.6%). Most subjects were white (86.6%) or black/African American (9.9%). All subjects had abnormal toenails, the mean number of DSO-affected toenails were 2.3 (1.6) on the left foot and 2.5 (1.6) on the right foot. The IGA of clinical disease involvement was estimated to be ≥25% to ≤50% in 79.5% of included subjects, ≥50% to ≤75% in 9.6% of included subjects and ≥10% to ≤25% in 11.0%.

Mycological status

The mycological status of the subjects included were investigated in both pivotal studies. The most frequently identified species was *Trichophyton rubrum*. The mycological status of the subjects at baseline was overall similar in study MOB015B-III conducted in Europe, and in study MOB015B-IV

which was conducted in North America. In both studies, *Trichophyton rubrum* was equally dominant, accounting for 86.3% of dermatophytes in the MOB015B-III study, and 96.2% of dermatophytes in the MOB015B-IV study.

In the MOB015B-III study, 27.6% subjects in the ciclopirox treatment group compared to 23.3% subjects in the MOB015B treatment group received treatment for tinea pedis at baseline and more subjects were treated in the ciclopirox group at Week 48 or early termination visit. In the MOB015B-IV study, approximately one third of subjects in either the test or vehicle groups were treated at baseline. Further on, more subjects were treated in the Vehicle group at Week 48 or early termination visit.

Efficacy results – Phase 3 study MOB015B-III
The pivotal study MOB015B-III showed a similar low efficacy level for the primary efficacy endpoint (complete cure of the target toenail) for the test product and the active comparator ciclopirox 80 mg/g, defined as negative fungal culture of dermatophytes, negative direct KOH microscopy and 0% clinical disease involvement when evaluated at week 52, 1.8% in the MOB015B group and 1.6% in the ciclopirox 80 mg/g group. Both treatments failed to show a clinically relevant complete cure rate, and since the complete cure rate of the active comparator arm (1.6%) was smaller than the non-inferiority margin (3%), no conclusion on non-inferiority can be made. However, although the NI-margin is considered obsolete, no alpha is considered to have been spent in the primary testing and secondary endpoints can still be evaluated in the formal testing sequence.

Although the applicant considers that non-inferiority has been shown, this opinion is not shared by the RMS. The minimal requirement for a non-inferiority trial to successfully lead to a non-inferiority claim is that efficacy over a (putative) placebo is established. To reach this, the comparator needs to perform in line with previous placebo-controlled trials (constancy assumption) and the NI margin be such that a reasonable proportion of the comparators effect over placebo is maintained. This is not fulfilled here.

Table 2. Complete cure at week 52 (PPS) – Study MOB015B-III

		MOB015B (n=224)	**Ciclopirox 80 mg/g (n=127)**	**Total (n=351)**
Complete cure	N (%)	4 (1.8%)	2 (1.6%)	Diff: 0.2%*
	95% CI	0.5, 4.5	0.2, 5.6	-2.6, 3.0
	p-value (non-inferiority)			0.0116

Total column shows the difference between MOB015B and ciclopirox 80 mg/g.
* Difference calculated with all decimals behind and not the rounded value for the treatments displayed in the table.
Complete cure of target toenail was defined as both complete clinical cure (0% clinical disease involvement) and mycological cure (defined as both negative direct KOH microscopy and negative fungal culture of dermatophytes).
CI = confidence interval, PPS = per protocol set
Source: CSR MOB015B-III, Table 14.2.2.2

The first key secondary endpoint, assessed the proportion of subjects with mycological cure (defined as negative KOH and negative dermatophyte culture) of the target toenail at week 52, was 83.5% in the MOB015B group and 41.7% in the ciclopirox 80 mg/g group, with a difference between the treatment groups of 41.7% (95% CI: 31.9, 51.6). The study was powered for non-inferiority testing, which was demonstrated since the lower boundary of the interval for the difference between the two proportions (31.9%) was substantially higher than -3%, ($p<0.0001$). However, there is a clear tendency for a more marked efficacy of MOB015B compared with ciclopirox 80 mg/g on mycological cure.

Table 3. Mycological cure at week 52 PPS) in study MOB015B-III (table from the SCE)

		MOB015B (n=224)	Ciclopirox 80 mg/g (n=127)	Total (n=351)
Mycological cure	N (%)	187 (83.5%)	53 (41.7%)	Diff: 41.7%*
	95% CI	78.0, 88.1	33.0, 50.8	31.9, 51.6
	p-value (non-inferiority)			<0.0001

Total column shows the difference between MOB015B and ciclopirox 80 mg/g.
* Difference calculated with all decimals behind and not the rounded value for the treatments displayed in the table.
Mycological cure was defined as both negative KOH and negative dermatophyte culture.
CI = confidence interval, PPS = per protocol set
Source: CSR MOB015B-III, Table 14.2.2.2

The second key secondary endpoint assessing treatment success (clinical disease involvement rated as "completely clear" [0%] or "almost clear" [less than or equal to 10%] and negative mycology) of the target toenail at Week 52, did not demonstrate non-inferiority of MOB015B versus ciclopirox 80 mg/g. Treatment success was achieved in 21.9% in the MOB015B group and 18.9% in the ciclopirox group (p=0.0890).

