Migraine Prophylaxis: The Race is On

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New York, NY
www.cancerprogressbyDH.com

**Therapeutic Insight**

BioEurope Spring
March 9-11, 2015
Paris, France
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

Prophylaxis is the Big Unmet Need in Migraine

• ~12% of the general population suffers from migraine (~36 million in the US), a disabling condition characterized by headache (unilateral, severe throbbing lasting 4 to 72 hours) often accompanied by nausea/vomiting, sensitivity to light (photophobia) and sensitivity to sound (phonophobia).

• An estimated 40% of migraine patients require preventive/prophylactic therapy.

• Although frequent/chronic migraine is associated with substantial disability and costs, few treatments have been shown to be effective.

Need for Migraine Prophylaxis:
• An unsatisfactory response to acute therapy
• Two or more attacks per month that interfere with patient’s daily routine
• Contraindications to acute treatments or adverse effects related to them
• The use of abortive medications > 2 times per week

Prophylactic Therapy is Needed Across the Spectrum of Migraine

♦ It is not only the truly chronic migraine patients (>15 headache days per month) that require prophylactic therapy.
♦ Intermediate frequency and high frequency migraines (and sometimes low frequency, depending on severity) may also require prophylactic therapy.
♦ In addition, migraines can progress to a higher frequency of attacks over time, often attributed to factors such as inadequate therapy and medication overuse.

~40% of Migraine Patients are Candidates for Prophylactic Therapy

♦ A recent Piper Jaffray report estimates that ~14 million migraine patients in the US are candidates for prophylactic therapy.

EM = episodic migraine, CM = chronic migraine
Currently Available Prophylactic Options for Episodic Migraine are Subpar, But Cheap

- There are many options available for prophylaxis of episodic migraine, all of which are generic, and all of which leave something to be desired.

**American Headache Society/American Academy of Neurology recommended agents for the prevention of episodic (not chronic) migraine**

<table>
<thead>
<tr>
<th>Level A: established as effective</th>
<th>Level B: probably effective</th>
<th>Level C: possibly effective</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Should be offered to patients requiring migraine prophylaxis</em></td>
<td><em>Should be considered for patients requiring migraine prophylaxis</em></td>
<td><em>May be considered for patients requiring migraine prophylaxis</em></td>
</tr>
<tr>
<td>Divalproex/sodium valproate</td>
<td>Amitriptyline</td>
<td>Candesartan</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Venlafaxine</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Atenolol</td>
<td>Cyproheptadine</td>
</tr>
<tr>
<td>Timolol</td>
<td></td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Topiramate</td>
<td><em>Supplements: Feverfew, Magnesium, Riboflavin</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>NSAIDS: Ibuprofen, Ketoprofen, Naproxen, Fenoprofen</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Misc: Histamine</em></td>
<td><em>NSAIDS</em></td>
</tr>
<tr>
<td>OTC Supplement: Petasites (butterbur)</td>
<td></td>
<td><em>Other</em></td>
</tr>
</tbody>
</table>

*2012 American Headache Society/American Academy of Neurology Guidelines for Prevention of Episodic Migraine*
Despite Significant Drawbacks, Topamax/Topiramate is the Agent of Choice for High Frequency Episodic Migraine

January, 2011 – Burlington, Mass.—Decision Resources, finds that, for the prophylactic treatment of chronic migraine, the highest proportion of surveyed neurologists select topiramate (Ortho-McNeil/Janssen-Cilag’s Topamax, generics) as having the best overall clinical profile when compared to other currently-available therapies.

- Cognitive dulling
- Nausea
- “Pins and needles”
- Etc.

- Moderate efficacy
- Weight loss
Candesartan is Making a Move to Become the Best of the Pack

♦ A recent study comparing candesartan (angiotensin II receptor blocker) to propranolol (beta-blocker), the most studied agent for the prophylaxis of migraine, showed comparable efficacy but a better side effect profile for candesartan.

A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomized, triple-blind, placebo-controlled, double cross-over study

Clinical implications
- Candesartan is effective for migraine prevention.
- The effect is similar to that of propranolol.
- The adverse event profile is different from that of propranolol.
- Candesartan may become a drug of first choice for migraine prevention.
In 2010, BOTOX (onabotulinumtoxin A) became the first agent approved for the prophylaxis of chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

- Revenues for the migraine indication are estimated at $300-400 M of the $2 billion in total sales for BOTOX.
- Payers are actively managing access via prior authorization and step edits through generic options that are not labeled for migraine prophylaxis (but are considered standard, albeit poor, of care).

In two randomized, placebo-controlled, double-blind, multi-center trials, 55% of Botox patients experienced a 50% reduction in migraine frequency vs. 25% in the placebo arm.

