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Article type : Original Article

An observer blinded randomised controlled pilot trial comparing localised immersion psoralen ultraviolet A (PUVA) with localised narrowband ultraviolet B (NBUVB) for the treatment of palmar hand eczema

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Running Head Hand eczema phototherapy pilot trial

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Conflict of interest nil

What's already known about this topic?

PUVA is widely used for the treatment of topical steroid resistant hand eczema. Despite the widespread use of NBUVB for whole body eczema there have been few investigations of NBUVB for hand eczema. Small studies have shown it to be safe but formal comparison with PUVA by RCT has not been performed.

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What does this study add?

This pilot study suggests that both immersion PUVA and NBUVB are effective treatments for palmar hand eczema. NBUVB appears more likely to cause mild side effects such as erythema. NBUVB for hand eczema is a safe and reasonable alternative to PUVA. Recruitment of sufficient numbers of patients to a non-inferiority study comparing PUVA with NBUVB may be challenging.

Summary

Background: Hand eczema is a common inflammatory dermatosis that causes significant patient morbidity. Symptoms such as pain, itch and localised swelling contribute to disruption of activities of daily living, lack of sleep, and missed days from work. The aetiology is often multifactorial. Previous studies comparing psoralen ultraviolet A (PUVA) and narrowband ultraviolet B (NBUVB) have been small, non-randomised and retrospective.

Objectives: To conduct an observer blinded randomized controlled pilot study using validated scoring criteria to compare immersion PUVA with NBUVB for the treatment of chronic hand eczema unresponsive to topical steroids.

Methods: 60 patients (22 male, 38 female), median age 50 years (range 22, 73), with hand eczema unresponsive to clobetasol propionate 0.05% (Dermovate®) (25 (42%) severe), were randomised to receive either immersion PUVA (n=30) or NBUVB (n=30) twice weekly for 12 weeks with assessments at intervals of 4 weeks. The primary outcome measure was the proportion of patients achieving a 'clear' or 'almost clear' Physician's Global Assessment (PGA) treatment response at 12 weeks. Secondary outcome measures included assessment of the modified Total Lesion and Symptom Score (mTLSS) and the Dermatology Life Quality index (DLQI)

Results: In both treatment arms, 23 patients completed the 12-week assessment for the primary outcome measure. In the PUVA group, 5 patients achieved 'clear', and 8 'almost clear' (ITT response rate 43% (95%CI: 26%, 61%)). In the NB-UVB group, 2 achieved 'clear' and 5 'almost clear' (ITT response rate 23% (95%CI: 8%, 38%)). For the secondary outcomes, median (IQR) mTLSS scores were similar between groups at baseline (PUVA 9.5 (6.8,11), NBUVB 9 (6.8,12)) and at 12-weeks (PUVA 3 (1,6), NBUVB 4(2,8)). Changes in DLQI were similar with improvements in both groups.

Conclusions: In this randomised pilot trial recruitment was challenging. Once randomised, there were acceptable levels of compliance and safety in each treatment schedule, but lower levels of retention. Using validated scoring systems; PGA, mTLSS and DLQI as measures of treatment response, the trial demonstrated that both PUVA and NBUVB improved the severity of chronic palmar hand eczema. The study was not designed to demonstrate superiority of one treatment and a larger adequately powered RCT will be required to investigate this.

Introduction:

Hand eczema (HE) is a common, relapsing inflammatory dermatosis characterised clinically by erythema, scaling, fissures, swelling and vesiculation¹. It is a condition that causes significant patient morbidity, with symptoms such as pain, itch and burning contributing to insomnia, disruption of activities of daily living and work absenteeism². The Scandinavian TOACS study estimate an incidence of 8.8 per 1000 persons per year, with a history of atopic dermatitis being the most significant risk factor³. Meding et al reported that up to 21% of patients take at least one period of absence of at least 7 days from work, and that 8% of patients will change their occupation due to hand eczema severity⁴. HE classification can be based on aetiology or morphology; with common sub-types including atopic, irritant contact, allergic contact, pompholyx, hyperkeratotic or mixed. Following failure of topical treatment, systemic therapy or phototherapy is often needed.

Phototherapy has several advantages over oral systemic treatment; no blood monitoring is required and avoidance of side effects associated with retinoids or immunosuppressant medication. Disadvantages include equipment setup and staffing costs, multiple patient hospital visits, risk of skin erythema and burning, and the potential to induce photo-damage and cutaneous malignancy.

Following the introduction of psoralen ultraviolet A (PUVA) for psoriasis, the use of PUVA for hand eczema emerged in the 1980s without any large scale clinical trials. The efficacy of narrowband ultraviolet B (NBUVB) for generalised atopic eczema has been demonstrated in RCTs⁵. The use of NBUVB for HE has been advocated by some Dermatologists but is not widespread. Studies comparing PUVA vs NBUVB for HE have been small, non randomised, retrospective and have often included other non-eczematous dermatoses. More importantly, standardised skin severity scoring systems were not used⁶⁻⁹. Perhaps due to concerns that hand NBUVB may not penetrate palmar skin and possible problems with erythema, PUVA has remained the phototherapy treatment of choice for hand eczema.