Table 4. Treatment success at week 52 PPS) in study MOB015B-III (table from the SCE)

		MOB015B (n=224)	Ciclopirox 80 mg/g (n=127)	Total (n=351)
Treatment success in target toenail	N (%)	49 (21.9%)	24 (18.9%)	Diff: 3.0%*
	95% CI	16.6, 27.9	12.5, 26.8	-5.7, 11.7
	p-value (non-inferiority)			0.0890

Total column shows the difference between MOB015B and ciclopirox 80 mg/g.
* Difference calculated with all decimals behind and not the rounded value for the treatments displayed in the table.
Treatment success was defined as clinical disease involvement rated as "completely clear" (0%) or "almost clear" (less than or equal to 10%) and negative mycology.
CI = confidence interval, PPS = per protocol set
Source: CSR MOB015B-III, Table 14.2.2.2

Efficacy results – Phase 3 study MOB015B-IV
Study MOB015B-IV is a vehicle-controlled study with superiority design. In the analysis of the primary efficacy endpoint (complete cure of the target toenail, defined as negative fungal culture of dermatophytes, negative direct KOH microscopy and 0% clinical disease involvement) based on the FAS, the proportion of subjects with complete cure of the target toenail at Week 52 was 4.5% in the MOB015B group and 0.0% in the vehicle group. This difference was statistically significantly different from the vehicle group (p=0.0195 and 0.0192, respectively), showing superiority of MOB015B versus vehicle. Data from the PPS supported the findings in the FAS.

The primary endpoint was met in study MOB015B-IV. The clinical efficacy level of MOB015B is however considered very modest.

Table 5. Complete cure at week 52 (PPS) – Study MOB015B-IV

		MOB015B (n=246)	Vehicle (n=119)	Total (n=365)
Complete cure	N (%)	11 (4.5%)	0 (0.0%)	Diff: 4.5%
	95% CI	2.3, 7.9	0.0, 3.1	1.9, 7.1
	p-value (Cochran-Mantel-Haenszel)			0.0195
	p-value (Chi-square)			0.0192

Note: Missing values were imputed by LOCF and Total shows the difference between MOB015B and Vehicle
Complete cure of target nail was defined as negative fungal culture of dermatophytes, negative direct KOH microscopy and 0% clinical disease involvement of the target toenail
The Cochran-Mantel-Haenszel test was the primary analysis, and the Chi-square test was exploratory
CI = confidence interval, FAS = full analysis set
Source: CSR MOB015B-IV, Table 14.2.2.1

The first key secondary endpoint assessing mycological cure at week 52, superiority of MOB015B versus vehicle was demonstrated. The proportion of subjects with mycological cure of the target toenail at Week 52 was 69.9% in the MOB015B group and 27.7% in the vehicle group, which based on the Cochran-Mantel-Haenszel test and Chi-square test resulted in a significance level of $p<0.001$ in both instances.

Table 6. Mycological cure at week 52 (FAS) in study MOB015B-IV

	MOB015B (n=246)	Vehicle (n=119)	Total (n=365)
N (%)	172 (69.9%)	33 (27.7%)	Diff: 42.2%
96.25% CI [adjusted p-value]	63.4, 75.9	19.5, 37.2	31.7, 52.7
p-value (Cochran-Mantel-Haenszel)			<0.001
p-value (Chi-square)			<0.001

Note: Missing values were imputed by LOCF, and Total shows the difference between MOB015B and Vehicle.
Mycological cure was defined as both negative KOH and negative dermatophyte culture.
The Cochran-Mantel-Haenszel test was the primary analysis, and the Chi-square test was exploratory.
CI = confidence interval, FAS = full analysis set
Source: CSR MOB015B-IV, Table 14.2.2.1

The second key secondary endpoint assessing treatment success at week 52, superiority of MOB015B versus vehicle was also demonstrated. The proportion of subjects with treatment success of the target toenail at Week 52 was 15.4% in the MOB015B group and 4.2% in the vehicle group, which based on the Cochran-Mantel-Haenszel test and Chi-square test results in a significance level of $p<0.0018$ in both instances.

Table 7. Treatment success at week 52 (FAS) in study MOB015B-IV

FAS		MOB015B (n=246)	Vehicle (n=119)	Total (n=365)
Treatment success	N (%)	38 (15.4%)	5 (4.2%)	Diff: 11.2%
	96.25% CI [adjusted p-value]	10.6, 21.3	1.2, 10.4	4.6, 17.9
	p-value (Cochran-Mantel-Haenszel)			0.0018
	p-value (Chi-square)			0.0018

Note: Missing values were imputed by LOCF, and Total shows the difference between MOB015B and Vehicle.
Treatment Success was defined as clinical disease involvement rated as 'completely clear' (0%) or 'almost clear' (less or equal to 10 %) and negative mycology.
The Cochran-Mantel-Haenszel test was the primary analysis, and the Chi-square test was exploratory.
CI = confidence interval, FAS = full analysis set
Source: CSR MOB015B-IV, Table 14.2.2.1

The two secondary efficacy endpoints support the outcome of the primary efficacy endpoint. MOB015B has a superior clinical efficacy versus placebo, most evident on mycological cure. The other secondary endpoint analysis overall supported the results with the primary and key secondary endpoints.

The beneficial efficacy of MOB015B and ciclopirox increase with time, it may take 9 months to one year before the result of treatment of onychomycosis can be observed.

Analysis performed across trials
In the pooled analyses of efficacy data from the two pivotal Phase 3 studies; 542 subjects received MOB015B, 156 subjects received ciclopirox 80 mg/g and 119 subjects received vehicle.

The dermatophytes identified in the target toenail prior to treatment was investigated and demonstrated that the most frequently identified species was *Trichophyton rubrum*, which was consistent between the treatment groups of the individual studies.

The most notable difference between the treatment groups was the high level of mycological cure in the MOB015B group. In both Phase 3 studies, treatment with MOB015B demonstrated a higher mycological cure rate than the comparator, ciclopirox 80 mg/g and vehicle, respectively. The mycological cure was 75.6% in the MOB015B group, 41.0% in the ciclopirox group and 27.7% in the vehicle group at week 52 following 48 weeks of drug treatment.