Administered every 12 weeks in the doctor’s office
Injections to 7 key areas of the head and neck; 31 total injections

http://www.botoxchronicmigraine.com/
Cefaly is the First Medical Device Approved for Migraine Prophylaxis in the US

- Cefaly (Stx-Med), approved in the US in March 2014, showed in a double-blind study of 67 EM patients with at least 2 attacks per month a reduction of ~ 2 headache days (not significant at the 5% significance level).

- Cefaly is the first medical device approved by the FDA for preventing EM.
- It is a small, non-invasive, wearable device that resembles a plastic headband.
- Cefaly is indicated to be used once per day for 20 mins.
- The device functions as a transcutaneous supraorbital nerve stimulator (tSNS) through an external adhesive electrode.
- The electrode covers bilaterally the origins of the supraorbital nerves, which are part of the trigeminal nerves.
- The electrode generates biphasic rectangular electrical impulses to stimulate the trigeminal nerves.

Source: www.cefaly.ca
CGRP Antagonists are the Next Big Thing in Migraine Prophylaxis

- CGRP (calcitonin gene-related peptide) is a 37 amino acid neuropeptide produced by alternative mRNA splicing of the calcitonin gene.
- CGRP acts as a neuromediator implicated in vasodilation, nociception, motor function, secretion and olfaction.
- CGRP receptors are expressed in both the central and peripheral nervous system.

Central Role of CGRP During Migraine

Peripheral Role of CGRP During Migraine

CGRP action at peripheral receptors

*Expert Reviews in Molecular Medicine © 2011 Cambridge University Press*
Oral CGRP Antagonists Establish Proof of Efficacy

With several chemically unrelated CGRP oral antagonists having been in the clinic, there is a substantial history of data to support efficacy of the mechanism, cardiovascular safety and better tolerability; however, liver toxicity has plagued development.

<table>
<thead>
<tr>
<th>Compound</th>
<th>DH Comments</th>
</tr>
</thead>
</table>
| Olcegepant /BI 44370TA (Boehringer Ingelheim) | • The first potent and selective non-peptide antagonist of the human CGRP receptor originally referred to as BIBN4096BS, renamed olcegepant.  
• Originally an IV formulation, followed with an oral version.  
• Completed 416pt P2 trial, eletriptan (Relpax) as active comparator. Highest dose (400mg) met pain-free endpoint after 2h in 27.4% of patients, compared to eletriptan’s 34.8%, and 8.6% in the placebo group.  
• No significant side effects reported..  
• No development has been reported since 2009.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Telcagepant (MK-0974, Merck)  | **Discontinued July 2011**  
• Oral, BID  
• Efficacy comparable to triptans.  
• Liver toxicity issues: 11 patients in a P2a exploratory chronic dosing, prophylaxis study (BID for 3 months) showed liver enzyme elevations more than 3x the upper limit of normal.  
• Large (4,500 patient) safety study completed May 2011 for prevention of perimenstrual migraine to counter concerns of liver toxicity. Results not published.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

*Several others discontinued.*
Next Generation Migraine Prophylaxis: CGRP Antibodies - The P2 Lineup

- Antibody-based therapies may address some of the safety issues associated with small molecule antagonists:
  - Not degraded in the liver
  - Few off-target effects
  - Longer plasma half-life
  - Peripheral activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Mechanism</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY 2951742</td>
<td>Artaeus/Lilly</td>
<td>MoAb, targets free CGRP molecules</td>
<td>P2, EM</td>
</tr>
<tr>
<td>ALD 403</td>
<td>Alder</td>
<td>MoAb, targets free CGRP molecules</td>
<td>PIb, EM</td>
</tr>
<tr>
<td>LBR-101</td>
<td>Labrys/Teva</td>
<td>MoAb, targets free CGRP molecules</td>
<td>P2, EM and CM</td>
</tr>
<tr>
<td>AMG 334</td>
<td>Amgen</td>
<td>MoAb, targets CGRP receptors</td>
<td>P2, EM and CM</td>
</tr>
</tbody>
</table>

EM = episodic migraine, CM = chronic migraine
CGRP Antibodies: The Race is On

Four P2 CGRP antibodies are neck-and-neck in a race to be first to market.

