Impact of treatment with high-concentration capsaicin (8%) (QTZ) topical system on sensory testing in patients living with painful diabetic peripheral neuropathy of the feet: a *post-hoc* analysis of the PACE trial

King M, Upperline Health, Nashville, TN; **Katz N**, WCG Analgesic Solutions and Adjunct Associate Professor of Anesthesia, Tufts University School of Medicine; **Allen S**, Averitas Pharma, Morristown, NJ, United States; **Carnevale A**, Averitas Pharma, Morristown, NJ, United States

Objectives

This *post-hoc* analysis of the PACE trial was conducted to further analyze changes in sensory function in the QTZ + SOC group after multiple applications of the topical system using the Brief Sensory Pain Examination. This instrument was used to assess sensory function at baseline, and to reassess following repeated applications of the QTZ topical system over a 52-week period. Since this is a *post-hoc* analysis of an open-label study, the results should be interpreted cautiously.

Conclusions

This *post-hoc* analysis of the PACE trial shows improved sensory function over time with repeated QTZ treatments compared with standard of care alone. This outcome may be linked to local vasodilatation resulting in better neuronal function. More research is warranted to confirm these findings and better understand the benefits of QTZ for patients with DPN.

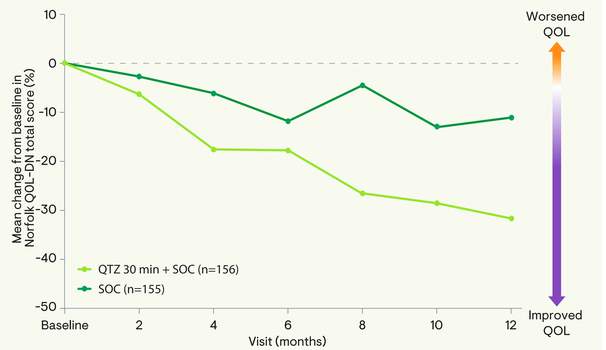
Background

Peripheral neuropathy is the most common microvascular complication of diabetes, occuring in about 50% of patients, and it typically presents as a loss of distal sensory function in the lower extremities.[1] The likelihood of patients developing diabetic peripheral neuropathy (DPN) increases with the duration of diabetes, and up to half of patients experience pain.[1-3]

Vascular supply to the peripheral nerves in patients with DPN is often compromised, resulting in distal axons that are unable to support the transport of nutrients, neurotrophic factors, and other signaling factors.[4] DPN represents a state of bioenergetic failure associated with impaired metabolism, which can lead to significant nerve damage which is length-dependent. Additionally, although DPN is progressive, the disease course is punctuated by small nerve fiber regeneration, which ultimately succumbs to net degeneration and underscores the crucial need for developing effective, broad-spectrum therapies.[5] These consequences of DPN can result in physical and chemical alterations of epidermal nerve fibers and changes in sensation in the extremities.[1,6] As patients combat both the loss of mechanical sensory information and increasing perception of pain, quality of life (QOL) is often negatively impacted.[1]

The PACE study was an open-label, Phase III, randomized, three-arm, multinational clinical trial, designed to assess the long-term (1-year) safety and tolerability of repeat administration of high-concentration capsaicin (8%) topical system (QUTENZA; QTZ) plus standard of care (SOC) vs. SOC alone in patients with painful DPN (30- or 60-min applications of QTZ with ≥8week intervals).[7,8] The primary endpoint was the change from baseline in the Norfolk QOL diabetic neuropathy (QOL-DN) total score, which is a validated, patient-reported outcome questionnaire.[7] This assessment was specifically developed to reliably measure effects of nerve function that translate into changes in QOL, activities of daily living, and health of the individual. Although the *a priori* goal of PACE was to assess sensory function in the QTZ + SOC group, a measurable improvement in QOL was observed in patients with DPN as evidenced by reduced QOL-DN total scores. Only the QTZ+SOC 30-minute group was included to reflect the current label in US (Figure 1).[7]

