Clinical Study Synopsis for Public Disclosure

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The information contained in this synopsis is not intended to substitute for informed medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a Healthcare Professional. Before prescribing any product mentioned in this Register, Healthcare Professionals should always refer to the specific approved product labelling information in their own respective country. The results from a single trial may not reflect the overall results and need to be considered in the context of the totality of the available clinical research for a product.

Study Synopsis

Name of Company/Sponsor	Nektr Technologies Ltd
Name of IMP	Mycosinate®
Name of Active Ingredients	Glucose Oxidase (CAS: 9001-37-0) Glucose (77938-63-7)
Name of Comparator Product	Curanail
Name of Comparator Active Ingredient	Amorolfine
Title of Study	A randomized, single-blinded, comparative study of Mycosinate and Curanail in the treatment of fungal nail infection

Methodology

Study Objective(s)

% Reduction in the Size of Infection

Photos taken during the trial will be analysed by the statistician who will measure both the entire size of the nail and the size of the infected portion of the nail. Using this data, the statistician will be able to calculate the % reduction in the size of the infection as the trial progresses.

Viability of the Infection (Mycological Cure Rate)

Confirmation testing will be carried out in a 3rd party contract laboratory and will be cultured to determine the viability of the infection at the various time points in the study.

Study Design and Clinical Phase

Single-Centre, Randomized, Single-Blinded, Comparative Study – Phase II/III

Study Centre(s)

Bray Chiropody and Podiatry (Primary Site)
Carlton Clinic (Medical Assessment Site)

Number of Subjects

Planned: 60
Enrolled and Completed Trial: 38

Diagnosis and Inclusion Criteria

Inclusion Criteria

- Confirmed presence of hyphae through microscopy of nail sample taken from patient.
- In good overall health (Subject to Health Assessment conducted by the responsible Physician).
- Male and Female aged between 18-65 inclusive.
- Fungal Infection on maximum of 2 nails per foot
- The fungal infection is seen across 20-75% of the nail with no involvement of the lunula.
- Subject is willing and available to return for study follow ups.
- Subject is willing to discontinue use of cosmetic nail products for the duration of the study.
- Subjects must agree to refrain from using other nail fungus treatments for the duration of the study.
- Physical examination without significant deviations.
- Non-smoker or past smoker (at least 6 months before dosing).

Exclusion Criteria

- Diabetics.
- Severe cases of onychomycosis (e.g. complete coverage of nail).
- Chronic conditions such as immune deficiency, chronic vascular disease or psoriasis.
- Currently involved in another clinical trial.
- Patients who are pregnant or breastfeeding.
- Severe secondary dermal infections.
- Patients suffering from proximal subungual onychomycosis.
- Any medical condition which may place the patient at risk of infection or delayed wound healing.
- Patients using immunosuppressant drugs.
- Smokers. (Protocol amendment accepted by HPRA on 17th July 2020 to remove this inclusion criteria)

- Other conditions known to cause an abnormal nail appearance.
- Known allergy to any of the ingredients in the study treatments.
- Patient has been using any antifungal therapy for the removal of the infection, either systemic or topical, in the past 6 months.
- Patients who have damaged or broken periungual skin.

Study Period:
June 2019 – February 2021

Investigational Products:

	Treatment A	**Treatment B**
Test Product Dosage Form	Mycosinate 0.5% Gel	Amorolfine 5%
Dosing Regime	Daily for 6 weeks then once weekly until 6 months	Once weekly for 9 months
Route of Administration	Topical	Topical
Treatment Duration	6 Months	9 Months

Criteria for Evaluation

- **Primary Endpoints**

% Reduction in the Size of Infection
Photos taken during the trial will be analysed by the statistician who will measure both the entire size of the nail and the size of the infected portion of the nail. Using this data, the statistician will be able to calculate the % reduction in the size of the infection as the trial progresses.

Viability of the Infection (Mycological Cure Rate)
Confirmation testing will be carried out in a 3rd party contract laboratory and will be cultured to determine the viability of the infection at the various time points in the study.

- **Secondary Endpoints**

Relapse Rates
The viability testing carried out from the month 6 follow up visit will form the relapse rate results. If the infection is viable at 9 month and was not viable at month 6 then the patient has relapsed.
Adverse Reactions
Any adverse reactions will be recorded, and serious adverse reactions will be reported directly to the HPRA via the sponsor's pharmacovigilance provider, Diamond PV Services.
Participant Satisfaction
Participants will answer the same set of questions at each assessment time point.

Results

Subject Disposition

A total of 38 patients with mild to severe presentations of onychomycosis infections completed this single centre, single-blinded, controlled trial. A breakdown of the screening process in given in the table below

There were 2 treatment arms, one received the Mycosinate product (Treatment A) while the other received Curanail (Treatment B).
Mycosinate was applied daily for 6 weeks, followed by weekly treatment for 18 weeks.
Mycosinate application was then ceased after the 6-month follow-up assessment. A final follow up appointment was completed 9 months from the initial dosing.

Curanail was applied as advised on the patient information leaflet for 9 months. A once weekly dosing scheme was used by subjects using Curanail for the duration of the study.

