Placebo response in randomised controlled trials of analgesics is common, often diluting the ability to detect potential drug effects. There are few definitive recommendations for mitigating placebo response, and the phenomenon remains poorly understood. Placebos with subjective measures of outcome, such as pain intensity, are particularly difficult to manage. In a recent randomised, double-blind, placebo-controlled, dose escalation study designed to evaluate safety and efficacy of a novel spidercytomycin derivative, KRN5500, in patients with end-stage cancer experiencing neuropathic pain, response was defined as the median percent change from baseline pain intensity. Nineteen patients received treatment flexibility dosed over 10 weeks (12 active 7 placebo). Baseline characteristics and achieved dose levels were similar across treatment groups. Withdrawal rates were also similar (80% for KRN5500 vs 81% for placebo). While depression was primarily treated as the endpoint, therapy also elicited reductions in placebo response. Of note, only 3 patients (16%) who could not complete the full 10-week dosing regimen as well as those that could. Of 12 patients receiving KRN5500, 9 (75%) had improved NRS pain scores, 4 (33%) had no change, and none had increased pain. Of 7 patients receiving placebo, 2 (29%) had improved pain scores (although one of these if only 1 post-baseline assessment due to study withdrawal) while 4 (57%) showed no change, and 1 (14%) reported increased pain. However, pain intensity was measured quantitatively as a percent change from baseline, placebo response was diminished. The median percent decrease from baseline in NRS pain scores was 24% (range 0 to100) in the KRN5500 group compared to 0% decrease (range -30 to 0) in the placebo group (p=0.03). Placebo response was higher, though erratic, for secondary outcome after treatment response; however, when placebo response was also taken into consideration, study design was no longer a predictor.

It has been suggested that enrolling subjects with higher baseline pain scores is one method of mitigating placebo response, as noted in NPQ scores. Study DTCL100 was positive despite the small sample size; there was lower variability within the placebo group and relatively low placebo response rates. Specific symptoms of NP may be more susceptible to placebo response, as noted in NPQ scores. Flexible dosing contributed to patients staying in the study until the highest possible dose was reached; it is unclear how placebo or medication response rates would have been affected if more patients had stayed in the trial for the full duration.

The study had only 2 treatment arms, and baseline pain level was moderate to severe; it is possible that one or both characteristics impacted sensitivity.

Placebo response was low and pain reduction in the medication group was statistically significant compared to placebo.

Evaluation of this study’s characteristics may offer insight for designing and conducting future analgesic trials, particularly those in patients with cancer who have NP.