Headache
© 2015 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.12744
Published by Wiley Periodicals, Inc.

Residents and Fellows

Clinical Trials Update 2015: Year in Review

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This section of *Headache* annually reviews the status of recently completed and ongoing major clinical trials involving common headache disorders. The review will focus on multicenter trials of new therapies, as well as novel formulations of previously approved therapeutics. The Table summarizes the major therapeutic headache trials that were ongoing at the end of 2015, according to data obtained from both the "ClinicalTrials.Gov" website and from corporate press releases and presentations.

Key words: clinical trials, headache, update

(*Headache* 2016;56:178-184)

2015 was a year of continued progress in the clinical development of a group of antibodies targeting calcitonin gene-related peptide (CGRP) and continued clinical development interest in neurostimulation techniques.

However, for the sixth year in a row, no new pharmacological therapeutic agents were approved by the US Food and Drug Administration (FDA) for the acute and/or prophylactic treatment of migraine.

FDA REVIEWS IN LATE 2014

Sumatriptan Intranasal (AVP-825, Formerly Called OPTINOSE).—In November, 2014, the FDA declined to approve a drug-device product combining low-dose sumatriptan powder delivered intranasally using a novel delivery technology for the treatment of migraine. The FDA reportedly requested that the Sponsor (Avanir Pharmaceuticals, Inc.) assess the cause or causes of device use errors observed during the clinical development of the product. The Sponsor reportedly planned to provide additional human use data sometime in 2015. However, the Sponsor was acquired shortly thereafter by Otsuka Pharmaceutical Co., Ltd. No further information is available at present concerning additional development plans for the product.

ACUTE TREATMENT OF MIGRAINE

Possible FDA Approvals in Late 2015 and 2016.—2016 should prove to be another lean year for new migraine products, as the only possible FDA approvals would appear to be for the intranasal formulation of sumatriptan (discussed above) and inhaled dihydroergotamine.

Dihydroergotamine Inhaled (Semprana®, Formerly Referred to as MAP0004 and Levadex®).—In June 2014, Allergan announced that the FDA had notified the Company of its third rejection of the inhalable migraine therapy. The Company announced that FDA approval will likely be delayed until the second quarter of 2015. However, since the corporate merger of Allergan, Inc. and Actavis plc in late 2014, there have been no public

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Accepted for publication November 3, 2015.

Conflict of Interest: None.

announcements about the status or future plans for the product. Therefore, an impending FDA approval remains a possibility although seems unlikely.

PRODUCTS IN THE PIPELINE

Lasmiditan (Formerly Referred to as COL-144).—CoLucid Pharmaceuticals, Inc. reached agreement with the FDA on a Special Protocol Assessment for a study designated the SAMURAI trial (NCT02439320), its first Phase 3 pivotal trial of lasmiditan in the acute treatment of migraine. Lasmiditan is a 5-HT1F receptor agonist that lacks the vasoconstrictor effects of other migraine therapies.

"A Study of Two Doses of LAsMiditan (100 mg and 200 mg) Compared to Placebo in the AcUte Treatment of MigRAIne: A randomized, double-blind, placebo-controlled parallel group study" plans to enroll 2225 subjects with risk factors for cardiovascular disease and some forms of stable cardiovascular disease. The primary endpoint of this study is the proportion of subjects who are headache pain free at 2 hours, and a key secondary endpoint is the proportion of subjects who are most bothersome associated symptom free at 2 hours. This large study is expected to be completed in mid-2016.

Topofen™ Gel (Topical Ketoprofen; Formerly Call ELS-M11).—Topofen™ gel is a topical cream formulation of ketoprofen being developed by Achelios Therapeutics. The results of a Phase IB, 12-week, randomized, double-blind, cross-over, placebo-controlled clinical trial entitled "Study to Determine the Efficacy and Safety of ELS-M11 in Acute Migraine" (NCT02057315) were reported in 2015.

The randomized, crossover, double-blind, placebo-controlled study involved 48 adult subjects with a history of episodic migraine with and without aura. Subjects were instructed to treat 5 moderate to severe migraines by applying the Topofen™ gel on the skin, over the 3 branches of the trigeminal nerve, and to record their symptoms on an electronic diary.

Compared with placebo, the ketoprofen gel resulted in greater improvement in pain assessments after study drug application, a faster time to pain response, a reduction of migraine-associated symptoms such as nausea, light and sound hypersensitivity, and greater suppression of pain over the 24-hour period that subjects were asked to follow each migraine after gel application. Of the severe migraine subjects, 45% had sustained pain relief from 2 to 24 hours after using the gel compared to 15% of placebo subjects. Also 50% of subjects who treated their severe pain with the ketoprofen gel were pain free at 24 hours compared to 25% of placebo-treated subjects. Adverse events were limited to application-site irritation, predominantly mild or moderate, that resolved quickly.