Summary Table 1 – Patient Enrolment and Status

PATIENT DISPOSITION	NUMBER OF PATIENTS (N)	GROUP A	GROUP B
PATIENTS SCREENED	88		
Screening Failures	39		
PATIENTS ACCEPTED AND RANDOMIZED	49	25	24

	Group A (N=21)	**Group B (N=17)**	**Total (N=38)**
Enrolled	25	24	49
Received at least one dose	24	17	41
Attended the clinic up until the month 6 follow up	21	17	38
Completed (T=9 Months Visit)	**21**	**17**	**38**
Withdrawn:	4	7	11
Lost to follow up/ Dropout	3	0	3
Adverse event	0	0	0
Death	0	0	0
*Non-Starter**	1	7	8
Other	0	0	0

*Primary cause of non-starters was that infection had spread to neighbouring toes between the time of screening and the subject's first treatment visit thus making them ineligible for the trial.

Summary Table 2 – Patient Demographics

		Treatment A	**Treatment B**	**Total**
Age	**N**	21	17	38
	Mean	52	53	n/a
	Median	53	58	n/a
	(Min, Max)	(28,65)	(27,65)	n/a
Gender	**Female**	8 (38.1%)	6 (35.3%)	14
	Male	13 (61.9%)	11(64.7%)	24
Toenail Infected	**Mean**	56.18%	53.08%	n/a
	Median	56.56%	51.30%	n/a

Baseline Data

Baseline data of the main efficacy criteria is shown in figures 1 & 2 below. Overall, treatment groups were well balanced at Baseline for demographics as well as for Baseline disease characteristics.

Infected Nail Area

The infected area was compared at baseline to ensure there was no significant difference in the toenails included in each of the treatment groups.

The mean infected area (mm2) of the toenails to be who received Treatment A (M=130.90, SD=88.995, n=34) was greater than that of mean infected area of the toenails to be who received Treatment B (M=108.46, SD=80.972, n=28) however this difference was not statistically significant (t(60)=1.029, p=0.308).

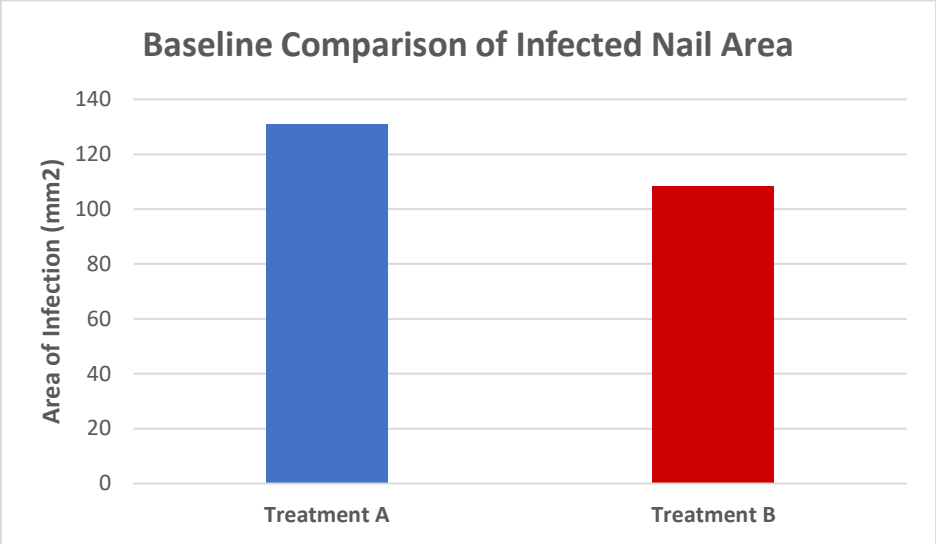

Figure 1: Above shows the mean infected area of both treatment groups at baseline. Although the starting level of infection at baseline was 17.14% lower in the treatment B group than the Treatment A group, this finding was not statistically significant.

% Nail Infected

The proportion of nail infected was compared at baseline to ensure there was no significant difference in the toenails included in each of the treatment groups.

The mean proportion of infected nail of the toenails to be who received Treatment A (M=0.57, SD=0.264) was greater than that of mean proportion of infected nail of the toenails to be who received Treatment B (M=0.56, SD=0.286, n=28) however this difference was not statistically significant (t(60)=0.174, p=0.862).

