

## INVESTIGATIVE REPORT

# Topical TrkA Kinase Inhibitor CT327 is an Effective, Novel Therapy for the Treatment of Pruritus due to Psoriasis: Results from Experimental Studies, and Efficacy and Safety of CT327 in a Phase 2b Clinical Trial in Patients with Psoriasis

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**Pruritus is an important symptom in psoriasis with no targeted treatment. Tropomyosin-receptor kinase A (TrkA) is associated with pruritus and psoriatic plaque formation. We report the efficacy of a TrkA inhibitor, CT327, on pruritus in psoriasis. A randomised, double-blind, vehicle-controlled Phase 2b clinical trial was conducted in 160 subjects. No effect was found on psoriasis severity using Investigator's Global Assessment (primary endpoint). However, clinically and statistically significant reductions in pruritus were observed in the 108 patient subset reporting at least moderate pruritus at baseline (37.1 mm visual analogue scale improvement (95% CI [-37.5, -6.2],  $p=0.0067$ ) for lowest dose; secondary endpoint). Significant modified Psoriasis Area and Severity Index reductions were found in this subset ( $p<0.05$ ). Experiments exploring capsaicin-mediated calcium influx, important in pruritus signalling, were performed in sensory neurons. CT327 inhibited capsaicin responses, indicating action at the nerve growth factor-TrkA-TRPV1 pathway. TrkA is a key target in pruritus, and CT327 has potential to become an effective and safe first-in-class treatment. *Key words: pruritus; psoriasis; Tropomyosin-receptor kinase A; nerve growth factor; Phase 2b; visual analogue scale.***

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Chronic pruritus, or itch, is a debilitating and underappreciated symptom of many dermatological diseases, including psoriasis, significantly affecting the quality of life of patients (1). Of patients with psoriasis 84–85% suffer from pruritus, with 77% having pruritus daily. Sleep is compromised in 81% of patients, and 75% of patients scratch until bleeding, with pruritus having a

general negative impact (1–3). There is significant unmet need, with pruritus reported to not be relieved by any therapy in 45% of psoriatic patients, 8% of patients on topical corticosteroids and 15% of patients on biologic therapy (2).

CT327 is a potent and selective Tropomyosin-receptor kinase A (TrkA) kinase inhibitor under investigation for the treatment of chronic pruritus in psoriasis and other dermatoses. CT327 exerts its effects through the Nerve Growth Factor (NGF) pathway by inhibiting the intracellular kinase domain of TrkA, the 140 kDa high affinity receptor for NGF. NGF is implicated in the pathology of chronic pruritus through the sensitization and sprouting of small diameter sensory nerve terminals in skin, the majority of which express TrkA (4–8) and Transient Receptor Potential cation channel subfamily V member 1 (TRPV1), a receptor activated by heat, low pH (acid) and capsaicin (9) (Fig. 1). NGF up-regulates the expression and sensitivity of TRPV1 via TrkA in rodent and human sensory neurons (10–12). While there are multiple peripheral and central neural mechanisms for pruritus and some are considered specific, increased cutaneous NGF-TrkA-TRPV1 signalling is considered a key mechanism, based on tissue studies in dermatological conditions.

There is evidence that increased local concentrations of NGF acting via TrkA may play an important role in the pathogenesis of psoriasis and associated pruritus. In psoriatic skin, NGF and TrkA expression are increased in the epidermis, which are in turn associated with the inflammatory mechanisms and hyperproliferation of keratinocytes, leading to formation of psoriatic lesions and symptoms (13–17). Keratinocytes from human psoriatic plaques synthesize higher levels of NGF compared to normal subjects (16). With regard to pruritus, psoriatic skin in pruritic patients is more richly innervated in the superficial dermis and epidermis, with significantly higher numbers of NGF-immunoreactive keratinocytes, NGF content, and expression of TrkA in nerve fibres, compared to non-pruritic lesions or non-lesional skin (17). Significant correlations have been found between

