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Capsaicin 8% patch for treprostinil subcutaneous infusion site pain in pulmonary hypertension patients

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Editor's key points

- This study investigated if capsaicin 8% patch can inhibit pain induced by subcutaneous treprostinil, a prostacyclin analogue used in pulmonary arterial hypertension (PAH).
- Local treatment with capsaicin 8% patches appeared to be safe in patients with PAH.
- This study did not achieve statistical significance for efficacy in the comparison of pain scores and the patient global impression of change across the two treatment arms.

Background. Treprostinil sodium improves haemodynamics and symptoms in pulmonary arterial hypertension (PAH) patients, but its subcutaneous (s.c.) administration can produce severe local site pain, and lead to discontinuation of vital treatment. Treprostinil is a prostacyclin analogue which stimulates prostacyclin receptors in skin nociceptor terminals, resulting in pain and cutaneous hypersensitivity, for which current pain remedies have limited effect. Capsaicin 8% patch relieves neuropathic pain for 3 months after a single 60 min cutaneous application; we investigated whether its pre-application can reduce s.c. trepostinil-induced pain.

Methods. A single-centre, double-blind, randomized, placebo-controlled, crossover study was conducted to assess the safety and efficacy of a single capsaicin 8% patch pre-application for s.c. treprostinil pain in 11 PAH patients, relative to control patch with low-dose capsaicin 0.075% cream.

Results. The primary efficacy endpoint, mean difference between the two treatment arms in an 11-point numerical pain rating scale from baseline to 2 weeks after patch applications, was significantly lower on the capsaicin 8% patch treatment arm [$P=0.01$, mean difference$=-1.47$ units, 95% credible interval (CI): -2.59 to -0.38] in the patients who completed the study per protocol, although intention-to-treat analysis did not show significant difference ($P=0.28$). Heat pain thresholds were decreased ($P=0.027$, mean difference$=5.43^{\circ}$C, 95% CI: 0.71–10.21) and laser Doppler flux increased ($P=0.016$, mean difference$=370$ units, 95% CI: 612 to 127.9) at the application site immediately after capsaicin 8% patch, confirming activity.

Conclusions. Further investigation of the efficacy of capsaicin 8% patch in this indication is warranted.

Clinical trial registration. ClinicalTrials.gov: NCT01393795.

Keywords: capsaicin 8%; clinical trial; pain; pulmonary arterial hypertension; treprostinil

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Pulmonary arterial hypertension (PAH) is a rare life-threatening disease characterized by increased vascular resistance and pressure in the pulmonary arteries, eventually leading to right ventricular failure and death.[1 2] Although seven medicinal products are approved for the treatment of PAH, there is still a need for safe, effective, and well-tolerated therapies.

Treprostinil sodium (Remodulin®, United Therapeutics, USA) solution for infusion is a prostacyclin analogue approved for the treatment of PAH in the USA and most European countries. Treprostinil improves haemodynamics and shortness of breath associated with physical activity in PAH patients.[3 4] The drug can be administered as a continuous i.v. infusion or subcutaneously (s.c.) through a microinfusion pump connected to a catheter implanted under the skin, usually in the abdominal area,[5–7] with gradual upward titration based on clinical response and adverse effects.[8 9]

While treprostinil improves exercise performance, when administered s.c., it can produce severe local pain and neurogenic skin hypersensitivity by stimulating prostacyclin (IP) receptors in skin nociceptor nerve terminals at the site of infusion.[5 10] Prostacyclin/PGI(2) acts via IP receptors to mediate pain in acute and arthritis pain models, and IP receptor antagonists reduce pain.[11]

This has been a major drawback in PAH patients, with local pain affecting dose titration during the pivotal study of s.c. treprostinil and resulting in dose lowering or even discontinuation

of s.c. treatment;[3 5] however, more recent studies have shown that the pain is not directly related to the dose.[12] The timing of onset of pain, its duration, and severity varies widely between and within patients, but is usually more severe during the first 2 weeks after site repositioning.[4] The effect of a wide range of pain remedies has been limited, including non-steroidal anti-inflammatory drugs, opioids, gabapentin, lidocaine gel, leaving the catheter in place longer than 2 weeks when the pain has reduced is a common pragmatic strategy.[7]

Capsaicin 8% patch (Qutenza®, Astellas Pharma Europe Ltd, UK) has been approved for the management of pain associated with post-herpetic neuralgia and painful peripheral neuropathies, excluding diabetic neuropathy.[13 14] Capsaicin 8% patches contain synthetic capsaicin, the pungent substance present in its natural form in chilli peppers that is known to activate heat pain receptors (TRPV1). Capsaicin 8% patches contain a high dose of capsaicin (640 μg cm^{-2}) which is released rapidly and overstimulates skin nerve terminals, which become desensitized and retract, and are no longer able to respond to the stimuli that cause pain.[15] After a single, 1 h application, each capsaicin 8% patch can provide pain relief for up to 3 months (the retracted nerve fibres regenerate during this period), with the maximum effect reached within 1–2 weeks. Only transient systemic exposure of capsaicin occurs, with the highest plasma concentrations immediately after patch removal, and undetectable 3–6 h later.[16]

We investigated whether pre-application of capsaicin 8% patch may reduce pain at the site of treprostinil s.c. infusion in PAH patients.

Methods

Study population

Thirteen patients with symptomatic PAH were recruited at Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK, and screened to provide data from eight patients completing each of two crossover periods. Patients were eligible to participate if they had a documented diagnosis of PAH according to standard criteria in WHO functional class II–IV and had been stable for at least 8 weeks before enrolment.[17] The patients were receiving stable doses of treprostinil s.c., continuously infused at a dose of at least 2.5 ng kg^{-1} min^{-1} for at least 8 weeks before enrolment.

