# Clinical trial results:
# A Phase IV, Randomised, Double-Blind, Controlled, Parallel Group Trial to Evaluate the Effectiveness and Safety of Balneum Plus vs Emollient in the Treatment of Uraemic Pruritus in Haemodialysis Patients.

## Summary

| | |
|---|---|
| EudraCT number | 2014-005594-36 |
| Trial protocol | GB |
| Global end of trial date | 26 December 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 October 2019 |
| First version publication date | 04 October 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | PHT/2014/107 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN13971661 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Portsmouth Hospitals NHS Trust |
| Sponsor organisation address | Queen Alexandra Hospital, Cosham, Portsmouth, United Kingdom, PO6 3LY |
| Public contact | Jacqueline Nevols, Portsmouth Hospitals NHS Trust, +44 02392286000, jacqueline.nevols@porthosp.nhs.uk |
| Scientific contact | Jacqueline Nevols, Portsmouth Hospitals NHS Trust, +44 02392286000, jacqueline.nevols@porthosp.nhs.uk |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 26 December 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 December 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare itch intensity as measured by a Visual Analogue Scale after 4 weeks treatment with Balneum Plus cream vs emollient control in patients with uraemic pruritus.

Protection of trial subjects:

Trial subjects had contact with study staff on a weekly basis - and had contact details to report problems outside of scheduled visits.

Background therapy:

All trial subjects were on maintenance haemodialysis for treatment of end-stage renal disease. Most of the trial subjects were on multiple medications -for example antihypertensives and phosphate binders. All medications were recorded at the time of study entry and subjects were stratified according to antihistamine use.

Evidence for comparator:

For the comparator group - a basic emollient was used (E45). There is no evidence in the literature that simple emollients (without active ingredients) improve the symptoms of uraemic pruritus.

| | |
|---|---|
| Actual start date of recruitment | 04 January 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 58 |
| Worldwide total number of subjects | 58 |
| EEA total number of subjects | 58 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 27 |

| | |
|---|---|
| From 65 to 84 years | 28 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited from the Wessex Kidney Centre's dialysis units. The research nurse visited each patient to inquire about symptoms of pruritus and their potential willingness to take part in a clinical trial.

### Pre-assignment

Screening details:

Potential subjects were screen according to the inclusion and exclusion criteria for the trial by the research nurse at the dialysis centre.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Assessor |

Blinding implementation details:

Randomisation list generated by the study statistician. The list was kept securely in the Trust Pharmacy. Study team (CI and research nurses) had no access to the randomisation list. Upon successful recruitment of a trial subject - the patient was randomised and prescribed the trial cream. Both the study cream and comparator looked identical and were dispensed in identical containers.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Treatment arm |

Arm description:

Balneum Plus - to be applied topically twice daily.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Balneum Plus |
| Investigational medicinal product code | PL33016/0010 |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Cutaneous use |

Dosage and administration details:

The cream was to be applied to affected areas of skin, topically, twice daily, for four weeks.

| | |
|---|---|
| **Arm title** | Comparator arm |

Arm description:

E45 cream was used as base cream/control cream

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | E45 |
| Investigational medicinal product code | PL00063/0404 |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Cutaneous use |

Dosage and administration details:

To be applied to affected areas of skin, topically, twice daily, for four weeks.

| **Number of subjects in period 1** | Treatment arm | Comparator arm |
|---|---|---|
| Started | 29 | 29 |
| Completed | 26 | 26 |
| Not completed | 3 | 3 |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | 1 | 2 |
| Not complete the course of treatment | 1 | - |
| Received transplant, no longer eligible | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Treatment arm |
| Reporting group description: | |
| Balneum Plus - to be applied topically twice daily. | |
| Reporting group title | Comparator arm |
| Reporting group description: | |
| E45 cream was used as base cream/control cream | |

| Reporting group values | Treatment arm | Comparator arm | Total |
|---|---|---|---|
| Number of subjects | 29 | 29 | 58 |
| Age categorical | | | |
| Adult haemodialysis patients. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 12 | 15 | 27 |
| From 65-84 years | 17 | 11 | 28 |
| 85 years and over | 0 | 3 | 3 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 64.0 | 63.4 | |
| standard deviation | ± 13.9 | ± 16.2 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | 18 |
| Male | 20 | 20 | 40 |
| Smoking status | | | |
| We documented smoking status as a baseline characteristic. | | | |
| Units: Subjects | | | |
| Never smoked | 11 | 11 | 22 |
| Ex-smoker | 13 | 12 | 25 |
| Current smoker | 5 | 6 | 11 |
| Cause of End-stage renal disease | | | |
| We identified the cause of end-stage renal disease in study participants. | | | |
| Units: Subjects | | | |
| Glomerulonephritis | 9 | 3 | 12 |
| Diabetic Nephropathy | 3 | 8 | 11 |
| Hypertension/renovascular disease | 8 | 4 | 12 |
| Obstructive Uropathy | 2 | 5 | 7 |
| Polycystic kidney disease | 1 | 2 | 3 |
| Other | 4 | 3 | 7 |