No further development plans for the ketoprofen gel have been announced by the Sponsor.

MK 1602 (Small Molecule CGRP Antagonist).—Allergan acquired worldwide rights from Merck & Co. to two clinical-phase migraine drug candidates for $250 million, plus milestone payments and royalties in mid-2015. The agreement gives Allergan rights to two small molecule oral CGRP receptor antagonists. The Sponsor reported that it is planning end of Phase II discussions with the FDA prior to launching a Phase III study of MK-1602, for which a Phase II study has been completed. More detailed clinical development plans for these molecules can be expected in 2016.

MIGRAINE PROPHYLAXIS AND CHRONIC MIGRAINE

Histamine Dihydrochloride.—BioHealthonomics Inc. filed an Investigational New Drug application for migraine prophylaxis in December 2013. A Phase 2 trial entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of Subcutaneous Histamine Dihydrochloride for Migraine Prophylaxis" (NCT02 021474) was scheduled to begin in late 2014, with a planned enrollment of 130 subjects. However, as of late 2015, the study is still listed as "not yet recruiting."

Intranasal Kinetic Oscillation Stimulation.—Chordate Medical is a medical device company based in Sweden that is developing a new neuromodulation technology

for the treatment of both acute and chronic migraine. The Company initiated a Phase 2 clinical trial in 2014 entitled "A Randomized, Placebo-controlled, Double-blind, Multi-center Pilot Study to Evaluate the Prophylactic Effect and Tolerability of Intranasal Kinetic Oscillation Stimulation (KOS) Using the Chordate System S200 in Patients Diagnosed With Migraine" (NCT02243865). The study was scheduled to be completed in mid-2015 so that the trial results can be expected in 2016.

TI-001 (Intranasal Oxytocin).—Trigemina, Inc. is developing TI-001, an intranasal formulation of the hormone oxytocin. A Phase 2 Study entitled "TI-001 (Intranasal Oxytocin) for Treatment of Chronic Migraine" (NCT01839149) was initiated by Trigemina, Inc. in 2013. The planned 240 subjects were expected to be enrolled by mid-2015 with investigators in Chile, Australia, and New Zealand. The study results can, therefore, be expected in early 2016.

Occipital Nerve Stimulation.—A study entitled "Occipital Nerve Stimulation (ONS) for Migraine: OPTIMISE" was initiated by the Boston Scientific Corporation in 2013 (NCT01775735). The primary objective of this study is to evaluate the safety and efficacy of ONS using the Precision™ System in the management of intractable chronic migraine, when used in conjunction with antimigraine medications. The study plans to enroll 180 subjects and final data collection is now expected in June 2017.

Neuromodulation System.—Scion NeuroStim is developing a noninvasive neuromodulation system for the treatment of migraine. A study entitled "A Non-Invasive Neuromodulation Device for Treatment of Migraine Headache" (NCT01899040) is now scheduled to complete in early 2016. In this study, a standardized active neuromodulation waveform was used for all active device subjects. The device was to be used twice daily. The results can be expected sometime in late 2016.

MLD10.—MLD10 is a novel formulation of magnesium L-lactate dehydrate for daily treatment that is being developed by Pharmalyte Solutions LLC. A Phase2/3 trial entitled "MLD10 in the Prevention of Migraine in Adults" was initiated in March, 2015 with a planned enrollment of 142 subjects. The study is scheduled to be completed in late 2016.

LY2951742 (Humanized CGRP Antibody).—Arteaus Therapeutics, LLC licensed worldwide development rights in 2011 from Eli Lilly and Co. to a humanized monoclonal antibody that potently and selectively binds to CGRP (ie, LY2951742). Eli Lilly and Company reacquired to commercial rights to the product in 2014.

The results from a Phase 2b, "Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients With Episodic Migraine" (NCT02163993) were reported in 2015. The Sponsor reported that LY2951742 met the primary endpoint in this study that evaluated the efficacy and safety of 4 different doses of LY2951742 given in a once-monthly, subcutaneous injection in more than 400 patients with episodic migraine (ie, people who experience between 4 and 14 migraine headache days per month). LY2951742 demonstrated a statistically significant reduction in migraine headache days and a safety and tolerability profile, thus confirming the previous results seen in a previous Phase 2a study.

Plans for possible Phase 3 trials of LY2951742 in migraine have not been announced, as of late 2015.

In addition to the migraine program, Lilly has initiated two Phase 3 trials (n = 162 subjects each) with LY2951742 in subjects suffering from episodic (NCT02397473) and chronic (NCT02438826) cluster headache. Based on the unmet medical need and significance of this disorder for patients, the FDA granted Lilly a granted Fast Track Designation for cluster headache.