All patients had a history of pain at the site of treprostinil s.c. infusion during the 8 weeks before enrolment and as assessed at screening on the 11-point pain intensity numerical pain rating scale (NPRS) from 0 to 10, where 0 represents 'No pain' and 10 represents 'Maximum pain imaginable'. Only patients with baseline pain intensity $\geq$3 NPRS points (as determined by the diary during a 7 day screening period) were eligible.

Patients enrolled were instructed to continue with their standard treprostinil s.c. treatment for the duration of the study administered as continuous s.c. infusion, via a catheter inserted preferably in a lower quadrant of the abdominal skin. They were also requested to change and reposition the catheter on the days they attended the hospital unit for the screening and study visits and, when needed, at their home according to their routine schedule. The use of systemic analgesics to relieve pain at the site of treprostinil s.c. infusion, including salicylates, paracetamol, non-steroidal anti-inflammatory drugs, and opioids, and also topical analgesic-containing gels or creams (such as capsaicin 0.025% and 0.075% cream), local anaesthetics such as lidocaine, were permitted for the duration of the study. Additional approved medications for treatment of PAH and other supplementary treatments were also permitted.

Study design and procedures

This was a single-centre, double-blind, randomized, placebo-controlled crossover study to assess the safety and efficacy of a single 60 min application of capsaicin 8% patch to improve site pain caused by a continuous s.c. infusion of treprostinil in PAH patients, in comparison with a positive control patch (Tegaderm film, 10 cm $\times$ 12 cm), in combination with low-dose 0.075% capsaicin cream (Axsain®, Cephalon, USA). The low-concentration capsaicin patch was used to provide blinding in the studies, since local low-dose topical capsaicin produces transient local erythema and a burning sensation, but unlike high-dose capsaicin 8% patch, requires topical applications several times daily for weeks to produce clinical pain relief.[15]

The study visits are shown in Figure 1. At screening, patients were asked to re-position their treprostinil s.c. catheter to a fresh site and underwent a series of pain and sensory tests (see below). They were also given a trial diary to record their 0-to-10 NPRS scores experienced at the infusion site twice daily for the following 7 days, as well any treprostinil repositioning and/or any concomitant pain medications. Eligible patients were randomly allocated 1:1 to receive either capsaicin 8% or control patches in combination with capsaicin 0.075% cream on day 1 of either treatment period. All patients (except one) received patch applications in a lower or upper quadrant of the abdominal skin according to their standard area of treprostinil cannula repositioning. One patient indicated the upper arm as the preferred site of repositioning; so, patches were applied in that area accordingly. Patients receiving a capsaicin 8% patch in treatment period 1 were crossed-over (after a washout interval of at least 1 week; minimum 7 days, maximum 26 days) to the control patch in treatment period 2 and vice versa. In treatment period 2, patches were applied to the area of the skin contralateral to the one chosen in treatment period 1.

Patients were pretreated with a topical anaesthetic (lidocaine 4%) for 30 min and then, to maintain blinding, a clinically qualified, unblinded member of the study team applied either capsaicin 8% patch or the control patch for 60 min while participants were temporarily blindfolded to prevent them from seeing which patch they received. Once the patch was applied, an opaque bandage was used to loosely cover the site of patch application to prevent the patient or blinded study members seeing the patch before it was removed. Patches were removed after 60 min and patients were monitored for up to 2 h thereafter. Patches were applied according to a study-specific standard operating procedure that

