Emerging Solutions in Pain

Therapeutic Advances and Evolving Treatment Strategies:
Novel Approaches to Migraine Management

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Dr. David Dodick: Welcome to *Therapeutic Advances and Evolving Treatment Strategies: Novel Approaches to Migraine Management*. This is supported by MediCom Worldwide. We appreciate their support throughout all of this, and it is also supported by an unrestricted educational grant from Teva Pharmaceuticals. So, we appreciate that support as well. In my 23 years in this field, never has there been a more exciting time in the field of migraine. Despite this 24 hour news cycle, the share of voice that migraine has right now is incredible with not only our move against migraine campaign, but all of the industry campaigns, and it just seems like every week there is a new press release on a positive clinical trial. So, it is a really exciting time in the field. We are going to talk a little bit about that today.

I am joined by two close friends and colleagues, Alan Rapoport, Clinical Professor of Neurology at the David Geffen School of Medicine at UCLA, and Stewart Tepper who is Professor of Neurology at Dartmouth. Stewart is on the Board of Governors of the American Headache Society, and Alan Rapoport is the immediate past president of the International Headache Society. Tremendous clinical experience and I could not ask for two better faculty people here today. This is a brief symposium. It is only an hour long. Dr. Tepper is going to talk to you about the migraine evolution process and treatment today. The science of migraine will be presented by him and will talk about from bench to practice expert perspectives on emerging strategies and novel agents for migraine prevention focusing on the small molecule receptor antagonists of CGRP and CGRP monoclonal antibodies. Then, we will take 10 minutes at the end for question and answer. So, without further ado, I am introducing Alan Rapoport who I have already introduced, but he is going to talk to us about the migraine evolution process and current treatments today. Alan?

Dr. Alan Rapoport: Thanks David and good morning everyone. The main barriers for preventive treatment of chronic migraine are consulting, you have to get to the doctor; proper diagnosis, you have to make the right diagnosis; and effective therapy. So, all three of them. What are the specific problems with migraine prevention today? There are barriers to consultation and accurate diagnosis as we just talked about. Most medications used are not FDA approved for migraine, and sometimes, we have a little trouble getting them. Dosing regimens are at least once a day, sometimes two or even three times a day. There is very low efficacy rate, the 50% responder rate for topiramate is somewhere around 50%, and everything is a little bit lower or quite a bit lower. There are numerous contraindications to our medications and many adverse events. So, it is very difficult to titrate our patients and keep them on this. There are very low adherence rates, and after adherence there is very low persistence, and I will show a good slide on that in a bit. These medicines do not often help the comorbid condition, so we need more than one medication for our patients.

I think you know the indications for preventive strategies. Everybody does it a little bit differently. Currently, we usually say if there is one attack a week, maybe four attacks a month, we might consider prevention, especially if the patient does not do really well on acute care medication. But also, we like to look at disability, even if it is one or two attacks a month. If there is a lot of disability and we cannot improve upon that, we might think about prevention, or if the patient's quality of life is just too low we would think about it. Sometimes acute care medications fail or are contraindicated or there are too many adverse events. Migraine sometimes interferes with the patient's daily routine and we have to do something to improve it. Some of our patients have hemiplegic migraine or migraine with brainstem aura, and many of our acute care medications are contraindicated. We may want to prevent medication overuse, or if the patient has medication overuse when they come to us we have to treat it and we do not want them to progress to chronic migraine. Sometimes, it is just patient preference not to have to take so many acute care medications, and there are pharmacoeconomic considerations at times.

Now, you all know the evidence-based guidelines. I do not like these that much only because this is based on the best literature there, not necessarily what is best for our individual patient. In the left column, you see the four medications that are approved for migraine: divalproex sodium, topiramate, propranolol, and timolol. Also in that list now is metoprolol. As you move to the right, a little less evidence. There are still medications that neurologists use a lot, amitriptyline, and many of us use nortriptyline, which I think may have fallen off this chart completely because it has not been studied that well. Even when you get over to the C column, candesartan is a medication that many of us use. I cut out the slide, but you will see it in your handout, what we used to

do at the New England Center for Headache, there are another 45 medications that we use, all of them off-label.