Table 8. Pooled Studies: Summary of Key Efficacy Endpoints at Week 52 (FAS) (table from SCE)

	MOB015B (n=542)	Ciclopirox (n=156)	Vehicle (n=119)
Complete cure, % (95% CI)	3.1 (1.8, 5.0)	1.3 (0.2, 4.6)	0.0 (0.0, 3.1)
Mycological cure, % (95% CI)	75.6 (71.8, 79.2)	41.0 (33.2, 49.2)	27.7 (19.9, 36.7)
Treatment success, % (95% CI)	17.5 (14.4, 21.0)	16.0 (10.6, 22.7)	4.2 (1.4, 9.5)

Missing values have been imputed using LOCF.
Source: Table 2.7.3.2.1, Table 2.7.3.2.2.1 and Table 2.7.3.2.3

The applicant is asked to elaborate on the relationship between mycological cure and treatment success (clinical disease involvement rated as “completely clear” [0%] or “almost clear” [less than or equal to 10%]). That is, will a higher mycological cure rate lead to a higher rate of treatment success and if so, if so when can treatment success be anticipated, since it was not observed following 48 weeks of treatment? The Applicant has in the response via modelling analyses shown that a higher

mycological cure rate led to a higher rate of treatment success, as could be expected. Moreover, the model implies that a further improvement in treatment success is anticipated for some time after cessation of treatment. Although the uncertainty in extrapolation of the model beyond the observation time is considered large, the plausibility of the assumption that successful treatment would depend on eradication of the causative pathogens is agreed.

Subgroup analysis
A comparison of results in sub-groups (gender; age <65 years/≥65 years; baseline disease severity: percent affected nail ≤50%/>50%) showed similar results in all sub-groups investigated. The results concerning disease severity is however hampered by the low number if subjects with >50% disease severity.

Persistence of treatment effect
The results of studies MOB015B-III and MOB015B-IV demonstrate a beneficial antifungal effect over a 48-week treatment period that improved further during the 4-week follow-up period (Weeks 48 to 52) without treatment.

Conclusions on clinical efficacy
A significantly superior efficacy for Terbinafin Moberg Pharma cutaneous solution compared with vehicle was demonstrated for the primary efficacy endpoint in the pivotal phase 3 study MOB015B-IV. The proportion of subjects with complete cure of the target toenail at Week 52 was 4.5% in the MOB015B group and 0.0% in the vehicle group which by the RMS is considered very modest. The magnitude of efficacy of Terbinafin Moberg Pharma is however in the same range as for other approved medicinal products with local application indicated for treatment of onychomycosis, including a terbinafine containing product, Terbinafine Sandoz® recently approved in the procedure DE/H/6404/01/DC.

The key secondary efficacy endpoints and other endpoints supported the efficacy of Terbinafin Moberg Pharma in study MOB015B-IV.

However, in the active comparator study MOB015B-III, no conclusion on non-inferiority can be made. It is concluded that both treatments failed to show a clinically relevant complete cure rate. Although the NI-margin is considered obsolete, no alpha is considered to have been spent in the primary testing and secondary endpoints can still be evaluated in the formal testing sequence.

When dosed as proposed in the SmPC, that is for 48 weeks with daily administration in the evening, the most notable effect of the test product is a high level of mycological cure. In both Phase 3 studies when data was combined, treatment with MOB015B demonstrated a higher mycological cure rate than with the comparator, ciclopirox 80 mg/g and with vehicle, respectively. The mycological cure rate was 75.6% in the MOB015B group, 41.0% in the ciclopirox group and 27.7% in the vehicle group at week 52 following 48 weeks of drug treatment.

The proposed indication of Terbinafin Moberg Pharma has been changed as requested by the RMS and CMS. The new proposed therapeutic indication is considered acceptable by the RMS.

Overall, the efficacy documentation presented for Terbinafin Moberg Pharma is considered adequate for approval of the product.

Clinical safety
The applied product, MOB015B, is a topical antifungal solution, containing 10% terbinafine hydrochloride. The product development is based on the established use of orally administered terbinafine. The Applied indication is for the treatment of adults of onychomycosis caused by dermatophytes. The recommended dosing is by covering each affected nail with a thin layer of solution once daily, preferably at bedtime, for a duration of about 6 months for treatment of fingernails and 9 to 12 months for toenails.

The treatment has been evaluated for efficacy and safety by data of two pivotal Phase III, multicenter, randomized, controlled studies with similar study design involving 48 weeks of treatment in a total of 817 subjects. In addition, safety and efficacy were also evaluated in a 48-week open Phase II study of 25 patients and in a 28-day systemic absorption study under maximal use conditions in 20 patients. Three Phase I dermal safety studies were also conducted in a total of 366 healthy volunteers.
Overall, 953 subjects have received MOB015B in the clinical development program. The safety analysis comprises an analysis of each of the individual studies and of pooled safety data from the two pivotal Phase III studies. A total of 542 patients were exposed to MOB015B for a mean of 302 days in the two pivotal phase 3 studies. There was a post-treatment follow-up for 4 weeks and evaluation of primary efficacy endpoint at Week 52. This duration and number of exposures seems acceptable from a safety point of view.

Similar proportions of subjects reported AEs across all treatment groups.
The proportions of subjects reporting serious adverse events (SAEs) were similar between the MOB015B and vehicle groups, but higher in the ciclopirox 80 mg/g group.