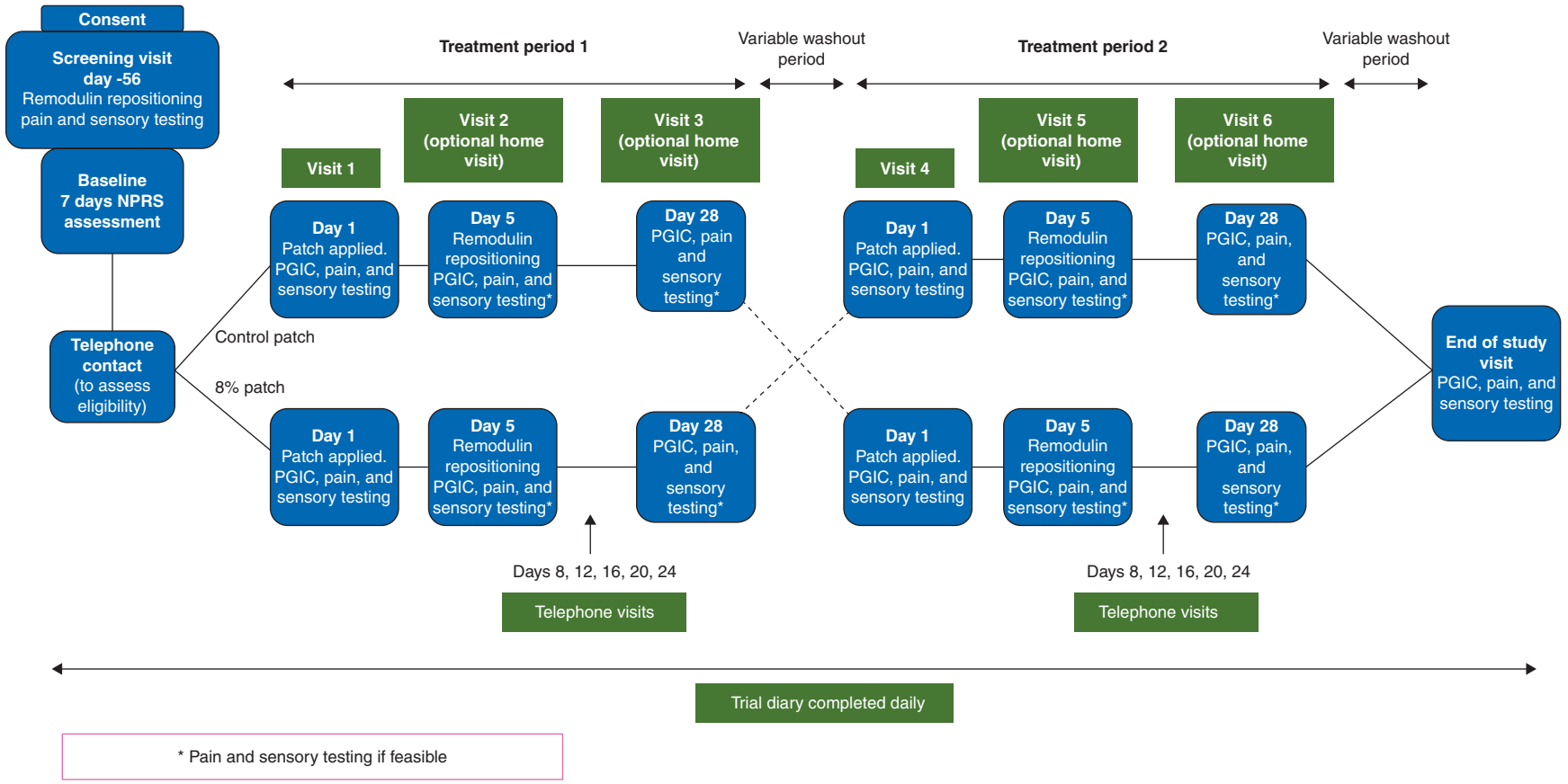

Fig 1 Study flow diagram. PGIC, patient global impression of change.

incorporated guidelines provided by the manufacturer (Astellas Pharma Europe Ltd). Patch procedures were always performed in side rooms or curtain-closed bays within the clinical research facility by unblinded members of the study team who undertook patch application training before study start. Investigators were not present during patch application, patch removal, and/or post-treatment patient monitoring.

On day 5 of each treatment period, patients were asked to change and reposition the treprostinil s.c. catheter (within the patch application site) and to continue scoring their daily NPRS score in the trial diary provided, until the end of the study period (day 28).

Patient global impression of change (PGIC) was assessed at every visit during the treatment periods using a scale of −3 (very much worse) to +3 (very much improved), with 0 being no change. Additional measures included sensory examination and tests performed at every visit on patch-treated, adjacent, and contralateral sites with: (i) cotton wool, (ii) brush, (iii) monofilaments, (iv) pin prick, and (v) thermal thresholds (i.e. warm perception, heat pain threshold, cool perception, and cold pain threshold). The area of skin axon reflex vasodilatation (skin flare) was assessed by laser Doppler fluxmetry. A detailed description of the sensory testing and fluxmetry methodology has been reported previously.[18 19]

The study was approved by the Institutional Review Board of Imperial College Healthcare NHS Trust, London (UK), the UK Medicines and Healthcare products Regulatory Agency (MHRA) (EudraCT number 2011-001312-59), and the Research Ethics Committee for Wales (REC reference number 11/WA/0083).

The study was registered on the public database ClinicalTrials.gov (reference number NCT01393795) and was conducted at The National Institute for Health Research (NIHR)-Wellcome Trust Imperial College Clinical Research Facility (ICRF) and Centre for Clinical Translation, Division of Brain Sciences, Imperial College London, in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participating patients before initiating any study-related procedures.

Statistical analysis

There was no formal calculation of power for this study. A sample size of eight subjects was chosen based on feasibility to allow preliminary characterization of the safety and efficacy of capsaicin 8% patch in PAH patients. The randomization sequences for this study were generated by standard statistical software (SAS PROC PLAN), and patients recruited into the study were randomized to receive treatments in the order indicated by this randomization list.

The safety and efficacy analyses were done on the intent-to-treat (ITT) analysis set, which was defined as all patients who received study medication and who completed NPRS scores for the baseline period.

Efficacy analyses included comparisons between the two treatment arms of the mean NPRS pain scores (averaged across the whole of the treatment periods) and the mean pre-patch to post-patch change in sensory and baseline mean flux measurements. For each of these analyses, a mixed-effects linear model was used, testing treatment, period, and sequence effects, with adjustment for baseline value, and with subjects treated as a random effect within sequence. Period, sequence, and baseline effects were not statistically significant in any of the analyses. *P*-values for the treatment arm comparison were derived, with the Bayesian estimates of mean differences and 95% credible intervals (CIs) for the treatment effect. Residuals from the linear models were examined graphically for departure from normality, and also tested for normality using the Shapiro–Wilk test. No statistically significant departures from normality were seen.

A comparison of total PGIC score in the two treatment periods was made using both a mixed-effects linear model and also a non-parametric Wilcoxon sign test.

Safety evaluation was based on the incidence, intensity, and type of adverse events (AEs) and clinically significant changes in examination findings and vital signs. Evaluation of safety was also based on signs and symptoms of PAH, routine clinical laboratory tests, ECG, and NYHA (WHO) classification at the screening and end of study follow-up visits. Patient characteristics, baseline clinical characteristics, and safety measures were summarized with descriptive statistics.

Results

Thirteen patients were screened to take part in this study between August 2011 and July 2012 (Fig. 2). One patient was not considered eligible and one was excluded before being randomized after hospitalization due to worsening of their disease-related clinical conditions. Of the 11 subjects that were randomized into the study, one withdrew at the end of treatment period 1 and two withdrew after patch application during treatment period 1 due to either AEs (burning pain at the application site), subjective lack of benefit from study medication, or personal reasons. The remaining eight subjects completed both treatment periods and all protocol-related procedures. The patient characteristic and treatment characteristics of the 11 randomized patients are shown in Table 1.