We identified a need to formally compare NBUVB with PUVA for HE in a prospective, randomised setting using validated scores. NBUVB has potential logistic advantages, including cheaper costs and faster patient turnaround time (no hand soaking required and shorter irradiation times) or avoidance of potential side effects if oral PUVA is used. If NBUVB were equivalent or superior to PUVA there would be a strong case to use it as first line treatment. We report the first randomised observer blinded pilot study to compare NBUVB vs immersion PUVA using validated outcome measurements.

Methods

The trial was conducted as single centre, observer blinded, prospective, randomised pilot trial. The primary objective was to demonstrate feasibility to recruit, treat and retain patients and obtain accurate data defining the clinical response of HE to NBUVB and immersion PUVA. Patients were recruited from clinics at Newcastle Dermatology at the Newcastle Hospitals NHS Trust. The department has 16 clinics per day and treats around 1000 patients per week. Hand eczema was diagnosed by history and examination and biopsies were not taken.

Eligibility and Exclusion Criteria

Patient eligibility and exclusion criteria are shown in Table 1. Eligibility included palmar hand eczema only to minimise the dosing complexity that would have been needed with different doses required for the thinner skin on the dorsal surfaces. One of the main inclusion criteria was “Not responding to topical treatments” targeting patients who, after treatment by a Dermatologist with standard topical treatments, had not improved and needed second line treatments. In practice, this will have included non-response to super potent topical steroids and often tacrolimus although there were not defined rules regarding prior treatment choices. Patients with mild eczema elsewhere on the body were eligible but those with more widespread eczema where palmar eczema was not the predominant problem were excluded from the study.

Randomisation and treatment details

Patients were randomised on a 1:1 basis using a random block allocation method, stratified by gender and eczema severity (Physicians global assessment(PGA) severe vs mild/moderate). Randomisation was administered centrally by a secure web-based system and the schedule produced by a statistician not involved with the trial. Flow of patients through the trial is shown in Figure 1. Patients were randomised into 2 groups as follows:

Group 1 (standard treatment) received immersion PUVA twice weekly. Patients' hands were immersed in psoralen solution (0.5ml of 1.2% 8-methoxypsoralen in 2L tap water) for 15 minutes followed by exposure to UVA radiation at an initial dose of 0.5 J/cm² according to British Photo-dermatology Group (BPG) guidelines¹⁰. Doses were then increased for each treatment (1.0, 1.5, 2, 3, 4, 5, 6). The maximum dose was 6 J/cm² and the maximum potential cumulative dose 125 J/cm² (incremental doses over 3 weeks plus 18 treatments x6J/cm²).

Group 2 (intervention treatment) received NBUVB twice weekly. Initial doses were 0.5 J/cm² and increased by 20% increments to a maximum of 10 J/cm². The maximum potential cumulative dose was 123 J/cm².

Phototherapy was delivered using Waldmann 181 units fitted with UVA or NBUVB bulbs. The devices were calibrated and maintained throughout the trial by the medical physics department at Newcastle Hospitals NHS Trust.

For both groups doses were reduced if erythema developed. Once symptoms had settled patients were re-started at the last dose that had been tolerated without side effects. Trial exit criteria for both groups were completing 12 weeks of treatment (24 separate treatments) or attaining 'clear' or 'almost clear' as defined by the Physicians Global Assessment (PGA) score. Patients were permitted to use unlimited emollients during the trial and had to stop using topical steroids for 48h before trial commencement and their first dose of UV irradiation. To allow for missed appointments, but avoid major disruption to dosing schedules, we allowed patients to complete their 12 weeks of treatment within a maximum 14-week time frame

Outcome measures

The primary outcome measure was the proportion of patients achieving a PGA 'clear' or 'almost clear' treatment response at 12 weeks (or at their last visit if they achieved this before 12 weeks). The 'index hand' was defined as either the worst affected hand at baseline or if both hands were the same at baseline, the hand with the best response was analysed for the primary outcome. The PGA score is described by Ruzicka et al¹¹.

Secondary outcome measures included (1) the modified total lesion severity score (mTLSS), a score with 7 components scored at 0 to 3 with a maximum of 21; (2) the patient reported Dermatology Life Quality Index (DLQI), a validated measure of the effect of skin disease on patient's daily activities and (3) safety measures.

The choice of outcome measures was influenced by those used in the largest randomised trial of hand eczema investigating the efficacy and safety of alitretinoin¹¹. In this trial, the PGA scoring was interpreted such that a patient could be classified as 'severe' either by symptoms or involved surface area criteria.