	MOB015B (N=542)	**Ciclopirox (N=156)**	**Vehicle (N=119)**	**Total (N=817)**
Subjects with at least one AE, n (%)	279 (51.5)	81 (51.9)	61 (51.3)	421 (51.5)
Subjects with at least one AE related to IMP[a], n (%)	100 (18.5)	12 (7.7)	19 (16.0)	131 (16.0)
Subjects with at least one AE related to study procedure[a], n (%)	48 (8.9)	8 (5.1)	7 (5.9)	63 (7.7)
Subjects with at least one SAE, n (%)	22 (4.1)	13 (8.3)	5 (4.2)	40 (4.9)
Subjects with at least one AE leading to discontinuation of IMP[b], n (%)	28 (5.2)	2 (1.3)	5 (4.2)	35 (4.3)
Subjects with at least one other important medical event as per protocol[c], n (%)	0	1 (0.6)	2 (1.7)	3 (0.4)
Subjects with at least one other significant event[d], n (%)	217 (40.0)	63 (40.4)	48 (40.3)	328 (40.1)
Subjects with at least one AE with outcome death, n	1	0	0	1

a Adverse events with causality assessed by the investigator in blinded manner as 'Possible', 'Probable' or 'Definite'.
b Where action taken was 'Drug withdrawn'.
c These events were unrelated to treatment: anaphylactic reaction in the Ciclopirox group (source: CSR MOB015B-III: Table 14.3.2), melanoma in situ and prostate cancer in the Vehicle group (Source: CSR MOB15B-IV: Table 14.3.1.7)
d Other significant event was defined as an AE that did not meet the SAE definition and was laboratory abnormalities or an AE that led to an intervention (including interruption or withdrawal of IMP, dose reduction, or significant additional concomitant therapy). These data include events already summarized in detail. They also include more specific data (e.g., subjects with at least one AE related to IMP [see below]). For clarification, the most relevant AEs experienced by ≥1% subjects in the pooled Phase III studies categorized as 'other significant events' are summarized by System Organ Class (SOC) and Preferred Term (PT) for Skin and Subcutaneous Tissue Disorders, and Infections and Infestations.

AE = adverse event; IMP = investigational medicinal product; N = number of subjects in group; n = number of subjects in category; SAE = serious adverse event.
Source: Table 2.7.4.2.1.1

The most common SOC was Infections and Infestations, reported by similar proportions of subjects in each of the treatment groups. The two most common PTs within this SOC for all treatment groups were tinea pedis and nasopharyngitis.

Table 9. Adverse Events Reported in Phase III Studies by ≥1% treated subjects in Any Group by System Organ Class and Preferred Term – Pooled Data, Safety Set

System Organ Class Preferred Term	MOB015B (N=542)			Ciclopirox 80 mg/g (N=156)			Vehicle (N=119)		
	n	%*	m	n	%*	m	n	%*	m
Infections and Infestations	**166**	**30.6**	**217**	**51**	**32.7**	**68**	**37**	**31.1**	**53**
Tinea pedis	55	10.1	61	32	20.5	36	23	19.3	27
Nasopharyngitis	42	7.7	50	14	9.0	16	6	5.0	7
Onychomycosis	18	3.3	19	4	2.6	4	1	0.8	2
Paronychia	13	2.4	14	0			0		
Upper respiratory tract infection	8	1.5	8	1	0.6	1	0		
Bronchitis	5	0.9	5	0			3	2.5	3
Influenza	4	0.7	4	1	0.6	2	3	2.5	3
Skin and Subcutaneous Tissue Disorders	**95**	**17.5**	**152**	**11**	**7.1**	**14**	**19**	**16.0**	**24**
Onychomadesis	16	3.0	22	0			6	5.0	7
Dermatitis contact	14	2.6	14	0			0		
Nail discolouration	13	2.4	13	2	1.3	2	1	0.8	1
Onycholysis	7	1.3	7	2	1.3	2	4	3.4	4
Erythema	6	1.1	9	0			2	1.7	2
Eczema	6	1.1	8	1	0.6	1	0		
Ingrowing nail	3	0.6	4	2	1.3	2	0		
Blister	2	0.4	2	0			2	1.7	3
Injury, poisoning and procedural complications	**26**	**4.8**	**35**	**10**	**6.4**	**10**	**8**	**6.7**	**10**
Limb injury	4	0.7	4	4	2.6	4	0		
Nervous System Disorders	**19**	**3.5**	**25**	**6**	**3.8**	**7**	**3**	**2.5**	**3**
Headache	4	0.7	5	3	1.9	4	1	0.8	1
Gastrointestinal disorders	**15**	**2.8**	**18**	**11**	**7.1**	**12**	**2**	**1.7**	**5**
Diarrhoea	4	0.7	4	2	1.3	2	0		
Respiratory, thoracic and mediastinal disorders	**13**	**2.4**	**14**	**4**	**2.6**	**4**	**4**	**3.4**	**5**
Cough	3	0.6	3	2	1.3	2	2	1.7	2
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	**12**	**2.2**	**15**	**4**	**2.6**	**4**	**4**	**3.4**	**5**
Dysplastic naevus	0			2	1.3	2	0		
Vascular Disorders	**10**	**1.8**	**10**	**4**	**2.6**	**5**	**0**		
Haematoma	1	0.2	1	2	1.3	3	0		
Cardiac Disorders	**4**	**0.7**	**6**	**3**	**1.9**	**4**	**2**	**1.7**	**2**
Atrial fibrillation	0			2	1.3	2	0		
Renal and Urinary Disorders	**2**	**0.4**	**2**	**1**	**0.6**	**2**	**3**	**2.5**	**3**
Nephrolithiasis	0			0			2	1.7	2

All other reported PTs were experienced by <10% of subjects within a treatment group. Other preferred terms reported by ≥2% of subjects in the MOB015B group were onychomycosis (3.3%), paronychia (2.4%), onychomadesis (3.0%), contact dermatitis (2.6%), and nail discoloration (2.4%). Of adverse events reported in phase III studies by ≥1% treated, local skin and nail reactions are

observed more commonly in the MOB015B group (17.5 %) compared to the active comparator Ciclopirox (7.1%) but only slightly more compared to the vehicle (16 %).

