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Preserved afferent small-fibre function is a pre-requisite for the analgesic efficacy of an oral inhibitor of transient receptor potential ankyrin 1 (TRPA1) in painful diabetic neuropathy

***Background*:** Diabetic peripheral neuropathy (DPN) causes chronic pain and disability and conventional therapies have had limited success. Transient receptor potential ankyrin 1 (TRPA1), a pain receptor expressed in small nerve fibres, holds promise for novel DPN therapies.
***Methods*:** This phase 2, proof-of-concept, multicenter trial investigated the efficacy and safety of oral TRPA1 inhibitor, ISC 17536, in 138 patients with painful diabetic peripheral neuropathy of 6 months to 5 years duration, randomized to receive either 50 mg of ISC 17536 (n=72) or placebo (n=66) twice daily for 28 days. The primary outcome was the change in the mean 24-hour average pain intensity (API) score based on an 11-point pain intensity numeric rating scale. Secondary outcomes included other pain measures, quality of life, sleep quality, and safety parameters from baseline to week 4. Somatosensory function and signs of pain were characterized using the quantitative sensory testing (QST) protocol established by the German Research Network on Neuropathic Pain, performed at baseline and week 4.
***Results*:** ISC 17536 was well-tolerated with no serious adverse events or discontinuations due to adverse events. Baseline API scores were similar between both groups, and both groups showed reduced API scores from the start of treatment to week 4. However, the difference in API score reduction between the ISC 17536 group and the placebo group was not statistically significant. There were also no significant differences between groups in secondary pain outcomes or quality of life measures. The study included a subgroup of 65 patients with preserved small nerve fiber function and moderate to severe pain (API>5) at baseline. There were no baseline differences in pain score between the ISC 17536 and placebo groups. The ISC 17536 group showed a statistically significant difference in pain score at week 4, with a LS (active minus placebo) mean difference of -0.96 (95% CI: -1.68 to -0.24), indicating efficacy in patients with high baseline pain. Additionally, statistically significant differences were observed in favour of ISC 17536 at weeks 1, 2, 3, and 6.
***Conclusions*:** ISC 17536 was safe and well tolerated but did not show efficacy for reducing pain in patients with DPN overall. However, ISC 17536 may have some analgesic effect in patients with preserved small nerve fibre function.

Comments. This randomized, double-blind, placebo-controlled trial shows that ISC 17536 was safe and well tolerated but did not significantly reduce pain scores compared with placebo in patients with painful DPN. However, the study also suggests that ISC 17536 may have some analgesic effect in patients with preserved small nerve fibre function, as measured by QST.
The study had limitations including a small sample size, a short treatment duration of 28 days, a heterogeneous study population, the lack of prospective stratification of patients, and the use of QST methods that were subjective and might be not sensitive enough for assessment of small fiber loss. Future clinical trials should consider incorporating objective and sensitive techniques such as corneal confocal microscopy to improve accuracy in identifying the small fibers preservation and the prediction models of treatment response.

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Reference. Jain SM, Balamurugan R, Tandon M, Mozaffarian N, Gudi G, Salhi Y, Holland R, Freeman R, Baron R. Randomized, double-blind, placebo-controlled trial of ISC 17536, an oral inhibitor of transient receptor potential ankyrin 1, in patients with painful diabetic peripheral neuropathy: impact of preserved small nerve fiber function. Pain. 2022 Jun 1;163(6):e738-e747. doi: 10.1097/j.pain.0000000000002470.
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