A final outcome measure was feasibility, defined as the number of patients randomised as a proportion of the number of potential eligible participants.

Hand eczema severity assessments and Blinding

At randomisation HE types, duration, presence at other sites, previous therapeutic interventions, and pre-existing medical conditions were recorded. At randomisation and at weeks 4, 8 and 12, patient HE severity (PGA and mTLSS) was independently assessed by one of 2 clinicians who were blinded to the treatment modality being used; whilst the attending nursing staff and patients receiving treatment were unblinded. The assessing clinicians were trained in utilising the PGA and mTLSS using standardised photographs of HE severity and real patients to improve parity¹². Patients were examined before their treatments in a closed office in an area of the department separate from the phototherapy equipment. At baseline, and each subsequent visit DLQI was determined via patient questionnaire.

Sample size and statistical analysis plan

As a pilot study, the sample size was chosen as an achievable target based on the minimum conventional threshold for making parameter estimates in pilot studies¹³, aiming to recruit 60 patients with baseline and 12 week scores. Allowing for 20% potential drop-outs and loss to follow up inflated the recruitment target to a total of 76 patients.

As a pilot study, the statistical analyses are focussed on descriptive statistics reporting primarily feasibility and response rates on an intention-to-treat (ITT) basis. Feasibility is calculated as the number of patients randomised as a proportion of the number of potential eligible participants. The primary outcome measure was PGA response rate at 12 weeks calculated as the number of 'clear' or 'almost clear' responders as a proportion of the number of patients randomised. Additional per protocol PGA response rates are reported as a planned sensitivity analysis. Longitudinal data, including PGA and mTLSS scores, are plotted over time. Patients with PGA response are assessed for duration of response. Patient reported quality of life is scored according to the Dermatology Life Quality Index (DLQI) and reported descriptively over time¹⁴.

Adverse event documentation

Expected phototherapy related side-effects include various grades of erythema. Adverse events were recorded and graded on a three-point severity scale of mild, moderate and severe; whilst causality for each event was assessed as unrelated, unlikely, possible, probable, definite or not assessable. (Mild: Discomfort noted with no disruption of activities of daily living (ADLs). Moderate: Discomfort sufficient to limit normal ADLs. Severe: Incapacitating discomfort with inability to work or perform ADLs.) The number of patients experiencing at least one severe episode is reported as a percentage of the total number of patients receiving treatment and as the total number of patients randomised.

Results

Recruitment and Randomisation

From August 2012 to April 2014, 105 patients were assessed via dedicated trial recruitment clinics where the diagnosis and categorisation of patients' hand eczema was made by a consultant dermatologist; 105 patients were screened; 73 patients fulfilled the eligibility criteria and 32 were excluded (Supplementary Table 1). 13 eligible patients declined to enter mainly (69%) due to inability to commit to twice weekly visits, travel difficulties and issues with work commitments. Three of the 13 were not entered due to specifically requesting PUVA treatment. A total of 60 patients were consented and randomised: 38 (63%) were female, 25 (42%) with severe disease, approximately balanced across randomised treatment groups through stratification. Feasibility, as assessed by recruitment rate, was 82.2% (95%CI: 73.4%, 91.0%). The total number of patients randomised was lower than the target of 76 due to difficulties to recruit and subsequent time and financial limitations.

Patient Demographics

The predominant type of HE was hyperkeratotic (47%). The median (range) duration of HE was 2.5 (0.3, 35) years, with 42% reporting eczema at body sites other than their hands (Table 2). It is unusual for there to be no cases of contact eczema reported. Patch testing was not part of the protocol and no analysis has been done based on subtype. We reported predominant HE type and it is possible that some patients may have had a contribution to their disease from contact allergy. In a full study it would be important to document contact allergy accurately with patch testing of all participants. None of the randomised patients had previously tried any systemic therapy for their hand eczema.

Treatment Received and Adverse Events

One patient randomised to PUVA decided not to participate in the study and did not start treatment. Median (IQR) number of treatments was 24 (17, 24) for the 29 PUVA patients and 22 (16, 24) for the 30 NBUVB patients (Supplementary Table 2). Most patients began treatment immediately and time on treatment was on average 85 days, in line with the protocol. Median (IQR) cumulative dose was 105.5 (66.0, 111.5) J/cm² for the 29 PUVA patients and 60.7 (28.1, 92.0) J/cm² for the 30 NBUVB patients.

A total of 54 adverse events were reported in 29 (49%) patients (Supplementary Table 3). Of these, 37 (PUVA n=10 (19%), NBUVB n=27, (50%)) were classed as mild (discomfort noted, no disruption to ADLs). A total of 17 moderate or severe events were reported in 13 (22%) patients; 14 events in 10 patients were in the NBUVB group (none were severe, 8 were treatment related) and 3 events in 3 patients were in the PUVA group (1 severe, none treatment related). Most of the NBUVB adverse events were predictable due to erythema or burning. There was one reported serious adverse event in the NBUVB arm due to abdominal pain requiring admission which was judged to be unrelated to the trial treatment.