Treatment related AEs were also reported by similar proportions of subjects in the MOB015B and vehicle groups, but in a lower proportion of subjects in the ciclopirox 80 mg/g group. Of treatment-related adverse events reported in more than 1% of subjects receiving MOB015B in two randomized controlled studies the most common SOC was Skin and Subcutaneous Tissue Disorders with nail discolouration, onycholysis, onychomadesis, paronychia, dermatitis contact and erythema being most common PTs. In section 4.8 of the SmPC Nail discolouration, Onycholysis, Onychomadesis, Paronychia, Dermatitis contact and Erythema are listed as common. This seems relevant.

Table 10. Treatment-Related Adverse Events in Phase III Studies Reported in ≥1% of Subjects in any Treatment Group – Pooled Data, Safety Set

System Organ Class Preferred Term	MOB015B (N=542)			Ciclopirox 80 mg/g (N=156)			Vehicle (N=119)		
	n	%*	m	n	%*	m	n	%*	m
Skin and Subcutaneous Tissue Disorders	**65**	**12.0**	**102**	**5**	**3.2**	**6**	**14**	**11.8**	**16**
Nail discolouration	13	2.4	13	2	1.3	2	1	0.8	1
Onychomadesis	12	2.2	17	0			4	3.4	5
Dermatitis contact	9	1.7	9	0			0		
Onycholysis	7	1.3	7	2	1.3	2	3	2.5	3
Erythema	6	1.1	9	0			2	1.7	2
Blister	2	0.4	2	0			2	1.7	3
Infections and Infestations	**30**	**5.5**	**33**	**6**	**3.8**	**7**	**4**	**3.4**	**5**
Onychomycosis	17	3.1	18	3	1.9	3	1	0.8	2
Paronychia	8	1.5	9	0			0		
Tinea pedis	3	0.6	3	3	1.9	4	3	2.5	3

AE = adverse event; m = number of AEs; N = number of subjects in group; n = number of subjects with at least 1 treatment-related AE
* percentage is calculated as n/N x100
Source: Table 2.7.4.2.2.2

SAEs were reported in 4.1 %, 8.3% and 4.2% of the MOB015B group, ciclopirox 80 mg/g group and vehicle group respectively. None of the reported SAEs, including one fatal reaction of COPD, were considered to be related to treatment.

Comparative safety data versus vehicle and versus ciclopirox 80 mg/g group show a higher incidence of adverse events grouped as local skin reactions including erythema, blister, skin irritation, and dermatitis in the MOB015B group compared to ciclopirox 80 mg/g. The conclusion by the Applicant is that this means the product has the potential to be irritating in some patients and care must be taken to limit application of the product to the nail only. This is agreed to. It should be clearly stated in the SmPC and PI to avoid application of MOB015B on surrounding skin.

There is a higher percentage of subject exposed to MOB015B who discontinue treatment due to adverse events compared to the active comparator (4.4% subjects in the MOB015B group, (1.9%) subjects in the ciclopirox 80 mg/g group and (2.5%) subjects in the vehicle group as stated by the Applicant).

Study MOB015B-V (Cumulative Skin Irritation Study)
The investigational products in the study were MOB015B and vehicle. The positive control was 0.2% SLS and the negative control was 0.2 mL of 0.9% saline, applied topically under occlusive conditions. The mean irritation score of MOB015B indicated that MOB015B was significantly more irritating than vehicle ($p<0.0001$), SLS 0.2% ($p<0.0001$), and saline 0.9% ($p<0.0001$). Mean irritation score of

the vehicle also indicated that it was significantly less irritating than SLS 0.2% (p=0.010) and more irritating than saline 0.9% (p<0.0001).

Study MOB015B-VI (Skin Sensitization Study)

This study performed in 208 subjects did not show dermal sensitization.

A photosensitization study was also performed. It was concluded that MOB015B seems not lead to sensitization or photoallergy.

Overall summary and conclusion
In summary, the treatment related safety profile is dominated by local reactions mainly of the skin and nails. The product is irritative when applied on the skin. This has been satisfactorily addressed in the proposed SmPC. The reported SAEs including one fatal case are considered not related to topical MOB015B.The extent of exposure in adults presented in submitted data is considered satisfactory.

Risk Management Plan
The MAH has submitted an updated risk management plan, version 0.1 with data lock point 28 May 2020 and signed off 11 March 2022 in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmaco-vigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Terbinafin Moberg.
Part I, part II module SI-SVIII and Part III-Part VII have been addressed.

Safety specification
Non-clinical
The Applicant has submitted a presentation of key safety findings from non-clinical studies.
The safety profiles of systemic and topical terbinafine are well characterised and terbinafine-containing products have been marketed in the EU and United States (US) for more than 20 years. The first terbinafine product (Lamisil®) was launched in Europe by Novartis Pharma in 1991. The dermal toxicity of terbinafine has been examined in several repeat-dose toxicity studies in rats and minipigs as well as in a dermal irritation study in rabbits. In addition, following feedback received from the US Food and Drug Administration (FDA), the bovine corneal opacity and permeation test for ocular irritation was conducted both with the drug substance terbinafine hydrochloride (HCl) and the drug product MOB015B. Lastly, the phototoxic potential of MOB015B was assessed.