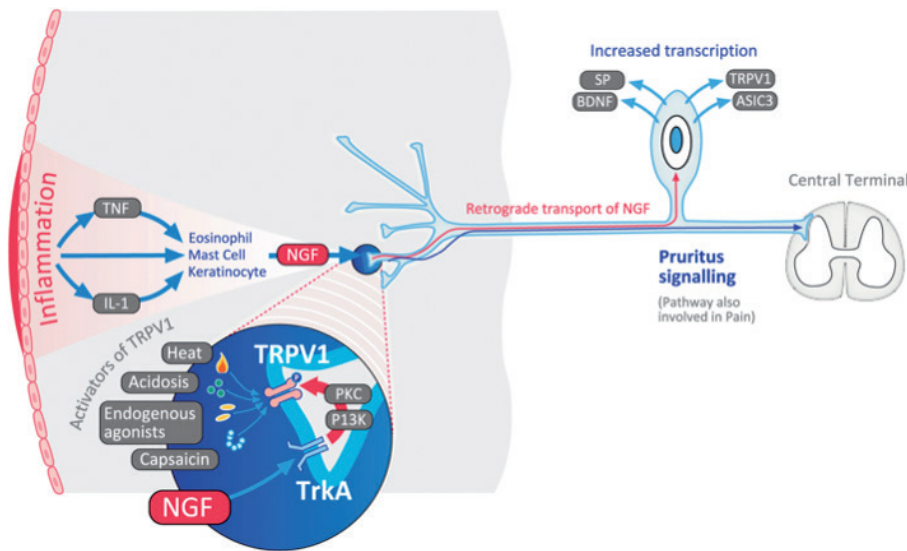


Fig. 1. Overview of the potential role of nerve growth factor (NGF) and Tropomyosin-receptor kinase A (TrkA) in chronic pruritus. NGF and TrkA are believed to play roles in the signaling of pruritus through transient receptor potential cation channel subfamily V member 1 (TRPV1) in the sensory neurons present in the skin of psoriasis patients.

pruritus severity and NGF-immunoreactive keratinocytes, expression of TrkA in the epidermis, and PGP 9.5-immunoreactive intraepidermal nerve fibres in psoriatic patients (16).

In this Phase 2b study, we explored the efficacy and safety of topical CT327 in the treatment of psoriasis and pruritus in patients with mild to moderate psoriasis. The primary endpoint was based on a change in psoriasis disease severity, as measured by the Investigator Global Assessment (IGA) score. A measurement of pruritus severity using a 100 mm Visual Analogue Scale (VAS) in patients with at least moderate pruritus at baseline (VAS  $\geq 40$  mm) was included as a pre-defined secondary endpoint, as was a different measure of psoriasis disease severity, the modified Psoriasis Area and Severity Index (mPASI). To our knowledge, this is the first clinical study of a specific TrkA inhibitor in any clinical disorder. To investigate the mechanism of action of CT327, the functional and morphological effects of CT327 were studied in cultured human and rat Dorsal Root Ganglion (DRG) sensory neurons with capsaicin-mediated calcium influx and neurite length assays. Immunostaining was used to localise TrkA expression in human DRG and skin.

## MATERIALS AND METHODS (see Appendix S1<sup>1</sup>)

### RESULTS

#### Experimental studies – in vitro and human tissue studies

The potential of CT327 in functionally affecting the sensory neurons that mediate pruritus was determined by performing capsaicin-mediated calcium influx and

neurite length assays in cultured human and rat Dorsal Root Ganglion (DRG) sensory neurons.

CT327 dose-dependently inhibited capsaicin responses in cultured rat neurons with  $IC_{50} = 10$  nM (Fig. 2, Panels A–E). In human neurons, treatment with 10 nM CT327 reduced capsaicin responses by  $78.8 \pm 9.4\%$  ( $n=6$  neurons), compared with  $14.3 \pm 5.9\%$  due to expected tachyphylaxis in vehicle treated neurons (Fig. 2, Panels F–H).

Neurite length or morphology was not affected after a 24 h treatment of rat neuronal cultures at the same doses of CT327 (1, 10, 100 nM and 1, 10  $\mu$ M; Fig. 2, Panels I and J).

Immunostaining using 3 different antibodies to TrkA was performed in normal (control) human DRG and skin tissues, and all revealed intense immunoreactivity of TrkA in a majority subpopulation of small diameter DRG neurons, and sub-epidermal nerve fibres in skin (data with Ab 379-sc118 in Fig. 2, Panels K–N).