What are the barriers for prevention of chronic migraine and what is chronic migraine? I think most of you know this. It is a migraineur who has at least 15 headache days a month for at least 3 months, and 8 of those days should be migraine days or the patient thought it would become a migraine day and successfully treated with a migraine-specific medication. About 1% of the world has chronic migraine. About 3% of people with episodic migraine in the population will morph to chronic migraine, and it will be a smaller percentage if we treat them really well. It is 3% anyway that is going to turn into chronic migraine, but if we give them really good acute care therapy, it is only 1.9% according to this article, and if you do not treat them well, it will be as high as 6.8%. We talked about the low adherence rate, and it is a real problem for our medications because even though we give them and hope the patients will stay on them and we follow them up, they do not stay on them. So, if we look at the proportion of days covered and we look at the antidepressants, only 26% of people stay on antidepressants for 6 months. The antihypertensive is only 27%, and the anticonvulsants 24%. What about 12 months? It gets down to 16%, 18%, and 17%, pretty shocking figures, but that is what is happening out there.

Further barriers for chronic migraine, we have these prescribing restrictions on us from insurance companies. We have to document the medications they have taken, their history, their diagnosis, and it takes us some extra time. There is a requirement for treatment failure of two, and in California sometimes three, categories of medications not even approved for chronic migraine before we can give the only medicine approved for chronic migraine, which is onabotulinumtoxinA. That is not right. Doctors are required to struggle with prior authorization. Sometimes, we spend extra money to get people to help us with that. Sometimes, we do not have those people and actually have to do it ourselves, and occasionally we have to pick up the phone and that does not usually work very well. We have medication overuse in a lot of our patients and we have to treat them in a special way, and it becomes more difficult and more time-consuming.

So, what do we need to do to overcome the barriers that we are talking about? Patients have to be consulting with any doctor and preferably a specialist, but very few of them get to us. An accurate diagnosis has to be made, and it often is not. Proper education and setting expectations is really important. We get a lot of phone calls immediately, "Why am I not better? It has been 3 days already." Optimal pharmacologic treatment with prevention of medication overuse or treatment if medication overuse is there. Treatment of comorbidities in addition to just the pain. Many of our patients have comorbidities. Behavioral therapy I believe is extremely important. Patients have to keep a very accurate headache calendar. They have to go for cognitive restructuring,

biofeedback training, and many other techniques, and we do not always have them available and the patients are not covered for them even though it is extremely important. Then, we need effective followup. Patients have to come back to see us regularly, or even if they are getting better they are going to fall off. What do we need for optimal migraine prevention? We need medications that can be given less frequently, have a high rate of adherence and persistence, have very few adverse events, are easy to administer, have efficacy to decrease headache days in the month, works when other preventive therapies do not work, and is cost-effective.

So, in summary, we have to overcome these three barriers. We have to consult, get our patients to consult; give them a proper diagnosis; and effective therapy. Thank you. Here is Stewart Tepper who I have had the pleasure of working with for 7 or 8 years at the New England Center for Headache, and even though he is from Yale, he is at my alma mater, Dartmouth.