Capsaicin 8% patch appeared to be safe and patients remained clinically stable during its application. AEs were reported by all of the 11 participants receiving the capsaicin 8% patch. The most common reaction was at the site of capsaicin 8% application and included a sensation of warmth, sensitivity to heat, burning pain, and erythema. Cutaneous irritation was severe in five patients (pain score between 6 and 10 on an 11-point scale), moderate in four patients (with a reported pain score between 3 and 5), and mild in two patients (below 3). All application site reactions resolved within 2 days, with the majority of patients requiring local cooling or oral analgesics predominantly on the treatment day. Three subjects discontinued the study because of the lack of tolerability of capsaicin 8% patch. There were no clinically significant changes in vital signs, clinical laboratory assessments, or physical findings. No serious AEs occurred.

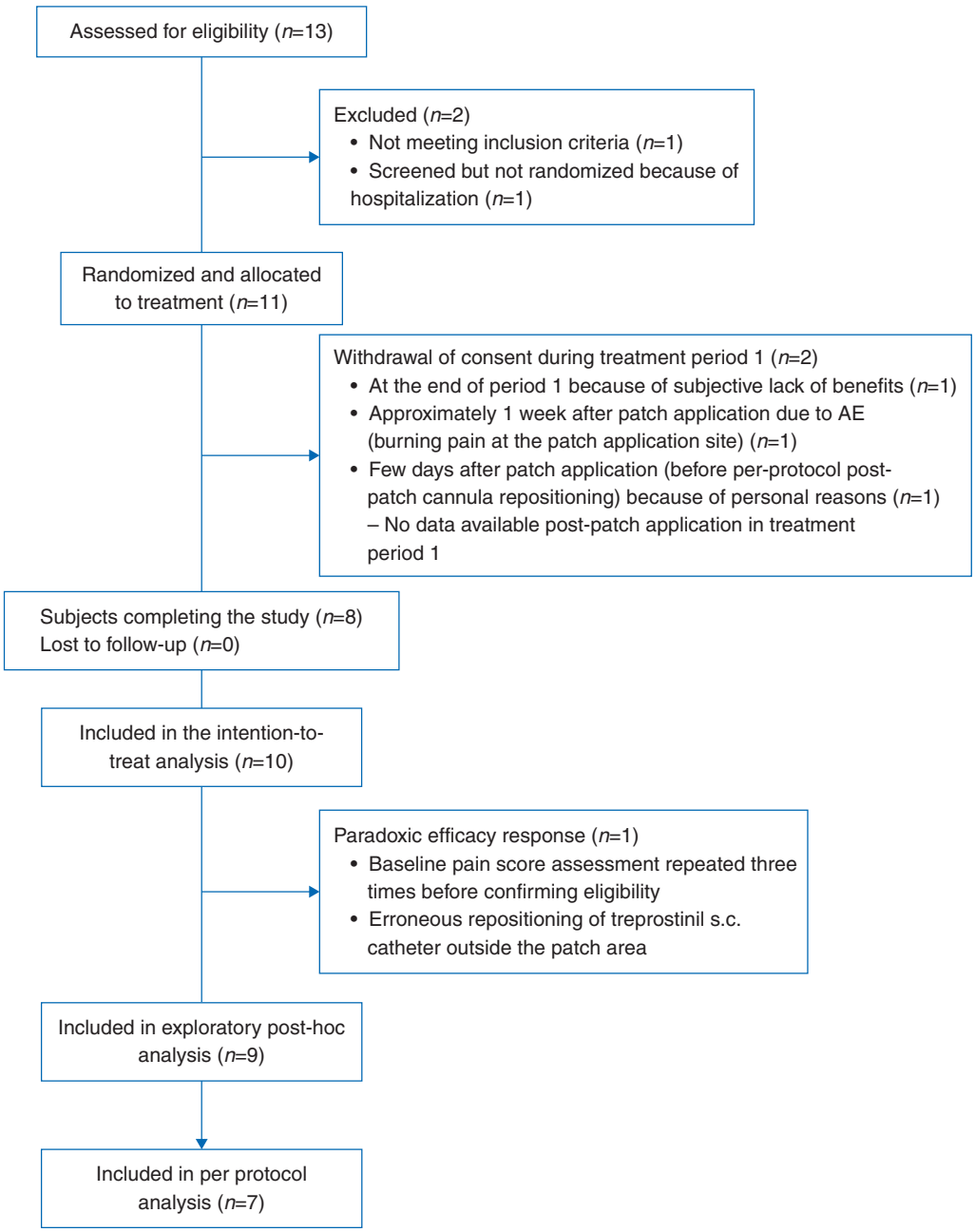

Fig 2 Patient disposition and data analysis.

Individual mean changes in NPRS scores post-capsaicin 8% patch treatment in the eight patients completing both treatment periods are shown in Figure 3A.

Examples of baseline pain responses and improvement after capsaicin 8% patch are shown in Figure 3B and C. The primary efficacy endpoint, mean difference between the two treatment arms in 11-point NPRS from baseline to 2 weeks after patch applications, was significantly lower on the capsaicin 8% patch treatment arm ($P=0.01$, mean difference $=-1.47$ units, 95% CI: -2.59 to -0.38) in the patients who completed the study per protocol.

