New Data on CGRP Monoclonal Antibodies for Migraine Prevention

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Washington, DC — New phase 2 data on the investigational calcitonin gene-related peptide (CGRP) monoclonal antibodies show significant efficacy in preventing migraine attacks with no major safety signals.

Phase 2 data for three different anti-CGRP drugs from Amgen (AMN 334), Teva Pharmaceuticals (TEV-48125), and Eli Lilly & Co (LY2961742) were presented here at the American Headache Society (AHS) 57th Annual Scientific Meeting by representatives from the three companies.

A fourth company, Alder Pharmaceuticals, is also developing an anti-CGRP agent but didn’t present data at this meeting. All four companies are planning to move their agents into phase 3 trials.

The drugs — administered as once-monthly injections — act by blocking CGRP, a vasodilator, without causing vasodilation. The Amgen product blocks the receptor for CGRP, while the other three are directed against the ligand itself. Lilly is developing its product for cluster headache as well as for migraine prophylaxis.

“They’re a new class to treat migraine preventatively,” AHS president Lawrence C. Newman, MD, professor of neurology at Icahn School of Medicine at Mount Sinai and director of The Headache Institute at Mount Sinai-Roosevelt Hospital, New York, told Medscape Medical News. “We’re excited because there hasn’t been a new medicine designed specifically to prevent migraine in over 50 years.”

Session moderator Robert Shapiro, MD, PhD, professor in the Department of Neurological Sciences at the University of Vermont, Burlington, told Medscape Medical News, “to have a new category developed specifically for migraine and to have them all show in these early-phase studies significant efficacy and at the same time not have significant signals that there’s a serious adverse events is very encouraging … This is not something we’ve experienced since 15 to 20 years ago when the triptans were rolling out.”

However, Dr Shapiro, who serves on the independent data monitoring committee for the Lilly drug, cautioned that these early studies are still too small and of short duration — none have data beyond 1 year — to fully establish efficacy and safety. “Any time there’s a new molecular entity, one has to be highly vigilant for safety concerns to emerge.”

Indeed, Thomas N. Ward, MD, professor of neurology at the Geisel School of Medicine, Dartmouth College, Lebanon, New Hampshire, and editor-in-chief of the AHS journal Headache: The Journal of Head and Face Pain, pointed out that CGRP is widely distributed throughout the body — in the kidney, lungs, eyes, liver, and gastrointestinal tract — as well as the brain.

“Could [the drugs] have a long-term effect on intracranial pressure, or renal function, or pulmonary function? CGRP is in your body for a reason and if you perturb it long enough, perhaps some people could accommodate well, but perhaps some people with underlying mild disease might not,” Dr Ward said. “It’s not really till you get to phase 3, with big, randomized, double-blind, placebo-controlled studies that you can really answer those questions.”
He pointed to previous experience with a related investigational drug that had generated similar excitement, Merck’s CGRP antagonist telcagepant. The company halted development in 2011 after liver toxicity was seen in a phase 3 study. “So far the [current agents] look safer... but things can appear that you weren't expecting,” Dr. Ward cautioned.

AMG 334

Results of a 1-year open-label extension of a 12-week randomized, double-blind, placebo-controlled, phase 2 study of AMG 334 for the prevention of episodic migraine were presented by Robert Lenz, MD, from the Department of Global Development at Amgen.

A total 483 patients with migraine on 4 to 14 days per month at baseline were randomly assigned to one monthly injection of placebo (n = 160 patients) or AMG 334 in doses of 7 mg (n = 108), 21 mg (n = 108), or 70 mg (n = 107). Most (80.5%) were female, with a mean age of 41 years.

The primary endpoint, a statistically significant change from baseline in monthly migraine days at week 12, was achieved with the 70-mg dose, with an average reduction of 3.4 days compared with 2.28 with placebo. Responses to lower doses were not statistically significant.

After the 12-week double-blind part of the trial, the 70-mg dose was given to all the study patients on-label. At 1 year, they had an average 4.9-day reduction in migraine days per month, down from 6.7 days at baseline, with no difference between those who had previously received the drug or placebo.