Dr. Stewart Tepper: Good morning, thank you. I'll talk a little bit about the science of migraine, and actually the two talks, mine and David's, will overlap and complement each other we hope without too much repetition. Those of you who attended the seminar yesterday saw the role that cortical spreading depression might play in the initiation of migraine pathophysiology, and one of the questions that is really not clear is where migraine originates, if there is one area. It may be deep brain structures. It may be cortical. It is really not clear, but following the activation of the migraine, there is activation of trigeminal vascular and meningeal fibers and release of CGRP (calcitonin gene-related peptide) from trigeminal vascular and meningeal nerve endings. The release of CGRP peripherally is associated, and I think this part is pretty unequivocal, with the peripheral pain mechanisms of migraine. Those include vasodilation of meningeal vessels and neurogenic inflammation in that region. That in turn activates nociceptive afferents that carry the signal back to the brainstem and where the pain process is integrated, processed, and ascends through the thalamus to the cortex and is perceived of as pain, and there is associated migraine symptomatology and central sensitization. This is a slide that Rami Burstein initiated and then was used in the Comprehensive Migraine Education Program for the American Headache Society that shows this. If we start at the left in the upper red, that is where the peripheral pain mechanisms are. Meningeal blood vessels dilate. There is a release of nasty neuro-inflammatory peptides, and calcitonin gene-related peptide is very important in initiating those processes. The signal then goes back to the brainstem. You can follow that on the red, goes through the trigeminal ganglion, and is processed at the level of the trigeminal nucleus caudalis. There are efferents going to the neck and out. As was discussed yesterday by Michael Moskowitz, parasympathetics go out to parasympathetic target organs, but the pain pathways ascend through the thalamus to the cortex. CGRP receptors occur at all of those sites. They occur at all of the sites

involved in migraine pathogenesis. There are CGRP receptors in cortex that probably enable and interact with NMDA glutamate receptors and are associated with the genesis of cortical-spreading depression and aura. There are CGRP receptors in small neurons in the vagus, in the trigeminal, in the dorsal root ganglion, in the trigeminal ganglion. I think the first person who taught me this was David Dodick. For years, CGRP has been a target because of its omnipresent locations. It is a match.

David is going to talk a little bit more about what CGRP looks like, how it operates, but it was its peripheral actions that led to our attention. Now, just a few pictures because pictures are always good. CGRP binds to the brainstem areas that are activated in migraine, and whether this represents a so-called central generator or a modulating area in the brainstem remains a question, but we really know that this area around the PAG and dorsal raphe is activated in migraine. fMRI data from Peter Goadsby's lab really shows that to be on the ipsilateral side in unilateral migraine. I mentioned CGRP binds in the trigeminal nucleus caudalis. It binds in the trigeminal ganglion. It binds where the action is. So, then, the question becomes what other evidence links it to migraine?

These are the links for CGRP in migraine. CGRP immunoreactive nerves innervate human cerebral arteries. CGRP is the most potent endogenous vasodilator, and it vasodilates human cerebral arteries. CGRP is released in migraine, and you can see a figure that David gave me on the upper right, resting CGRP levels, and then CGRP levels during a migraine attack. CGRP infusion as you knew evokes migraine. CGRP levels are elevated in migraine. They are persistently elevated in chronic migraine. It looks like it may be a marker, a biomarker for that, and headache relief after sumatriptan coincides with normalization of the CGRP levels. Finally, we get to the action, right? CGRP receptor antagonists, small molecule gepants effectively terminate migraine attacks. If you can block the CGRP receptor at the time of a migraine, you can stop the attacks. Anti-CGRP and anti-CGRP receptor monoclonal antibodies prevent both episodic and chronic migraine, which is really why we are here. CGRP infusion, there is an immediate headache and then a delayed headache, and the delayed headache looks like migraine without aura, and that occurs in almost two-thirds of people who get a CGRP infusion. I am sure we do not have a lot of volunteers for that anymore.

Let's talk a little bit about gepants. Seven gepants have actually been studied in humans, and gepants have never failed on efficacy. So, those questions, obviously not the right answer. Gepants have been studied in both acute treatment trials and in preventive treatment trials. Olcegepant was the first gepant that was studied. It was studied in Europe, and yes, Olesen published the results in the *New England Journal of Medicine*. IV, it worked in a manner comparable to a triptan in terminating acute attacks. A Boehringer Ingelheim oral compound was next published in phase 2, although no further studies have been done on it. The most studies were done on telcagepant which

