

# First Non-Invasive Combined Occipital & Trigeminal Nerve Stimulation Digital Therapeutics System for Treatment of Migraine: A Randomized, Sham-Controlled, Double-Blind Clinical Trial

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## INTRODUCTION

Until recently, Combined Occipital and Trigeminal Nerve Stimulation (COT-NS) was only available with implanted technology. We conducted a randomized, double-blind, sham controlled clinical trial to assess the safety and efficacy of the first non-invasive, self-administered, multi-channel COS-NS device (Relivion<sup>®</sup>, Neurolief Ltd) for acute treatment of migraine. The head-worn device delivers precise stimulation to six branches of both the occipital and trigeminal nerves via three adaptive output channels. During treatment, the Relivion mobile application gathers treatment data from the device and upload it to a cloud database for analysis and treatment optimization.

## OBJECTIVES

To evaluate the safety and efficacy of non-invasive Combined Occipital and Trigeminal Nerve Stimulation (COT-NS) device in the acute treatment of episodic and chronic migraine.

## METHODS

This was a prospective, randomized, double-blind, parallel-group, sham-controlled clinical study. Subjects initiated self-administered one-hour treatment with the device soon after onset of their migraine episode. The primary endpoint was to assess the change in VAS pain score from baseline to 1-hour post treatment initiation. Pain intensity (VAS) was recorded before treatment and then at 1, 2 and 24-hours post treatment initiation. Subjects were asked to refrain from medications for at least 2 hours post treatment initiation.

## RESULTS

55 subjects with episodic or chronic migraine were randomized to receive either an active or a sham treatment. Following one-hour of treatment, pain decreased significantly more in the treatment group compared to the sham group at all time points (group difference at 1-hour 41%,  $p=0.0002$ , at 2-hours 33%,  $p=0.03$ , at 24-hours 36%,  $p=0.02$ ). Responder rate ( $\geq 50\%$  pain reduction) was significantly higher in the treatment group than in the sham group at 1-hour (67% ver. 20%,  $p=0.001$ ), 2-hours (67% ver. 32%,  $p=0.02$ ) and 24-hours (78% ver. 48%,  $p=0.04$ ). Pain free at 2-hours for subjects with a baseline pain level of severe-moderate was significantly higher in the treatment group than in the sham group (43% ver. 11%,  $p=0.02$ ). Headache relief rate (subjects which improved from severe or moderate pain at baseline to mild or no pain) was significantly higher in the treatment group compared to the sham group at 1-hour (66.7% ver. 26.32%,  $p=0.01$ ) and 2-hours (76.19% ver. 31.58%,  $p=0.01$ ) test points. No serious adverse events were reported.

## CONCLUSIONS

Self-administered treatment of acute migraine with a non-invasive combined occipital and trigeminal nerve stimulation device was safe and highly effective. We hypothesize that the synergistic neuromodulatory effect elicited by concurrent activation of the occipital and trigeminal neural pathways contributes to the superior therapeutic results shown in this study.