ALD403 (CGRP Antibody).—ALD403 is a genetically engineered humanized anti-CGRP antibody being developed for the treatment of migraine by Alder Biopharmaceuticals Inc.

A Phase 2b entitled "A Parallel Group, Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Phase 2 Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of ALD403 Administered Intravenously in Patients With Chronic Migraine" (NCT02275117) was initiated in late 2014. The study planned to enroll 600 subjects and "Top-line" 12-week data are anticipated by the first quarter of 2016.

The Sponsor has also reported initiating a Phase 1 study in healthy volunteers to investigate quarterly self-administration dosing of ALD403. Following the expected top-line data announcement of this study in the first quarter of 2016, the Sponsor plans to initiate a Phase 2b follow-on study to determine optimal dosing for efficacy over a 12-week period for frequent episodic migraine patients.

The Sponsor has also disclosed that it plans to initiate a first pivotal Phase 3 trial of ALD403 in late 2015. The planned 600-patient double-blind, randomized, placebo-controlled, multidose trial will study 3 dose levels of ALD403 and placebo administered quarterly with 150 frequent episodic migraine patients per group. In 2016, the Sponsor plans to initiate a second pivotal Phase 3 trial. The 450-subject double-blind, randomized, placebo-controlled, multidose trial will study 2 dose levels of ALD403 and placebo administered quarterly with 150 chronic migraine patients per group. The primary endpoint for both trials is the change in migraine days between ALD403 and placebo as determined by the difference in responder rates over a 12-week period.

TEV-48125 (Formerly LBR-101, PF-04427429, and RN-307) (Humanized CGRP Antibody).—Teva Pharmaceuticals acquired Labrys Biologics Inc. in June 2014 and thereby obtained the rights to develop TEV-48125 for the prevention of chronic migraine and other disorders. TEV-48125 (formerly called LBR-101, PF-04427429, and RN-307) is a humanized monoclonal antihuman antibody that binds to CGRP itself, thereby blocking its ability to interact with the CGRP receptor. The data from 2 different Phase 2 clinical trials with TEV-18125 were published in 2015.

The first study, entitled "A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group, Multi-Dose Study Comparing the Efficacy and Safety of Subcutaneous LBR-101 With Placebo for the Preventive Treatment of Chronic Migraine" (NCT02021773), enrolled 264 subjects.[1] Both assessed doses of TEV-48125 (loading of 675 mg followed by monthly injections of 225 mg or 900 mg) were significantly superior to placebo in reducing the number of headache-hours (primary endpoint: $P = .038$ and $P = .0057$) and the number of headache days of moderate or severe intensity in month 3 (secondary endpoint: $P < .0345$ and $P = .0237$). Approximately, 15% of study drug-treated subjects were totally free of headaches at month 3. No significant safety or tolerability concerns were identified. No serious treatment-related adverse events were seen.

The second study, entitled "A Multicenter Assessment of TEV-48125 in High Frequency Episodic Migraine" (NCT02025556), enrolled 297 subjects.[2] The subjects reported having had migraine for nearly 2 decades, with a mean of 11.4 migraine-days per month, and 12.5 headache-days per month. Over a period of 12 weeks, both doses of TEV-48125 (225 mg and 675 mg) met the primary and secondary endpoints, achieving statistically significant reductions in mean monthly migraine days and monthly headache days, as well as significantly diminished number of days and hours of headaches of at least moderate severity. A decrease of at least 50% of migraine days for the duration of the study were seen in 53% ($P = .0005$) and 59% ($P < .0001$) of the individuals given 225 mg and 675 mg correspondingly vs 28% of those receiving placebo. A decrease of at least 75% in episodic migraine days was observed in 11%, 34% ($P = .0001$) and in 31% ($P = .0008$) of the individuals given placebo, 225 mg and 675 mg, respectively. No treatment-related serious adverse events were reported with use of TEV-48125.

The Sponsor has yet to announce its plans for pivotal Phase 3 trials.

AMG 334 (Fully Human CGRP Receptor Antibody).—AMG 334 (from Amgen) is a fully human monoclonal antibody that is selective for the CGRP receptor complex (as opposed to the 3 other antibodies being developed that target CGRP itself). This ability to block the CGRP receptor (as opposed to CGRP) might be advantageous as binding to the CGRP receptor might prevent receptor activation, independent of CGRP release.