Primary outcome measure: PGA

The PGA scores at baseline for the index hand were 11 (18%) mild, 24 (40%) moderate and 25 (42%) severe (Table 3). A total of 46 (77%) patients (23 in each randomised group) had final assessment data available for analysis. The most common reason for patients not reaching the end of the study was being unable to attend assessments due to work commitments. A total of 13 patients randomised to PUVA had PGA response at 12-week assessment (5 clear, 8 almost clear). A total of 7 patients randomised to NBUVB had PGA response at 12-week assessment (2 clear, 5 almost clear) (Table 3). Intention-to-treat analysis (ITT) PGA response rates demonstrated 43% (95%CI: 26%, 61%) response in the PUVA group and 23% (95%CI: 8%, 38%) in the NBUVB group. A planned per-protocol sensitivity analysis of the primary outcome measure demonstrated a 57% (95%CI: 36%, 77%) and 30% (95%CI: 12%, 49%) PGA response for PUVA and NBUVB respectively (Table 3).

Secondary outcome measures

The secondary outcome measures were recorded at baseline, week 4, week 8 and at the end of the study (week 12-14). Median mTLSS scores decreased during the treatment period in both randomised groups (Figure 2) where decreased score indicates decreased severity. The sizes of reductions were similar in both groups: median (IQR) mTLSS scores at randomisation and end of study were 9.5 (6.8, 12) and 3 (1, 6) for PUVA; 9 (6.8, 11) and 4 (2, 8) for NBUVB.

There was a marked reduction in mTLSS scores for both treatments in patients who achieved the primary PGA response compared to those patients who did not (Supplementary Figure 1).

There was a progressive reduction in DLQI in both groups over time where reduced DLQI indicates improving quality of life (Figure 3). The size of the reductions was similar in both groups: median (IQR) DLQI scores at randomisation and end of study were 9.5 (7.8, 15.5) and 2 (0, 11) for PUVA; 10.5 (7, 16) and 4 (2, 7) for NBUVB.

Only 19 patients (32%) were followed to the 26 weeks follow up due to lack of patient availability giving too small a data set for meaningful analysis.

Discussion

We have conducted a pilot study investigating NBUVB and immersion PUVA for the treatment of palmar hand eczema resistant to topical therapy. Both treatment modalities were shown to be safe with good patient acceptability. The higher rate of treatment related AE in the NBUVB group was not unexpected. NBUVB is more likely to cause erythema than PUVA. The degree of erythema experienced by an individual patient is related to dose but also epidermal thickness, UV penetration, local factors which influence photoadaptation and biochemical factors influencing erythema. No patients withdrew from the study due to AE; however, further work on dosimetry may succeed in reducing the episodes of NBUVB mediated erythema.

Almost twice as many patients in the PUVA group (43%, 95%CI: 26%, 61%) achieved the primary outcome (clear or almost clear PGA) compared with the NBUVB group (23%, 95% CI: 8%, 38%), although with wide over-lapping confidence intervals. A similar difference was not seen in the mTLSS and DLQI data. The mTLSS is a 21-point score and provides a more sensitive and detailed description of the hand eczema severity. Patients with only small differences in the mTLSS can be allocated different PGA scores. The categorical nature of the PGA score may therefore amplify the differences between groups. We recommend that future studies use a scoring system with a continuous measurement as the primary outcome measure, rather than the categorical PGA. As with the mTLSS, the DLQI scores were similar between both groups suggesting that the large PGA determined primary outcome difference is possibly misleading. Due to the relatively small size of the study firm conclusions cannot be made on response by hand eczema subtype. However, the majority of patients had hyperkeratotic hand eczema and their thickened epidermis may have influenced the penetration of the UV with UVA penetrating more readily than UVB. Any future studies will need to carefully balance the groups for HE types.

The design of this trial was in part based on the Ruziicka et al alitretinoin study¹¹. In retrospect, a better primary outcome would have been a continuous scale such as , the HECSI (Hand eczema clinical severity index)¹⁵. Advantages of the HECSI include more accurate recording of area involved and a lack of subjective measures such as itch but the disadvantage is increased complexity and a longer scoring time. Future studies could consider its use in addition to PGA, mTLSS and DLQI.

For ethical reasons, there was no control group and it is therefore possible that some patient improvement may have been through regression to their mean severity values (i.e. recruited at their most severe and through the natural fluctuation of inflammatory skin disease were better 12 weeks later at the end of the trial). However, clinical experience of patients with severe chronic hand eczema suggests that without treatment most remain severely affected and so most improvements seen in this study are likely to be a result of the interventions. One option would be to only treat one hand and monitor the untreated hand for any concomitant severity changes although HE is often asymmetric in severity which limits this study design.

