How are new drugs and devices integrating into treatment strategies

HCOP 2020

January 26, 2020

ALAN M. RAPOPORT, M.D.

Clinical Professor of Neurology
The David Geffen School of Medicine at UCLA
Los Angeles, California

Past-President of the IHS

Founder and Director-Emeritus
The New England Center for Headache
Stamford, Connecticut

DR. RAPOPORT'S DISCLOSURES

SPEAKERS BUREAU

- Amgen
- Teva

October 2, 2019

ADVISOR

- Allergan
- Amgen
- Amneal
- Autonomic Technologies
- Biohaven
- Cala Health
- Neurolief
- Novartis
- Promius
- Satsuma
- Teva
- Theranica
- XOC
- Zosano

Agenda – New Acute Care Therapies for Migraine

CGRP – Why Block It and what happens?
Small Molecule CGRP Receptor Antagonists (Gepants)
Monoclonal Antibodies to CGRP or its Receptor

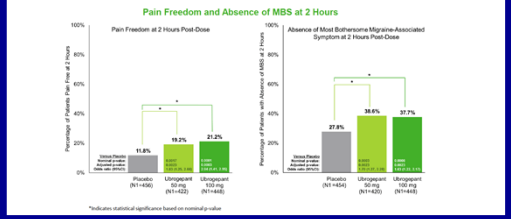
Ditans (lasmiditan)

Devices
Transcranial Magnetic Stimulation - sTMS
Transcutaneous Supraorbital Nerve Stimulation – tSNS
Remote Upper Arm Neuromodulation - REN
Combined Occipital and Trigeminal Neuromodulation
Caloric Vestibular System - CVS
Sphenopalatine Ganglion Stimulation - SPG Stim
Non-invasive Vagal Nerve Stimulation - nVNS
Micro-needle zolmitriptan Intradermal Patch
Sumatriptan NS with Permeation Enhancer
DHE Nasal Powder and Nasal Spray
BRIEF DISCUSSION OF: New methysergide, meloxicam 20/rizatriptan 10

Ubrogepant Co-Primary Endpoints

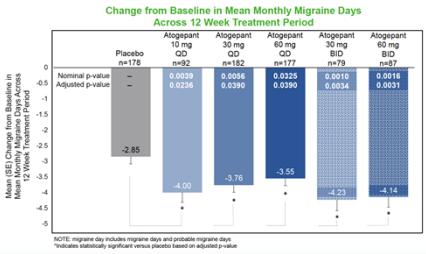
Co-Primary Efficacy Endpoints

- 2 hours post-initial dose, the percentage of ubrogepant-treated patients (50 mg and 100 mg) achieving pain freedom was significantly greater vs. placebo
- Percentage of ubrogepant-treated patients (50 mg and 100 mg) achieving absence of MBS at 2 hours post-initial dose was significantly greater vs. placebo



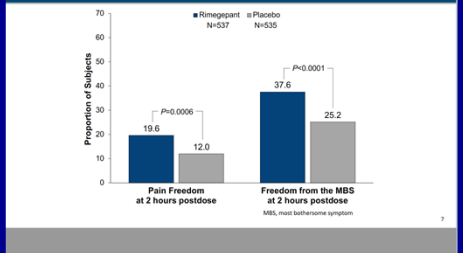
Atogepant Primary Endpoint

Primary Efficacy Endpoint: Reduction in Migraine Days *(mITT Population)*



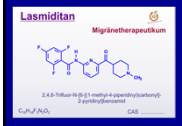
Rimegepant Phase III

Superior to Placebo on Both Coprimary Efficacy Endpoints



A new class of “ditans” – Serotonin$_{1F}$ receptor agonists

- Lasmiditan, the first “ditan”, has clear proof of principle in 2 studies and 1 Phase III study
- Oral tablet 50-400 mg
- AEs: dizziness, drowsiness, par.
- It does not constrict vessels



Lasmiditan Primary Endpoints

Primary Endpoint: Headache Pain-Free (First Dose)
Double-Blind Period, mITT Population (SAMURAI and SPARTAN)

SAMURAI[1,3]	PBO (N=524)		LTN 100 mg (N=503)	LTN 200 mg (N=518)
% of patients pain free at 2 hours[a]	15.3		28.2	32.2
Odds ratio*			2.2 (1.6, 3.0)	2.6 (2.0, 3.6)
p-value*			<0.001	<0.001
SPARTAN[2,3]	**PBO (N=540)**	**LTN 50 mg (N=556)**	**LTN 100 mg (N=532)**	**LTN 200 mg (N=528)**
% of patients pain free at 2 hours[a]	21.3	28.6	31.4	38.8
Odds ratio*		1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	2.3 (1.8, 3.1)
p-value*		0.003	<0.001	<0.001

*vs. PBO.
[a]Headache pain-free is a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the indicated assessment time.
Lasmi=Lasmiditan; MBS=Most Bothersome Symptom; mITT=Modified Intent-to-Treat; PBO=Placebo.
1. Kuca B, et al. Presented at: AHS 2017. Abstract IOR11B. 2. Wietecha LA, et al. Presented at: IHC 2017. Abstract PO-02-180. 3. Data on File, Eli Lilly and Company.

Lasmiditan MBS Freedom

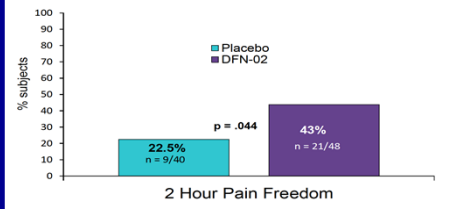
Key Secondary Endpoint: MBS-Freedom at 2 hours
Double-Blind Period, mITT Population (SAMURAI and SPARTAN)

SAMURAI[1,3]	PBO (N=524)		LTN 100 mg (N=503)	LTN 200 mg (N=518)
% of patients MBS free at 2 hours[a]	29.5		40.9	40.7
Odds ratio*			1.7 (1.3, 2.2)	1.6 (1.3, 2.1)
p-value*			<0.001	
SPARTAN[2,3]	**PBO (N=540)**	**LTN 50 mg (N=556)**	**LTN 100 mg (N=532)**	**LTN 200 mg (N=528)**
% of patients MBS free at 2 hours[a]	33.5	40.8	44.2	48.7
Odds ratio*		1.4 (1.1, 1.8)	1.6 (1.2, 2.0)	1.9 (1.4, 2.4)
p-value*		0.009	<0.001	<0.001

*vs. PBO.
[a]Most Bothersome Symptom of nausea, phonophobia or photophobia.
Lasmi=Lasmiditan; MBS=Most Bothersome Symptom; mITT=Modified Intent-to-Treat; PBO=Placebo.
1. Kuca B, et al. Presented at: AHS 2017. Abstract IOR11B. 2. Wietecha LA, et al. Presented at: IHC 2017. Abstract PO-02-180. 3. Data on File, Eli Lilly and Company.

DFN-02 (Tosymra) Sumatriptan 10 mg NS with Permeation Enhancer

Primary Endpoint: 2-Hour Pain Freedom, DFN-02



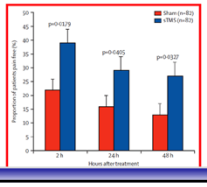
Lipton et al. *Headache* 2018;58:676-687.

Neuromodulation for Migraine & Cluster

- FDA approved:
  - Transcranial magnetic stimulation for acute and preventive treatment of migraine with and without aura (sTMS) – (sTMS mini)
  - Transcutaneous supraorbital neurostimulation (tSNS) for prevention and acute care of migraine (Cefaly)
  - Non-invasive vagal nerve stimulation (nVNS, gammaCore) for acute treatment of Cluster Headache and Migraine
  - Remote Neuromodulation – (REN, Nerivio)
  - DFN-02 Sumatriptan NS with Permeation Enhancer (Tosymra)
- Not FDA approved:
  - Occipital and Supraorbital Neuromodulation – Relivion
  - Sphenopalatine ganglion stimulation (SPG, Pulsante) – Cluster and Migraine
  - Zolmitriptan intradermal patch (ADAM)
  - DHE Nasal Powder and spray + a few others

Single Pulse Transcranial Magnetic Stimulation (sTMS)

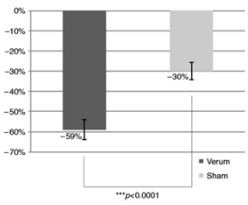
- Magnetic pulses disrupt cortical spreading depression (CSD), the basis for aura, and down-regulate thalamocortical pain pathways
- 1 RCT for acute treatment of migraine with aura, N=167
  - 2 hours pain-free: 39% sTMS vs 22% sham (*P*=0.0179)
- 2 open label studies for prevention of migraine with prn extra pulses for acute use, N=249
  - 4-25 headache days for inclusion; 4 pulses BID with extra prn up to 17 pulses per day
- FDA-approved in 2017 as nonsignificant risk device for preventive and acute treatment of migraine
- Rental cost $225/month



Andreou et al. *Brain*. 2016;139:2002-2014.
Lipton et al. *Lancet Neurol*. 2010;9:373-380.
Bhola et al. *J Headache and Pain*. 2015;16:535.
Starling et al Cephalalgia 2018;38:1038–1048.

Primary Outcome Measure: Change in Pain Score on VAS at 1 hour Compaired to Baseline (n=99)

Outcome measures are detailed in Table 2. The primary outcome (mean change in pain score at 1 hour compared to baseline) was significantly decreased ($p<0.0001$) in the verum and sham groups, but much more in the verum (–59%) than in the sham group (–30%); the effect size was large, with a Cohen's *d* value of 0.88 (Figure 4). Applying the aforementioned post hoc ANCOVA sensitivity analysis, the treatment effect defined by the primary outcome measure remained highly significant ($p<0.0001$).



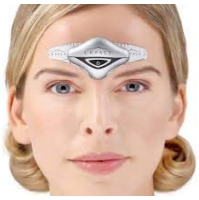
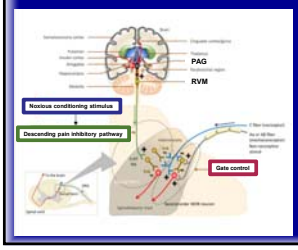


Figure 4. Relative change in pain intensity at 1 hour.

Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial
Denise E Chou, Marianna Shnayderman Yugrakh, Dana Winegarner, Vernon Rowe, Deena Kuruvilla, Jean Schoenen. *Cephalalgia* 2018.
DOI: 10.1177/0333102418811573

Nerivio for the Acute Treatment of Migraine (REN)

- A novel remote electrical neuromodulation device controlled by an app (Theranica Bio-Electronics Ltd., Israel)
  - FDA allowed
- Peripheral nerves of the upper arm are stimulated to induce conditioned pain modulation (CPM) – a descending endogenous analgesic "pain inhibits pain" mechanism
  - Peripheral nociceptive information just below the perceived pain threshold can activate the descending pain inhibitory pathway and inhibit the headache

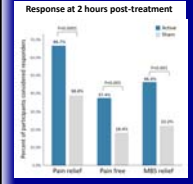


	Clinical manifestation	Signaling	Spatial effect	Duration
CPM	Pain inhibits pain	Noradrenalin serotonin	Global	A few minutes after stimulus exposure
Gate control	Touch inhibits pain	GABA	Local	Only during stimulus exposure

Nerivio for the Acute Treatment of Migraine

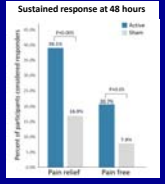
- A prospective, randomized, double-blind, sham-controlled, multi-center study
  - 252 adult participants (18-75 years) were randomized to active or sham treatment
  - The efficacy analyses were performed on 202 participants (99 active and 103 sham)

Response at 2 hours post-treatment



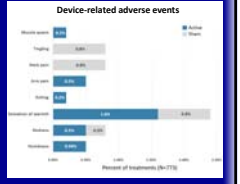
Remote neuromodulation provides superior clinically meaningful relief of migraine pain and MBS

Sustained response at 48 hours



Pain relief and pain free responses were sustained 48 hours after treatment

Device-related adverse events

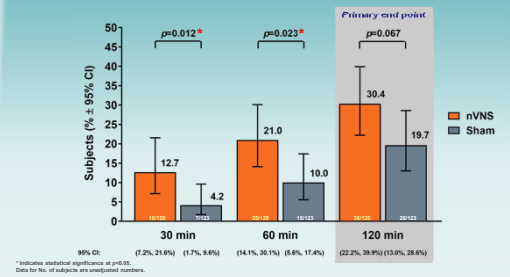


The incidence of device-related adverse events was low (3.6%)

Non-Invasive Vagal Nerve Stimulator (gammaCore, nVNS)

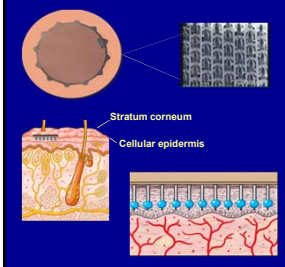
- Handheld, patient-controlled device, which preferentially activates afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction
- Multiple possible MOAs related to headache/pain
  - Inhibits CSD
  - Decrease in Glutamate
  - Suppresses Neuronal firing in TCC
  - Modulates Trigeminal Autonomic Reflex
- CE Mark for Primary Headache
- FDA Approved
  - Acute treatment of episodic cluster (ACT1 & ACT2 RCTs)
  - Prevention of Cluster (PREVA and Real World OL Study vs. SoC)
  - Acute treatment of migraine (PRESTO RCT, Class I Evidence)

PRESTO: 1st Attack % Pain Free in EM



* Indicates statistical significance at p=0.05.
Data for No. of subjects are unadjusted numbers.

ADAM - A New Delivery System



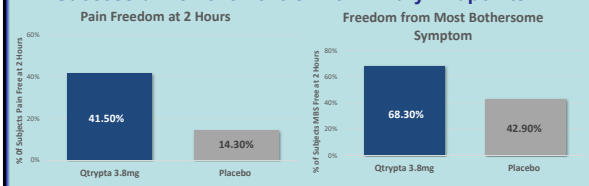
ADAM™ : Adhesive Dermally Applied Microneedle System

- Novel transdermal patch containing 340µm sized micro-projections (ADAM™)
- Micro-projections can be coated with both large and small molecules
- Drug delivery via ADAM™ allows for rapid and consistent dissolution of drugs into capillary bed
- Shallow depth of penetration of proprietary micro-projections into superficial skin layers minimizes stimulation of nerve endings
- Quarter size patch designed to be simple, easy to use and discreet

18

Zoltrip Study: Primary Endpoint Results

Successful Achievement Of Co-Primary Endpoints



p=<0.0001
Therapeutic Gain = 27.2

p=<0.0009
Therapeutic Gain = 25.4

Spierings ELH *et al*. Randomized, double-blind, placebo-controlled, parallel-group, multi-center study of the safety and efficacy of ADAM zolmitriptan for the acute treatment of migraine. *Cephalalgia* 2018 Feb;38(2):215-224. 19

Satsuma

STS101 DRUG-DEVICE COMBINATION FOR ACUTE MIGRAINE

STS101

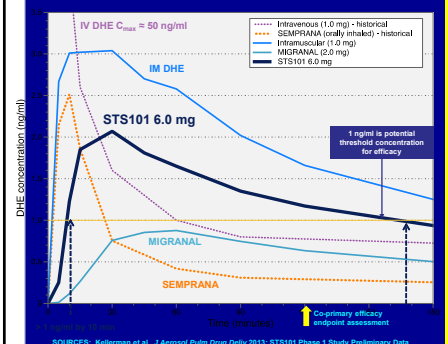
DHE NASAL *POWDER*

Single-use nasal delivery device
- Simple intuitive use; no assembly or priming
- Discreet & disposable

Mucoadhesive powder formulation
- Proprietary formulation that facilitates rapid drug absorption

STS101 achieves desired results in Ph1 study,

predicting strong Ph3 clinical performance and favorable safety/tolerability



SOURCES: Kellerman et al., *J Aerosol Pulm Drug Deliv* 2013; STS101 Phase 1 Study Preliminary Data

Achieves target PK
- ✓ STS101 >1 ng/ml within 10 min and remains above to nearly 3 hrs
- ✓ High early and late AUCs, (88% $AUC_{0\text{-}inf}$ of IM DHE)
- ✓ Low variability

Predicting strong clinical performance
- ✓ Rapid onset of action (≤ 30 min)
- ✓ Robust early and late efficacy
- ✓ Consistent and dependable efficacy

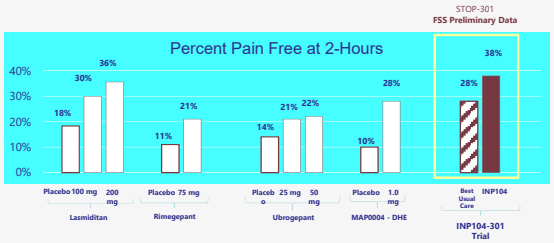
Demonstrates favorable safety & tolerability
- ✓ All AEs mild, transient, & not clinically relevant
- ✓ No nausea, vomiting, or CV AEs

INP104 Strong Position with CMC

- No changes in manufacturing from initiation of clinical PROGRAM to commercialization

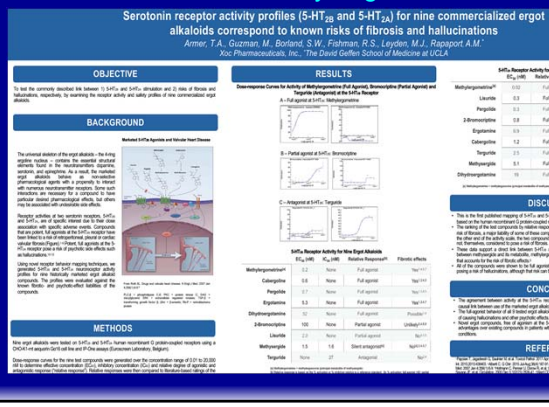
- **Drug product:**
- Utilizing established manufacturer who has provided commercial drug product/primary container to the market for over 25 years.
- Expected 2-3 year shelf life.
- **Precision Olfactory Delivery device:**
- Stable supply chain and released product consistently exceeds performance requirements from FDA
- Simple Device with low cost-of-goods
- **Human Factors:**
- Multiple human factor studies and long-term use in Phase 3 study demonstrate simplicity, reliability and ease of use of INP104

INP104 Demonstrates Unsurpassed Benefit with 38% Pain Freedom at 2 hours



- *Each of the drugs were tested in different clinical trials and direct comparisons may not be accurate.*

The New Methysergide



Serotonin receptor activity profiles (5-HT$_{2B}$ and 5-HT$_{2A}$) for nine commercialized ergot alkaloids correspond to known risks of fibrosis and hallucinations

Armer, T.A., Guzman, M., Borland, S.W., Fishman, R.S., Leyden, M.J., Rapaport, A.M.
Xoc Pharmaceuticals, Inc., The David Geffen School of Medicine at UCLA