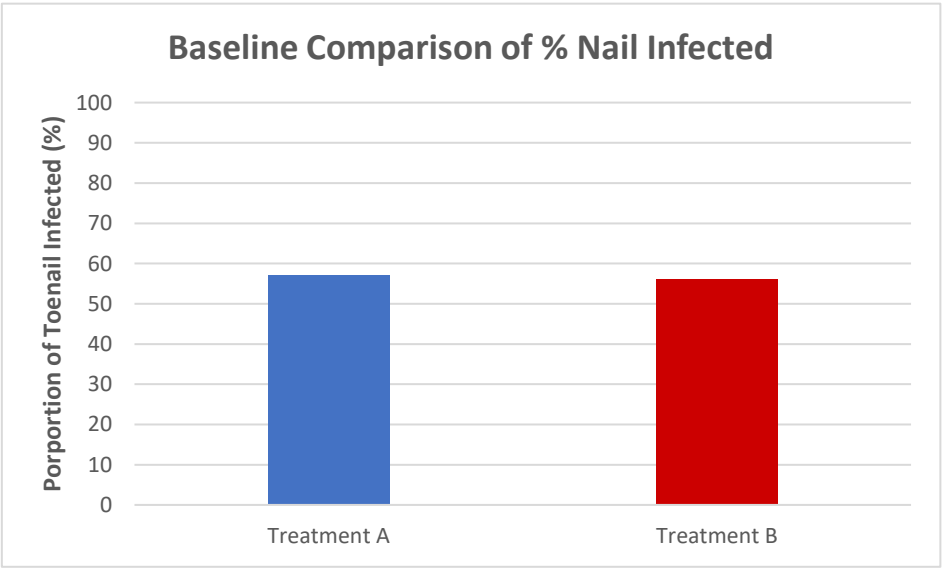

Figure 2: Above shows the proportion of toenail infected comparing both groups at baseline. Although the proportion of toenail infected at baseline was slightly higher in the Treatment A group, this finding was not statistically significant.

Treatment Performance Based on Infected Nail Area (Both Groups)

In this section the measurements taken of all patients, regardless of gender or age group, are compared from the baseline visit to all subsequent clinical visits.

Table 1: Treatment A - Comparison of **Total Infected Area of Toenail** (mm^2) at Baseline to Total Infected area at 5 other clinical appointments. Data is Mean±SD. n represents the number of patient toenails measured at that clinical visit. There were statistically significant reductions in the size of the infection at the 6 week and 12 week timepoints with very significant reductions observed at the 6 month timepoint.

Visit	n	Size at Baseline (mm^2)	Size at Visit (mm^2)	p-value
3 Week	*29*	*133.615±91.549*	*130.537±93.826*	*0.700*
6 Week	*29*	*126.030±89.694*	*105.984±71.267*	*0.038**
12 Weeks	*29*	*128.325±92.325*	*107.267±80.473*	*0.045**
6 Months	*28*	*129.194±94.409*	*100.402±81.855*	*0.006***
9 Months	*27*	*139.649±92.039*	*146.597±106.542*	*0.540*

Patients measured at the 6-week visit had a significant mean reduction of 20.046mm2 (95% CI: 1.224, 38.869) in the total infected area of the toe infected compared to their baseline measurements. Patients measured at the 12-week visit had a significant mean reduction of 21.058mm2 (95% CI: 0.457, 41.660) in the total infected area of the toe infected compared to their baseline measurements. Patients measured at the 6-month visit had a significant mean reduction of 28.792mm2 (95% CI: 8.996, 48.588) in the total infected area of the toe infected compared to their baseline measurements. Patients measured at the 9-month period showed an increase in the size of the infected area compared to baseline however this deterioration was not statistically significant, and the patients had completed treatment at 6 months.

Table 2: Treatment B - Comparison of **Total Infected Area of Toenail** (mm^2) at Baseline to Total Infected area at 5 other clinical appointments. Data is Mean±SD. n represents the number of patient toenails measured at that clinical visit.

Visit	n	Size at Baseline (mm^2)	Size at Visit (mm^2)	p-value
3 Week	*27*	*111.765±80.565*	*120.081±93.903*	*0.297*
6 Week	*27*	*111.297±81.083*	*99.091±86.072*	*0.176*
12 Weeks	*26*	*115.288±79.938*	*107.041±88.553*	*0.345*
6 Months	*24*	*103.933±81.446*	*97.598±78.631*	*0.565*
9 Months	*27*	*104.231±79.302*	*118.083±90.661*	*0.188*

Table 2 shows that there were reductions in the mean total infected area of the toenails on patients who received Treatment B at the 6-week, 12-week and 6-month visits, however these reductions were not statistically significant. There were increases in the mean total infected area of the toenails at the 3-Week and 9-month visits, but these increases were not statistically significant.

Treatment Performance Based on the Proportion of Infection (Both Groups)

Table 3: Treatment A - Comparison of **Proportion (%) of Toenail showing infection** at Baseline to Proportion (%) of Toenail showing infection at 5 other clinical appointments. Data is Mean±SD. n represents the number of patient toenails measured at that particular clinical visit.

Visit	n	% Toe Infected at Baseline	% Toe Infected at Visit	p-value
3 Week	29	57.0±25.6	54.0±27.1	0.091
6 Week	29	54.0±25.9	48.0±24.4	0.009**
12 Weeks	29	54.0±25.6	47.0±26.2	0.002**
6 Months	28	56.0±26.9	44.0±27.5	<0.005***
9 Months	27	57.4±25.1	56.9±30.1	0.848

Table 3 above shows that there were statistically significant reductions in the mean Proportion (%) of Toenail showing infection for patients who received Treatment A at the 6-week, 12-week and 6-month visits. Patients measured at the 6-week visit had a significant mean reduction of *6.37% (95% CI: 1.73, 11.02)* in the proportion of toenail infected compared to their baseline measure. Patients measured at the 12-week visit had a significant mean reduction of *6.65% (95% CI: 2.66, 10.63)* in the proportion of toenail infected compared to their baseline measure. Patients measured at the 6-month visit had a significant mean reduction of *12.03% (95% CI: 7.14, 16.92)* in the proportion of toenail infected compared to their baseline measure.