The literature regarding phototherapy for hand eczema is fragmented, consisting of small, non-randomised studies, retrospective case series and inclusion of patients with non-eczematous dermatoses; making it difficult to draw definite conclusions regarding best practice. Numerous small studies have demonstrated the benefits of PUVA for hand eczema and are consistent with the wide clinical experience of this treatment¹⁶⁻¹⁸. There have been other comparisons of PUVA vs UVB but most of the studies were small and did not use validated scoring systems. *Rosen et al* compared broadband UVB with oral PUVA in a randomised, non-blinded study that recruited 35 patients with various forms (predominantly ACD) of hand eczema¹⁸. Using a non-validated scoring method, they concluded that oral PUVA was superior to UVB treatment. However, it is unlikely that the sample size used was sufficient to make a statistically significant conclusion.

In 1997 *Simons et al* performed a right-left comparison of topical PUVA vs NBUVB in 13 patients with chronic hand eczema and concluded that there was no statistical difference in efficacy, although the PUVA treated hands suffered more episodes of burning¹⁷. In 2007, *Sezer et al* performed a randomised, prospective right-left comparison study on 15 patients with chronic hand eczema, treating them with either immersion PUVA or NBUVB 3 times a week for 9 weeks with similar results seen for both treatments⁹.

Adhering to standard dosimetry schedules, the short-term safety profile of both therapies appears limited to episodes of erythema. However, the long-term safety of repeated treatment courses to the hands is yet to be elucidated for both immersion PUVA and NBUVB. Further work is needed to investigate the optimal dosing regimen for NBUVB in HE. Whilst this study only treated the palms, the thinner dorsal surfaces may be more prone to erythema and careful investigation will be needed to determine the starting doses and increments when using NBUVB in this area.

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Ultimately, a non-inferiority study comparing PUVA against NBUVB would help to determine the order of treatment choice. This would be challenging due to patient numbers required to provide sufficient statistical power. The introduction of an effective licensed oral agent for hand eczema, alitretinoin, may also lead to a reduced demand for phototherapy. The UK NIHR is currently conducting the ALPHA study comparing PUVA vs alitretinoin and these results may also have a big impact on treatment choice and the current widespread use of phototherapy for HE¹⁹. For these reasons, the need for a definitive non-inferiority trial of NBUVB vs immersion PUVA will be reviewed following the results of ALPHA.

This randomised pilot trial has confirmed feasible levels of randomisation and retention, acceptable treatment schedules demonstrating high compliance and acceptable safety profiles for each arm. It has quantified the variation in disease. This trial has shown that whilst NBUVB did result in more frequent episodes of erythema, overall it was safe and well tolerated and did produce improvements for some patients. Immersion PUVA was well tolerated. NBUVB is proposed as a safe treatment option for patients desiring a shorter hospital visit for their treatment or when PUVA has not been effective. Further investigation is needed to determine if one treatment is superior to the other.

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1. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J, et al. Guidelines for diagnosis, prevention and treatment of hand eczema. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*. 2015;13(1):e1-22.
2. Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis*. 2010;62(2):75-87.
3. Mortz CG, Bindsvlev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood. *Br J Dermatol*. 2014;171(2):313-23.
4. Meding B, Jarvholm B. Incidence of hand eczema-a population-based retrospective study
Hand eczema in Swedish adults - changes in prevalence between 1983 and 1996. *J Invest Dermatol*. 2004;122(4):873-7.
5. Reynolds NJ, Franklin V, Gray JC, Diffey BL, Farr PM. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet*. 2001;357(9273):2012-6.
6. Nordal EJ, Christensen OB. Treatment of chronic hand dermatoses with UVB-TL01. *Acta Derm Venereol*. 2004;84(4):302-4.

7. Kuhl JT, Davis MD, McEvoy MT. Narrowband ultraviolet-B phototherapy for hand and foot dermatoses. *Photodermatol Photoimmunol Photomed*. 2008;24(3):152-3.
8. Sezer E, Erbil AH, Kurumlu Z, Tastan HB, Etikan I. Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *J Dermatol*. 2007;34(7):435-40.
9. Sezer E, Etikan I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. *Photodermatol Photoimmunol Photomed*. 2007;23(1):10-4.
10. Halpern SM, Anstey AV, Dawe RS, Diffey BL, Farr PM, Ferguson J, et al. Guidelines for topical PUVA: a report of a workshop of the British photodermatology group. *Br J Dermatol*. 2000;142(1):22-31.
11. Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol*. 2008;158(4):808-17.
12. Coenraads PJ, Van Der Walle H, Thestrup-Pedersen K, Ruzicka T, Dreno B, De La Loge C, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol*. 2005;152(2):296-301.
13. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *Journal of evaluation in clinical practice*. 2004;10(2):307-12.
14. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-6.
15. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. *Br J Dermatol*. 2005;152(2):302-7.
16. Hawk JL, Grice PL. The efficacy of localized PUVA therapy for chronic hand and foot dermatoses. *Clin Exp Dermatol*. 1994;19(6):479-82.
17. Simons JR, Bohnen IJ, van der Valk PG. A left-right comparison of UVB phototherapy and topical photochemotherapy in bilateral chronic hand dermatitis after 6 weeks' treatment. *Clin Exp Dermatol*. 1997;22(1):7-10.
18. Rosen K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands: a comparison of PUVA and UVB treatment. *Acta Derm Venereol*. 1987;67(1):48-54.
19. Smith IL, Brown S, Nixon J, Cowdell FC, Ersser S, Fernandez C, et al. Treatment of severe, chronic hand eczema: results from a UK-wide survey. *Clin Exp Dermatol*. 2017;42(2):185-8.