OBJECTIVE

BACKGROUND

METHODS

RESULTS

DISCU

CONCL

REFER

Comparison of XC101-D13H and Historical Migraine Preventive

	Target Activity	Effects	XC101-D13H	Methysergide	Methysergide Metabolite
5-HT$_{1B}$	Weak Agonist	Target activities collectively induce migraine prevention effects			
5-HT$_{1D}$	Agonist				
5-HT$_{1F}$	Agonist				
5-HT$_{2A}$	Antagonist				
5-HT$_{2B}$	Antagonist				
5-HT$_{2C}$	Antagonist				
Side Effect/Safety Receptors					
5-HT$_{1B}$	Antagonist	Agonism causes fibrotic side effects			
5-HT$_{2A}$	Antagonist	Agonism causes psychotic side effects			
α_{1A}	Inactive	Agonism causes CV side effects			

Note: XC101-D13H has no major metabolites

25

Meloxicam 20/Rizatriptan 10

IHC-PO-124 19TH CONGRESS OF THE INTERNATIONAL HEADACHE SOCIETY, 5-8 SEPTEMBER 2019, DUBLIN, IRELAND

AXS-07 (MoSEIC™ Meloxicam/Rizatriptan): Novel Oral Therapeutic in Clinical Development for the Acute Treatment of Migraine

Cedric O'Gorman[3], Amanda Jones[3], Karen TenHuisen[3], Mark Jacobson[3], Richard B. Lipton[1], Stewart J. Tepper[2], Herriot Tabuteau[3]

[1]Albert Einstein College of Medicine, New York, NY, USA; [2]Geisel School of Medicine at Dartmouth, Hanover, NH, USA; [3]Axsome Therapeutics Inc. New York, NY, USA

Introduction

- Migraine is a disabling neurological disorder characterized by recurrent attacks of pulsating head pain accompanied by nausea and sensitivity to light and sound. These symptoms are often severe and incapacitating, requiring bed rest.
- Current treatments are suboptimal, with more than 70% of sufferers reporting dissatisfaction with existing acute treatments. The most commonly reported reasons for patient dissatisfaction are slow onset of pain relief, inconsistent pain relief, and recurrence of pain during the same day.[1,2]
- Suboptimal acute treatment is associated with a significantly increased risk of new-onset chronic migraine, which may be prevented by improving acute treatment outcomes.[3]
- AXS-07 is a novel, oral, investigational medicine, with distinct dual mechanisms of action, under development for the acute treatment of migraine. AXS-07 consists of MoSEIC™ meloxicam and rizatriptan. Meloxicam is a potent, COX-2 preferential NSAID which is limited by slow

Phase 1 Results

- MoSEIC™ meloxicam was rapidly absorbed after oral administration of AXS-07 (20 mg MoSEIC™ meloxicam/10 mg rizatriptan), with a median time to therapeutic plasma concentration (T_{max}) of 17 minutes, the primary endpoint (**Figure 2** and **Table 1**). Median T_{max} was 1 hour compared to 4.5 hours for 15 mg standard meloxicam (Mobic®).
- Mean plasma elimination half-life ($T_{1/2}$) for MoSEIC™ meloxicam was 19.2 hours after administration of AXS-07, which compares to 21.5 hours for standard meloxicam.

Figure 2: Mean Meloxicam Concentrations over Time for AXS-07 versus Standard Meloxicam*

MOMEN AXS-07 in of Inac

A Phase 3 trial o migraine in adults

Conclusions

- *CGRP small molecule receptor antagonists (gepants) for both acute care and prevention of migraine +*
- *mAb to CGRP or the its receptor for prevention of migraine, appear to be promising treatments with few significant AEs*
- *Several older drugs are back with new routes of administration making them faster, better with fewer AEs*
- *Lasmiditan, a 5-HT$_{1F}$ agonist is coming*
- *Magnetic, caloric and electrical stimulation are here to stay and seem to be effective with few AEs*
- *We will soon have a lot more treatment possibilities*

Thanks for your attention!