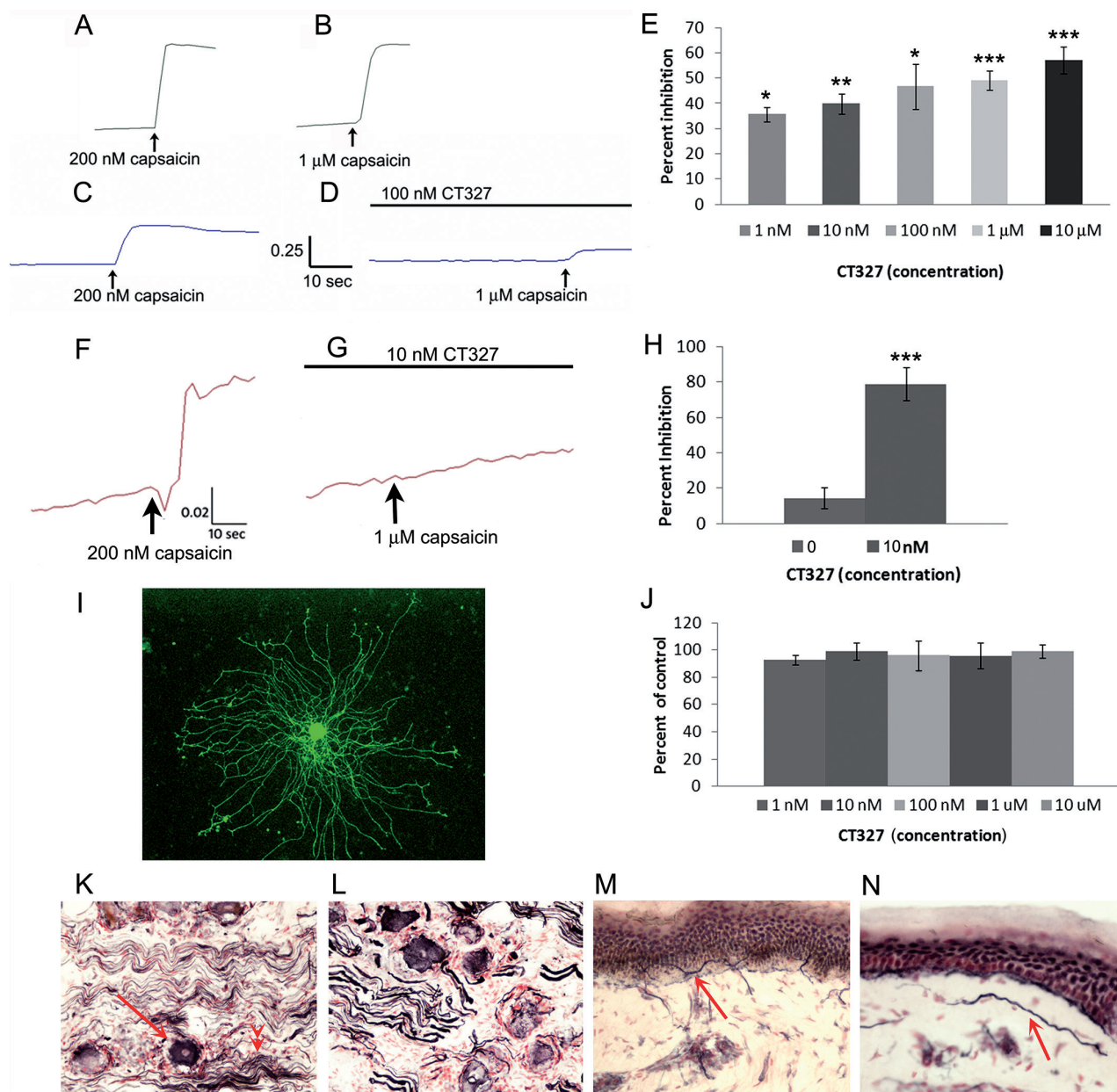
#### Phase 2b clinical study

**Patients.** One hundred and thirty-four patients out of 160 completed the clinical study, representing an 84% completion rate. Data was available from 153 patients using the Last Observation Carried Forward criteria. A summary of the study demographics of patients for each study arm is provided in Table S1<sup>1</sup>. A summary of patient disposition is presented in Fig. S1<sup>1</sup>.

**Efficacy, psoriasis, and IGA.** No improvements in controlled disease response rates were seen for any dose of CT327 compared to vehicle, the primary endpoint of the study; controlled disease at 8 weeks was achieved by 2.5–5% and 10% of patients on CT327 0.05–0.5% and vehicle, respectively. There was no evidence of a linear dose-response relationship.