The Company initiated 3 different Phase 2 studies of AMG 334. The first, "A Phase 2 Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention" (NCT01952574), enrolled 483 subjects with episodic who were randomized to subcutaneous monthly placebo or AMG 334 (7 mg, 21

Table 1.—2016 Ongoing Clinical Trials in Migraine

Title	Conditions	Interventions	Phases	Planned Enrollment	Start Date	Expected Completion Date	NCT Number
Chordate system prophylactic migraine clinical investigation	Migraine	Chordate system S020	Phase 2	80	Sep 2014	Jun 2015	NCT02243865
TI-001 (intranasal oxytocin) for treatment of chronic migraine	Chronic migraine	TI-001	Phase 2	240	May 2013	Aug 2015	NCT01839149
A noninvasive neuromodulation device for treatment of migraine headache	Migraine headache, episodic	Neuromodulation for episodic migraine headache	Phase 2	76	Aug 2013	Jan 2016	NCT01899040
A multicenter assessment of ALD403 in chronic migraine	Prevention of migraine headache in chronic migraineurs	ALD403	Phase 2	600	Oct 2014	Jul 2016	NCT02275117
Lasmiditan compared to placebo in the acute treatment of migraine	Acute migraine	Lasmiditan	Phase 3	2225	Apr 2015	Jul 2016	NCT02439320
A study of LY2951742 in participants with episodic cluster headache	Cluster headache	LY2951742	Phase 3	162	May 2015	Aug 2016	NCT02397473
A study to assess the long-term safety and efficacy of AMG 334 in chronic migraine prevention	Treatment for prevention of chronic migraine	AMG 334	Phase 2	490	Jun 2014	Dec 2016	NCT02174861
A study to evaluate the efficacy and safety of AMG 334 in chronic migraine prevention	Treatment for prevention of chronic migraine	AMG 334	Phase 2	651	Feb 14	Jan 2017	NCT02066415
A multicenter assessment of ALD403 in frequent episodic migraine	Frequent episodic migraine	ALD403	Phase 3	600	Jul 2015	Apr 2017	NCT02559895
A study to evaluate the efficacy and safety of AMG 334 compared to placebo in migraine prevention	Migraine	AMG 334	Phase 3	540	Jul 2015	Oct 2017	NCT02483585
A study of LY2951742 in participants with chronic cluster headache	Cluster headache	LY2951742	Phase 3	162	Jun 2015	Dec 2017	NCT02438826
Occipital nerve stimulation (ONS) for migraine: OPTIMISE	Migraine disorders	Occipital nerve stimulator	Phase 2	180	Jan 2013	Jun 2017	NCT01775735

Table 1.—*Continued*

Title	Conditions	Interventions	Phases	Planned Enrollment	Start Date	Expected Completion Date	NCT Number
MLD10 in the prevention of migraine in adults	Migraine	MLD10	Phase 2	142	Mar 2015	TBD	NCT02322333
A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of subcutaneous histamine dihydrochloride for	Migraine prophylaxis	Histamine dihydrochloride	Phase 2	130	Sep 2015	TBD	NCT02021474

mg, or 70 mg) in a 3:2:2:2 ratio, respectively. Subjects had a mean baseline of 8.7 migraine days per month. The primary endpoint was the change from baseline in monthly migraine days at week 12. Subjects who were randomized to the 70-mg dose group observed a statistically significant 3.4-day reduction in monthly migraine days compared with 2.28 days observed in the placebo group ($P = .021$). Secondary study endpoints included a 50% responder rate, monthly migraine attacks, and safety and tolerability. AMG 334 demonstrated a statistically significant increase in the 50% responder rate compared with placebo (47% vs 30%, respectively). The dose tolerability profile of AMG 334 was similar to placebo across all dosing groups.

The second, "A Study to Evaluate the Efficacy and Safety of AMG 334 in Chronic Migraine Prevention" (NCT02066415), was initiated in early 2014 with a planned enrollment of 651 subjects. The third, "A Study to Assess the Long-term Safety and Efficacy of AMG 334 in Chronic Migraine Prevention" (NCT02174861), was initiated in mid-2014 with a planned enrollment of 490 subjects. The results from these Phase 2 chronic migraine studies are expected in 2016.

In 2015, a Phase 3 trial entitled "Study to Evaluate the Efficacy and Safety of AMG 334 Compared to Placebo in Migraine Prevention" was initiated with a planned enrollment of 540 subjects. Results are expected in 2018.

COMING ATTRACTIONS: KEY DATA EXPECTED IN 2016 AND BEYOND

The continued clinical development progression of multiple CGRP antibodies should provide a novel class of treatment agents for the treatment of chronic migraine and potentially other subtypes of headache within the next few years.

The pending Phase 3 data from multiple companies should provide a definitive test of the hypothesis that was first developed over 25 years ago that CGRP plays a key role in the pathophysiology of migraine.

Nonetheless, the clinical improvement (in terms of the net reduction in number of migraine

days) reported with the CGRP antagonists has been relatively modest (ie, an average of ∼1 net day of headache per month in subjects with very frequent headache). As a result, there remains a clear need for improved therapeutic agents for migraine and other headache disorders. The reported successes of the past few years offer hope that additional clinical and scientific insights will allow the treatment of migraine and other types of headache to progress even more significantly in the future.

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