Table 4: Treatment B - Comparison of **Proportion (%) of Toenail showing infection** at Baseline to Proportion (%) of Toenail showing infection at 5 other clinical appointments. Data is Mean±SD. n represents the number of patient toenails measured at that particular clinical visit.

Visit	n	% Toe Infected at Baseline	% Toe Infected at Visit	p-value
3 Week	27	56.4±28.8	57.9±32.7	0.549
6 Week	27	54.0±27.8	52.6±33.3	0.633
12 Weeks	26	55.8±26.7	56.5±33.2	0.809
6 Months	27	54.4±28.5	54.2±34.7	0.938
9 Months	27	54.4±28.5	59.7±33.0	0.100

Table 4 above shows that there were reductions in the mean proportion (%) of Toenail showing infection for patients who received Treatment B at the 6-week and 6 month visit when compared to baseline measurements. There were increases in the mean proportion (%) of Toenail showing infection at the 3-week, 12-week and 9-Month visit. None of these changes in mean proportion (%) of toenail showing infection were statistically significant.

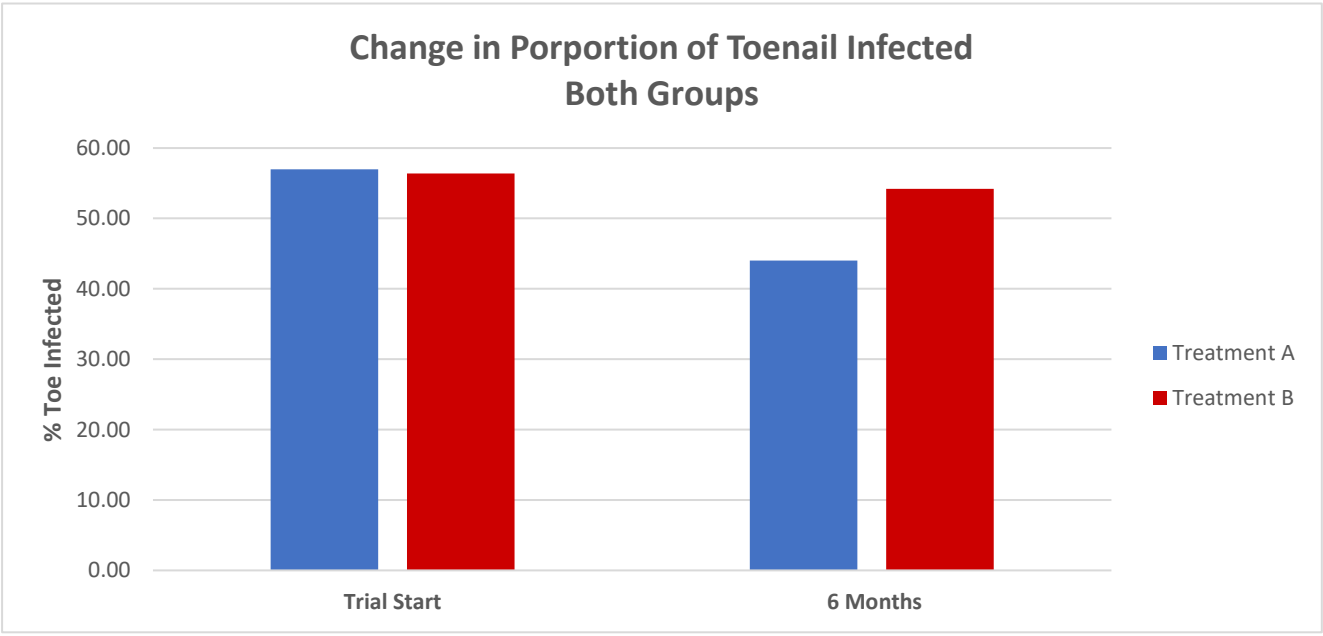

Figure 3: Comparison between both treatment groups in the proportion of toenail infected from Trial Start to the 6-month timepoint. Patients in the Treatment A group reduced in proportion of infection from 57.0% at baseline to 44% at the 6-month timepoint while patients in the Treatment B showed no significant change from 56.4% toe infected to 54.2%infected at the 6-month timepoint.

Overall Comparison Between Groups - % Change in % of Nail Infected

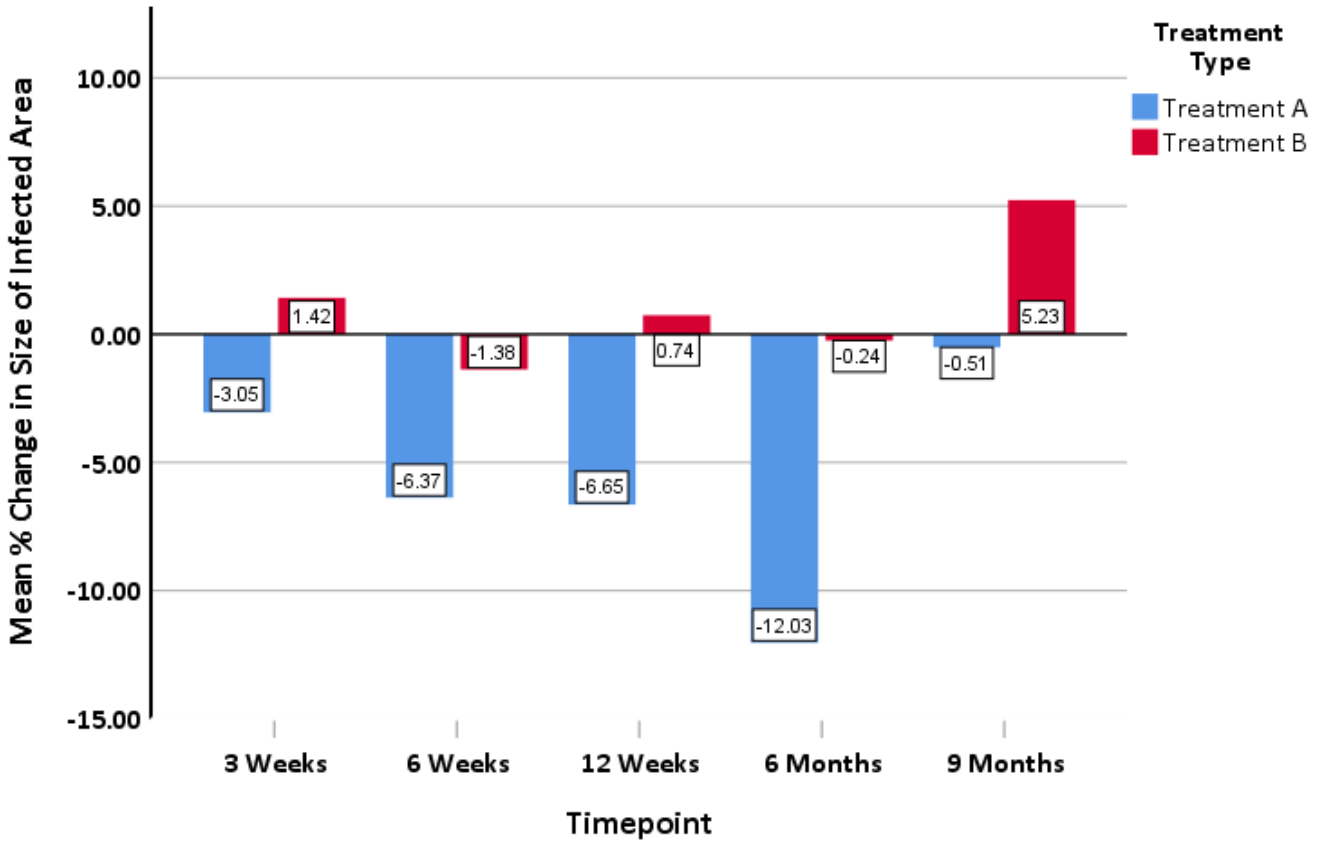

Figure 4: Mean % change in the % of nail showing infection at each timepoint compared to baseline measurements split by Treatment Type.

***Note:** All % changes are calculated from the relevant timepoint to the baseline measurements.

Figure 4 shows the mean % change in the percentage area of the nail showing visual signs of infection at each timepoint in the trial compared to the baseline measurements broken down by treatment type. After 3 weeks it can be seen that the mean % change in the % nail infected of patients on Treatment A (M=-3.05%, SD=9.37) showed a reduction compared to patients on Treatment B which showed an increase (M=1.42%, SD=12.13), however this difference was not statistically significant (t(54)=-1.547, p=0.128). After 6 weeks the mean % change in the % nail infected of patients on Treatment A (M=-6.37%, SD=12.22) showed a reduction compared to patients on Treatment B which also showed a reduction (M=-1.38%, SD=14.79), however this difference was not statistically significant (t(54)=-1.382, p=0.173). After 12 weeks the mean % change in the % nail infected of patients on Treatment A (M=-6.65%, SD=10.48) showed a reduction compared to patients on Treatment B who showed an increase (M=0.74%, SD=15.52), a statistically significant difference of 7.39% (95% CI: 2.92%, 14.49%) (t(53)=-2.088, p=0.042). After 6 months the mean % change in the % nail infected of patients on Treatment A (M=-12.03%, SD=12.61) showed a larger reduction compared to patients on Treatment B (M=-0.24%, SD=16.22), a statistically significant difference of 11.78% (95% CI: 3.94%, 19.62%)(t(53)=-3.015, p=0.004). After 9 months the mean % change in the % nail infected of patients on Treatment A (M=-0.51%, SD=13.67) showed a reduction compared to patients on Treatment B who showed an increase (M=5.23%, SD=15.94), however this difference was not statistically significant (t(52)=-1.421, p=0.161).

Please note Treatment A patients ceased treatment at the 6-month timepoint.

Negative % change in this instance indicates a reduction in the infection nail area while positive % change indicates an increase in infected nail area.

Overall Comparison Between Groups - % Change in Area of Clear Nail Visible

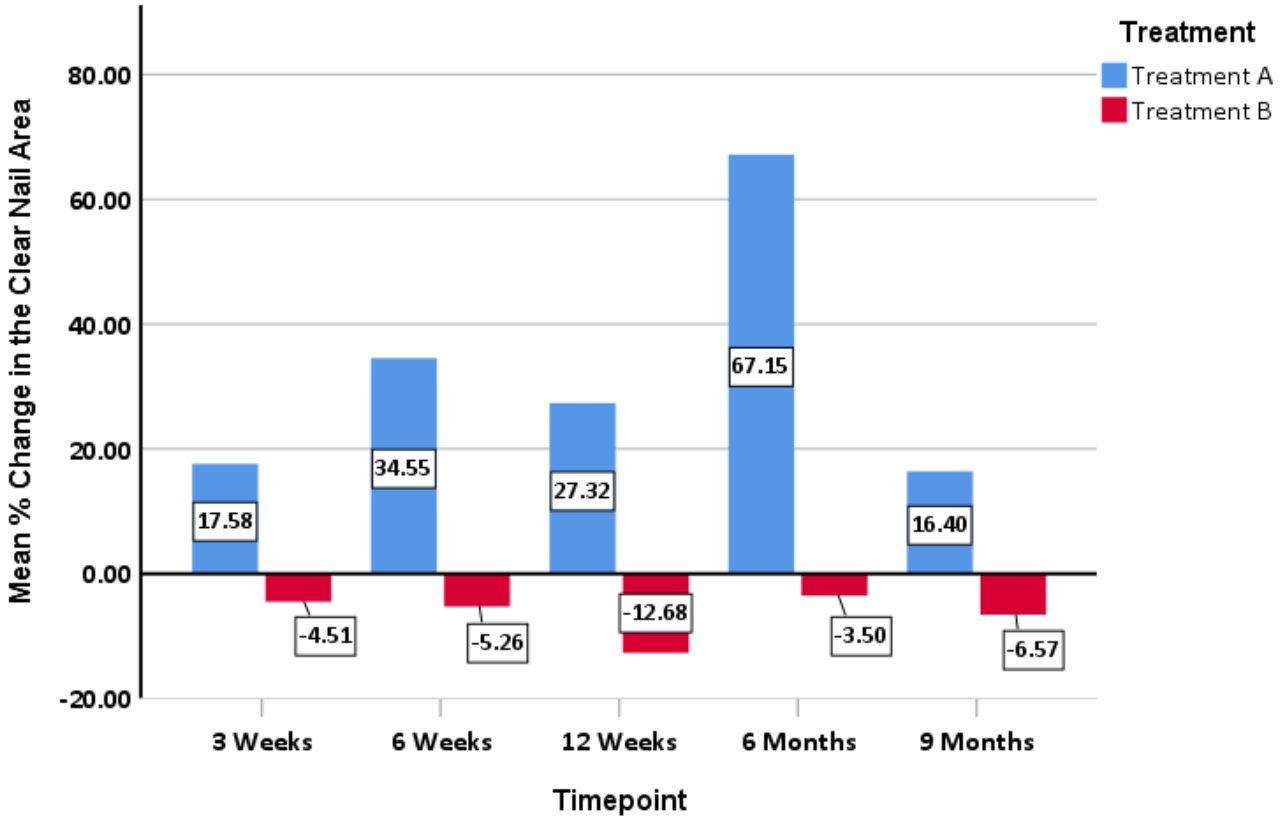

Figure 5: Mean % change in area of clear nail at each timepoint compared to baseline measurements split by Treatment Type.

Figure 5 shows the mean % change in the area of clear nail at each timepoint in the trial compared to the baseline measurements broken down by treatment type. After 3 weeks the clear nail on the toenails of those getting Treatment A had shown a mean % increase of 17.58%±53.69%(±SD) compared to a mean % decrease of 4.51%±33.65%(±SD) for those on Treatment B, however this difference was not statistically significant (t(51)=1.750, p=0.086). After 6 weeks the area of clear nail on the toenails of those getting Treatment A had shown a mean % increase of 34.55%±66.53%(±SD) compared to a mean % decrease of 5.26%±40.07%(±SD) for those on Treatment B, a statistically significant difference of 39.81% (95% CI: 10.18%, 69.43%) (t(46.847)=2.703, p=0.010). After 12 weeks the area of clear nail on the toenails of those getting Treatment A had shown a mean % increase of 27.32%±48.86%(±SD) compared to a mean % decrease of 12.68%±37.03%(±SD) for those on Treatment B, a statistically significant difference of 40.00% (95% CI: 16.29%, 63.71%) (t(50.651)=3.388, p=0.001). After 6 months the area of clear nail on the toenails of those getting Treatment A had shown a mean % increase of 67.15%±106.22%(±SD) compared to a mean % decrease of 3.50%±51.89%(±SD) for those on Treatment B, a statistically significant difference of 70.65% (95% CI: 24.12%, 117.19%) (t(41.274)=3.065, p=0.004). After 9 months the area of clear nail on the toenails of those getting Treatment A had shown a mean % increase of 16.40%±59.37%(±SD) compared to a mean % decrease of 6.57%±50.77%(±SD) for those on Treatment B, however this difference was not statistically significant. (t(49)=1.475, p=0.147).

Please note Treatment A patients ceased treatment at the 6-month timepoint.

Negative % change in this instance indicates a reduction in the healthy nail area while positive % change indicates an increase in healthy nail area.