**mPASI.** A small non-significant difference in mPASI, the pre-defined secondary endpoint of the study, was

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**Fig. 2.** *In vitro* and tissue studies. A. Sample trace of a calcium influx response to 200 nM capsaicin challenge stimulus in rat Dorsal Root Ganglia (rDRG) neuron. B. Trace showing the second response to 1 μM capsaicin, in rDRG neuron shown in Panel A, this is slightly reduced due to repeat stimulation (i.e. tachyphylaxis, as previously described including in nociceptors, e.g. Anand et al 2008). C. Trace of 200 nM capsaicin challenge stimulus response in rDRG neuron, prior to response described in Panel D. D. Trace showing a significantly reduced response to 1 mM capsaicin in the presence of 100 nM CT327 (the response of this neuron to test challenge with 200 nM capsaicin is described in Panel C). E. Graph showing dose-related percent inhibition of capsaicin responses by CT327 in rDRG neurons (\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  unpaired *t*-test). F. 200 nM capsaicin challenge trace in hDRG neuron followed by G. inhibition of capsaicin test stimulus in the presence of 10 nM CT327. H. Graph showing percent inhibition of capsaicin responses by CT327 in human DRG neurons ( $n = 6$ , \*\*\* $p < 0.001$ , unpaired *t*-test). I. Immunofluorescence image of rDRG neuron in culture positive for Gap43 antibody labelling soma and neurites, for assessment of neurite lengths. J. Graph showing lack of effect of CT327 on neurite lengths at different concentrations. K. TrkA immunostaining in neuron soma (arrow) and nerve fibres (double arrowheads), in normal human DRG tissue section. L. Neurofilament expression in neuron soma and nerve fibres in DRG tissue section. M. Human skin sections showing TrkA positive intra-epidermal nerve fibres (arrow), and N. sub-epidermal nerve fibres (arrow). K, L, M, N: magnification  $\times 20$ .

observed with the 0.1% w/w and 0.5% w/w CT327 doses, with the 0.05% w/w CT327 dose reaching statistical significance. At week 8, CT327 treatment groups achieved a mean of 37.1–42.8% mPASI reduction compared to a mean 29.8% reduction on vehicle.

### Pruritus

*Pruritus in patients with at least moderate pruritus at baseline.* A reduction in VAS from baseline was observed for all CT327 treatment groups compared

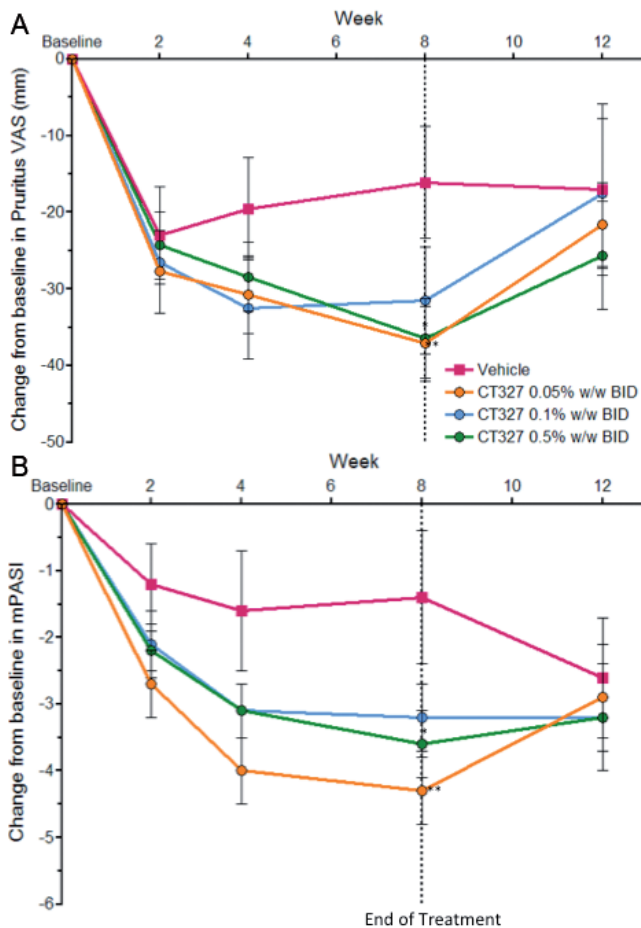


Fig. 3. Mean (SE) change from baseline in pruritus visual analogue scale (VAS) in subgroup with pruritus VAS  $\geq 40$  mm at baseline. \* $p < 0.02$ ; \*\* $p < 0.01$  (A). Mean (SE) change from baseline in modified Psoriasis Area and Severity Index (mPASI) in subgroup with pruritus VAS  $\geq 40$  mm at baseline. \* $p < 0.02$ ; \*\* $p < 0.001$  (B).

to vehicle in patients with at least moderate pruritus at baseline (VAS  $\geq 40$  mm), a pre-defined secondary endpoint for the study (Fig. 3A). This represented 70.6% of the study population (108 out of 153 patients; see Table SI<sup>1</sup> for study demographics for this patient population). At week 8, mean reductions in VAS from baseline were 37.1 mm, 31.5 mm, and 36.4 mm for CT327 0.05%, 0.1%, 0.5% groups, respectively, versus 16.1 mm for the vehicle group (Fig. 3A and Table SII<sup>1</sup>). Compared to vehicle, the mean reductions were statistically significant for the CT327 0.05% and 0.5% treatment groups ( $-21.8$  mm, 95% CI  $[-37.5, -6.2]$ ,  $p = 0.0067$  and  $-19.8$  mm, 95% CI  $[-35.2, -4.4]$ ,  $p = 0.0124$ , respectively; CT327 0.1%:  $-15.9$  mm, 95% CI  $[-31.9, 0.2]$ ,  $p = 0.052$ ). Differences between the treatment groups and vehicle were observed by week 4. In the follow-up visit at week 12, 4 weeks after patients completed treatment (week 8), a worsening of pruritus towards baseline levels was observed for all active treatment groups (Fig. 3A).

