# Lasmiditan and sumatriptan: comparison of in vivo vascular constriction in the dog and in vitro contraction of human arteries

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* (R)-isometheptene is being investigated in the US for tension-type headache under a US IND and is not approved for any indication.

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Disclosure statement:
This study was supported by Tonix Pharmaceuticals

## EHMTC-0155
## POSTER SESSION D

## NON-INVASIVE VAGUS NERVE STIMULATION (NVNS) FOR THE ACUTE TREATMENT OF MIGRAINE WITHOUT AURA IN ADOLESCENTS: PRELIMINARY CLINICAL EXPERIENCE

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**Background:** Recent study results and clinical experience have demonstrated the safety, tolerability, and efficacy of non-invasive vagus nerve stimulation (nVNS; gammaCore®) for the acute and prophylactic treatment of migraine. nVNS has a favorable adverse event profile, making it an attractive option for sensitive patient populations.

**Aim:** To explore the safety, tolerability, and efficacy of nVNS as an acute treatment of migraine without aura in adolescents.

**Methods:** Eight 13- to 18-year-old patients with migraine without aura according to *International Classification of Headache Disorders, 3rd edition (beta version)* criteria (4 to 8 migraine days per month) were recruited. In a one-hour training workshop, the patients and their parents were instructed to treat attacks acutely with nVNS for one month. Each attack was treated with one 2-minute stimulation on the right side of the neck; a second stimulation was allowed within one hour of the first treatment. Patients recorded the pain intensity of the treated attack at several prespecified time points between 30 minutes and 24 hours after treatment. Rescue medication was allowed after 2 hours from device use.

**Results:** Of the 44 treated migraine attacks, 17 (38.6%) were pain free at one hour. Pain intensity for an additional 4/44 (9.1%) attacks decreased to mild at 2 hours. These attacks (21/44; 47.8%) did not require rescue medication. No device-related adverse events were recorded.

**Conclusions:** In this preliminary evaluation, nVNS had favorable safety and tolerability and was practical and effective in acutely treating migraine without aura in adolescents.

Conflict of interest
Disclosure statement:
Licia Grazzi, MD, has received consultancy and advisory fees from Allergan, Inc., and electroCore, LLC. Gabriella Egeo, MD, PhD, has nothing to disclose. Eric Liebler is an employee of electroCore, LLC, and receives stock ownership. Piero Barbanti, MD, PhD, has received consultancy fees from Allergan, Inc., electroCore, LLC, Janssen Pharmaceuticals, Inc., and Lusofarmaco and advisory fees from Abbott Laboratories and Merck & Co., Inc.

## EHMTC-0329
## POSTER SESSION D

## LASMIDITAN AND SUMATRIPTAN: COMPARISON OF IN VIVO VASCULAR CONSTRICTION IN THE DOG AND IN VITRO CONTRACTION OF HUMAN ARTERIES

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Antimigraine triptans are vasoconstrictive 5-$HT_{1B/1D}$ receptor agonists that are contraindicated in patients with coronary artery disease. In contrast to sumatriptan, lasmiditan is a selective 5-$HT_{1F}$ receptor agonist that lacked in vitro vasoconstrictive effects in rabbit saphenous vein. To further assess the cardiovascular effects of lasmiditan, we studied the vascular effect of lasmiditan in dogs and in human isolated arteries and compared it to sumatriptan.

Anesthetized female beagle dogs (5.4–7.9 kg) were implanted with carotid and coronary artery crystals for measurement of vascular diameter. Lasmiditan, sumatriptan and vehicle were administered by intravenous infusion over 20 minutes in escalating cumulative doses ranging from 0.03 to 11.13 mg/kg (n = 6/group). Statistically significant decreases in both coronary and carotid artery

diameters occurred in the sumatriptan-treated group at clinically relevant doses compared to the vehicle control ($p < 0.025$). Conversely, lasmiditan was devoid of any vasoconstrictive activity at all doses tested.

In human isolated blood vessels, sumatriptan induced contractions in the proximal ($E_{max}$ 44% of contraction to 100 mM KCl, $pEC_{50}$ 6.29, $n = 2$) and distal ($E_{max}$ 139%, $pEC_{50}$ 6.45, $n = 2$) coronary artery. In internal mammary artery, sumatriptan also induced contractions ($E_{max}$ $30 \pm 16\%$, $pEC_{50}$ $5.86 \pm 0.56$, $n = 5$). and contractions were augmented ($E_{max}$ $79 \pm 19\%$, $pEC_{50}$ $6.42 \pm 0.66$, $n = 5$) after precontraction with threshold concentrations of U46619. Vehicle and lasmiditan did not contract any of the arteries studied, either from baseline or after precontraction with U46619.

Thus, in canine and most importantly, in human blood vessels, the lack of vasoconstrictive properties of lasmiditan may be a cardiovascular safety advantage compared to the triptans.

Conflict of interest
Disclosure statement:
This study was supported by CoLucid Pharmaceuticals

## EHMTC-0010
## POSTER SESSION D

## PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF DFN-02, AN INTRANASAL SUMATRIPTAN SPRAY CONTAINING A PERMEATION ENHANCER, COMPARED WITH SUBCUTANEOUS (SC) SUMATRIPTAN IN HEALTHY ADULTS

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**Objective:** To compare the pharmacokinetic characteristics of two commercial sumatriptan products, 4 mg and 6 mg SC sumatriptan with DFN-02, an intranasal formulation comprised of sumatriptan 10 mg plus 0.20% permeation enhancer 1 O n Dodecyl-β-D-Maltopyranoside (DDM, Intravail® A3) in healthy adults.

**Background:** Intranasal sumatriptan (Imitrex®) may be an alternative for patients who refuse injections and cannot tolerate oral agents, but low bioavailability and slow absorption limit the clinical utility of the currently marketed formulation, highlighting an unmet need for an effective non-oral migraine medication with a rapid onset of action.

**Methods:** We conducted an open-label, randomized, single-dose, three-way crossover bioavailability study comparing DFN-02 with 4 mg and 6 mg SC sumatriptan in 78 healthy, fasted adults. Subjects received a single dose of each treatment with at least three days between treatments. Blood was sampled for pharmacokinetic evaluation of sumatriptan and DDM through 24 hours post-dose.

**Results:** Median tmax was 10 minutes for DFN-02 compared to 15 minutes for 4 mg and 6 mg SC sumatriptan ($P < .0001$). Mean sumatriptan exposure metrics were similar for DFN 02 and 4 mg sumatriptan: AUC0–2 values were 35.12 and 44.82 ng*hr/ml, respectively; AUC0-$\infty$ values were 60.70 and 69.21 ng*hr/mL, respectively; Cmax values were 51.79 and 49.07 ng/mL, respectively. DDM exposure was low (mean Cmax = 1.63 ng/ml), tmax was 30 minutes, and DDM was undetectable by 4 hours. There were no serious adverse events, discontinuations due to adverse events, or any clinically remarkable findings.

**Conclusions:** Plasma sumatriptan concentrations of DFN-02 peaked five minutes earlier than 4 mg and 6 mg SC sumatriptan. The rapid absorption of DFN-02 suggests that its efficacy will be comparable to that of 4 mg SC sumatriptan.

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Document not received

## EHMTC-0069
## POSTER SESSION D

## VITAMIN B COMPOUND COULD BE EFFECTIVE IN MENSTRUAL RELATED MIGRAINE

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**Background:** Migraine headaches are disabling problem for women with many of them experience more severe attacks before menstruation. Homocysteinemia results in overproduction of homocysteic acid which in turn stimulates the trigeminovascular system and provokes