Proportion of Toes Showing a Decrease in Infected Area

As seen in **Table 5** below there were statistically significant differences between Treatment A and Treatment B for the percentage of toenails showing decreases in the proportion of the toe with a visible infection between baseline and the 12-week visit and between baseline and the 6-month visit.

Table 5: Comparison of the number and proportion of toes in each treatment arm showing a decrease in the proportion of toe with a visible infection. Data is count(%).

	Treatment A	Treatment B	p-value
Baseline to 3 Weeks	*16 (55.2)*	*12 (44.4)*	*0.442*
Baseline to 6 Weeks	*21 (72.4)*	*13 (48.1)*	*0.063*
Baseline to 12 Weeks	*21 (72.4)*	*11 (42.3)*	*0.024**
Baseline to 6 Months	*22 (81.5)*	*11 (40.7)*	*0.002***
Baseline to 9 Months	*17 (56.7)*	*9 (33.3)*	*0.077*

Patients who received Treatment A were *1.71 (95% CI RR: 1.04, 2.83)* times more likely (71% increase in the likelihood) to show a decrease in the size of the infected area of the toenail than those who received Treatment B for 12 weeks. **Patients who received Treatment A were *2.00 (95% CI RR: 1.24, 3.26*) times more likely (100% increase in the likelihood) to show a decrease in the size of the infected area of the toenail than those who received Treatment B for 6 months.**

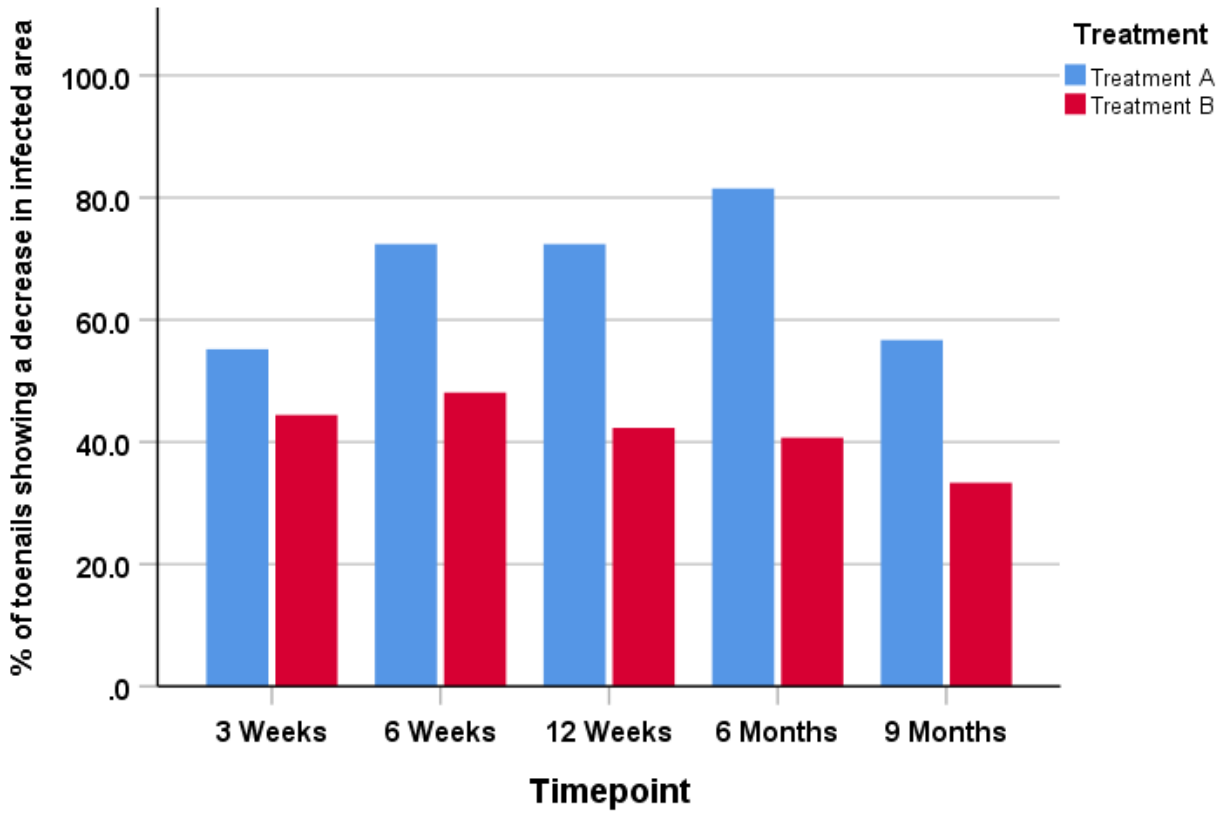

Figure 6: Comparison of % of toenails showing a decrease in infected area compared to visit 1 over time by treatment type.

Please note Treatment A patients ceased treatment at the 6-month timepoint.

Mycology Analysis – Culturing (Both Groups)

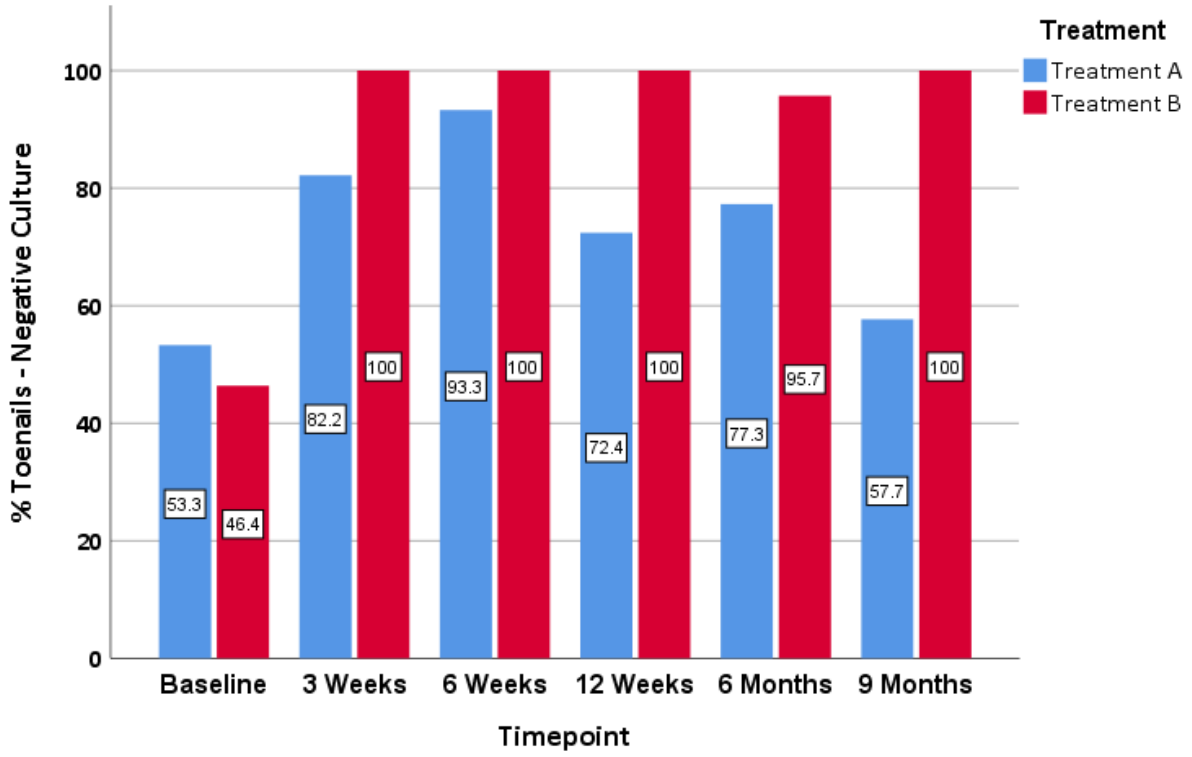

Figure 7: Comparison of culturing results by Treatment at each timepoint.

Figure 7 compares the culture results from each treatment at the six different timepoints of the trial. At the beginning of the trial 53.3% (n=16) of the toenails getting Treatment A showed negative culture compared to 46.4% (n=13) of the toenails getting Treatment B, however this difference was not statistically significant (z=0.53, p=0.596). After 3 weeks 82.2% (n=24) of toenails getting Treatment A had negative culture compared to 100.0% (n=28) of toenails getting Treatment B, a statistically significant difference of 17.8% (z=-2.30, p=0.021). After 6 weeks 93.3% (n=28) of toenails getting Treatment A had negative culture compared to 100.0% (n=6) of toenails getting Treatment B, however this difference was not statistically significant (z=-1.37, p=0.187). After 12 weeks 72.4% (n=21) of toenails getting Treatment A had negative culture compared to 100.0% (n=27) of toenails getting Treatment B, a statistically significant difference of 27.6% (z=-2.95, p=0.003). After 6 months 77.3% (n=17) of toenails getting Treatment A had negative culture compared to 95.7% (n=22) of toenails getting Treatment B, however this difference was not statistically significant (z=-1.81, p=0.070). After 9 months 57.7% (n=15) of toenails getting Treatment A had negative culture compared to 100.0% (n=26) of toenails getting Treatment B, a statistically significant difference of 42.3% (z=-3.74, p<0.001).

Safety

In total there were 4 AE's recorded during the trial, **none** were found to be related to the IMP or comparator product.

No deaths occurred during the trial and no Serious Adverse Events (SAE's) were reported by any patient in either treatment group. A summary of the AE's reported is given below.

AE No	Description	SAE
1	Local reaction from inappropriate use of plasters not prescribed as part of the trial	No
2	Fracture of right 2nd toe	No
3	Haematoma L2 middle toe following 18km walk	No
4	COVID-19	No

Conclusion
The superiority of Treatment A(Mycosinate) over its comparator Treatment B (Curanail) was clearly demonstrated. Treatment A demonstrated statistically significant reductions in the levels of infection while Treatment B showed no significant changes. The aim of this study was to demonstrate that Mycosinate is both safe and effective for the treatment of fungal nail infection. Our future direction will aim to run a treatment study for a longer duration so that complete cure rates can effectively be measured. Both products were well received with zero SAE's or drug related AE'S reported during the trial.

For those wishing to read our full clinical study report please contact us using the details below:

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