Within each treatment group, up to 62% of patients on CT327 had at least a 50% reduction in VAS from baseline by week 8 of treatment (62% response rate for CT327 0.05% ( $p = 0.0483$ ), 46% for CT327 0.1% ( $p = 0.3820$ ), 61% for CT327 0.5% ( $p = 0.0514$ )), compared to 32% of patients on vehicle.

*Pruritus (full analysis set).* A reduction of pruritus was also observed in all CT327 groups compared to vehicle in the entire study population (Table SIII<sup>1</sup>; *post-hoc* analysis). At week 8, mean reductions in VAS from baseline were 31.0 mm, 24.9 mm, and 30.8 mm for CT327 0.05%, 0.1%, 0.5% groups, respectively, versus 10.5 mm for the vehicle group (Table SIII<sup>1</sup>). Compared to vehicle, the mean reductions were statistically significant for the CT327 0.05% and 0.5% treatment groups ( $-16.4$  mm, 95% CI  $[-27.5, -5.3]$ ,  $p = 0.0040$  and  $-13.5$  mm, 95% CI  $[-24.8, -2.2]$ ,  $p = 0.0194$ , respectively; CT327 0.1%:  $-11.0$  mm, 95% CI  $[-22.1, 0.2]$ ,  $p = 0.0537$ ).

*mPASI change in patient subgroup with at least moderate pruritus (VAS  $> 40$  mm) at baseline.* A *post-hoc* analysis of mPASI in patients with at least moderate pruritus at baseline was performed. All CT327 subgroups showed greater mean reductions in total mPASI scores than vehicle (Fig. 3B). At week 8, mean reductions in mPASI from baseline were 4.3 (46.4% change from baseline), 3.2 (36.4% change), and 3.6 (37% change) for CT327 0.05%, 0.1%, 0.5% groups, respectively, versus 1.4 (17.3% change from baseline) for the vehicle group. Compared to vehicle, the mean reductions were statistically significant for the CT327 0.05% and 0.5% treatment groups ( $-2.9$ , 95% CI  $[-4.5, -1.3]$ ,  $p = 0.0006$  and  $-2.0$ , 95% CI  $[-3.6, -0.4]$ ,  $p = 0.0153$ , respectively; CT327 0.1%:  $-1.6$ , 95% CI  $[-3.3, 0.0]$ ,  $p = 0.0571$ ). In this sub-group, 13 (45%), 9 (35%), and 11 patients (35%) in the CT327 0.05%, 0.1%, 0.5% groups, respectively, achieved mPASI-50 ( $\geq 50\%$  change in mPASI from baseline) compared to 5 (23%) in the vehicle group.

### Safety

CT327 was well tolerated, and no application site reactions were reported by patients. Seventy-three patients experienced treatment emergent adverse events (AEs). The most frequently reported AEs are reported in Table SIV<sup>1</sup>. Fifteen patients reported pruritus as an AE. Of these, 9 (7.5%) were treated with CT327 ( $n = 120$ ) and 6 (15%) received vehicle ( $n = 40$ ). Eight patients withdrew from the study due to worsening of pruritus; 5 (12.5%) received vehicle whilst only 3 patients (2.5%) receiving CT327 withdrew. Two serious AE were reported, a ruptured uterine cyst and depression. Neither was related to study medication (both patients were treated with vehicle). No systemic CT327 was detected.

## DISCUSSION

While no significant improvements in psoriasis severity were found in the entire study population using the IGA instrument, we present here the first clinical evidence that inhibiting TrkA kinase has a significant effect in reducing chronic pruritus in patients with psoriasis.

The NGF-TrkA pathway has been considered to play an important role in the pathogenesis of chronic pruritus, propagating and sustaining the pruritogenic signal that evokes the “itch-scratch cycle” (8). The histological and experimental studies performed in human and rat DRG support this hypothesis. The histological studies showed that neural expression of TrkA in human tissues was localised in sub-epidermal and epidermal nerve fibres in skin, and in the majority of small diameter DRG neurons, a sub-population of which mediate pruritus and express TRPV1 (4, 5). The DRG experiments showed the functional inhibition of capsaicin-induced responses in capsaicin sensitive small diameter rat and human sensory neurons *in vitro* by CT327, sensitized by NGF, and support a mechanism of action through the NGF-TrkA-TRPV1 axis. Signalling in this pathway may be reduced by the inhibition of TrkA by CT327, thus reducing pruritus.