The mean difference between the two treatment arms was not statistically significantly different for the ITT analysis set ($P=0.2761$; mean difference $=-0.86$ units, 95% CI: -2.91 to 1.15). One patient (004) was required to repeat the 7 day baseline assessment on three separate occasions before meeting the NPRS inclusion criterion. Further, the patient's laser Doppler fluxmetry showed elevated values across the abdomen, suggesting low-grade inflammation (see below). This patient showed an atypical response to the two treatments (i.e. considerable worsening of treprostinil s.c.-induced site pain after capsaicin 8% patch, and no pain, a major

Table 1 Patient characteristics and clinical characteristics of the ITT study population

Patient randomization number	Sex and age (yr)	Diagnosis of PAH (yr)	WHO functional class	Start of treprostinil treatment	Dosage of treprostinil at screening	Average NPRS at baseline (0–10 point scale)	Daily pain medications at baseline	Notes
002	Female (34)	2000	II	2009	0.026 ml h^{-1}, 40 ng kg^{-1} min^{-1}	4.0	Gabapentin (200 mg) b.d., cocodamol (30/500 mg) q.d.s.	Early withdrawal at the end of treatment period 1
003	Female (46)	2007	III	2007	0.030 ml h^{-1}, 45 ng kg^{-1} min^{-1}	3.6	Gabapentin (400 mg) t.d.s., tramadol (50 mg) p.r.n.	Level of improvement in quality of life being reported=high
004	Female (77)	2008	IV	2010	0.020 ml h^{-1}, 30 ng kg^{-1} min^{-1}	4.0	Tramadol (50 mg) o.d., paracetamol (500 mg) p.r.n.	Baseline pain score assessment repeated three times before inclusion. Erroneous repositioning of treprostinil s.c. catheter outside patch area on three occasions while on capsaicin 8% patch arm
006	Female (33)	2003	III	2008	0.26 ml h^{-1}, 31 ng kg^{-1} min^{-1}	6.0	Morphine sulphate (10 mg) b.d., paracetamol (1 g) p.r.n.	
007	Male (52)	2008	III	2010	0.02 ml h^{-1}, 35 ng kg^{-1} min^{-1}	3.2	Gabapentin (400 mg) t.d.s., paracetamol (1 g) p.r.n.	Early withdrawal 1 week after patch application in treatment period 1. No NRPS diary completed from the day of patch application
008	Female (47)	2002	III	2004	0.62 ml h^{-1}, 115 ng kg^{-1} min^{-1}	3.7	Paracetamol (1 g) p.r.n.	
009	Female (38)	2006	III	2006	0.029 ml h^{-1} 26 ng kg^{-1} min^{-1}	4.7	Gabapentin (100 mg) t.d.s., paracetamol (500 mg) p.r.n.	
010	Female (26)	2005	III	2009	0.050 ml h^{-1}, 60 ng kg^{-1} min^{-1}	4.0	Buprenorphine 5 μg h^{-1} patch, codydramol (10/50 mg) p.r.n.	Early withdrawal 1 week after patch application in treatment period 1
011	Female (43)	2004	II	2005	0.030 ml h^{-1}, 33 ng kg^{-1} min^{-1}	6.0	Gabapentin 300 mg o.d., cocodamol (500 mg) p.r.n.	Level of improvement in quality of life being reported=high
012	Female (28)	2006	III	2009	0.028 ml h^{-1}, 25 ng kg^{-1} min^{-1}	4.3	Paracetamol (500 mg) t.d.s., gabapentin (400 mg) t.d.s.	
013	Male (46)	2003	III	2004	0.026 ml h^{-1}, 40 ng kg^{-1} min^{-1}	8.0	Gabapentin (600 mg) t.d.s., paracetamol (1 g) p.r.n.	
Mean (SD)						4.68 (1.43)		

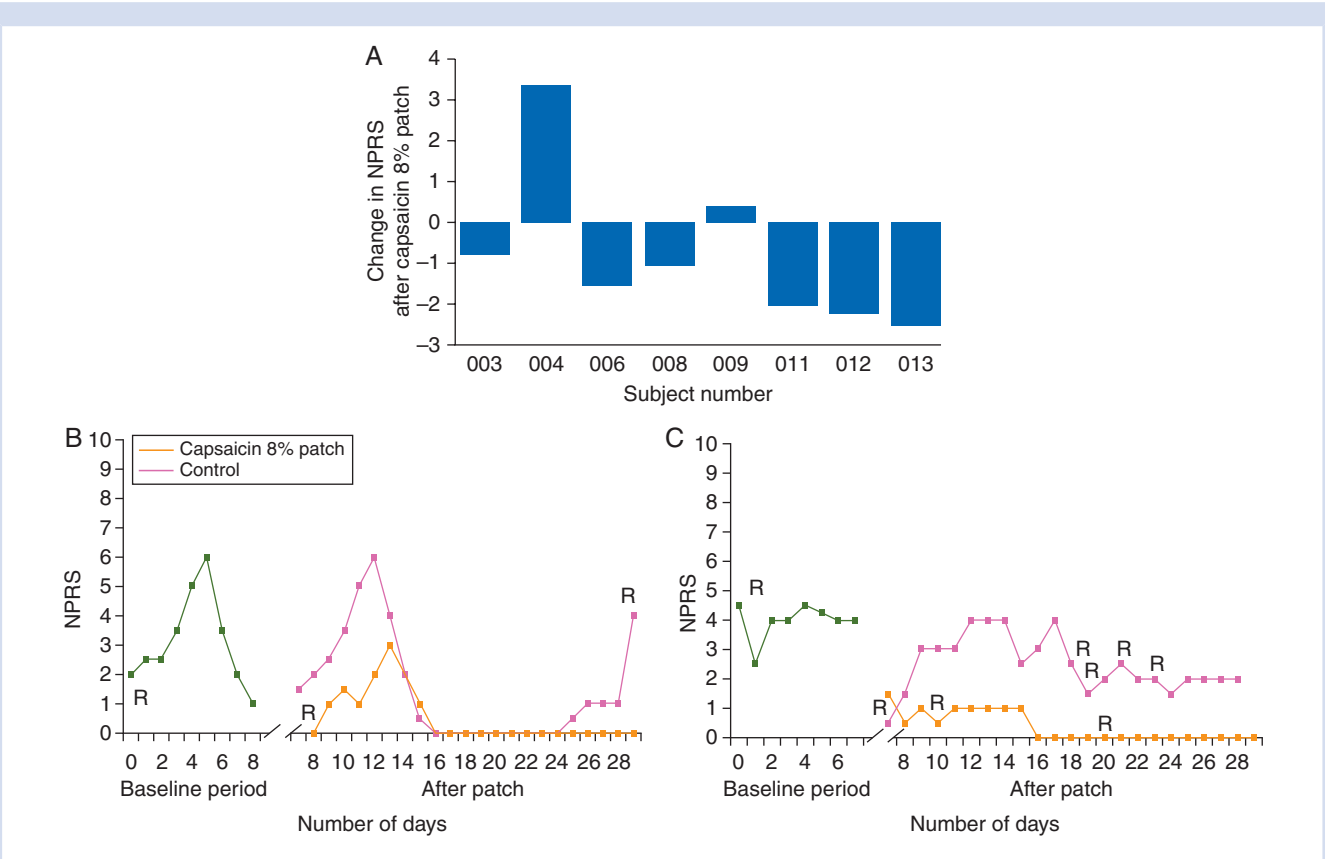

Fig 3 (A) Individual mean changes in NPRS pain score after capsaicin 8% patch application relative to baseline in eight PAH patients completing both treatment periods; (B) and (C) examples of capsaicin 8% patch and control effects in two different patients.

Table 2 Descriptive statistics [least squares (LS) means (standard errors), mean differences, and 95% CIs] of the ITT and per-protocol analyses

	LS mean (SE) capsaicin 8% patch Period	LS mean (SE) control period	Mean difference (Bayesian estimate) (capsaicin 8% patch *vs* control)	95% CI for mean difference
NPRS (ITT; $n=10$)	2.37 (0.64)	3.23 (0.69)	−0.86	−2.91 to 1.15
NPRS (ITT excluding subject 004; $n=9$)	2.32 (0.63)	3.77 (0.65)	−1.45	−2.49 to −0.36
NPRS (per-protocol; $n=7$)	2.53 (0.73)	3.36 (0.75)	−1.47	−2.59 to −0.38
Heat threshold (ITT)	4.19 (1.52)	−1.24 (1.52)	5.43	0.71 to 10.21
Doppler flux (ITT)	−388 (79.5)	−18 (84.3)	−370	−612.0 to −127.9

improvement from baseline, after control treatment). The treprostinil infusion site was erroneously repositioned outside the patch area by this elderly patient on three separate occasions while on capsaicin 8% patch. In an exploratory *post hoc* analysis of the ITT excluding patient 004, there was a statistically significant lower pain score on the capsaicin 8% patch treatment arm ($P=0.0094$, mean difference$=-1.45$ units; Bayesian 95% CI: −2.49 to −0.36). Analyses of the median for the pain score change showed similar statistical results of the ITT and *post hoc* groups. Descriptive statistics (least squares means, standard errors, mean differences, and 95% CIs) of the ITT and per-protocol analyses are presented in Table 2.

An additional *post hoc* analysis was done to assess the potential effect of any imbalances in the use of concomitant pain medications and/or number of treprostinil s.c. site repositioning during the two treatment periods (Table 3). These variables were tested in the mixed-effects crossover models, but the effects were not statistically significant for either the ITT analysis or the *post hoc* analysis excluding patient 004 ($P>0.25$ in all cases).

Results from the mean PGIC analysis after patch application showed no statistically significant difference between treatments arms ($P=0.7486$), although more patients reported an improvement in pain scores after capsaicin 8% patch than control.

Heat pain thresholds were significantly decreased ($P=0.0269$; mean difference$=5.43$°C, 95% CI: 0.71 to 10.21) in patients who received capsaicin 8% patch application (Fig. 4). The other sensory tests were not affected significantly. Two patients who

Table 3 Use of concomitant pain medication and frequency of treprostinil s.c. repositioning, in PAH patients completing both treatment periods. Dashes indicate no data available due to early withdrawal

Patient number	Screening (7 days)		Capsaicin 8% patch Period (28 days)		Control period (28 days)	
	Days on concomitant PRN medications	Number of treprostinil repositioning	Days on concomitant PRN medications	Number of treprostinil repositioning	Days on concomitant PRN medications	Number of treprostinil repositioning
002	0	1	1	2	1	4
003	0	3	0	10	0	9
004	0	1	1	1	9	3
006	0	2	—	—	—	—
007	0	1	0	3	1	3
008	0	3	1	5	0	10
009	0	2	—	—	—	—
010	0	1	0	2	5	1
011	2	1	6	4	2	5
012	4	1	0	2	4	1
013	3	1	7	4	—	—
Mean (SD)	0.82 (1.47)	1.54 (0.82)	1.78 (2.73)	3.67 (2.69)	2.75 (3.10)	4.5 (3.38)

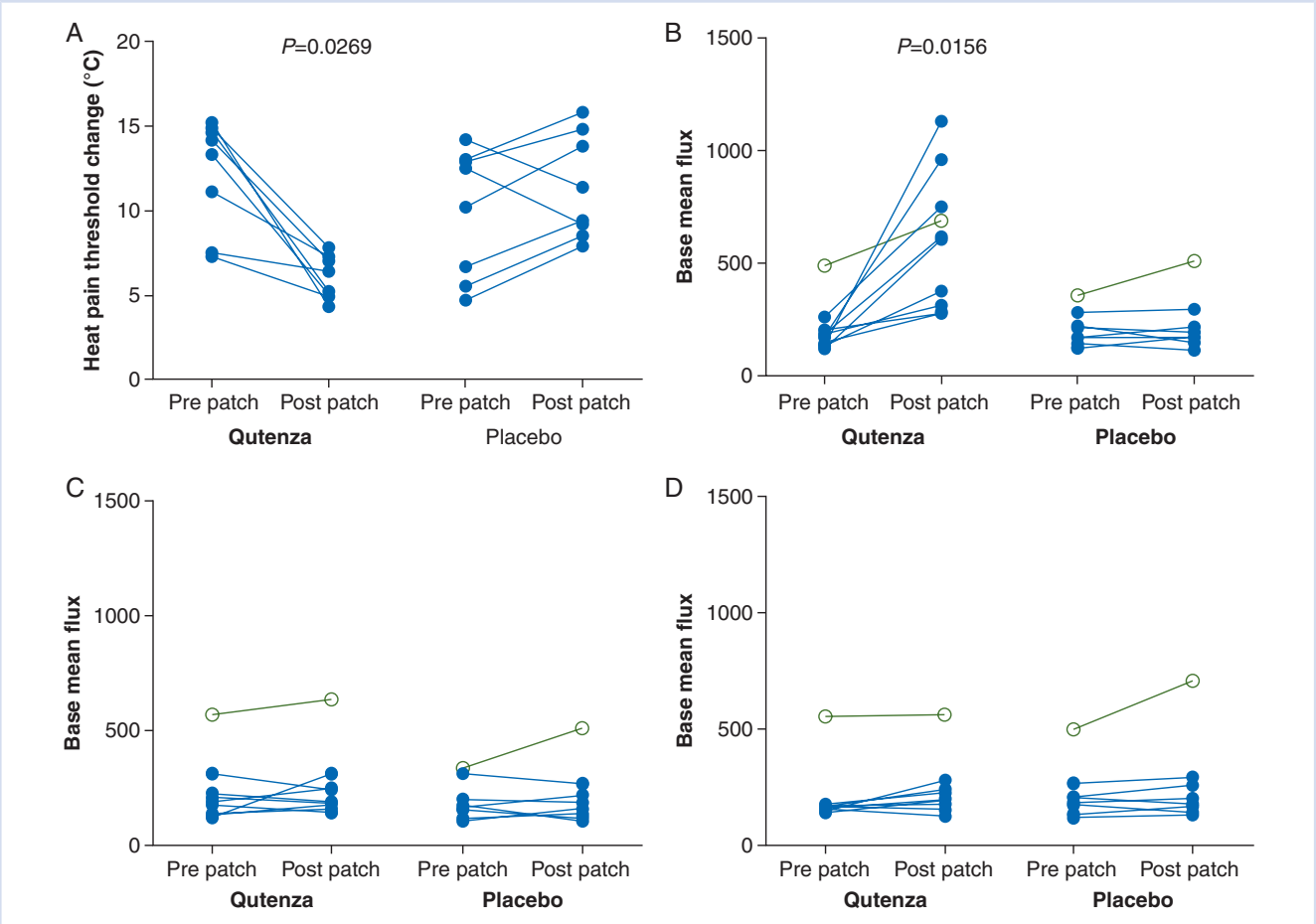

Fig 4 (A) Heat pain threshold change in patients pre- and post-capsaicin 8% and control patch applications. Base mean flux change in patients pre- and post-capsaicin 8% patch and control patch applications in (B) target, (C) adjacent, and (D) contralateral areas. Base mean flux change values for patient 004 are depicted with open circles.

received capsaicin 8% patch had severe post-patch pain and were unable to complete the quantitative sensory testing. One patient found it difficult to perform the quantitative sensory tests, and had highly variable and inconsistent readings.

The mean laser Doppler flux change for patients was significantly increased [P=0.0156; mean difference=370 units (95% CI: 612 to 127.9)] post-application of capsaicin 8% patch at application site when compared with control. No significant changes were observed in areas adjacent and contralateral to the application area. Patient 004 had high baseline levels of laser Doppler flux in all areas (Fig. 4, open circles). Representative photographic and laser Doppler flux images after control and capsaicin 8% patch applications are shown in Figure 5.

Discussion

Chronic s.c. treprostinil infusion is one therapeutic option for patients with severe PAH[17 20] when i.v. epoprostenol is contraindicated. The benefits of treatment with treprostinil need to be weighed against adverse reactions, the most common being local infusion site pain, which affects up to 80% of the patients and leads to permanent treatment discontinuation in 5–23%.[6 9] Prostanoid receptor-mediated sensitization of nociceptor fibres