Toxicity
The dermal toxicity of terbinafine has been examined in several repeat-dose toxicity studies in rats and minipigs as well as in a dermal irritation study in rabbits. In these studies, terbinafine was applied as a nail lacquer, i.e. in alcoholic solution with 0.5% dodecyl-2-N,Ndimethylaminopropionate. Thus, the studies characterize the dermal toxicity of the active pharmaceutical ingredient terbinafine. While the formulation used in these studies was not identical to that of MOB015B, systemic exposure was about 10-50x (minipigs) and up to ~200x (rats) higher than in patients treated with MOB015B. This suggests that there were also high local concentrations of terbinafine in the skin of the animals. Thus, these dermal repeat-dose toxicity studies confirm that terbinafine penetrates the skin and no dermal toxicity was observed with the same or higher concentration of the active substance as used in MOB015B. Therefore, the studies are considered representative for MOB015B. Skin findings were only observed in the 28-day dermal toxicity studies. The findings comprised minimal to mild epidermal hyperplasia, hyperkeratosis, and epidermal surface exudates in rats and very slight erythema, peeling or skin flaking in minipigs exposed to active or vehicle control. No such findings were made in the chronic studies (6-month and 9-month dermal toxicity studies in rat and minipigs, respectively), despite the administration of higher concentrations of terbinafine.

Local tolerance
In rabbits very slight or no skin irritation (i.e., erythema or edema) was observed on either the intact or abraded skin sites treated with the 1% Terbinafine HCl Nail Lacquer over 29 days of dosing, which was not significantly different from the control sites. However, very slight to well-defined erythema

and/or very slight edema were noted for most test sites in animals treated with 5% Terbinafine HCl Nail Lacquer and in animals treated with 10% Terbinafine HCl Nail Lacquer at various intervals over the 29 days of dosing. These slight skin responses produced by the 5 and 10% Terbinafine HCl Nail Lacquer, on the combined intact and abraded sites, were significantly greater ($p< 0.05$) than the Placebo Terbinafine HCl Nail Lacquer treated sites, beginning on Day 7, and persisted for the duration of the 29 days of dosing. Both Terbinafine HCl and the drug product MOB015B were categorized as severe/corrosive eye irritants in the bovine corneal opacity and permeability test.

Summary of conclusions by the applicant:
Topical administration of MOB015B leads to very low systemic exposure. Therefore, the risk for systemic toxicity is minimal. Altogether, the dermal findings were minimal to mild, and they were only observed in some of the studies. The local tolerance of MOB015B is further supported by the well documented safety of other topical terbinafine products and by its clinical development program. It should be further noted that MOB015B is intended for the administration onto finger and/or toenails, and not the skin. Therefore, exposure of the skin in patients using MOB015B is limited. Contact with eyes and mucous membranes should be avoided as addressed in the proposed SmPC.

Genotoxicity:
A standard battery of in vitro and in vivo genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.

Phototoxicity:
In an EpiDermTM Phototoxicity Assay, MOB015B applied to cultured skin did not elicit any ultraviolet radiation (UV) A-induced cytotoxicity.

Reproductive and developmental toxicity
No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

Safety pharmacology and other toxicity related information or data
The pharmacology of terbinafine is well characterized and no additional non-clinical studies were performed to assess the pharmacology of MOB015B. Due to the very low systemic exposure to terbinafine following application of MOB015B onto the nails, the risk of side effects related to secondary pharmacology or the cardiovascular, respiratory, or central nervous systems as well as for pharmacodynamic drug interactions is negligible.

Part IV
Limitations in respect to populations typically under-represented in clinical trial development programmes

Pregnancy and breast-feeding
Pregnant and breastfeeding women were excluded from the clinical development program. Orally-administered terbinafine has been in use for many years for treatment of onychomycosis. There is a large amount of data on the use of terbinafine in pregnant women that indicate lack of malformative or feto/neonatal toxicity. In a propensity score–matched comparison study conducted in Denmark including 4065 terbinafine-exposed pregnancies as well as 40,650 unexposed pregnancies, no significant differences in the risk of major malformations or spontaneous abortion were identified between oral terbinafine-exposed, topical terbinafine-exposed, and unexposed pregnancies. While it is known that terbinafine is excreted into breast milk, it has been shown that the systemic absorption of terbinafine from this topical formulation MOB015B is negligible, in contrast to higher systemic levels obtained following ingestion of terbinafine through the oral route. The use of MOB015B in breast-feeding women has not been studied; however, based on the negligible absorption of terbinafine following topical use of MOB015B, it may be concluded that any possible risks to infants from exposure to breast milk are negligible.

Clinical

The summary of safety concerns as presented by the Applicant can be seen in the table below.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

No important identified or potential risks have been identified for MOB015B. Adverse reactions for MOB015B, all considered to have minimal clinical impact on patients (in relation to the severity of the indication treated).

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant.

Plans for post-authorisation efficacy studies

Not applicable. There are no planned or ongoing post-authorization efficacy studies.

Risk minimisation measures (RMM)

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the Applicant.

Part VI Summary of the risk management plan

This includes the table below as well as a summary of the details presented in the RMP.

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

Assessor's comment:

A summary of the medicinal product and what it is authorised for, safety concerns and missing information, and information of risk minimisation measures including tables has been provided. Additional pharmacovigilance activities are not planned. The updated summary is acceptable.

Summary of the RMP

The submitted Risk Management Plan, version 0.1 with data lock point 28 May 2020 and signed off 11 March 2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet for Terbinafin Moberg Pharma has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet for Terbinafin Moberg Pharma meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Disease or condition and available therapies

Onychomycosis is a highly prevalent fungal infection of the nail unit including nail matrix, nail bed and nail plate. It is estimated that approximately 10% of the population has onychomycosis and it is most common in older men, with toenails approximately 10-times more often infected than fingernails. Several factors may contribute to the development of onychomycosis, including history of athlete's foot, peripheral arterial diseases, and diabetes mellitus. Nail trauma, older age, family history and chronic exposure to moist environment are also major risk factors for fungal nail infections.