The NGF-TrkA-TRPV1 axis is also involved in pain, suggesting potential similarities mechanistically with pruritus. Multiple peripheral and central neural mechanisms exist for pruritus and pain, and while some are considered specific for pruritus, particularly in rodents (21, 22), in the periphery both sensations involve activation of small diameter primary sensory nerve fibres which can be sensitized by increased NGF-TrkA-TRPV1 signaling. Pruritus evoked by histamine or cowhage is reduced by topical capsaicin desensitization, while punctate cutaneous application of capsaicin, histamine and cowhage evoke similar pruritic and nociceptive (pain) sensations, indicating shared cutaneous neural mechanisms (6). These potentially mechanistic similarities between pruritus and pain raise the possibility that TrkA inhibition could also have broader applications in the treatment of cutaneous pain and hypersensitivity.

The clinical trial results revealed that CT327 applied topically significantly reduced the chronic pruritus of psoriasis patients as measured by VAS, whilst exhibiting a good safety profile and being well tolerated. In patients with at least moderate pruritus at baseline (i.e. VAS  $\geq$  40 mm), mean VAS changes of up to 37.1 mm were observed by week 8, corresponding to up to a 59% reduction. These results were also clinically meaningful. 62%, 46% and 61% of patients on CT327 0.05%, 0.1%, and 0.5%, respectively, had at least a 50% reduction in pruritus VAS, compared to 32% on vehicle (an emollient). No apparent dose response was observed between the 0.05% and 0.5% CT327 concentrations. The doses tested are thought to

have been at the top of the dose-response curve, and it is therefore possible that lower concentrations would have had an equally beneficial effect. Further studies will explore dose response.

The changes in pruritus at week 2 were similar for CT327 groups compared to vehicle, a petrolatum-based ointment and an emollient in its own right, before separating at the week 4 and week 8 time points. This highlights the role that an emollient can play in initially improving pruritic symptoms. A possible explanation for the initial emollient response observed with vehicle could be due to patients not being allowed to use any therapies (including emollient) for a minimum of 2 weeks prior to the start of the study, which could have resulted in increased skin dryness that immediately responded to a vehicle emollient upon start of therapy.

Pruritic symptoms were reassessed 4 weeks after study treatment completion (week 12). For each of the CT327 treatment groups, a worsening of pruritus was observed, although not fully returning to baseline values. This further demonstrates a pharmacological action of CT327 in the treatment of chronic pruritus.

With regard to treating psoriasis severity, no significant improvements in controlled disease were found in the entire study population using the IGA instrument, the primary endpoint of the clinical trial. A small difference was observed in mPASI, but this was not clinically meaningful. Our results suggest that inhibition of keratinocyte hyperproliferation and sensory neuron function via TrkA kinase in this study may not be sufficient to alter the entire psoriatic disease state over 8 weeks of dosing, as measured by changes in either the IGA or mPASI instruments.

TrkA kinase inhibition, however, appeared to be sufficient for statistically significant and clinically meaningful reductions in pruritus. The effect of CT327 on pruritus should be relevant for psoriasis patients, given the impact of pruritus on their quality of life and unmet need, with no approved targeted anti-pruritic therapies and reported lack of efficacy of existing therapies (1–3).

Interestingly, in the subset of patients with at least moderate pruritus at baseline, clinically meaningful and statistically significant reductions in mPASI were observed in patients treated with CT327 compared to vehicle. The magnitude of response observed was similar to those in recent studies involving calcipotriol (23). The effects observed in mPASI in addition to those observed in pruritus raise the possibility that by inhibiting pruritus and breaking the itch-scratch cycle at its source, broader benefits on psoriasis can result. Another explanation for the reductions in mPASI observed with CT327 in pruritic patients could lie in inhibition of the autocrine loop of NGF effects in keratinocytes (7), or a combination of these anti-proliferative effects of TrkA inhibition in keratinocytes and its anti-pruritic effects in sensory neurons.