Table 1.

Inclusion criteria	Exclusion criteria
Written informed consent	Inability to give informed consent.
Palmar eczema not responding to topical treatments	Significant eczema on the dorsal surface of the hands
Any type of hand eczema	Phototherapy within the last 3 months
Over 18 years of age	Sunbed use within the last 3 months
No systemic treatments for 3 months	Current involvement in other investigational studies
	Pregnant
	Clinical evidence of infection

Table 1

Inclusion and exclusion criteria for study.

Table 2

		PUVA n=30	NBUVB n=30	Total n=60
Sex	Male	12 (40%)	10 (33%)	22 (37%)
	Female	18 (60%)	20 (67%)	38 (63%)
Severity	Severe	12 (40%)	13 (43%)	25 (42%)
	Mild /moderate	18 (60%)	17 (57%)	35 (58%)
Age	Median (yrs)	51	44	50
	Range	(22, 73)	(22, 72)	(22, 73)
	IQR	(33, 61)	(34, 61)	(34, 61)
Predominant type of HE				
	Allergic Contact Dermatitis	0 (0%)	0 (0%)	0 (0%)
	Irritant Contact Dermatitis	5 (17%)	3 (10%)	8 (13%)
	Allergic and Irritant	1 (3%)	1 (3%)	2 (3%)
	Atopic HE	4 (13%)	5 (17%)	9 (15%)
	Atopic and Irritant	4 (13%)	3 (10%)	7 (12%)
	Vesicular	2 (7%)	4 (13%)	6(10%)
	Hyperkeratotic	14 (47%)	14 (47%)	28(47%)
Duration: years				
	Median (Range)	2 (0.5,35)	2.75 (0.3,10)	2.5(0.3,35)
Eczema at other sites				
	No	20 (67%)	15 (50%)	35 (58%)
	Yes	10 (33%)	15 (50%)	25(42%)

Table 2 Patient Characteristics at Randomisation

Table 3

Number of patients reaching clear or almost clear on the PGA score at the end of the study (shaded).

	PGA Score at Baseline					
	0. Clear	1. Almost	2. Mild	3. Mod	4. Severe	Total
PUVA	0	0	4	15	11	30
NBUVB	0	0	7	9	14	30
TOTAL	0	0	11	24	25	60
	Final PGA Response					
	0. Clear	1. Almost	2. Mild	3. Mod	4. Severe	Total
PUVA	5	8	3	4	3	23
NBUVB	2	5	10	5	1	23
TOTAL	7	13	13	9	4	46

Table 3 b) Proportion of patients reaching clear or almost clear on the PGA score at the end of the study

	% Achieving PGA response at final assessment (95% CI)	
	Intention-to-treat NBUVB =30, PUVA =30	Per protocol NBUVB=23, PUVA=23
primary outcome response PUVA =13	43% (26%, 61%)	57% (36%, 77%)
Primary outcome response NBUVB = 7	23% (8%, 38%)	30% (12%, 49%)