| | | | |
|---|---|---|---|
| Unknown | 2 | 4 | 6 |
| Dialyser size | | | |
| We documented the size of dialyser for each participant. | | | |
| Units: Subjects | | | |
| Small | 6 | 7 | 13 |
| Medium | 11 | 12 | 23 |
| Large | 12 | 10 | 22 |
| Allergic drugs<br>Units: Subjects | | | |
| No | 20 | 21 | 41 |
| Yes | 9 | 8 | 17 |
| Antipruritics<br>Units: Subjects | | | |
| No | 17 | 17 | 34 |
| Yes | 12 | 12 | 24 |
| Emollient use<br>Units: Subjects | | | |
| No | 16 | 14 | 30 |
| Yes | 13 | 15 | 28 |
| Antihistamines use<br>Units: Subjects | | | |
| No | 26 | 26 | 52 |
| Yes | 3 | 3 | 6 |
| Other medication<br>Units: Subjects | | | |
| No | 0 | 0 | 0 |
| Yes | 29 | 29 | 58 |
| Allergies<br>Units: Subjects | | | |
| No | 20 | 21 | 41 |
| Yes | 9 | 8 | 17 |
| Time on Haemodialysis<br>Units: Years | | | |
| median | 1.5 | 2.6 | |
| inter-quartile range (Q1-Q3) | 0.7 to 3.4 | 0.9 to 4.7 | - |
| C-reactive protein<br>Units: milligram(s)/litre | | | |
| median | 12 | 10 | |
| inter-quartile range (Q1-Q3) | 6 to 20 | 5 to 19 | - |
| Phosphate Level<br>Units: millimole(s)/litre | | | |
| arithmetic mean | 1.7 | 1.7 | |
| standard deviation | ± 0.6 | ± 0.6 | - |
| Urea Level<br>Units: millimole(s)/litre | | | |
| arithmetic mean | 18 | 17 | |
| standard deviation | ± 6 | ± 5 | - |
| Visual Analogue Scale<br>Units: Arbitrary Unit | | | |
| median | 6.5 | 6.3 | |
| inter-quartile range (Q1-Q3) | 4.4 to 8.0 | 5.1 to 7.3 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Treatment arm |
| Reporting group description: | |
| Balneum Plus - to be applied topically twice daily. | |
| Reporting group title | Comparator arm |
| Reporting group description: | |
| E45 cream was used as base cream/control cream | |

### Primary: Visual Analogue Scale score

| | |
|---|---|
| End point title | Visual Analogue Scale score |
| End point description: | |
| Patients marked their Itch symptom score on a visual analogue scale. | |
| End point type | Primary |
| End point timeframe: | |
| VAS score after four weeks treatment. | |

| End point values | Treatment arm | Comparator arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 26 | | |
| Units: cm | | | | |
| number (not applicable) | 2.6 | 2.0 | | |

### Statistical analyses

| Statistical analysis title | Visual Analogue Scale at 4 weeks |
|---|---|
| Statistical analysis description: | |
| Primary outcome was compared between groups using ANCOVA. The itch intensity at end of the study was considered as the outcome variable, with the itch intensity at baseline and the use of anti-histamines used as covariates in the analysis. The VAS scores were found to have a positively skewed distribution, and to meet the assumptions of the analysis methods, a log transformation of scores was made, with the analysis performed on the log scale. | |
| Comparison groups | Treatment arm v Comparator arm |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.64 |
| Method | ANCOVA |
| Parameter estimate | Adjusted difference ratio |
| Point estimate | 1.1 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.64 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Data on adverse events were collected weekly during the study period and for one week afterwards.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | Not used |
| Dictionary version | 0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Balneum Plus |
| Reporting group description: - | |
| Reporting group title | Control Emollient |

Reporting group description: -

| Serious adverse events | Balneum Plus | Control Emollient | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 3 / 29 (10.34%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Dyspnoea | Additional description: Patient presented at hospital with breathlessness due to previously known heart failure. Patient prescribed bisoprolol and eplerenone and was discharged home later. | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | Additional description: Patient admitted with Non ST elevation myocardial infarction in a patient with known ischaemic heart disease. | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | Additional description: End stage cardiac disease, not fit for further angiography/ intervention. Patient died at home under DNAR order | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Surgical and medical procedures | | | |
| Surgery | Additional description: Patient was treated on Day Case Unit and was admitted overnight. Admitted for formation of left bracho basilic transposition fistula. This was considered routine surgery. | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access malfunction | Additional description: Patient admitted with blocked dialysis access. Patient required new tunnelled dialysis line (haemodialysis continues). | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transplant | Additional description: Patient admitted for planned transplant surgery. Patient withdrawn from trial as now transplanted and there is an improvement expected in uraemic pruritus. Patient remains in hospital for post surgery monitoring. | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | Additional description: Patient presented at hospital with diarrhoea as a known clostridium difficile carrier. Patient prescribed oral vancomyn and was considered for faecal transplant, but no longer needed it when symptoms resolved. | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dysphonia | Additional description: Patient admitted with shortness of breath and possible pleural effusion. Patient had a chest x-ray | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| urge to urinate & mild hematuria | Additional description: Patient experienced urgency in urinating and passed small amount of blood. Patient referred to urologist for cystoscopy | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Balneum Plus | Control Emollient | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 1 / 29 (3.45%) | |
| Surgical and medical procedures | | | |
| fistuloplasty | Additional description: Planned fistuloplasty | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Surgery | Additional description: Planned admission for removal of ischaemic finger | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Inflamed spots | Additional description: Inflamed spots on abdominal skin. | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| itching | Additional description: Itching around cannula site | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 01 August 2017 | The amendment includes: 1) change of Chief Investigator from Dr Robert Lewis to Dr Jacqueline Nevols, Consultant Nephrologist, who is currently a Co-Investigator and protocol author on the trial; 2) Changes to the study management team due to changes in staffing and their roles; 3) protocol update with the changes from the latest summary of product characteristics for Balneum Plus cream with the safety profile of the drug and expected adverse events; 4) Amended the study inclusion and exclusion criteria to widen the available patient population so that further recruitment is possible; 5) to allow patient questionnaires and case report form to be completed by the patient and returned to the study team by post, with a follow up phone call for any data queries; 6) update to the study questionnaires - a body outline has been replaced by tick boxes for patients to indicate where on the body they are itching in order to make data entry on the study database simpler and more consistent across all patients. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported