Trends-in-Medicine

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by Lynne Peterson

SUMMARY

GlaxoSmithKline/Pozen's Treximet is getting off to a strong start, and doctors predicted that 12% of their migraine patients, on average, will be taking it in 6 months. Use may drop when generic sumatriptan is available later this year, but doctors expect use to pick up again because they don't believe the generic will work as well as Treximet. ♦ Doctors are excited about Merck's CGRP, telcagepant (MK-0974), and they predicted that an average of 19% of their migraine patients will be on that 6-12 months after approval, particularly patients who can't take triptans or have suboptimal response to them. The lack of cardiovascular side effects also is likely to make this a popular drug with primary care doctors. ♦ Allergan's Botox is used very sparingly off-label in chronic migraine both because reimbursement is extremely difficult but also because many doctors have had disappointing results. ♦ MAP Pharmaceuticals' inhaled DHE, MAP-0004, is likely to find a niche given its fast onset of action – if it can get FDA approval.

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AMERICAN HEADACHE SOCIETY (AHS)

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Headache specialists were upbeat at the meeting this year, and they were excited about GlaxoSmithKline/Pozen's newly approved triptan, Treximet (sumatriptan RT/naproxen), and the accumulating data on CGRP (calcitonin gene-related peptide) inhibitors, with Merck's telcagepant (MK-0974) likely to be the first in that class. There was a sense that migraine therapy is really starting to move forward. "Migraine is now where cardiovascular disease was 20 years ago," said Dr. Richard Lipton, director of the Montefiore Headache Center at Albert Einstein College of Medicine.

As a practical matter, Dr. Lipton said, it is of little significance which headache definition gets used, "Migraine has a clinically variable course. Patients with a progressive course worsen over months or years." Common definitions are:

- **Chronic daily headache** (CDH) of long duration = 15 or more headache days/month for at least 3 months with headaches lasting ≥4 hours.
- **Transformed migraine** = CDH with a link to migraine (the least restrictive definition).
- **Chronic migraine** = CDH with ≥15 attacks/month meeting the criteria for migraine without aura.
- **Chronic migraine-R** = CDH with ≥8 days/month meeting the criteria for migraine without aura or responding to migraine-specific medication.
- **Chronic migraine-alternative** = CDH with at least half the days per month meeting the criteria for migraine without aura or probable migraine.

Interesting facts about migraine:

- The medication class which makes the greatest contribution to migraine progression is barbiturates.
- Among individuals with episodic migraine, 2.5%/year convert to chronic migraine/transformed migraine.
- Iron in the periaqueductal gray matter has been implicated in the longevity of migraine.
- Central neurons in the thalamus, peripheral neurons in the trigeminal ganglion, and central neurons in the nucleus caudalis are all directly involved in the mediation of central sensitization.
- Migraine frequency may increase over time in some individuals.
- NSAIDs appear to be protective.

- Predictors of response to botulinum toxin-A (Allergan's Botox) include unilateral headache, scalp allodynia, and muscle allodynia.

There was considerable discussion at AHS about the role of cortical spreading depression (CSD) in headache. In rats, CSD appears to be a model for migraine and possibly migraine with aura. CSD has nothing to do with psychological depression; it is a depression of electrical activity in the cortex. There are various drugs that suppress CSD in rats, including: amitriptyline, memantine (Forest's Namenda), propranolol, and topiramate (Johnson & Johnson's Topamax).

Medication Use in Year 1
Predicts Chronic Migraine in Year 2

Drug	Adjusted odds ratio		
	Overall	Women	Men
Acetaminophen (reference)	1.0	1.0	1.0
Prescribed medication + NSAIDs	0.96	0.97	0.93
Triptans	1.05	0.93	2.11
Barbiturates	1.73	1.97	1.29
Opiates	1.44	1.28	2.76
Isometheptene compounds	0.93	0.85	1.60

Triptans are the mainstay of migraine treatment. Doctors said that compliance is generally very good in patients in whom they work, but that is only about 60% of migraine patients. One of the problems, though, is that patients often don't take them or wait too long to take them. A Pennsylvania doctor said, "Triptan compliance is very good. The real problem is insurance coverage." A New England doctor said, "If a patient tolerates the side effects, then 60% are satisfied (with efficacy)."

NIH-Funded Projects

Time period	1987-1991	1992-1996	1997-2001	2002-2006
Mean number of projects	16.8	18.4	34.2	42.0
Headache type	**Migraine**	**Cluster**	**Tension**	**Other**
Share of funding dollars	69.4%	1.8%	0.6%	28.2%
Investigators	**Academic**	**Industry**	**NIH**	**Private, non-academic**
Percent of research	77.4%	7.5%	7.5%	7.5%
Disease category	**Headache**	**Epilepsy**	**Asthma**	**Diabetes**
Total NIH 2007 spending	$13 million	$105 million	$294 million	$1.04 ***billion***
Per person funding adjusted for disease prevalence	$0.36	$36.00	$12.25	$49.38
Per year NIH funding per $1,000 cost to society	$0.41	$8.40	$18.36	$5.96

Not surprisingly, headache specialists would like to see the National Institutes of Health (NIH) spend more on headache research. Dr. Todd Schwedt, a neurologist from Washington University, presented a review of NIH headache funding over the last 20 years. He found 111 NIH headache research projects funded in those 20 years, with the majority investigating migraine. He reported that NIH headache funding increased steadily over that time period, but still lags way behind where he computed it should be (>$100 million/year).

New Headache Guidelines

Dr. Stephen Silberstein of Thomas Jefferson University reviewed the changes in the evidence-based guidelines for the preventive treatment of episodic migraine in adults. The guidelines make no recommendations on how long a patient should be treated. Among the key changes were: The criteria for treatment of episodic migraine was changed from 2 attacks per week to one attack per week, Topamax was rated effective, and Botox was downgraded to probably ineffective. Doctors predicted that the new guidelines on Botox would make an already difficult reimbursement situation even more challenging.

Comparison of Triptan Efficacy *

Drug	Initial response at 2 hours	Recurrence	24-hour sustained pain relief	Triptans per migraine	Net success rate
Sumatriptan 25 mg	56.0%	26.7%	16.7%	1.18	41.3%
Sumatriptan 50 mg	62.4%	29.0%	16.2%		
Sumatriptan 100 mg	59.4%	35.0%	13.9%		
AstraZeneca's Zomig (zolmitriptan) 2.5 mg	61.3%	38.0%	10.4%	1.22	39.7%
AstraZeneca's Zomig (zolmitriptan) 5 mg	62.0%	34.2%	21.9%		
GlaxoSmithKline/Pozen's Treximet (sumatriptan RT/naproxen)	61.2%	12.6%	23.8%	1.08	53.5%
GlaxoSmithKline's Amerge (naratriptan)	48.6%	21.4%	15.9%	1.1	38.2%
Merck's Maxalt (rizatriptan) 5 mg	62.4%	39.3%	18.9%	1.25	40.6%
Merck's Maxalt (rizatriptan) 10 mg	68.6%	36.9%	25.3%		
Pfizer's Relpax (eletriptan) 20 mg	48.9%	28.4%	10.6%	1.15	40.3%
Pfizer's Relpax (eletriptan) 40 mg	62.5%	27.0%	20.2%		
Johnson & Johnson's Axert (almotriptan) 12.5 mg	61.2%	26.2%	25.9%	1.16	45.2%

*** Source: GSK poster at AHS**

Episodic Headache Guideline Changes

Group	Category	Recommendation	Change
1	Effective	Should be used	Topiramate added
2	Probably effective	Should be considered	Candesartan added
3	Possibly effective	May be considered	Carbemazapine and verapamil downgraded from Group 2
4	No significant evidence	No recommendation	Lamotrigine downgraded from Group 3
5	Probably ineffective	Should ***not*** be considered	Botulinum toxin-A, clonazapen, oxycarbamazepine, acetazolimine downgraded from Group 4

MENSTRUALLY-RELATED MIGRAINE

Menstrual migraine (without aura) is divided into 2 categories:

- Menstrually-related migraine (60%). Typically occurs on Day -2 to Day +3. PMS (premenstrual syndrome) headaches resolve with the onset of menses; menstrually-related migraines do not.
- Premenstrual migraine (14%) – only occurs with migraine.

There are no FDA-approved medications for menstrually-related migraine. In September 2007 the FDA issued a "not approvable" letter for Endo Pharmaceuticals/Vernalis' application for a supplemental indication for Frova (frovatriptan) for prevention of menstrual migraines, and in April 2008 Endo pulled the application. The FDA reportedly questioned the significance of the trial findings submitted in support of the application. Sources said Endo is still considering how to proceed, but the company can still promote Frova for treatment of pain associated with menstruation and is doing that. An expert said, "Preventive use is off-label, but, practically speaking, people are using it."

Endo presented a poster at AHS on an open-label German study of Frova for acute migraine associated with menstruation. The study of women in a primary care setting found that the effectiveness and tolerability of treatment were improved with Frova vs. prior therapies. Intra-patient analyses found that a woman was ~25- and 35-fold more likely to report improved effectiveness and tolerability, respectively, after switching from a previous migraine therapy to Frova.

NEW/INVESTIGATIONAL MIGRAINE DRUGS

A variety of prophylactic and therapeutic drugs are in development, including:

- **New anticonvulsants**, such as GlaxoSmith-Kline/Xenoport's XP-13512.
- **Gap junction inhibitors**, such as Minster Pharmaceuticals' tonabersat.
- **NMDA receptor antagonists**, such as Forest's Namenda (memantine).
- **Long-acting triptans**.
- **Botulinum toxin-A**.
- **CGRP inhibitors.** Doctors said these are the most promising agents on the near horizon. There hasn't been a good rodent model, but an expert said a mouse model finally has been developed:
  - Merck's telcagepant (MK-0974) – which clearly is the farthest along.
  - Bristol-Myers Squibb – in Phase I.
  - Boehringer Ingelheim's olcegepant (BIBN-4096-BS) – an IV CGRP, but this is not likely to be the CGRP going forward. Rather, the company is working on oral follow-ons.
- **Substance P** – This appears not to work and development has stopped.
- **TRPV-1 receptor blockers** – These were predicted "not to have legs in migraine."
- **Cannabinoid receptor inhibitors –** A speaker said he doesn't know if they will work and if one can be found that gets away from the cognitive problems.
- **Nitric oxide synthesis blockers –** GSK's GW-274150 has completed a clinical trial, but the results have not been released, leading experts to suggest the trial failed.
- **iGlu5 kainate receptor antagonists**, such as Lilly's LY-466195.

Efficacy of Treatment Options for Menstrually-Related Migraine

Drug *	Dose	Menstrually-related migraine	Level of evidence	Placebo
Sumatriptan	6 mg injectable	73% - 81%	B – good	29% - 31%
GlaxoSmithKline's Imitrex (sumatriptan RT)	50 mg - 100 mg tablets	50% - 67%	B – good	22% - 33%
Merck's Maxalt (rizatriptan)	10 mg	70% - 73%	B – good	50% - 53%
AstraZeneca's Zomig (zolmitriptan)	1.25 mg - 5.0 mg	48% - 66%	C – fair	27% - 33%
GlaxoSmithKline's Amerge (naratriptan)	1.0 mg - 2.5 mg BID	50% - 61%	I – insufficient	25% - 38%
Endo Pharmaceuticals' Frova (frovatriptan)	2.5 mg BID	39% - 50%	B – good	26%

*** None are FDA-approved for menstrually-related migraine**

ALEXZA PHARMACEUTICALS' Staccato (inhaled loxapine), a dopamine antagonist

The results were presented from a randomized, double-blind, placebo-controlled, multicenter, single-dose Phase IIa trial of Staccato in 168 patients with moderate-to-severe migraine. The study showed the two highest doses (2.5 mg and 5 mg) provided significant pain relief at 2 hours vs. placebo, and nausea was reduced at all dose levels. However, there was no significant difference in photophobia or phonophobia. The company is now planning a larger Phase IIb outpatient study. Sources were not impressed with this data.

Staccato Phase IIa Results

Measurement	Staccato 1.5 mg	Staccato 2.5 mg	Staccato 5 mg	Placebo
Primary endpoint: Pain relief at 2 hours post-dose *	67.4% (Nss, p=0.1774)	79.1% (p=0.0106)	76.7% (p=0.0212)	51.3%
Sustained freedom from pain at 2 hours	Nss	p<0.05	Nss	---
Nausea relief	<0.05	<0.05	<0.05	---
Dysgeusia, the most common side effect	19%	23%	37%	1%
Somnolence	5%	23%	23%	13%
Fatigue	0	7%	14%	8%

*** Defined as a drop in severity to none or mild**

Staccato comes in a small, hand-held inhaler that was described as "very different" from, and simpler than, either a metered dose inhaler or dry powder inhaler used for asthma patients. The disposable, one-use device is loaded at the factory, but the company has a multi-use device in development.

ALLERGAN's Botox (botulinum toxin-A)

Botox safety is not an issue, doctors agreed. Most doctors questioned said they use Botox occasionally for chronic daily headache – not for episodic headache, but they said their use is rare and usually only for the "worst of the worst" patients who respond to nothing else. Comments included:

- *New York #1:* "Botox works better in patients with a lot of myofascial pain along with headache."
- *Florida:* "Botox is not for everyone, but it is helpful."
- *California:* "My personal take is it works in a subgroup, and the challenge is to define the subgroup."
- *Maryland:* "I gave up on it."
- *New York #2:* "I use it for the worst patients with transformed or chronic migraine. Those are where it seems to work."
- *Pennsylvania #1:* "It ***may*** be effective in very refractory chronic migraine patients, but there are no data on that."
- *Pennsylvania #2:* "Botox doesn't work in episodic migraine, so the guidelines are right."

Several doctors said they tried Botox and were disappointed with the results, but doctors who have used it successfully said this may be an issue of patient selection. A Canadian doctor said, "I used Botox but stopped. I'm not sure it is effective. There is no logic on why it should work." A New England doctor said, "I haven't had great success with Botox, and it is very hard to get it covered (by insurance)."

Reimbursement is a significant issue, with very few insurance companies paying for it, and then only for very selected patients. They predicted the reimbursement situation will worsen with the new treatment guidelines, even though those only apply to episodic headaches, not chronic daily headaches. Comments on reimbursement included:

- "The guidelines will give the insurance companies more ammunition and make it harder to get it covered."
- *Florida:* "Right now most big insurance companies aren't covering Botox for migraine. Patients have to pay for it themselves. What we did to offset the cost is we found the pharmacy with the best price, and we tell the patient to get it there. We think there is tremendous value in Allergan pursuing an on-label indication for Botox."
- *New York:* "Reimbursement in New York is very difficult. A few companies pay because they realize it can save money on acute medications, but that is the exception. Botox is not for the occasional migraineur."
- *Pennsylvania:* "It is already hard to get insurance coverage for Botox, and the new guidelines will make that harder, but it won't stop use in patients who can pay."

Allergan has done a Phase III chronic daily headache trial, and that is in the data analysis phase, with results expected soon. Sources were optimistic that this trial would be successful because it is limited to (1) patients not on other preventive medications that might confound the results and (2) patients with chronic migraine-alternative, the study group most likely to respond.

The FDA has never approved a drug to treat chronic migraine, but sources were hopeful that Botox could be the first to get that indication. An expert said, "Because nothing has ever been approved for chronic migraine, Allergan will be covering new and vital ground. I think these are the most disabled patients. The hope is that, in the face of clear cut data, the FDA will consider chronic migraine an approvable indication." Even if Botox gets FDA approval for the treatment of chronic daily headache, doctors predicted that use would remain very limited.

Dr. Ninan Mathew – a professor of neurology at the University of Texas Medical School at Houston, director of the Houston Headache Clinic, and former president of the American Headache Society – said, "No one doubts there are

patients who responded to botulinum toxin-A, but can we predict who will respond? We did a study looking at predictors, and we found that predominantly unilateral headaches, patients with scalp allodynia and muscle allodynia (tenderness and spasm of the muscles of the neck along with headache pain) were predictors – patients who characterize their headaches as coming from inside out."

What is the mechanism of action for Botox in headache? Dr. Mathew said, "We don't know fully, but I can tell you that for a long time we thought the effect was due to just relaxation of the muscles. That is probably not the whole story. There is a great deal of scientific literature showing an anti-nociceptive effect of botulinum toxin-A…It has been shown in animals to have anti-nociceptive effect at the periphery, and that may be why it is effective in patients with chronic migraine. We need to learn more…We don't know if there is any central effect."

Dr. Mathew said a 60-patient study of Botox vs. Topamax found that patients responded to both drugs, with no statistically significant difference between them at either 6 or 9 months. Likewise, another study comparing Botox to divalproex found no statistically significant difference between those two drugs, though Botox did better numerically. In both comparisons, though, there were fewer adverse events with Botox.

Asked about combining Botox with other medications, Dr. Mathew said, "We looked at a group of patients not on any medication and found their response to botulinum toxin-A was better than those already on preventive medications while the study was ongoing. It was not the primary analysis…It was a subset analysis…but the practical importance is we still don't know if botulinum toxin-A should be monotherapy or add-on therapy. That has to be studied…The new botulinum toxin-A studies are all monotherapy, not any preventive medications."

Dr. Keith Edwards and a colleague from the Neurologic Research Center in Bennington VT presented a poster on a single case of a patient who had chronic cluster headache with associated hemifacial spasm for 15 years and was helped by Botox. They said that within two weeks the hemifacial spasm (an on-label use of Botox) and cluster headache (an off-label use) both resolved completely. They suggested that it may be a good idea to consider Botox treatment earlier in the course of refractory cluster headache or trigeminal pain syndromes.

A poster by Dr. Michael Marmura of Jefferson Headache Center in Philadelphia and colleagues provided some insight into how headache clinics are using Botox off-label for prophylactic treatment of headache. This was an investigator-initiated observational study of 703 patients conducted at 10 headache centers in the U.S. They reported:

- 68.6% of patients continued Botox treatment, and 0.4% discontinued due to adverse events.
- ~56% of patients were using a triptan at enrollment, but >70% characterized their response to triptans as less than optimal.
- Botox was given for (multiple diagnosis possible): chronic migraine 65.6% of patients, migraine without aura 41.0%, 12.5% migraine with aura, 10.0% chronic tension-type headache, 6.0% tension-type headache, 3.7% new daily persistent headache, and 1.8% cluster headache.
- Treatment was initiated as (multiple treatments possible): 73% patient refractory to preventive medication, 57% patient preference, 32% pericranial tenderness, 19% adverse events with previous preventive medication, 5% contraindications to other preventive medication, 4% presence of co-existing conditions, and 2% for age.

Dr. Suzanne Christie of the University of Ottawa and Canadian colleagues presented a poster on the effects of prophylactic treatment with Botox on the cost of acute headache medication and health-related quality of life in chronic migraine patients. This was an open-label, multicenter, pilot study in 53 patients. They found:

- Botox significantly decreased the total cost of acute prescription medications by an average of $106.32/month vs. prior triptan use ($291.68/month).
- There was a significant decrease in mean days on triptans and triptan dose.
- Days worked with migraine symptoms increased significantly at both Month 3 and Month 6, and daily activities affected by migraine symptoms significantly decreased at both time periods.

Another study looked at Botox in the treatment of chronic tension-type headache with cervical myofascial trigger points. This was a randomized, double-blind, placebo-controlled study. The number of headache days per month (the primary endpoint) were reduced significantly (p=0.013), but headache intensity was not significantly affected. Additionally, range of motion, maximum tolerated pressure (MTP) sensitivity, and psychological measures were not significantly improved. In a responder analysis, 62.5% of patients had their headache days per month reduced vs. 46.9% placebo patients, and the relief lasted longer for Botox patients. The researcher concluded that Botox reduced headache frequency by ~5 days per month at peak effect, but the effect dissipated over time. Headache intensity was not significantly changed (25% for Botox, 20% for placebo), "Our findings show some beneficial, albeit short-lived, effect."

FOREST LABORATORIES' Namenda (memantine)

Experts generally agreed that memantine is very promising in migraine. Dr. Andrew Charles, director of the Headache Research and Treatment Program at UCLA, said, "Initial open-label results with use (of memantine) as a migraine preventive agent have been encouraging…Memantine has been used in 200-300 patients so far (in small studies), and it is well tolerated and provided a great benefit. It is not a cure, but it is another arrow in our sling." A Canadian doctor said, "Memantine works, but it is too broad. I don't have any hopes for it."

The problem, the experts said, is that Forest has taken no interest in studying memantine in migraine since the drug goes off label in March 2012. Two doctors said they are working on grant proposals to try to get NIH to sponsor a trial.

GLAXOSMITHKLINE/POZEN's Treximet (sumatriptan RT/ naproxen)

The FDA approved Treximet in April 2008, and most doctors questioned at AHS have already been detailed on Treximet (formerly called Trexima) and/or have started prescribing it. So far, they are satisfied with the results, but they said it is really too early to have much feedback from patients. In six months, they estimated that an average of 12% of their migraine patients will be taking Treximet.

Comments included:

- "I've put about 20 patients on Treximet. I've heard back from 12, and they said (migraine) recurrence is less… There is a niche for it if you ask the patients the right question: Do you have a headache that keeps coming back?"
- "Treximet is more effective than triptans alone for headaches that need treatment more than once."
- *Colorado:* "Clinically, patients either say it works, it works better, or thanks – if you pick the patient right."
- *Florida:* "Treximet works quite well…Cost is an advantage, and compliance is easier."
- *Maryland:* "Treximet is a winner. The feedback is good. There are no more side effects than Imitrex alone. It works faster, and people don't have the added side effects."
- *Pennsylvania:* "Treximet has the efficacy of a triptan without the cardiovascular side effects."
- *Illinois:* "It is too early for feedback from my patients, but I'm using it in patients where Imitrex wears off and they need multiple doses…Use will take off, especially when GSK starts direct-to-consumer advertising."

Doctors estimated that an average of 20% of their patients on GlaxoSmithKline's Imitrex (sumatriptan RT) also take naproxen – either over-the-counter (OTC) or prescription. However, doctors don't always know when Imitrex patients are using naproxen if the patient buys OTC naproxen.

The biggest advantage to Treximet, according to these headache specialists, is that it takes away a patient's choice about the timing and order of taking Imitrex + naproxen. Ideally, patients should take the Imitrex first and very early in the migraine, with the naproxen taken just a little later. However, patients generally don't do that. As several doctors explained: Because of the cost of the triptans and insurance company limits on how many tablets they will cover per month, patients tend to take the naproxen first in the hopes that it will do the trick. That means they take the Imitrex too late and in the wrong order. In contrast, the pharmacokinetics of Treximet mean that the sumatriptan is released earlier, and then the naproxen is timed to release 4 hours later.

Patients doing well on GlaxoSmithKline's Imitrex (sumatriptan RT) generally will not be switched to Treximet, but doctors said many patients aren't doing well on Imitrex or Imitrex + naproxen. One doctor said, "Treximet is good for patients who get some benefit from triptans but the triptans are not working any more."

Although Treximet is priced about 10% below Imitrex, pricing is not the factor driving use. Doctors said they have plenty of samples, and $50 coupons they can give patients, who can also get additional coupons from the pharmacy. One doctor said some smaller pharmacies are trying to take advantage of the lower Treximet price by marking it up. Another commented, "Price won't drive Treximet use because it is still not cheap." A Pennsylvania doctor said, "I use Treximet because of the samples."

Reimbursement for Treximet is somewhat challenging. Doctors said that most insurance companies have put it on Tier 3, and many fight paying for it but eventually give in. Comments included:

- "Most patients have insurance, so the price difference is not significant."
- "Blue Shield requires a 4-page form that most doctors don't want to fill out, and then they probably will reject it anyway."
- "The insurance companies are cutting back on the number of doses permitted. We hoped for 10-12/month, and the insurance companies were approving 6-9, but now we find a lot of payors are limiting doses to 4/month."
- "A couple of insurance companies don't like it."
- "Reimbursement is a little difficult. There is some payors push back, and a lot have put it on Tier 3."

When generic Imitrex is available in late 2008, doctors predicted that Treximet use will decrease – but only temporarily. Comments included:

- "The generic probably will be inferior because it won't have the RT technology in Imitrex, which makes absorption better (more rapid), and that will probably boost Treximet use."
- *New York:* "Many patients are very brand loyal, especially migraine patients. I guarantee there will be migraine patients who know Imitrex or Treximet works and won't want to try something else."
- *Florida:* "With generic sumatriptan plus prescription naproxen, there would be two co-pays, but they would only be $10 each – or $4 at Wal-Mart – and the co-pay for Treximet is $35."

- *Colorado:* "Treximet is different than the two pills separately...It looks like there is synergy from the combination in Treximet…Poor patients will get sumatriptan plus naproxen, and I think what will happen is that the results won't be as good – either because of the pills, compliance, or timing. A lot of patients will go on the generic when it is available, but this is the old Imitrex, not the RT technology. Then, we will see the results, which is why it is important for patients to try Treximet now."
- *Maryland:* "I will still write Treximet because what patients will do is try naproxen alone and wait too long for the sumatriptan, and Treximet takes that choice away, so they get their triptan sooner."
- *New York:* "What happens depends on if a generic is truly equivalent to Imitrex with RT. In epilepsy bioequivalence wasn't there. Some managed care companies may mandate a generic before any brand."
- "When Imitrex goes generic, insurance companies won't cover Treximet."
- *Illinois:* "I'm not sure patients will want the generic…but I heard that the generic will have the RT technology, and if it does, that would make the generic more appealing."

Reportedly, GSK has a menstrual migraine treatment study underway with Treximet. Dosing in the study is on an as-needed basis, not as a prophylactic. Data are expected at the end of the year.

Posters at AHS on Treximet included a study led by Dr. Paul Winner of West Palm Beach FL which found that body mass index (BMI) does not appear to impact the responsiveness or tolerability of Treximet in the acute treatment of migraine.

Another poster by Dr. Stephen Landy of the Wesley Headache Clinic in Memphis and GSK researchers looked at the use of the combined endpoint of "sustained pain freedom and no adverse events" (SPFNAE). They used this endpoint to analyze the results of two pivotal trials of Treximet, and they found that this new endpoint was a more rigorous and more clinically meaningful endpoint – and it confirmed the original trial conclusions, indicating it is a valid endpoint.

GLAXOSMITHKLINE/XENOPORT's XP-13512, a prodrug of gabapentin

This is under investigation in migraine as well as restless leg syndrome. The companies reportedly plan another Phase II trial in migraine before moving into Phase III.

Doctors asked about their experience with gabapentin generally agreed it has been disappointing in headache. A Massachusetts doctor said, "I use it sometimes for very intractable cases. The evidence doesn't suggest it is very effective, but some patients respond when I add it." A New York doctor said, "I don't find it very effective because of the side effects at the dose required (1800-2400 mg). I've also had limited success with Lyrica (Pfizer, pregabalin)." An Illinois doctor said, "I use gabapentin as a preventive and a lot with patients who have trouble sleeping. It works but not as well as Topamax."

JOHNSON & JOHNSON's Topamax (topiramate)

The use of Topamax for chronic migraine is ***not*** supported by randomized, double-blind, placebo-controlled trials – yet. And J&J is not pushing Topamax heavily because it goes off patent soon. However, doctors believe it works, and it has been added to the Group 1 (effective, should use) guidelines for episodic headache.

The National Institutes of Health is planning a multi-month trial of topiramate ± propranolol (a beta blocker) in chronic migraine, though the protocol has not yet been approved. The expectation is that this will be conducted in the offices of community-based neurologists.

Dr. Ninan Mathew said two open-label studies, one large and one small, found Topamax effective in menstrual migraine, but there was a high incidence of "some very unpleasant" side effects, which included parethesia and difficulty with concentration/attention, "The cognitive side effects are quite variable from person to person…I think there is an individual sensitivity to topiramate. But the side effects remain a problem with long-term use."

MAP PHARMACEUTICALS' MAP-0004, inhaled dihydroergotamine (DHE)

Valeant Pharmaceuticals sells a nasal spray, DHE (D.H.E. 45), but MAP claims its inhaled DHE, using its proprietary Tempo device, has a faster onset of action. The advantage to both DHE preparations is that they can be given at any time during a migraine vs. triptans which need to be taken early.

Doctors generally thought MAP-0004 would have a place if it gets approved, though some suggested the regulatory path could be difficult. One said, "Inhaling DHE is like an IV, so it will give a quick zap…The concern will be whether it has more side effects than nasal DHE." Another commented, "I don't know how patients will take to it. I have some patients on nasal DHE, and I don't know if they will change unless they don't like nasal sprays."

There weren't any other alternate delivery forms for DHE or other ergots presented or discussed at AHS. However, MAP presented several posters at AHS, including:

1. **QTc effect.** A 3-period, single-dose, dose-escalation study in healthy adults found that MAP-0004 appears to have no greater potential to cause clinical signs or QT or QTc prolongation than the approved 1.0 mg IV DHE dose. T_{max} was ~13-37 minutes (0.2-0.6 hours). No patients had QTc prolongation >450 ms, and there was no QTc prolongation >60 ms from baseline to 10 minutes. Six patients had QTc prolongation >10 ms at 10 minutes

post-dose, but there was no QT difference between any inhaled dose and IV DHE.

2. **Chronic inhalation toxicity.** A study in 40 dogs found no significant respiratory tract toxicity at doses up to 29 times the maximum safe daily IV human dose administered for 6 months. Signs of ergotism were reported at the highest doses only. Abrasions and/or scabbing of the tips of the ear as well as vomiting and excessive salivation were seen only when the dose exceeded 5 times the human therapeutic dose. No evidence of organ weight change, heart valve changes, or macroscopic or microscopic changes were found.

3. **Asthmatics.** A Phase II, double-blind, randomized, placebo-controlled, 2-arm, 3-period, incomplete block crossover study in 19 asthmatics at sites in the U.S. found that MAP-0004 appears safe and effective in asthmatics. Asthma did not delay absorption of MAP-0004, and the presence of chronic lung disease or asthma had no appreciable effect on the PK of MAP-0004. PK profiles were similar between asthmatics and non-asthmatics in previous studies. Mean T_{max} was 9.6 minutes.

MAP-0004 Safety in Asthmatics

Measurement	Placebo n=18	MAP-0004 first dose n=19	MAP-0004 second dose n=17
Any adverse event	27.8%	42.1%	35.3%
Nausea	5.6%	21.1%	5.9%
Vomiting	5.6%	10.5%	11.8%
Dysgeusia	0	10.5%	5.9%
Headache	0	10.5%	11.8%
Treatment-related adverse event	50%	73.7%	87.5%
Adverse event causing discontinuation	5.6%	0	0
Change in FEV_1	-2.2 to +4.2	-3.8 to +4.4	-4.6 to +4.5

4. **Blood levels.** The mean T_{max} of MAP-0004 was compared to published PK results for other DHE formulations.

Blood Levels of Various DHEs

Measurement	T_{max}
Oral 2 mg	75 min.
D.H.E. 45 1 mg	~ 56 min.
D.H.E. 45 2 mg	~ 42 min.
IM 0.5 mg	~ 35 min.
IM 1 mg	~ 21 min.
Subcutaneous injection 0.5 mg	~ 19 min.
MAP-0004 (1 mg or 2 mg)	~ 12 min.
IV 1 mg	~ 5 min.

5. **Sustained pain relief (SPR) and sustained pain freedom (SPF) over 24 and 48 hours.** The sustained pain relief and sustained pain freedom seen with MAP-0004 was compared to previously published results for other drugs with a similar trial design.

MAP-0004 Sustained Efficacy vs. Other Therapies

Measurement	MAP-0004 1 mg	MAP-0004 2 mg	Treximet	Telcagepant 300 mg
Pain relief at 2 hours	~ 39%	~ 32%	~ 28% - 38%	~ 22%
SPR 2-24 hours	~ 30%	~ 32%	~ 28% - 31%	~ 30%
SPR 2-48 hours	~ 25%	~ 28%	---	---
Pain freedom at 2 hours	~ 37%	~ 28%	~ 20% - 25%	~ 31%
SPF 2-24 hours	~ 31%	~ 14%	~ 15% - 16%	~ 29%
SPF 2-48 hours	~ 30%	~ 5%	---	---

MAP is planning two large Phase III trials, each of 1,000 patients at 120 U.S. centers. The first is scheduled to start in mid-July in acute headache treatment, with results expected by the end of the year. This is a 12-week trial, with 52-week follow-up for safety. The second Phase III trial will start after the first Phase III trial ends.

How does MAP-0004 compare to Alexza's inhaled loxapine? A MAP official said, "Their PK is in 2 minutes vs. 10 minutes for ours, but their clinical efficacy is 2 hours, and we have it in 10 minutes. And we reduce photophobia and phonophobia, and they don't. Their drug is just an anti-nausea drug."

MERCK's telcagepant (MK-0974), a CGRP receptor antagonist

Headache specialists at AHS were very excited about telcagepant. A Merck-sponsored satellite session on new neuronal therapies filled a large lecture room even though it started at 6:15 am on a Saturday morning.

Doctors predicted that within 6-12 months of approval 19% of their migraine patients, on average, would be taking telcagepant. Most sources said their patients doing well on triptans would probably not be switched to telcagepant, but they said that older patients, patients with cardiac conditions, and other patients who can't take a triptan would be likely candidates for telcagepant. The biggest use may come, they pointed out, from primary care physicians (PCPs) who currently avoid triptans because of the side effects – if those PCPs get educated about telcagepant.

Physician comments on telcagepant included:

- *California #1:* "Where it will fit remains to be seen. In some patients it may replace triptans or be used in triptan failures. We need to get our hands on it and see. It doesn't constrict blood vessels, so there is a perception of more safety."
- *Canada:* "CGRP blockers are very exciting and opening a new field. There is no cardiovascular issue. But triptans won't disappear."
- *New York:* "Primary care doctors won't use triptans, and they won't use telcagepant. Cost is a barrier."

- *Maryland:* "I'm looking forward to telcagepant. It will start with headache specialists and then move down to primary care doctors. If Merck spends the money to get us to teach the primary care doctors, it will get there faster."
- *Pennsylvania #1:* "I'm very impressed. There is a large subset of patients who can't use a triptan because of high cardiovascular risk or age. Why not use something without cardiovascular risk? Telcagepant will be good for older patients, patients with a family history of cardiovascular disease, and diabetics. Many of these have never even been on a triptan. Whether or not patients switch from a triptan will depend on the cost of telcagepant."
- *California #2:* "This will be huge…I don't fix what's not broken, so there is no reason to switch a patient doing well on a triptan to telcagepant. But there are people who don't tolerate a triptan or who don't get an adequate response from one. SPF with a triptan is ~25%...Primary care doctors will buy in quickly…If they don't have to discuss cardiovascular risk with patients, this will be the choice of primary care doctors…Telcagepant will be first line with primary care doctors because it is easier to prescribe, and headache specialists will use it."
- *Texas:* "Telcagepant won't replace triptans, but it can be used in patients with contraindications for triptans… Primary care doctors may take this up."
- *Pennsylvania #2:* "Telcagepant is a big deal, mainly because it has no cardiovascular complications. All suboptimal triptan patients will try it, and if primary care doctors learn about it, they will use it."
- *Illinois:* "Telcagepant is very exciting. If there really are no cardiovascular side effects, it will be a nice new option. It won't replace the triptans unless the data get better. It would be good for patients who are older, can't take a triptan or ergot because of cardiovascular side effects, or have chest side effects from a triptan."

Dr. Tony Ho of Merck pointed out that telcagepant is different from the triptans because it is ***not*** a direct vasoconstrictor. He said the drug has been reformulated from a "rather large" liquid-filled capsule to a smaller tablet because of concern patients with nausea might have trouble swallowing the capsule. He also said Merck is not investigating other doses.

A third and ongoing Phase III trial is using the new tablet formulation (at both 150 mg and 300 mg), looking at efficacy over time (over several migraine attacks), which Dr. Ho said European regulators (but not the FDA) require. Merck is expected to submit telcagepant to regulatory authorities in 1Q09, and Dr. Ho said a decision on whether or not to submit both doses will be made when the results of the third Phase III trial are available.

New Phase III data were presented at AHS from a randomized, double-blind, placebo- and active-controlled, parallel group, 1,380-patient study in adults with a single moderate or severe migraine attack indicating that the 300 mg dose of telcagepant is as effective as – not more effective than – triptans but with a safer side effect profile (no cardiovascular side effects). The lower dose (150 mg) was not impressive, raising questions about why it was included in Phase III, but a source indicated the FDA requested both doses.

Phase III Results with Telcagepant

Measurement	Telcagepant 150 mg n=333	Telcagepant 300 mg n=354	Zomig 5 mg n=345	Placebo n=348	p-value telcagepant 150 mg/300 mg vs. placebo
***Primary endpoints* at 2 hours post-dose**					
Pain freedom	17.2% *	26.9%	31.3%	9.6%	<0.010 / <0.001
Pain relief	49.8%	55.0%	56.4%	27.7%	<0.001 both doses
Absence of photophobia	53.8%	57.8%	55.3%	36.8%	<0.001 both doses
Absence of phonophobia	45.0%	51.0%	50.0%	28.9%	<0.001 both doses
Absence of nausea	67.0%	65.1%	71.3%	55.3%	<0.001 / <0.01
Secondary endpoints					
Sustained pain freedom at 2-24 hours	10.7% *	20.2%	18.2%	5.0%	<0.010 / <0.001
Total migraine freedom at 2 hours	13.3% *	22.9%	27.2%	8.7%	Nss / <0.001
Total migraine freedom at 2-24 hours	8.2% *	17.4%	15.8%	4.7%	Nss / <0.001
Exploratory analysis					
Sustained pain freedom 2-48 hours	7.7% *	18.4% *	13.2%	4.1%	<0.05
Adverse events within 14 days					
Any	31.4%	37.2%	50.7%	32.1%	---
Drug-related	21.0%	24.7%	40.9%	18.6%	---
Serious adverse event	0	0	0	---	---
"Triptan-like" sensations	2.1%	4.3%	10.4%	3.4%	---
GI	13.8%	17.6%	21.7%	14.3%	---
General disorders	7.5%	9.4%	20%	7.2%	---
Nervous system disorders	12.0%	15.1%	22.6%	12.0%	---

* p<0.001 vs. Zomig

The trial found:

- 300 mg telcagepant is comparable in efficacy to Astra-Zeneca's Zomig (zolmitriptan).
- 150 mg and 300 mg telcagepant were both more effective than placebo.
- Telcagepant was well tolerated, with less parethesia, chest pain, chest pressure, throat tightness, fatigue, and myalgia than Zomig – but more dizziness (4%), fatigue (4%), and dry mouth (6%) than placebo.
- In some measures, Zomig was superior to 150 mg telcagepant.
- A subgroup analysis found telcagepant is effective in migraine with aura as well as without aura.

Why was Zomig 5 mg chosen as the comparator? Dr. Ho said Zomig is considered a high efficacy triptan, and that is the most commonly prescribed dose of Zomig.

Merck appears to be giving strong support to telcagepant. The company even had a booth at AHS encouraging investigator-initiated preclinical studies of telcagepant – which Merck is willing to fund or at least provide free drug. Areas of particular research interest for 2008 are: the role of CGRP in the pathophysiology of migraine, CGRP and migraine progression, CGRP and medical overuse, migraine awareness, and migraine as a neurobiologic disorder.

A poster by Belgian researchers found no negative impact of telcagepant on sublingual nitroglycerin. This was a double-blind, randomized, placebo-controlled, 2-way crossover study in 22 healthy males given a single 500 mg dose or placebo followed 1.5 hours later by the nitroglycerin.

Telcagepant Effect on Response to Sublingual Nitroglycerin

Measurement	Pre-Nitroglycerin		Post-Nitroglycerin	
	Placebo	Telcagepant	Placebo	Telcagepant
Systolic blood pressure	120	121	118	121
Diastolic blood pressure	74	74	67	68
Heart rate	53	53	57	58
Brachial artery diameter (BAD)	6,445 µm	6,425 µm	1.13 fold	1.14 fold
Augmentation index (AIx)	13.92%	13.95%	-16.88%	-17.93%

SPFNAE as an Endpoint

Measurement	Telcagepant 150 mg n=328	Telcagepant 300 mg n=351	Zomig 5 mg n=341	Placebo n=343
SPF 2-24 and no adverse events 0-24 hours	9.1% *	14.2% **#	8.8% *	4.4%
SPR 2-24 and no adverse events 0-24 hours	20.4% **	24.6%**##	17.1% *	11.7%
Pain freedom at 2 hours and no adverse events 0-24 hours	12.7% *	17% **	14% *	7.9%
Pain relief at 2 hours and no adverse events 0-24 hours	34.7% **##	36.5% **###	25.4%	21%

* p<0.05 vs. placebo, ** p<0.001 vs. placebo
# p<0.05 vs. Zomig, ## p<0.01 vs. Zomig, ### p<0.001 vs. Zomig

Merck presented a poster on the effect of 300 mg telcagepant on spontaneous ischemia in patients with stable cardiovascular disease from a double-blind, randomized, placebo-controlled, 2-period, 2-dose trial. They found that two doses of telcagepant was safe and tolerable in stable coronary artery disease patients and did not appear to exacerbate spontaneous ischemia. Three patients had ST segment depression (2 with placebo and 1 on telcagepant). Another 2 patients (one each with placebo and drug) had chest pain. There was slightly more fatigue, headache, and dizziness with telcagepant.

Dr. David Dodick of the Mayo Clinic and Merck researchers also presented a poster on the use of the combined endpoint of sustained pain freedom and no adverse events (SPFNAE), this time with telcagepant vs. Zomig using patient-level data from a Phase III trial. In this post-hoc analysis, telcagepant was "nominally superior" to placebo on SPFNAE, and Zomig was superior to placebo on most of the same measures but to a smaller extent than telcagepant 300 mg.

MIGRALEX's Migralex, an over-the-counter combination of aspirin and magnesium

Dr. Alexander Mauskop of the New York Headache Center developed this treatment. As an over-the-counter combination of two common drugs, he said it does not require FDA approval. It is being formulated as a rapid-dissolve tablet. Manufacturing is getting ready to start, and the expectation is it will be on the market in about 6 months. Initially, it will be marketed on the internet and through samples sent to headache specialists. At AHS Dr. Mauskop presented a poster on an open-label, 50-patient trial of Migralex which found that when Migralex was taken in lieu of the patient's usual acute treatment:

- 50% of patients found Migralex to be better/much better than their current treatment, 32% the same, 18% worse.
- 54% said they would definitely take it again, 26% would probably take it again, and 20% would not take it again.
- The only side effect was gastric irritation, reported by one patient.

MINSTER PHARMACEUTICALS' tonabersat, a gap junction blocker

Paul Durham PhD, director of the Center for Biomedical and Life Sciences at Missouri State University, said a completed Phase II trial in migraine prophylaxis showed a significant increase in the number of responders vs. placebo, with decreased use of rescue medications and few side effects. He said, "Tonabersat may function as an anti-migraine drug by inhibiting neuronal-satellite glial cell signaling via gap junctions and blocking cellular events likely involved in peripheral sensitization of trigeminal neurons."

Mayo's Dr. Dodick said the preclinical data showed no effect of tonabersat on blood pressure, heart rate, or cerebral blood flow, so from a cardiovascular safety standpoint it appears to be well tolerated. A double-blind, placebo-controlled trial was presented at the International Conference on Headache (ICH) in Stockholm last year but has not yet been published. That study did not meet the primary endpoint (change in mean monthly migraine days from baseline to Week 12) but there was a very high placebo responder rate, and he speculated that the trial may need to be run longer and/or at a higher dose.

TORREYPINES THERAPEUTICS' tezampanel, an AMPA/ kainate receptor inhibitor (iGluR1-2-5)

Dr. Neil Kurtz, president/CEO of TorreyPines, pointed out that tezampanel, which is injected subcutaneously, would be a first-in-class, and he emphasized that it has shown several advantages:

- No evidence of constriction of blood vessels.
- No evidence of interaction with serotonin receptors.
- Non-opioid and no evidence of abuse potential.
- No direct effect on the gastrointestinal mucosa or the heart.

In a single-dose, double-blind, parallel group Phase IIb dose-ranging study, three doses – 40 mg, 70 mg, and 100 mg – were compared to placebo. The study was done in clinics, not by patients at home, and patients were given a single subcutaneous dose. The trial met the primary endpoint, but there was a huge placebo effect that raised questions with doctors.

The lowest dose was the most effective, and it appeared that there was an inverse dose response curve, but Dr. Kurtz insisted that this was not the case, "We have a wealth of data now with absolutely no evidence for an inverse dose response…We think it is a flat dose response from 40 mg to 100 mg…This drug has been extremely well studied now in a large number of animal models – of platelet aggregation, epilepsy, etc...and the effect is never inverse…This is the first (tezampanel) clinical trial to even suggest a lack of dose response…This would have to be a real outlier if we see an inverse dose response."

Dr. Kurtz also said the trial was not powered to show statistical significance but justifies proceeding to a Phase III trial, and the FDA has given the company the green light to do a pivotal Phase III.

Results of Phase IIb Trial of Tezampanel

Measurement	Placebo n=75	Tezampanel 40 mg n=78	Tezampanel 70 mg n=74	Tezampanel 100 mg n=77
Primary endpoint: Mean headache response at 2 hours	58.7%	78.2%	63.5%	57.1%
Absence of photophobia	47%	47.3%	N/A	N/A
Absence of phonophobia	38.5%	53.3%	N/A	N/A
Absence of nausea/vomiting	60.7%	83.3%	N/A	N/A
Sustained headache response	45%	64.1%	N/A	N/A
Adverse events				
Any adverse event	50.7%	38.5%	44.6%	50.6%
Injection site pain	2.0%	5.1%	12.2%	10.4%
Injection site burning	6.7%	3.8%	2.7%	5.2%
Somnolence	6.7%	7.7%	6.8%	5.2%
Dizziness	5.3%	6.4%	4.1%	9.1%
Headache	2.7%	2.6%	1.4%	6.5%
Blood pressure increase *	0	2.6%	4.1%	5.2%

* the amount of increase was not specified

DEVICE-BASED MIGRAINE THERAPY

Four device therapies that are under investigation were mentioned. A speaker said, "It is too early to recommend any of them for routine use. We need better results, better controlled trials. Maybe in another two years we will have better answers."

- **Occipital nerve stimulation.**
- **Vagal nerve stimulation.**
- **Patent foramen ovale (PFO) closure.** NMT Medical halted its MIST-II trial, but other companies, including AGA Medical and St. Jude, have PFO closure/migraine trials underway. Headache specialists said the ongoing trials are having trouble recruiting patients. An expert said, "The PFO evidence is getting pretty strong on the correlation of large PFO and migraine with aura. I'm convinced there is a connection. The microbubbles (that get through) could use the CSD waves. I'm convinced PFO is a trigger, but is it a primary trigger where closing it is sufficient? That may be true for ***some*** patients."
- **Motor cortex stimulation.**

MEDTRONIC's occipital nerve stimulator (ONS) for refractory chronic migraine

The results of the 67-patient, randomized, multicenter, prospective, single-blinded ONSTIM trial showed that neurostimulation cut headache days by a ***non-significant*** 27% over three months in patients with medication-refractory chronic migraines. Headache days were defined as days with headaches rated >3 on a 0-10 headache pain scale. The trial also failed to show any statistically significant improvement in photophobia or phonophobia.

Thin lead wires are placed under the skin near the occipital nerves and connected to an implanted neurostimulator. The neurostimulator delivers controlled electrical pulses to the occipital nerves, which branch out across the back of the head.

Patients were randomized to receive either (1) a neurostimulator that allowed them to control the level of stimulation, (2) a neurostimulator as a control (in the off position), or (3) standard medical management with no implant. A positive response was defined as ≥50% reduction in the number of headache days in a month, or a

reduction in the pain intensity of at least three points on a standard 0-10 pain scale. This was a 3-month trial, but patients will continue to be followed out to three years for safety.

The principal investigator, Dr. Joel Saper, director of the Michigan Head Pain and Neurological Institute in Ann Arbor, reported that when patients in the adjustable stimulation group did have headaches, the headaches were less painful than before ONS treatment. Participants in the adjustable stimulation group also fared better than patients assigned to the device and non-device control groups. He said, "Based upon the responder rate of 39%, ONS may be a promising therapy for ***some*** refractory chronic migraine headache patients…Better outcomes may result from enhanced product development, refinement of implant technique, and targeted patient selection."

The most common adverse events were device-related lead migration, which occurred in 24% of patients. Dr. Saper said, "We are looking at ways to improve that." There were also 3 serious adverse events: an implant site infection, lead migration, and post-op nausea. Non-device-related adverse events were mainly worsened migraine vs. baseline, which occurred mostly in the preset stimulation arm and less in the medical management arm.

Doctors were intrigued with the results but want to see more data. A Midwest doctor said, "The ONS data were exciting. I will look into the accessibility of that, but the side effects – the lead migration – were concerning."

3-Month ONSTIM Trial Results

Measurement	Adjustable stimulation n=33	Pre-set stimulation n=29	Medical management n=17	Ancillary device n=6
Primary endpoint: Average change in the number of headache days per month	27%	29%	19%	40%
p-value	---	Nss, 0.32	Nss, 0.058	Nss, 0.503
Responder rate *	39%	6%	0	40%
p-value	---	0.030	0.003	N/A

*** ≥50% reduction in headache days per month or ≥3-point reduction in overall pain intensity**

NEURALIEVE's transcranial magnetic stimulation (TMS) for acute treatment of migraine with aura

Dr. Richard Lipton presented the results from a randomized, double-blind, parallel group, sham-controlled, outpatient study evaluating the efficacy of TMS in the acute treatment of migraine with aura. The study used a portable, rechargeable TMS device weighing <3 pounds. In the study, patients were treated for up to 3 migraine attacks, but the first treated attack was the per protocol primary. The hypothesis was that TMS would relieve migraine, perhaps by disruption of cortical spreading depression. Dr. Lipton reported that one of the two primary endpoints (pain relief) was met, and TMS had mixed results on the other primary endpoint, meeting the criteria for non-inferiority to sham for photophobia but not phonophobia or nausea. He said the finding established the safety of the device and demonstrated that TMS is a promising treatment for migraine with aura.

Neuralieve's TMS Trial Results

Measurement	Sham stimulus n=82	Active TMS n=82	p-value
Primary endpoint #1: Pain-free 2 hours post-treatment for first rated episode (*by ITT*)	22%	39%	0.018
Primary endpoint #2: Photophobia, phonophobia, and nausea at 2 hours	---	Photophobia: -8.5% Phonophobia: -6.1% Nausea: -2.4%	Photophobia met non-inferiority, but phonophobia and nausea did not
SPF 2-24 hours	15.9%	29.3%	0.040
SPF 2-48 hours	13.4%	26.8%	0.033
Treatment-emergent adverse events	9.1%	13.7%	---

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