Figure 1

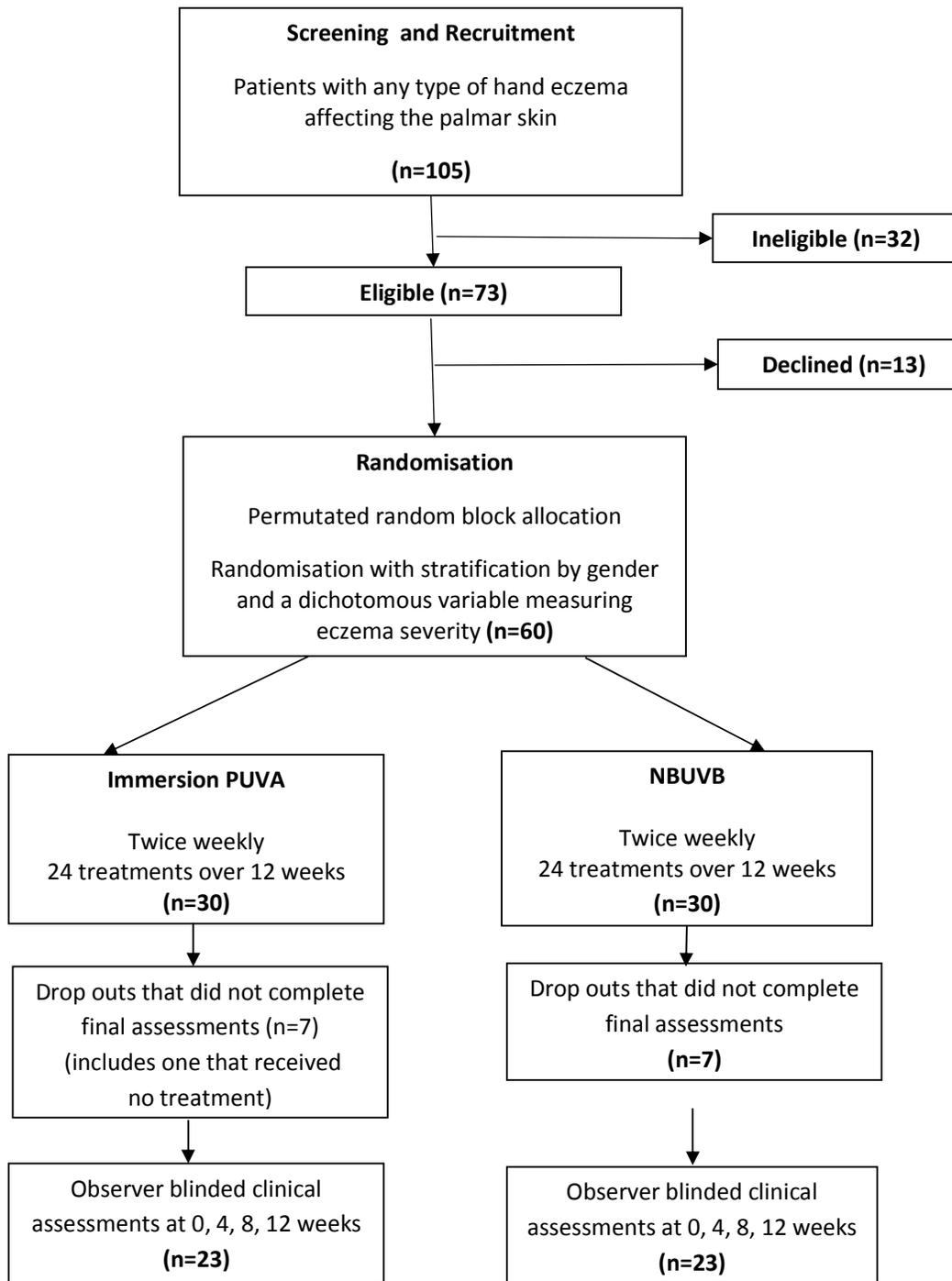
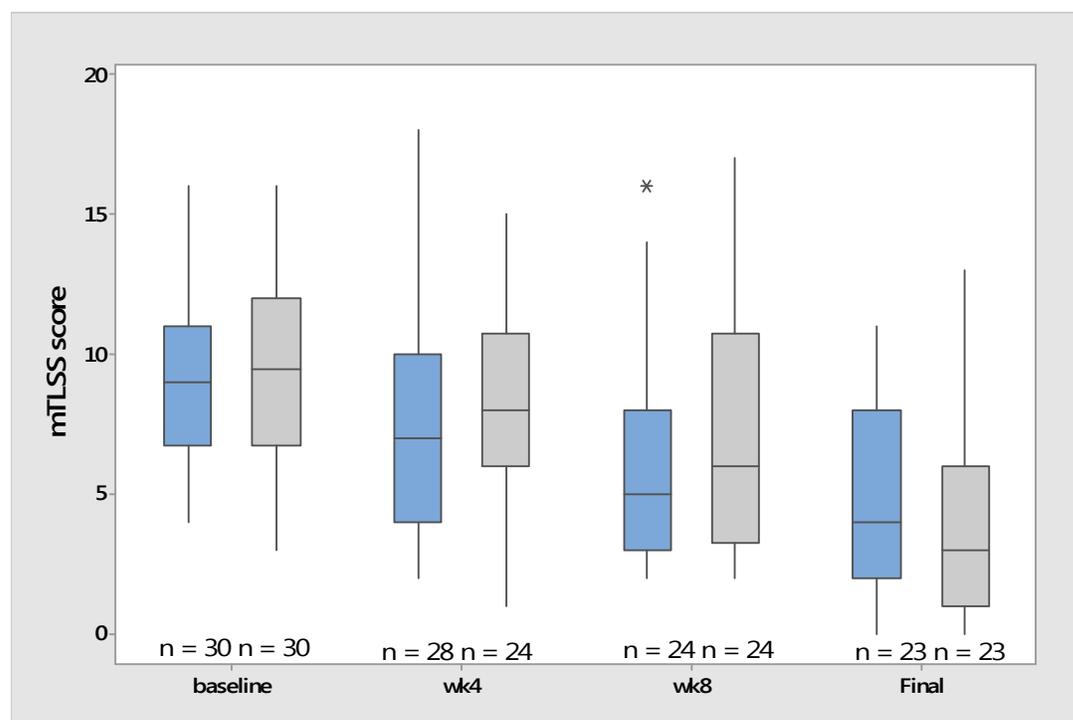


Figure 1

The trial flowchart shows the distribution of patients between the two intervention arms of the trial. The details of reasons for ineligibility and declining to participate are shown in supplementary table 1.