Figure 1 - Mean change (%) from baseline in Norfolk QOL-DN total scores with QTZ + SOC vs. SOC alone over 52 weeks in patients with painful DPN[7,8]



Methods

High-concentration capsaicin (8%) topical systems were applied at bimonthly visits (or at unscheduled visits at intervals of at least 8 weeks). The Brief Sensory Pain Examination assessed sensory function by rating evoked sensations from five predefined areas on both feet compared with an asymptomatic control site. It involved the assessment of five stimuli: heat, cold, sharp sensations, vibrations, and deep tendon reflexes. Although multiple locations on the foot were examined for heat, cold, and sharp sensation, for the purpose of this publication all results are from the mid-plantar location. These data seemed most consistently representative of the entire foot. Examinations were performed by neurologists as well as non-neurologist physician-investigators (given appropriate training) and findings were captured using pre-defined scales (footnote to Table 1).

The *post-hoc* analysis included two subgroups of patients (listed below) and the original ITT population (Table 1):

- Subgroup 1: comprised patients reporting abnormally low sensations at baseline in each of the five modalities.
- Subgroup 2: comprised patients with a reported score of zero (no sensation) at baseline in each of the five modalities.

Comparative statistics were not performed and all data are presented descriptively as percentages. The initial analysis was conducted to determine any positive or negative sensory shifts with repeated applications. The percentage of sensory tests in the two subgroups that shifted to either some positive or normal sensation, respectively, were collected in patients treated with QTZ for 30 min + SOC.

Table 1 - Any shift in sensation in the Brief Sensory Pain Examination following consecutive administrations of QTZ + SOC for the ITT population

Sensory modality	Tx 1	Tx 2	Tx 3	Tx 4	Tx 5	Tx 6	EOS - LOCF
Heat at mid-plantar, % positive shift	11.2	22.5	19.4	23.6	28.8	31.7	**28.0**
Heat at mid-plantar, % negative shift	11.6	12.7	15.1	12.4	12.4	12.2	**14.0**
Cold at mid-plantar, % positive shift	16.3	21.8	23.3	25.2	31.2	29.3	**29.7**
Cold at mid-plantar, % negative shift	11.2	15.6	15.9	10.8	14.0	17.5	**17.0**
Sharp at mid-plantar, % positive shift	16.3	18.2	21.3	26.4	28.8	28.5	**27.0**
Sharp at mid-plantar, % negative shift	11.2	9.5	11.2	10.8	11.6	15.0	**15.7**
Vibration, % positive shift	10.2	20.4	22.1	26.4	26.8	30.9	**27.3**
Vibration, % negative shift	6.1	8.8	8.1	6.8	10.0	11.0	**12.3**
Reflexes, % positive shift	5.8	6.5	8.5	10.4	12.8	14.2	**13.0**
Reflexes, % negative shift	5.8	7.3	7.0	4.9	6.8	5.3	**8.7**
n=number of sensory assessments	294	275	258	250	250	246	300

Scoring involved the assessment of five modalities: vibration, heat, cold, and sharp sensations, and the assessment of deep tendon reflexes. The left and right sides were assessed separately as:

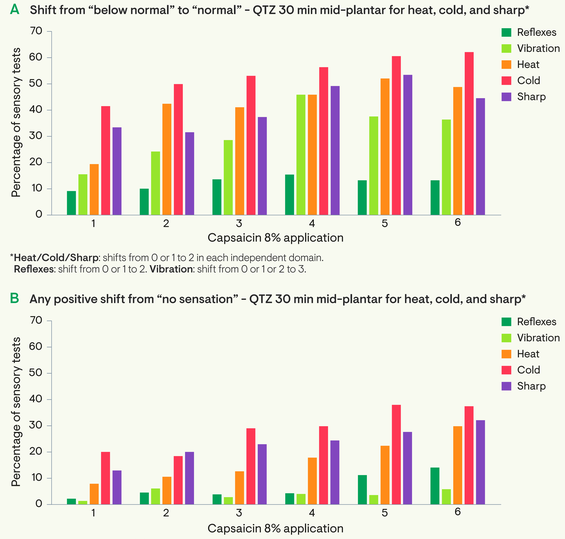
- **Heat** at each of ball of foot, mid-plantar, dorsal first toe, dorsal foot, medial malleolus: not warm (= 0), slightly warm (= 1), warm or hot (= 2, normal), painfully hot (= 3)
- **Cold** at each of ball of foot, mid-plantar, dorsal first toe, dorsal foot, medial malleolus: not cold (= 0), slightly cold (= 1), cold (= 2, normal), painfully cold (= 3)
- **Sharp** at each of ball of foot, mid-plantar, dorsal first toe, dorsal foot, medial malleolus: not felt (= 0), dull (= 1), sharp (= 2, normal), painfully sharp (= 3)
- **Vibration sensation**: not felt (= 0), <6 sec (= 1), 6 to 10 sec (= 2), >10 sec (= 3, normal)
- **Reflexes**: no response (= 0), hypoactive (= 1), normal (= 2), hyperactive (= 3), clonus (= 4)

EOS: end of study; LOCF: last observation carried forward.

Results

More positive shifts were consistently observed across all five domains in the QTZ + SOC study ITT population (Table 1). To determine treatment effect on sensation more accurately for QTZ in patients with abnormally low sensation and no sensation at baseline, two subgroup analyses were conducted. The proportion of sensory tests in each subgroup treated with QTZ + SOC reporting improved sensory perception increased with repeated applications. In subgroup 1 (abnormally low sensation at baseline), the shift to normal sensation was also increased by the 6th application in all five sensory modalities (Figure 2A). In subgroup 2 (score of zero at baseline), the percentage of sensory tests in all five modalities increased with repeated applications (Figure 2B).

Figure 2 - Mean percent responses to QTZ + SOC in the Brief Sensory Pain Examination in patients with abnormally low sensation at baseline (A), or no sensation at baseline (B)



*Heat/Cold/Sharp: shifts from 0 or 1 to 2 in each independent domain. Reflexes: shift from 0 or 1 to 2. Vibration: shift from 0 or 1 or 2 to 3.

*Heat/Cold/Sharp: any shift from 0 to 1 or 2 in each independent domain. Reflexes: any shift from 0 to 1 or 2. Vibration: any shift from 0 to 1 or 2 or 3.

Discussion

Improvements in sensory perception were observed over time with repeated applications of QTZ + SOC in patients with DPN. Treatment with QTZ ensures sufficient selective binding to transient receptor potential vanilloid 1 (TRPV1)–expressing nociceptive fibers, resulting in a reversible chemical ablation leading to significant pain relief.[9-12]

A secondary effect of capsaicin is the release of calcitonin gene-related peptide (CGRP) in the skin, which is likely the main initiator of neurogenic inflammation, characterized by increased blood flow resulting in edema and erythema.[13,14] When the pharmacokinetic properties of QTZ were determined, it was hypothesized that the matrix technology in the topical system should ensure the formation of a reservoir of capsaicin in the stratum corneum.[15] This reservoir may underlie some longer-term effects of QTZ such as nerve regeneration, improvements in sensory function, and nociception. This hypothesis has been supported by recent data showing increased epidermal nerve fiber density (ENFD) at 3 months following an application of QTZ in patients with DPN as compared with baseline ENFD biopsies.[12] Furthermore, axon-reflex vasodilation in the skin was significantly increased after 3-month follow-up in the subset of subjects tested.

Additionally, there was a positive correlation between the increase of axon-reflex vasodilation and ENFD at 3 months post QTZ application. These positive effects on ENFD were time-dependent and began to revert to baseline values within 6–9 months, which should be expected due to the progressive nature of DPN.[5,12] Given these findings, it is reasonable to assume a long-term secondary effect of capsaicin on blood flow may result in healthier nerves distally in diabetic patients.

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Disclosures

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