705569450 - Annex B to RCloud Tasking Form (Part B) Supplier Technical Summary – Supplier Technical summary

The condition now termed Non-freezing cold injury (NFCI) was previously called Trench Foot, and it has been known since World Wars I and II to be a vaso-neuropathy. An underlying small fibre neuropathy with neuro-vascular changes have been demonstrated recently in skin biopsies, which may account for the chronic pain and persistent cold hypersensitivity (Anand P, et al, Front Neurol. 2017).

Currently prescribed oral treatments for neuropathic pain generally have limited efficacy, with multiple side effects (Anand and Bley, Br J Anaesth, 2011, Anand P et al, Pain Manag. 2019, Anand et al, Front Neurol, 2021). Further, there are no treatments that can cure or even modify the underlying condition.

An effective treatment, licensed in the UK / EU for neuropathic pain, is the Capsaicin 8% patch ("Qutenza 179 mg cutaneous patch"), which may relieve pain for up to 3 months after a single 30-minute application. This treatment is localised to skin, and not associated with significant systemic absorption or generalised side effects.

Capsaicin is an active compound of chilli peppers, which mediates their "hot" sensation. Traditional topical low dose capsaicin creams have been used in post-herpetic neuralgia and diabetic neuropathy at 0.025-0.075% concentrations. They need to be applied multiple times per day for weeks. While a meta-analysis of clinical data suggests mild efficacy (Hempenstall et al. 2005), compliance is poor due to the slow response (2-6 weeks), frequency of dosing and clothing contamination.

The Capsaicin 8% patch (Qutenza) can be applied every 2 to 3 months if needed; in a 1/3 of patients with diabetic neuropathic pain the pain does not return (Martini et al, 2012), unlike with cessation of oral medication. In our recent study, Capsaicin 8% patch treatment in subjects with NFCI led to regeneration and restoration of nerve fibres, shown for the first time in NFCI, and which correlated with pain relief (Anand et al, 2021).

Repeated Capsaicin 8% patch applications may provide progressive benefit. In a large clinical trial of Capsaicin 8% patch versus "standard of care" (SOC) alone, in diabetic peripheral neuropathy, repeated patch applications over 12 months showed sustained and progressive improvement of pain relief compared to SOC alone (Snijder et al 2015).

Hence this study aims to specifically evaluate the efficacy of repeated Capsaicin 8% patch applications in NFCI, to examine whether these provide progressive pain relief, and if this is mediated via an effect on nerve fibre regeneration.

A key feature of NFCI with neuropathic pain is a reduction in intra-epidermal nerve fibre density in the skin, with dysfunction of the residual small sensory nerve fibres, as in many other causes of painful neuropathy (Anand and Bley, Br J Anaesth, 2011, Anand et al, Front Neurol, 2017, and 2021). Thus, neuropathic pain associated with NFCI can be treated with the Capsaicin 8% patch, as licensed.

We recently conducted a single-centre open label study including military participants with NFCI (mean duration 49 months), who received 30-minute Capsaicin 8% patch treatment, as licensed, to the feet and calf (Anand P, et al, Front Neurol. 2021). Pain symptoms were

assessed using a pain diary (with the 11-point Numerical Pain Rating Scale, NPRS) and questionnaires, the investigations included skin biopsies, performed before and three months after treatment.

Participants showed significant decrease in spontaneous pain (**p=0.006), and cold-evoked pain (**p=0.006). The time-course of pain relief over 3 months was similar to other painful neuropathies. Patient Global Impression of Change showed improvement (***p=0.0001). Post-patch application skin biopsies showed significant increase of nerve fibres with structural marker PGP9.5 (***p<0.0001), and of regenerating nerve fibres with their selective marker GAP43 (***p=0.0001). The increase of nerve fibres correlated significantly with reduction of spontaneous (Spearman r: -0.55; p=0.027) and cold-evoked pain (Spearman r: -0.57; p=0.019). Our findings show that Capsaicin 8% patch provides an exciting new prospect for treatment of NFCI, with regeneration and restoration of nerve fibres, for the first time, in addition to pain relief.

This previous study had MoDREC approval (Application No: 890/MoDREC/2018). In the new study, for which MoDREC approval is now sought, the only differences from the previous published study are that the participants will: 1) receive *repeated* Capsaicin 8% patch treatments (3-monthly for a year, *as licensed*), and 2) be *randomised* to receive either Capsaicin 8% patch treatment, or a placebo patch (with no drug).

In this new proposed randomised placebo-controlled clinical trial, we aim to investigate the effect of repeated applications of Qutenza patch treatment in subjects with NFCI related painful neuropathy, as licensed, and applied 3-monthly over 1 year, vs placebo patches. In a recent study, described above, Capsaicin 8% patch treatment in NFCI led to regeneration and restoration of nerve fibres, for the first time, in addition to pain relief. Repeated applications of the Qutenza patch over 1 year have been shown to provide progressive pain relief in a clinical trial for painful diabetic peripheral neuropathy.

Our hypothesis is that repeated topical application of Capsaicin 8% patch will progressively reduce pain and induce nerve fibre regeneration, to restore skin nerve fibre density and function, and hence lead to a “cure” in NFCI.

NFCI and the associated chronic neuropathic pain are a particular health burden to military personnel. NFCI may lead to a downgrading of military functional status, and in many cases early discharge from the armed services. It is also a financial burden for the Ministry of Defence.

[redacted]

If successful this treatment could be rapidly exploited for service personnel (SP) to improve symptoms, improve functional status and ultimately allow return to work, and thereby a reduction in litigation costs.