Also at 1 year, 62% of the patients achieved greater than a 50% reduction in monthly migraine days, 38% achieved greater than a 75% reduction, and 19% achieved a 100% reduction.

Adverse events occurred in about half of the drug and placebo groups and serious adverse events in less than 1% overall.

Events leading to discontinuation occurred in 2.8% with 70 mg vs 1.3% with placebo. Injection site pain or other problems occurred in less than 2% in all groups.

TEV-48125

Marcelo E. Bigal, MD, PhD, vice president of clinical development at Teva and formerly the chief medical officer at Labrys Biologics, where TEV-48125 was developed, presented the data for a randomized, double-blind, double-dummy, placebo-controlled, multidose, parallel-group study of once-monthly injections of the drug in patients 8 to 14 days of migraine per month.

Patients could also take triptans and other acute migraine drugs for up to 14 days, but no more than 4 days per month of opioids or barbiturates were permitted.

A total 297 patients were randomly assigned to 225 mg or 675 mg of TEV-48125 or to placebo once monthly for 3 months.

For both doses, there was more than a 6-day decrease in the number of monthly migraine days, a highly significant difference from baseline (P < .0001) and also superior to placebo at months 1 and 2 (P < .001). Results were similar for the secondary endpoint of decrease in headache days (P < .001).

The proportion experiencing at least 50% improvement during the study were 59% with the 675-mg dose and 53% for the 225-mg dose, compared with 26% for placebo (P < .001). More than 75% improvement was seen in 31%, 34%, and 11%, respectively (P < .001).

Tolerability was similar to that seen with placebo, and no treatment-related serious adverse events occurred.

LY2951742

Phase 2b data on efficacy and safety for LY2951742 in a randomized, double-blind, placebo-controlled, dose-ranging study were presented by Aaron Schacht, global brand development leader for Lilly’s pain portfolio. Study participants had 4 to 14 migraine headache days and at least two attacks per month.
Subcutaneous injections of LY2961742 doses of 5 mg (n = 68), 50 mg (n = 68), 120 mg (n = 70), 300 mg (n = 67), or placebo (n = 137) were given once every 28 days for 12 weeks.

All four doses were numerically superior to placebo for the change from baseline in migraine headache days, although only the 120-mg dose achieved statistical significance in the last 28-day period of the 12-week treatment phase (P = .004).

Also statistically significant were the proportions achieving responses of at least 50% (P = .038), 75% (P = .003), and 100% (P = .038).

Treatment-emergent adverse events occurring in 5% or more of patients in any LY2961742 group and seen more often than in the placebo group included injection site pain, upper respiratory tract infection, nasopharyngitis, dysmenorrhea in women, and nausea. None of these occurred in more than 15% in any group.

Lilly is enrolling patients for phase 3 trials of LY2961742 for both chronic and episodic cluster headache and has received fast-track designation from the US Food and Drug Administration for cluster headache, Schacht said.

Awaiting Phase 3

Dr Shapiro noted that it's also too early to be able to determine whether there are significant differences among the four anti-CGRP drugs, including whether the different target for the Angen drug makes any difference in efficacy or safety.

"It's way too soon on the basis of phase 2 trials to make significant comparisons between these agents," he said. "It really requires larger numbers in phase 3 trials and sorting out inclusion/exclusion criteria… All of them have positive data, and some have extraordinary signals for subsets of patients, but we can't yet draw conclusions."

However, Dr Ward noted, "If this class of medications pans out, it's almost essentially the holy grail of prevention for migraine because we wouldn't have a lot of side effects that we have with our current medications, such as weight gain, hair loss, or cognitive abnormalities. It might allow people to live a relatively normal life."

Dr Newman is an advisor for Teva and Lilly. Dr Shapiro serves on the independent data safety monitoring board for the Lilly anti-CGRP drug trials. Dr Ward has disclosed no relevant financial relationships. Dr Lenz, Dr Bigai, and Mr Schacht are employees of Amgen, Teva, and Lilly, respectively.