showed promise in efficacy comparable to triptans for acute treatment, and development was stopped due to liver toxicity. A second compound within that same shoot was also liver toxic and was also effective in acute treatment of migraine, but has been abandoned. Rimegepant was effective versus placebo in a phase 2 trial which is fully published and is being readied for a phase 3 acute randomized control trial right now. Ubrogepant has been published in a phase 2 trial and is in phase 3 currently for acute treatment of migraine. Telcagepant was studied preventively. It was studied in two incomplete studies, one of which was terminated due to hepatotoxicity as the drug was dosed b.i.d., and the other was an evaluation of liver function in menstrually related migraine prevention, which also showed a liver signal, and so, the development of telcagepant was discontinued. Atogepant, another gepant, is currently in phase 2 for migraine prevention. That would be a way of taking the gepant every day and blocking the receptor every day with an oral drug for prevention. I do not think we have seen the end of the gepants. I think we are still in a time of fast development, and there will be three gepants in clinical trials probably by this time early next year, as long as the liver problems have been eliminated. Remember gepants go through the liver. They are metabolized in the liver. That is where the problems can occur. David gave me this slide showing the various gepants, and what I like about it is in the middle three you actually see the gepants not only in comparison to placebo but also in comparison to triptans. So, the Tony Ho study was with telcagepant compared to zolmitriptan acutely. Right? The Diener study was the second Boehringer Ingelheim oral drug and that was compared to eletriptan, and the Marcus study, I think it is rimegepant and that was compared to sumatriptan, and the Voss study that you see on the far right is the ubrogepant phase 2 trial. So, that would be the trial that you are looking at. This is for pain freedom at 2 hours, and these acute treatments really behave like triptans. Tolerability appears to be better, but they behave like triptans from an acute efficacy standpoint.

So, in conclusion, migraine pathogenesis may involve cortical spreading depression as you heard yesterday in that long symposium that was so fantastic. The big question remained, is cortical spreading depression at the beginning of all of these migraine attacks or part of these migraine attacks, and is it at the root of how many of our preventive drugs work or all of them? We clearly recognize that the peripheral pain mechanisms of meningeal and dural vasodilation and neurogenic inflammation are pivotal in the genesis of pain, and they in turn activate nociceptive and neuronal afferents that go centrally for processing. The CGRP receptors are found at every single one of these locations, and CGRP infusion evokes migraine, and CGRP goes up in migraine, and CGRP goes down after migraine is treated. The gepants, these antagonist small molecules, effectively abort migraine attacks, which brings us to the monoclonal antibodies and the fact that they prevent episodic and chronic migraine and allows me to gracefully segue to the president of the International Headache Society, David Dodick.

Dr. David Dodick: Thank you very much, Stewart. This is like déjà vu all over again. When sumatriptan came along, sumatriptan was extensively developed to constrict intra- and extracranial blood vessels. This is the beautiful thing that with new therapy comes new knowledge and new insights into disease mechanism and new targets for treatment. Because what has happened since the introduction of the triptans, now we understand receptor pharmacology of the serotonin system much better, and while they were designed to constrict blood vessels because we thought that was the mechanism of action of an acute drug, it turns out that is probably not how they work or where they work. Most likely, they stop pain transmission and signaling through trigeminal afferents peripherally, and possibly through the central trigeminal vascular pathway. With new therapy comes new knowledge. So, we have new therapy here, CGRP receptor antagonists, and now the CGRP monoclonal antibodies, and we have no idea where they work. They were developed extensively because CGRP is a potent vasodilator, and we want to inhibit that dilation because in the past we thought that that dilation led to pain. It turns out that that is probably not their mechanism of action. You have heard from Dr. Tepper that these receptors are ubiquitous. They are located throughout the central and peripheral nervous system and indeed throughout the body, but where these drugs actually work, we simply do not know yet. But the proof of principle is in, they definitely work, and so over the next 5, 10, 15 years, we are going to have a lot of fun figuring out where they work, and as we figure that out, undoubtedly what is going to happen is we are going to have new insights into the mechanism of the disease and undoubtedly new targets are going to be teed up for other therapies.