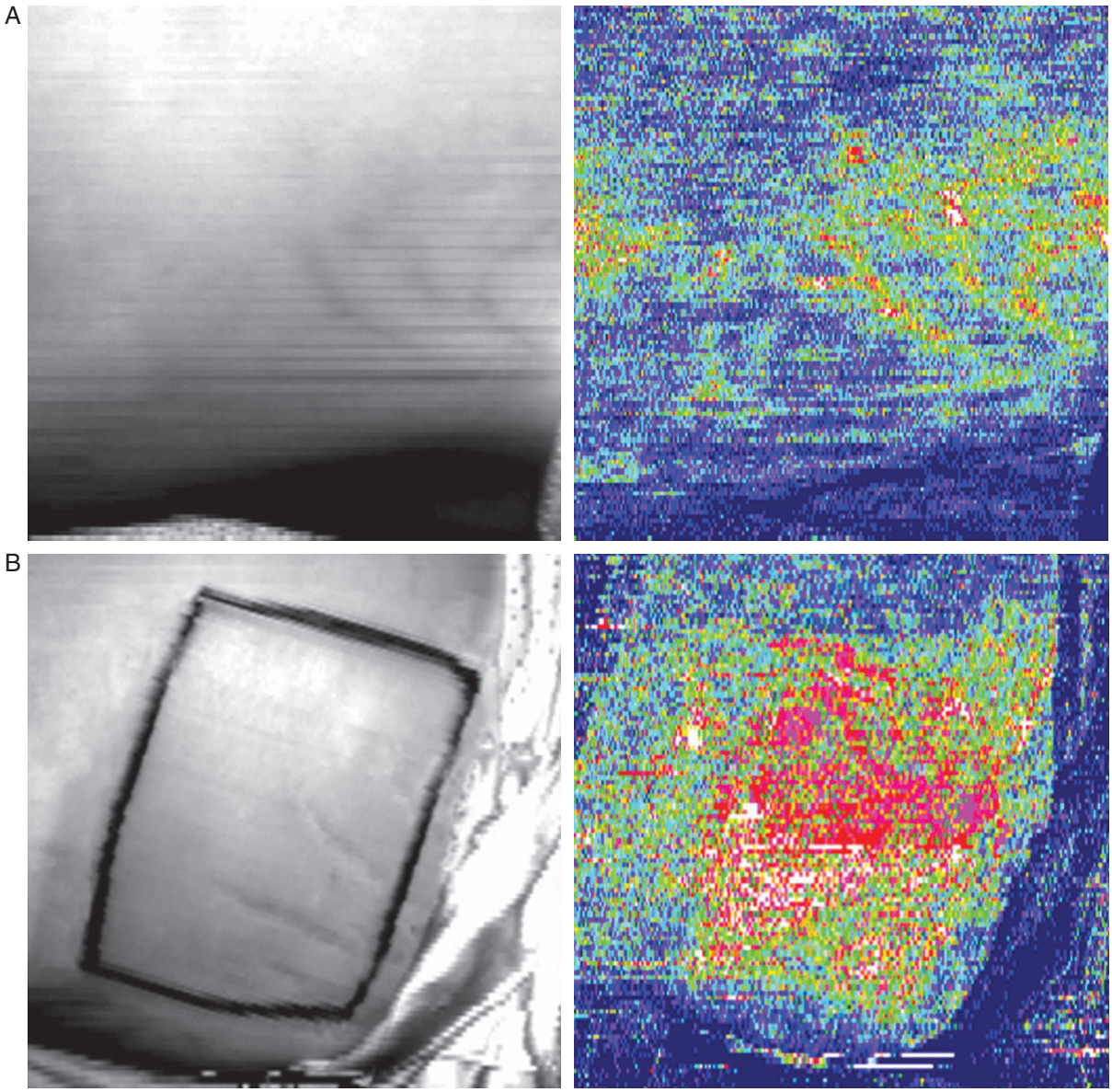

Fig 5 Representative photograph (left) and laser Doppler flux (right) images of patients post-control (A) and post-capsaicin 8% patch (B) application.

is a major contributor to the generation of pain and hyperalgesia.[10] Prostacyclin/PGI (2), the primary endogenous agonist for the IP receptor, is produced by tissue injury and inflammation, and considered to be of at least equal importance to PGE2 for inflammatory pain. IP receptors are expressed by sensory neurones, and transgenic mice lacking the IP receptor indicate its key role in oedema and pain.[21]

In our study, local treatment with capsaicin 8% patches appeared to be safe in patients with PAH. An important advantage of the topical capsaicin approach is that this drug is poorly absorbed transdermally in humans and there appear to be few systemic adverse effects or even local effects other than transient application-site reactions such as pain and erythema.[1] In accord with previous studies, application site irritant reactions were the most prevalent drug-related AEs, which led to early withdrawal in three patients. Application site reactions were mostly short-lived and could be managed by local cooling or oral analgesics. Overall, the safety profile of capsaicin 8% patches was consistent with the previous reports in neuropathic pain studies.[13 14 22–25]

Based on ITT analysis, our study did not achieve statistical significance for efficacy in the comparison of pain scores and PGIC across the two treatment arms. The results need to be considered in view of the small sample size and the responses observed in one subject (004), who reported a significant worsening of the pain scores while on active treatment, but improvement on control treatment compared with baseline, unlike the majority of study participants. It is notable that the patient was elderly, did not comply with the protocol, and had high baseline levels of laser Doppler flux across the abdomen. Evaluation of the completers data set showed that a reduction in pain scores was achieved in six out of seven subjects who completed both arms per protocol (85%), after active treatment (Fig. 3A).

Sensory tests showed heat pain thresholds were significantly decreased and laser Doppler flux significantly increased at the application site in patients after capsaicin 8% patch, both expected findings,[19] which confirmed its action at the site. No significant changes were observed in skin areas adjacent and contralateral to the application area, indicating a local peripheral mechanism of patch action and efficacy. While a low-concentration capsaicin control patch was used to maintain blinding, local application-site reactions were undoubtedly higher after capsaicin 8% patch, we therefore cannot exclude that they positively influenced patient perception of efficacy.

Since completion of the trial, six patients requested and have continued to use the capsaicin 8% patch for the management of their treprostinil s.c.-induced site pain (in line with the Ethics Committee approved protocol and recommended dose of capsaicin 8% patch, four applications 3 monthly at a single site). These patients reported improved level of analgesia, reduced skin hypersensitivity, and better quality of life, with reduced use of concomitant pain medications. One patient has been treated with capsaicin 8% patch on four separate occasions since participation in the trial, and the patient's site pain has been reduced from a historical and trial baseline daily score of 6–8/10 points to 1–2/10 points.

The reports of pain relief with the capsaicin 8% patch in some PAH patients suggest that a further evaluation in larger studies is warranted.

Authors' contributions

Trial conceived by P.A. and J.S.R.G., and designed by V.L. and P.A.; clinical project management (R.H.K.); patient recruitment (R.H.K., W.G.-S.); data collection (D.J.P., T.I.); data analysis (L.H.); construction of tables and figures (R.H.K.; T.I.); writing up of the first draft of the paper (V.L.); paper review (P.A., L.H., J.S.R.G., R.H.K., D.J.P.).

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Declaration of interest

V.L., J.S.R.G., and P.A. have attended advisory boards and/or have received consultancy or speaker fees from United Therapeutics and/or Astellas.

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