Approximately 60 to 80% of onychomycosis is caused by dermatophytes, mainly *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Onychomycosis is a chronic condition that does not resolve without prolonged treatment to eradicate the fungus. If left untreated, the fungus will spread and can eventually destroy the nail.

Current therapeutic options for onychomycosis include mechanical or chemical nail avulsion, topical therapy, oral therapy or a combination of all of these modalities. Treatment decision depends on the clinical pattern of onychomycosis, the thickness, and the number of affected toenails, as well as patient's age, use of other medications, motivation and preferences.

Terbinafine was first launched in 1991 as tablet formulation under the brand name Lamisil® (Novartis) and is available worldwide in both topical and oral formulations for different indications. In Sweden there is a topical nail lacquer, Terbinafine Sandoz® containing 78.22 mg terbinafine, approved in 2020 during the procedure DE/H/6404/01/DC.

There are several products approved for topical treatment of onychomycosis which all are afflicted with a modest clinical efficacy. There is a medical need for more efficient topical treatment of fungal nail infections.

Product proposed for marketing

Terbinafin Moberg Pharma is a cutaneous, propylene glycol-based solution intended for application on the nails. It is presented in 5- or 10-mL plastic tubes, each with a silicone tip applicator. Excipients are

propylene glycol (solvent), urea (hydrating agent), lactic acid (buffer), sodium hydroxide (pH-adjusting agent), and disodium edetate (chelating agent).

Terbinafine is an allylamine antifungal that inhibits biosynthesis of ergosterol, an essential component of fungal cell membrane, via the inhibition of squalene epoxidase enzyme. Terbinafine has activity against a broad spectrum of dermatophytes including *Trichophyton rubrum* the most commonly observed dermatophyte in onychomychosis, yeasts, molds and other fungi.

The claimed indication is: '*Terbinafin Moberg Pharma is indicated in adults for the treatment of onychomycosis caused by dermatophyte'*.

Terbinafin Moberg Pharma should be applied by covering each affected nail with a thin layer of solution once daily, preferably at bedtime. In general, the duration of treatment for fingernails is approximately 6 months, while for toenails it is 9 to 12 months.

Quality aspects
The development, manufacture and control of the drug substance and drug product have been acceptably described from a pharmaceutical perspective.

Main clinical studies

The efficacy of Terbinafin Moberg Pharma is supported by three Phase 1 studies, one PK systemic absorption study, one open-label Phase 2 pilot study and two pivotal Phase 3 efficacy and safety studies in the target population, i.e., patients with onychomycosis.

The first pivotal study, MOB015B-III, evaluated efficacy and safety following 48 weeks treatment with the test product MOB015B and an active comparator, ciclopirox (product name Miclast®). The second pivotal study MOB015B-IV had a similar design but was vehicle controlled without active comparator. The pivotal studies MOB015B-III and MOB015B-IV had overall replicate protocol designs.

Favourable effects

In the pivotal study MOB015B-IV, a significant superior efficacy of MOB015B cutaneous solution compared to vehicle solution was demonstrated for the primary endpoint; complete cure of the target toenail at Week 52. The proportion of subjects with complete cure of the target toenail was 4.5% in the MOB015B group, and 0.0% in the vehicle group at Week 52 which was statistically significant. Superiority of MOB015B cutaneous solution versus vehicle solution was demonstrated, and the primary end-point was met.

The key secondary endpoints mycological cure and treatment success reached statistical significance in favor of MOB015B cutaneous solution, $p<0.001$ for mycological cure and $p<0.0018$ for treatment success, respectively. Moreover, the results for the key secondary endpoints obtained in the non-inferiority study MOB015B-III supported the results with the primary and key secondary endpoints from study MOB015B-IV.

The beneficial efficacy of MOB015B and ciclopirox increase with time, it may take 9 months to one year before the result of treatment of onychomycosis can be observed.

A high level of mycological cure in the MOB015B group was noted in the pooled analysis of both pivotal studies. The mycological cure was 75.6% in the MOB015B group, 41.0% in the ciclopirox group and 27.7% in the vehicle group at week 52 following 48 weeks of drug treatment. A higher mycological cure rate led to a higher rate of treatment success, as could be expected.

A comparison of results in sub-groups (gender; age <65 years/≥65 years; baseline disease severity: percent affected nail ≤50%/>50%) showed similar results in all sub-groups investigated. The results concerning disease severity is however hampered by the low number if subjects with >50% disease severity.

The product is easy to use with no nail filing or removal of old product with solvent needed before application of new drug product is performed. Since treatment of nail onychomycosis with a topical product requests a dedicated mind during a long treatment period, a convenient use of the product is of favor.

The proposed indication of Terbinafin Moberg Pharma is considered acceptable by the RMS.

Uncertainties and limitations about favourable effects

It can be noted that only 8% of treated subject's regard themselves as totally cured following treatment with MOB015B, and 18% regard themselves as almost cured, at week 52 end of treatment visit following 48 weeks of daily treatment with MOB015B.

The pivotal study MOB015B-III showed a similar low efficacy level for the primary efficacy endpoint (complete cure of the target toenail) for the test product and the active comparator ciclopirox 80 mg/g, defined as negative fungal culture of dermatophytes, negative direct KOH microscopy and 0% clinical disease involvement when evaluated at week 52, 1.8% in the MOB015B group and 1.6% in the ciclopirox 80 mg/g group. Both treatments failed to show a clinically relevant complete cure rate, and since the complete cure rate of the active comparator arm (1.6%) was smaller than the non-inferiority margin (3%), no conclusion on non-inferiority can be made. However, Terbinafin Moberg Pharma is despite of this deficiency considered approvable (see below Balance of benefit and risks).