Again, the prescient prediction of Dr. Lars Edvinsson back more than 30 years ago now when CGRP was discovered in trigeminal meningeal nerve fibers that innervate the cerebral vasculature, and it was known to be a potent dilator, the prediction was that CGRP must be or may be of considerable importance in the regulation of cerebral blood flow and in the migraine syndrome. So, he was prescient in that prediction at that time. He was right, but maybe not for the right reason. CGRP is a 37-amino acid peptide, again, located ubiquitously throughout the body, and it binds to a CGRP receptor, which is made up of a calcitonin-like receptor and a RAMP1 or receptor activity modifying protein. For a functional receptor, it must contain both components. Pretty simple? Not so simple. The calcitonin receptor family has turned out to be like the serotonin receptor family, quite complex. There are CGRP receptors, there are adrenomedullin receptors, there are calcitonin receptors, and there are amylin receptors in this calcitonin receptor family, and they are made up of different calcitonin-like receptors or calcitonin receptors plus different RAMP proteins that can further specificity. The importance of that is that CGRP binds equally potently as amylin does at the amylin receptor, and amylin binds with some degree of potency, albeit not nearly as potent as CGRP at the CGRP receptor. I will come back to whether or not that is going to have therapeutic advantages or whether there are any safety issues concerning that, but the

important take-home message is that CGRP binds not just to the CGRP receptor, but to other receptors, including the amylin receptor.

What is the difference between small molecules and monoclonal antibodies? Well you can see the size difference right off the bat. These are big proteins that do not readily cross the blood-brain barrier. The target specificity of these monoclonal antibodies is extremely high. They are highly precise therapeutics designed to meet a very precise target. The target specificity obviously of the small molecules is not quite as specific. The clearance of small molecules is through the liver and kidney, most of these are hepatically metabolized, whereas the clearance of the peptides, these monoclonal antibodies, are through the reticuloendothelial system. They do not go through the CP450 system. Obviously, size is a big difference, and because of that size, in part, monoclonal antibodies have to be parenterally administered either subcutaneously, at least insofar as the CGRP antibodies are concerned, or intravenously. We certainly do not think they enter the blood-brain barrier to any appreciable degree, but as we saw yesterday, if cortical spreading depression really does open up the blood-brain barrier and some attacks, is it possible that during attacks of aura that the blood-brain barrier opens up and these antibodies have access? We do not know, but they certainly do not enter the blood-brain barrier in native subjects to any great extent. The half-life is different. The half-life of small molecules is measured usually in minutes to hours, sometimes days. The half-life of these antibodies is around a month, maybe give or take a week or two. Small molecules should not have immunogenicity, but the monoclonal antibodies may have immunogenicity. The development of anti-drug antibodies is obviously an issue whenever infusing an antibody into a patient. The distribution of monoclonal antibodies in the CNS is minimal because of that blood-brain barrier, it is thought. These are just different tissue penetration figures for the monoclonal antibodies, and I guess what you will notice is that there is very little penetration into the brain. Again, we do not know what happens during migraine attacks, but there is also very little penetration into other tissues in the body as well, mainly confined into the systemic circulation.

Well, as I said, the proof of principle is in, and now, this is actually an old slide that was put together to just summarize the phase 2 studies. All of the phase 2 studies of these monoclonal antibodies have been positive. In fact, all the pivotal studies have been positive for three of the four antibodies. We will get into that in a moment. I highlighted just two things on the slide. One is that the Amgen monoclonal antibody, or erenumab, targets the receptor, and the other three antibodies target the peptide itself. That is one major difference. The other major difference is that the Alder antibody, or eptinezumab, is administered at least at this time intravenously whereas the others are administered subcutaneously. The half-life is roughly equivalent, around a month, and as I said, all of the phase 2 and now many of the phase 3 trials are positive. I cannot obviously get into

all of the details in the primary and secondary endpoints from each of these trials in the interest of time, but suffice it to say, when we look at responder rates, the responder rates of these monoclonal antibodies look equivalent to or superior than currently available therapies, with responder rates ranging from the mid 40s to the mid-70s when we look at 50% responder rates. Perhaps unique to these antibodies, a unique attribute, and it speaks to the disease specificity, is that the responder rate for some of these antibodies, 75% responder rates are appreciable actually. We are not used to seeing 75% responder rates that look quite like this. Obviously some of these look higher than others, but if you actually look at the therapeutic gain taking active compared to placebo, they all look very similarly effective.