The earliest time-point for collecting data on the anti-pruritic effects of CT327 in patients was at 2 weeks onwards. Topically applied CT327 could be expected to bind to TrkA receptors expressed by cutaneous epidermal afferents to provide symptom relief, in the acute phase through inhibition of NGF-TrkA-TRPV1 signalling at cutaneous nerve terminals (as modeled in the cultured sensory neuron studies which demonstrate on-target activity), but also chronically, involving down-regulation of TRPV1 and neuropeptide expression over several days/weeks via inhibition of retrograde transport of NGF by TrkA from cutaneous nerve terminals to the DRG soma. A recent report on the lack of efficacy of topical TRPV1 inhibitor SB705498 on acute itch in a healthy human volunteer study (24) suggests that chronic sensitization and phenotypic changes in this pathway, including expression of other NGF-TrkA dependent putative mediators of itch such as TRPA1, may be important in clinical pruritus (21). In support, the greatest effects on pruritus observed in our Phase 2b trial were after 4–8 weeks of treatment with CT327. The paravertebral location of the cell bodies of cutaneous afferents in the DRG, the terminals of which are at a great distance from the soma, may explain the long time-course of effectiveness in patients. The latter may be more important for full clinical efficacy in chronic pruritus, in view of the time-course of effects in our clinical trial.

CT327 exhibited a good safety profile, with a low incidence of AE and no CT327 detected in blood, suggesting that CT327 has low to no systemic exposure. Furthermore, in the cultured DRG experiments performed, established neurites were not adversely affected by CT327, and no deleterious morphological effects were observed, indicating lack of a toxic effect at the neuronal level at doses that inhibited capsaicin responses. NGF affects neurite extension in developing neurons, but its role switches to maintenance of the nociceptive phenotype in adults. We used adult neurons with established neurites in our study, where NGF was used to sensitise the neurons; our findings are in agreement with a study showing lack of effect of TrkA inhibition *in vivo* on the maintenance of adult sensory and sympathetic nerve fibres, while demonstrating analgesic efficacy, in a rodent model of non-malignant skeletal pain (25).

Loss of protective sensation/nociception remains a concern with long-term systemic blockade of the NGF-TrkA pathway (26), which may be avoided by restricted topical delivery, as with CT327, for chronic pruritus and other cutaneous hypersensitivity disorders (e.g. neuropathic pain).

Anti-inflammatory therapies are currently used to treat all aspects of psoriatic and other dermatological conditions, including pruritus. It would thus be reasonable to expect a correlation between psoriasis disease severity and pruritus severity. Reports in the literature give differing results as to whether there is

a correlation (1, 22). In our previous reported study, a correlation analysis of the psoriasis disease severity as measured by mPASI and pruritus severity using the VAS scale found no correlation between the two (27). Interestingly, and in support, in a recently published Phase 2b study with oral tofacitinib, at baseline, patients had a similar severity of pruritus to the subpopulation of patients with at least moderate pruritus at baseline in our study with CT327, despite those patients in the tofacitinib study having moderate to severe psoriasis rather than the mild to moderate psoriasis in our study (28). This lack of correlation between mPASI and pruritus severity reported previously by us highlights the need for targeted anti-pruritic therapies in patients with psoriasis, and other dermatological conditions. This is especially important given 43% of US and European psoriasis patients reported that pruritus was their most bothersome symptom, ahead of more typical symptoms such as scaling (23%) or flaking (20%) (29).

The results from the Phase 2b trial with CT327 described indicate the potential for an effective and safe topical TrkA inhibitor treatment for chronic pruritus. Effective treatment of chronic pruritus could make a significant difference to the quality of life in patients suffering this often overlooked but debilitating symptom.

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DR (Chief Medical Officer, Creabilis), JS (Head of Development, Creabilis), RW and VM are employees of Creabilis and hold share options in the company. PA is a member of the Scientific Advisory Board of Creabilis, for which he receives an honorarium, and has contributed to the pre-clinical and clinical development of CT327. In the past 24 months his lab has received a research grant from Creabilis. He did not receive any compensation for his work on the present article. GY is a member of the Scientific Advisory Board of Creabilis, for which he receives an honorarium, and has contributed to the clinical development of CT327. He did not receive any compensation for his work on the present article. The authors have no other conflict of interests to report.

#### REFERENCES

1. Yosipovitch G, Goon A, Wee J, Chan YW, Goh CL. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. *Br J Dermatol* 2000; 143: 969–973.
2. Prignano F, Ricceri F, Pescitelli L, Lotti T. Itch in psoriasis:

- epidemiology, clinical aspects and treatment options. *Clin, Cosm Invest Derm* 2009; 2: 9–13.
3. Reich A, Hrehorów E, Szepietowski JC. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. *Acta Derm Venereol* 2010; 90: 257–263.
  4. McCoy ES, Taylor-Blake B, Zylka MJ. CGRP-expressing sensory neurons respond to stimuli that evoke sensations of pain and itch. *PLOS One* 2012; 9: 1–11.
  5. Han L, Ma C, Liu Q, Weng HJ, Cui Y, Tang Z, et al. A subpopulation of nociceptors specifically linked to itch. *Nature Neuroscience* 2013; 16: 174–182.
  6. Rukweid RR, Main M, Weinkauff B, Schmelz M. NGF sensitizes nociceptors for cowhage- but not histamine induced itch in human skin. *J Invest Dermatol* 2013; 133: 268–270.
  7. Raap U, Stander S, Metz M. Pathophysiology of itch and new treatments. *Curr Opin Allergy Clin Immunol* 2011; 11: 420–427.
  8. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wei E, Biro T. Neurophysiological, neuroimmunological and neuroendocrine basis of pruritus. *J Invest Dermatol* 2006; 126: 1705–1718.
  9. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, et al. The cloned capsaicin receptor integrates multiple pain producing stimuli. *Neuron* 1998; 21: 531–543.
  10. Winter J, Forbes CA, Sternberg J, Lindsay RM. Nerve growth factor regulates the adult rat cultured dorsal root ganglion neuron responses to the excitotoxin capsaicin. *Neuron* 1988; 1: 973–981.
  11. Anand U, Otto WR, Casula MA, Day NC, Davis JB, Bountra C, et al. The effect of neurotrophic factors on morphology, TRPV1 expression and capsaicin responses of cultured human DRG sensory neurons. *Neurosci Lett* 2006; 399: 51–56.
  12. Bley K, Anand P. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011; 107: 490–502.
  13. Anand P, Foley P, Navsaria HA, Sinicropi D, Williams-Chestnut RE, Leigh IM. Nerve growth factor levels in cultured human skin cells: effect of gestation and viral transformation. *Neurosci Lett* 1995; 184: 157–160.
  14. Anand P. Neurotrophic factors and their receptors in human sensory neuropathies. *Prog Brain Res* 2004; 146: 477–492.
  15. Bracci-Laudiero L, Pincelli C. Nerve growth factor is increased in psoriatic skin. *J Invest Dermatol* 1995; 105: 854–855.
  16. Nakamura M, Toyoda M, Morahashi M. Pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors. *Br J Dermatol* 2003; 149: 718–730.
  17. Yamaguchi J, Aihara M, Kobayashi Y, Kambara T, Ikezawa Z. Quantitative analysis of nerve growth factor (NGF) in the atopic dermatitis and psoriasis horny layer and effect of treatment on NGF in atopic dermatitis. *J Dermatological Science* 2009; 53: 48–54.
  18. Anand U, Otto WR, Anand P. Sensitization of capsaicin and icilin responses in oxaliplatin treated adult rat DRG neurons. *Mol Pain* 2010; 6: 1–11.
  19. Anand U, Otto WR, Sanchez-Herrera D, Facer P, Yiangou Y, Korchev Y, et al. Cannabinoid receptor CB2 localisation and agonist-mediated inhibition of capsaicin responses in human sensory neurons. *Pain* 2008; 138: 667–680.
  20. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. *Acta Derm Venereol* 2012; 92: 497–501.
  21. Bautista D, Wilson S, Hoon M. Why we scratch an itch: the molecules, cells and circuits of itch. *Nat Neurosci* 2014; 17: 175–182.
  22. Szepietowski C, Reich A, Wisnicka B. Itching in patients suffering from psoriasis. *Acta Dermatovenerol Croat* 2002; 10: 221–226.
  23. Fleming C, Ganslandt C, Guenther L, Johannesson A, Buckley C, Simon JC, et al. Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double blind, exploratory study. *Eur J Dermatol* 2010; 20: 465–471.
  24. Gibson R, Robertson J, Mistry H, McCallum S, Fernando D, Wyres M, Yosipovitch G. Randomised trial evaluating the effects of the TRPV1 antagonist SB705498 on pruritus induced by histamine, and cowhage challenge in healthy volunteers. *PLOS One* 2014; 9: 1–11.
  25. Ghilardi J, Freeman K, Jimenez-Andrade J, Mantyh W, Bloom A, Bouhana K, et al. Sustained blockade of neurotrophin receptors TrkA, TrkB and TrkC reduces non-malignant skeletal pain but not the maintenance of sensory and sympathetic nerve fibers. *Bone* 2011; 48: 389–398.
  26. Indo Y. Nerve growth factor, pain, itch and inflammation: lessons from congenital insensitivity to pain with anhidrosis. *Exp Rev Neurother* 2010; 10: 1707–1724.
  27. Roblin D, Wickramasinghe R, Yosipovitch G. Pruritus severity in patients with psoriasis is not correlated with psoriasis disease severity. *J Am Acad Dermatol* 2014; 70: 390–391.
  28. Mamolo C, Harness J, Tan H, Menter A. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, improves patient-reported outcomes in a phase 2b, randomized, double-blind, placebo-controlled study in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol* 2013 Jan 7. [Epub ahead of print].
  29. Lebwohl M, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley R, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol* 2014; 70: 871–881.