<table>
<thead>
<tr>
<th>Compound</th>
<th>LBR-101</th>
<th>AMG334</th>
<th>LY2951742</th>
<th>ALD403</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>EM prophylaxis</td>
<td>CM prophylaxis</td>
<td>EM prophylaxis</td>
<td>Migraine prophylaxis</td>
</tr>
<tr>
<td>Stage</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Randomized, double-blind, placebo-controlled</td>
</tr>
<tr>
<td>Patient #</td>
<td>270</td>
<td>225</td>
<td>468</td>
<td>490</td>
</tr>
<tr>
<td>Baseline Migraine Days Per 28 Days</td>
<td>&gt;=8 &amp; &lt;15</td>
<td>&gt;=15</td>
<td>&gt;=4 &amp; &lt;15</td>
<td>&gt;=15</td>
</tr>
<tr>
<td>Doses</td>
<td>Sub-Q injection once every 4 weeks; 2 different doses</td>
<td>Sub-Q injection once every 4 weeks; 2 different doses</td>
<td>3 different doses</td>
<td>1 sub-Q injection per month; 2 different doses</td>
</tr>
<tr>
<td>Duration</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>24 weeks (12-week follow-up)</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Mean change in migraine headache days per 28 days</td>
<td>Mean change in monthly cumulative headache hours per 28 days</td>
<td>Mean change in migraine headache days per 28 days</td>
<td>Mean change in migraine headache days per 28 days</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>Jan 2015</td>
<td>Feb 2015</td>
<td>End-2014</td>
<td>2015</td>
</tr>
</tbody>
</table>
Data Presented at the 2014 AAN Meeting for Two CGRP Antibodies Showed Similar Efficacy Profiles

- Data on two CGRP antibody programs were released at the 2014 AAN meeting.
- Both of these MoAbs target free CGRP receptor molecules; both targeting frequent episodic migraine (versus chronic migraine).

### CGRP Antibodies in Clinical Development for Migraine Prophylaxis

<table>
<thead>
<tr>
<th>Compound / Company</th>
<th>Phase</th>
<th>Patient #</th>
<th>Dosing</th>
<th>Baseline (headache days/month)</th>
<th>Headache reduction per month</th>
<th>Percent reduction headache days per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY 2951742 (Artaeus/Lilly)</td>
<td>P2, EM</td>
<td>217</td>
<td>Biweekly, SubQ</td>
<td>6.7 vs. 7 (placebo)</td>
<td>4.2 vs. 3.0 (p&lt;0.003)</td>
<td>62.5% vs. 42.3%</td>
</tr>
<tr>
<td>ALD 403 (Alder)</td>
<td>P1b, EM</td>
<td>163</td>
<td>Single IV</td>
<td>8.5 vs. 8.9 (placebo)</td>
<td>5.6 vs. 4.6 (p=0.03)</td>
<td>66% vs. 52%</td>
</tr>
</tbody>
</table>

*Note: % reduction in headache days per month on par with Botox in CM patients.*
CGRP Antibodies Look Tolerable, But Longer-Term Safety is Still a Question

- Clinical data thus far suggests that CGRP antibody therapy has a good side effect profile.
- However, long-term safety, particular liver toxicity, is the big unknown.

### Tolerability of CGRP Antibodies

<table>
<thead>
<tr>
<th>Compound / Company</th>
<th>Side Effects</th>
<th>Percent Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY 2951742 (Artaeus/Lilly)</td>
<td>Injection site pain, upper respiratory infections, abdominal pain</td>
<td>72% vs. 67%</td>
</tr>
<tr>
<td>ALD 403 (Alder)</td>
<td>Tooth abscess</td>
<td>56% vs. 50%</td>
</tr>
</tbody>
</table>
With the exception of CGRP antibodies, the migraine pipeline is largely focused on acute therapies.

- Triptan delivery alternatives (e.g., OptiNose sumatriptan, Avanir; sublingual rizatriptan, RedHill)
- Inhaled DHE (Levadex, Allergan/Map Pharmaceuticals)
- 5HT-1f agonist (Lasmiditan, CoLucid)
- Devices (e.g., Cefaly supraorbital nerve stimulator, gammaCor handheld VNS)
Key Takeaways

♦ CGRP monoclonal antibodies are promising to be an exciting new therapy for the prophylaxis of migraine – a major unmet need for a large patient population.
  • P2 data shows impressive efficacy, a durable effect and good tolerability.
♦ However, questions remain, particularly in terms of long-term safety.
♦ With four competitors entering the market, potential to differentiate will be based on efficacy, certainly, but may also be in the form of differences in tolerability, frequency/ease of administration, presence of neutralizing antibodies, etc. (similar to multiple sclerosis injectable therapies).
♦ In addition, understanding the potential value and/or limitations for the different target patient populations (e.g., headache frequency, severity, disability, medication overuse) will be critical in understanding market potential.
♦ A broader consideration of the competitive environment is warranted, particularly in light of the new data for candesartan and the entry of devices (e.g., Cefaly supraorbital nerve stimulator, gammaCor handheld VNS).
♦ Pricing and market access will be driven by the ability to support a strong value proposition and cost-effectiveness argument (improved quality of life and disability, reduced health resource utilization and cost).
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- **ASH Annual Meeting** | December 6 - 9, 2014 | San Francisco | http://dfndhlth.com/ASH-2014