I just want to highlight some of the unique therapeutic attributes of some of these antibodies, which I think is probably a class effect. Galcanezumab, Eli Lilly antibody, has been shown, at least in the post hoc analysis, to have a rapid onset of efficacy. This is a post hoc analysis done by Peter Goadsby showing that within 1 week in episodic migraine these antibodies have shown efficacy already and separate from placebo. The same thing has been shown with fremanezumab, the Teva antibody. That shows a rapid onset of efficacy not only within 1 week but even within as short a time as 3 days or 72 hours. That is a major difference when we are sitting there counseling our patients, because right now, well forever, we tell patients that you need to titrate the dose slowly and you need to wait for 2 months to see if it is going to be effective, and the full effect of the drug may not be until 6 months. Well, this is transformative because we will not be having that conversation anymore with patients, at least in those where we are able to prescribe these antibodies. There is no titration effect, and we may not have to wait nearly as long to see a therapeutic effect. They may also have a long duration of effect, and this is some of the data from eptinezumab, the Alder antibody, and I will just draw your attention to the 6-month response after a single intravenous infusion. You can see the 50% response is about 50%, 75% response is about a quarter, and about 11% had a 100% response after single intravenous infusion. So, the duration, not only is the onset rapid, but the duration may be a quite long for some of these antibodies.

The other interesting thing which we are paying more attention to now is the interictal burden. Of course, we defined the disability conventionally of migraine based on the attack and based on the disability associated with the attack, but the interictal symptoms, which I guess include both, and by that I mean prodromal, postdromal, as well as interictal symptoms when you are not in the postdromal or prodromal phase, because patients have symptoms referable to migraine and disability associated with migraine because of the state of the brain and trait of the brain in a migrainous subject even in between attacks. Some people spend a lot of time symptomatic in these in this interictal phase, and Juliana Vanderpluym who works with us did analysis of the Teva database showing that on headache-free days, in those who received the antibody

compared to those who received placebo, there was a significant difference in what we initially called wellness or at least in functional performance. So, patients were able to think more clearly and get things done. Their activities of daily living were much better on non-headache days compared to placebo. It suggests that these antibodies are not only having an effect in reducing attack frequency and in the genesis of an attack, but they are doing something else which we do not yet understand on non-headache days as well.

Another unique attribute of these antibodies and one that we all should be excited about, and our patients I know are excited about, is that the side-effect profile of these appears to be relatively benign. If you look at the dropout rates in patients exposed to conventional therapies compared to these monoclonal antibodies, it is not even close. That is true in the phase 2 studies and as well as in the phase 3 studies where you have dropout rates from 1% to 3% compared to 20% to 30% with some of the more conventional therapies that we use. There appears to be at least in all of the phase 2 and phase 3 studies, and I think there are now over 13,000 patients that have been exposed to these antibodies, no unique adverse events and no serious treatment-related adverse events.