If data on the primary endpoint was missing at the week 52 visit, LOCF were used for handling of missing data based on pre-defined criteria. This might not be a conservative way to handle missing data. In the responses to questions the applicant presented the number of missing data at week 52 and the number of those imputed as success using the LOCF for primary and key secondary endpoints for both pivotal studies. The number of "imputed successes" are low and similar between treatment groups. Hence, the method used is considered acceptable.

It is not acceptable to exclude outliers from analysis, as this could introduce a bias in the treatment comparison. The Applicant has clarified that no data was classified as outlier and excluded from analysis.

Unfavourable effects

The extent of exposure in adults presented in submitted data is considered satisfactory. The safety profile is dominated by adverse events of infections (nasopharyngitis and oncychomycosis) and of local reactions mainly of the skin and nails. In dermal studies the product is shown to be irritative to the skin when applied under occlusion. None of the reported SAEs including one fatal case are considered related to topical MOB015B. AEs were reported by similar proportions of subjects in the topical MOB015B group and ciclopirox 80 mg/g group though treatment related AEs were reported in a lower proportion of subjects in the ciclopirox 80 mg/g group compared to the topical MOB015B group and vehicle group. Of treatment-related adverse events reported in more than 1% of subjects receiving MOB015B in two randomized controlled studies the most common SOC was Skin and Subcutaneous Tissue Disorders with nail discolouration, onycholysis, onychomadesis, paronychia, dermatitis contact and erythema being most common PTs. There is a higher percentage of subject exposed to MOB015B who discontinue treatment due to adverse events compared to the active comparator (4.4% subjects in the MOB015B group, (1.9%) subjects in the ciclopirox 80 mg/g group and (2.5%) subjects in the vehicle group.

Uncertainties and limitations about the unfavourable effects

Most of the uncertainties have been clarified.

Topical MOB015B in performed studies has demonstrated a potential to be irritating. The impact of this in clinical use may limit the use. The majority of the local ADRs considered related to the treatment and causing a higher percentage of subject exposed to MOB015B to discontinue treatment were associated with dermatitis and local irritation of the skin surrounding the treated nail. Care must be taken to apply the product mainly on the nail. In order to limit irritative reactions the Applicant has committed to add the sentence “Do not apply Terbinafin Moberg Pharma on the surrounding skin.” to section 4.2 Posology and method of administration of the SmPC. Furthermore, the rationale for the use of adverse reactions listed in Table 1, section 4.8 of the proposed SmPC based on chosen MedDRA PT:s and Reported terms is in large acceptable.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

A significantly superior efficacy for Terbinafin Moberg Pharma cutaneous solution compared with vehicle was demonstrated for the primary endpoint in the pivotal phase 3 study MOB015B-III. The key secondary efficacy endpoints from both pivotal clinical studies and other endpoints supported the efficacy of Terbinafin Moberg Pharma. The magnitude of efficacy demonstrated in the study is not large, but in the same range as for other topical products approved for treatment of nail onychomychosis. The subject’s own ratings of response to treatment was also rather small. The importance of favourable effects are in the same range as for other comparative products on the market with therapeutic indication nail onychomychosis.

Terbinafin Moberg Pharma has a fairly marked efficacy on mycological cure rate compared with ciklopirox 80 mg/g and vehicle which could be of importance of the product.

Although AEs in general were reported by similar proportions of subjects in the topical MOB015B group and ciclopirox 80 mg/g group, treatment related AEs -mainly local reactions-were reported in a lower proportion of subjects in the ciclopirox 80 mg/g group compared to the topical MOB015B group and slightly less in the vehicle group. Terbinafin Moberg Pharma is shown to be irritative to the skin when applied under occlusion but overall, the reported local treatment related adverse events are dominated by mild to moderate local reactions of the skin and nails. The recommendation not to apply Terbinafin Moberg Pharma on surrounding skin has been added to the SmPC.

Balance of benefit and risks

Overall, the efficacy and safety documentation presented for Terbinafin Moberg Pharma cutaneous solution is considered adequate.

Approval of the product can be accepted based on the overall efficacy data submitted; most importantly a statistically significant effect of the test product compared to vehicle in the vehicle-controlled study MOB015B-IV. Supportive efficacy results are obtained with the key secondary endpoints, most notable on mycological cure. In study MOB015B-III, both test product and the active comparator treatments failed to show a clinically relevant complete cure rate, and since the complete cure rate of the active comparator arm (1.6%) was smaller than the non-inferiority margin (3%), no conclusion on non-inferiority could be made. Although this a deficiency of the clinical program submitted in support of the application, a comparison with active comparator would not be a formal requirement for approval of the product. The product can be approved based on vehicle controlled clinical data only if the results in the study are convincing enough.

There is product already on the market containing terbinafine approved for local treatment of nail onychomycosis, Terbinafine Sandoz®. Pharmacokinetic data demonstrate a low systemic absorption of terbinafine in Terbinafin Moberg Pharma in line with Terbinafine Sandoz®.

Safety data show a benign safety profile with local adverse event mainly of the skin and nails. The product has the potential to be irritating in some patients and care must be taken to limit application of the product to the nail and not on the surrounding skin.

Conclusion

The overall B/R of Terbinafin Moberg Pharma is positive.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	**Due date**
Tier B sediment organism toxicity study in accordance with the appropriate OECD test guideline.	2025-06-27
Bioconcentration (BCF) study with terbinafine in accordance with OECD test guideline 305.	2025-06-27
Phase II Tier B assessment.	2025-06-27

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Terbinafin Moberg Pharma, 98 mg/ml, Cutaneous solution was positively finalised on 2023-06-28.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se