Figure 2

Boxplots of patient's mTLSS score at baseline, week 4, week 8 and final assessment at week 12 (max 14 weeks) for NBUVB (blue) and PUVA (grey). Boxplots show median (band inside box), the interquartile range (top and bottom of box), whiskers extend to 1.5 X IQR and outliers (asterisk). The mTLSS is a hand eczema score with 7 components scored at 0 to 3 with a maximum of 21. Median mTLSS scores decreased during the treatment period in both randomised groups

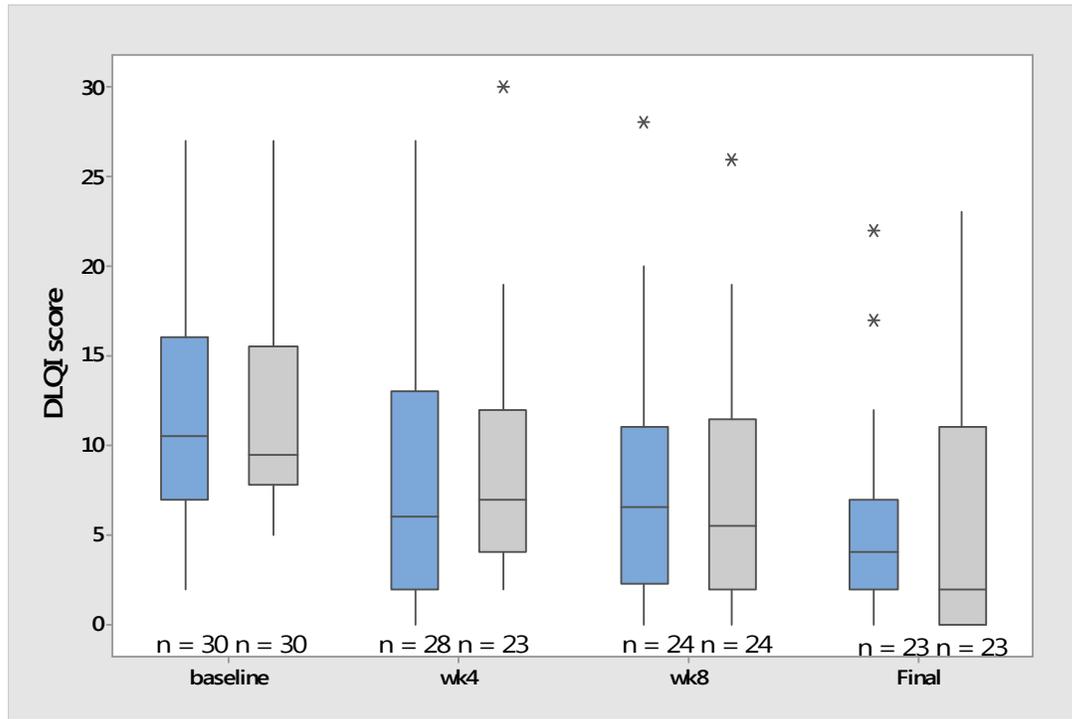


Median mTLSS scores and (IQR) for patients with baseline PGA scores

Arm	Baseline: median (IQR)	Wk4: median (IQR)	Wk8: median (IQR)	Final: median (IQR)
NBUVB	9 (6.8,11)	7 (4,10)	5 (3,8)	4 (2,8)
PUVA	9.5 (6.8,12)	8 (6,10.75)	6 (3.3,10.8)	3 (1,6)

Figure 3

Boxplots of patient's DLQI score at baseline, week 4, week 8 and final assessment at week 12 (max 14 weeks) for NBUVB (blue) and PUVA (grey). Boxplots show median (band inside box), the interquartile range (top and bottom of box), whiskers extend to 1.5 X IQR and outliers (asterisks). Reductions in DLQI were seen in both groups over the course of the 12 weeks.



Median DLQI score and (IQR) patients with baseline PGA scores.

Arm	Baseline: median (IQR)	Wk4: median (IQR)	Wk8: median (IQR)	Final: median (IQR)
NBUVB	10.5 (7,16)	6 (2,13)	6.5 (2.3,11)	4 (2,7)
PUVA	9.5 (7.8,15.5)	7 (4,12)	5.5 (2,11.5)	2 (0,11)