I am going to give you just a little bit of update on what was presented at the American Academy of Neurology. There were several erenumab presentations at the American Academy of Neurology. These were the pivotal studies in both episodic and chronic migraine. Both doses separated from placebo. I am showing you the 50% responder rates in both episodic and in chronic migraine. Eptinezumab, which is the IV antibody from Alder, presented their data in chronic migraine, and their primary endpoint was 75% responder rate, and as you can see, about a third of the patients had a 75% response and at least two doses separated from placebo. So, they met their primary endpoint as well. They also showed that the intravenous formulation of this drug may work even quicker than 72 hours. There was a 50% reduction in the incidence of migraine within 48 hours after the infusion. That should not be surprising because Dr. Tepper just told us that the six small molecule oral receptor antagonists all showed acute treatment efficacy. So, it should not surprise us that either subcutaneously or intravenously administering one of these antibodies would have acute efficacy. That is my walk through the data. It should be said that last month, as I said earlier, there seems to be a press release every week, galcanezumab, the Lily antibody, announced positive pivotal trial results in both episodic and chronic migraine, and within the last week, including the last 72 hours, Teva announced in their episodic and chronic migraine studies positive results. They all met their primary endpoint, and indeed, Teva announced 48 hours ago that their episodic and chronic migraine trials met all 25 primary and secondary endpoints. So, the proof is in. As Dr. Tepper said, there has not been a single small molecule that has failed with respect to acute treatment efficacy,

and there has not been a single trial with any of these antibodies that has failed for episodic or chronic migraine prevention.

Now, that is the good news. There is no bad news, but there is some theoretical concern with blocking such a ubiquitous and potent vasodilator. That is because it has to be there for a reason. Is it there to provide compensatory dilation when the individual is under stress, for example, myocardial stress or cerebrovascular stress or hypertension? We do not know the answer to that, but we do know that CGRP is important for, to some extent, in maintaining vascular tone and for compensatory dilation. I think we are becoming increasingly reassured when you have over 13,000 patients exposed and you are not seeing any significant or serious adverse events, including cardiovascular adverse events, that these may be safe from a cardiovascular standpoint.

This was data presented actually in Boston last month during the American Academy of Neurology meeting, which showed that delivering erenumab 140 mg IV had no effect on the PK of sumatriptan, had no effect on resting blood pressure, and had no effect on any hemodynamic parameter when combined with 12 mg of subcutaneous sumatriptan, so that is relatively reassuring that when you combine a supramaximal dose of sumatriptan to a high dose of the antibody, there is no effect on blood pressure or heart rate. So, it should give some reassurance. All of these clinical trials, at least in those patients who did not get a 100% response, were of course treating their acute attacks, many of which were treating them with triptans, and so no adverse events were seen or were suggested that there is a problem when you combine a triptan with a CGRP monoclonal antibody, and this was reassuring data. This was actually presented at EHMTIC (European Headache and Migraine Trust International Conference), but erenumab does not induce contraction of coronary arteries nor does it interact with the contraction caused by sumatriptan. Looking at distal and proximal coronary arteries, you will see what happens with respect to constriction in blue caused by sumatriptan. You see that blue curve shows the contraction of coronary arteries when exposed to sumatriptan, and what you find in the green when you combine sumatriptan to AMG-334, in this case erenumab, it does not amplify or augment the constriction. That should be relatively reassuring as well. When you just give AMG-334 or expose the coronary arteries to AMG-334, there is no contraction of the coronary vessels. At least up to now, there is some reassurance at least through the clinical trial program and through some of these safety studies that there does not appear to be a major cardiovascular risk, at least in the population of patients that were studied. What we need now is data in diseased populations, patients with ischemic heart disease, patients with cerebrovascular disease. It is like the triptans. That was a healthy population in those triptan trials. What happens when you start to expose disease populations? That remains to be seen.

In the interest of time, I am just going to skip over that and end with this slide. There is evidence to believe that these antibodies may be effective for other headache syndromes as well, such as cluster headache, and we are looking forward to seeing the results of the cluster headache trials that are ongoing now with galcanezumab and fremanezumab, and in post-traumatic headache where we struggle with these patients almost on a daily basis to try to manage them. It appears that CGRP at least may be important initially in the pathogenesis of posttraumatic headache. Finally medication-overuse headache. Could these antibodies be effective in not only preventing the medication-overuse headache but in reversing medication-overuse headache? We are looking forward to, hopefully, some phase 3B and phase 4 studies that evaluate the effect, the efficacy, and safety of the antibodies in these patient populations where there is also a significant unmet treatment need.