Hello. My name is James Howard, Chip Howard to many of you, Professor of Neurology, Medicine, Allied Health at the University of North Carolina. Welcome to the CME activity, where we explore clinical research highlights presented at the AAN 2025 meeting on myasthenia gravis. What is myasthenia gravis? It's not a single disease, it's a group of rare disorders characterized by a disorder of synaptic transmission affecting the post-junctional membrane, most commonly due to antibodies directed against some component of the acetylcholine receptor. The trademark sign is fluctuating muscle weakness made worse by activity, improved with rest, only to recur when that activity is resumed. First described back in the 1600s. Ocular weakness is typically the most common presenting symptom, though other individuals may present with bulbar or limb weakness, and in the majority of cases, there is a progression from ocular symptomatology to generalized weakness typically within two to two and a half years, though rarely, it can extend much longer than that.

We have seen a transformation in the management of myasthenia, and since 2017, we've had six approved drugs here in the US. Eculizumab, efgartigimod, ravulizumab, rozanolixizumab, zilucoplan and nipocalimab, all essentially monoclonal antibodies or small proteins directed to target very specific entities causal in the development of myasthenia. Well, let's jump in and see what AAN provided us. In the first paper, I'd like to discuss, here by Thawani, is the global MG management and how things have changed over the years. We know that, in this study, which was a survey of 210 individuals in multiple countries around the world, thymectomy was recommended by the majority, but not all, typically more common in those with more experience and in developed countries. There did not appear to be any consensus in the management of MuSK myasthenia in terms of first-line therapy, and this highlights therapeutic uncertainty to some degree, though many of us would argue that B-cell depletion therapy, rituximab, is what we've had available to us being used off-label, was the most common therapy or the most efficacious therapy that we have.

Another topic of interest was pregnancy and the role of mycophenolate mofetil. It was surprising to me in reading this study that only 61% recommended discontinuation of the drug and a quarter of individuals continued the drug at a lower dose. There is a black box warning, at least in the United States, that this drug should be discontinued because of the risk of first trimester pregnancies, but to my knowledge, there is no good data as to whether the dose itself plays any role in that. In my practice, we discontinued the drug. Many individuals were treated with intravenous immunoglobulin as a way to carry them over during their pregnancy and pregnancy exacerbations.

What was also interesting to me was the role of cesarean section, most likely to be recommended in developed countries, and that's different from our own personal belief here, where we'd like the woman to have a natural childbirth, if at all possible, and safe for the individual, rather than a surgical intervention to deliver the fetus. I think both of these last things reflect the differences in practice norms around the world. Another real-world treatment pattern was a study by Grover and her team, looking at over 6,000 patients who've had disease in almost three years, and notice that there was a reduction in the role of cholinesterase inhibitors. Corticosteroids were quite prominent, up to 60% plus of patients. Non-steroidal immunosuppressants were increasing, originally from about 11%, 12%, up to 42%, and I think the practice is that, while steroids are a beautiful drug to treat the disease, it's a double-edged sword, given the adverse event profiles, and we're seeing a trend away from that in the role of non-steroidal immunosuppressant drugs.

Immunoglobulin also increased slightly, doubling from six to 16%, and the new targeted therapies, neonatal FcRn inhibitors, complement inhibitors, are slowly increasing in their use, around 3%, and I think this reflects the newness of the drugs, and I would anticipate that these will increase in use over

time. One of the difficulties we have is the payer perspective and what they will and will not allow in the treatment of at least US patients, and I think that has suppressed the use of these drugs as well.

What we're seeing is that, from the time or duration of disease to the time these targeted therapies are initiated, is quite prolonged. 18 months, 20 months, almost two years, and I think it's because we have to cycle through other therapeutics before we're allowed to use these drugs. Myasthenic patients exacerbate, and many do, more than half, typically within the first year and then decline yearly, but I think any patient exposed to a certain stress, infection, surgery, sometimes emotional stress may precipitate an exacerbation, particularly if their disease is not well-controlled.

Then what also surprised me was that a small number of patients had MG crisis, about 3%. This is atypical when compared to our research studies, our clinical trials, where we're seeing well over 25% of those patients who've had myasthenic crisis within the preceding one or two years, and I think that reflects the individual who wants to participate in a clinical trial, sicker to some degree, therefore, at greater risk for these exacerbations and crises.

Let's switch gears a little bit and look at clinical trial data, and the first I want to talk about is nipocalimab. This slide talks about nipocalimab, a recently FDA-approved drug for the treatment of myasthenia gravis and for children over the age of 12. What you see on the slide are the outcome measures and the response to the investigational product, nipocalimab, versus placebo over a period of a blinded phase, as well as at other areas or other time points.

2.8 placebo adjusted change in the QMG is quite in line with what we've seen with many of our other targeted therapeutics in the FcRn and complement class. Time to improvement is very rapid, as are our new targeted therapies, often within a few weeks, and this is no different. One sees that there is significant change in the overall QMG, what we call QMG responder analysis, where more than 70% of patients are improving, relative to those in the placebo arm of over 40%. Yes, myasthenic clinical trials have a significant, if not huge, placebo response, and we have to take that into account when we design our clinical trials, and a number of reasons for this. Not the least of which is the fact that this is a fluctuating disease, moment by moment, hour by hour, day by day, and when you examine them, may reflect how well they're doing. What side of the bed do they get up on? If they get up grumpy, they may do worse than if they came up happy and all smiley. But no question, nipocalimab performed quite well, as have our other FcRn inhibitors.

Zilucoplan is a small peptide, a 15 amino acid macrocyclic peptide that targets complement protein C5, and it's been approved for the use in generalized ACHR-positive myasthenia gravis. In this analysis by Michael Weiss at the University of Washington, we looked at the response to the various domains, ocular, bulbar, respiratory, and axial, based on the quantitative MG score, the MG-ADL score, and one sees that favorable responses were seen in each of these domains relative to the placebo arm of the trial. This post-hoc analysis gives proof that the effects of these drugs are over all parts of the MG axis, if you will, and not restricted to simply limb weakness or bulbar weakness, that we're seeing global effects of improvement, and this improvement was consistent across all aspects of the trial.

The other trial I want to talk to you about is inebilizumab, an ACHR-positive in MuSK MG, the MINT trial led by Richard Nowak at Yale University. Here, 119 patients received drug, 119 received placebo, one of the largest trials ever in myasthenia gravis, and clearly, there was beneficial response in both the ACHR-positive arm and in the MuSK arm at the primary endpoint of 26 weeks. Further analysis extending to 52 weeks for the ACHR-positive group was also significant. This drug depletes B cells by targeting CD-19, much like rituximab targeting CD-20, and this has an effect on a broader range of our B cell population. The results were encouraging, and through the blinded portion, we saw additional improvement as we rolled over into the open label clinical part of the trial.

The other trial was by Kelly Gwathmey at the VCU, Virginia Commonwealth University, in Richmond. Looking at a flexible dosing pattern for efgartigimod, an IgG1 fragment targeting the neonatal FC receptor. Originally, this drug was dosed in a cyclical fashion, dosing once a for four weeks, observing the patient, re-dosing when there was a return of symptoms, and that produced a bouncing rolling hill construct, which we found, as clinicians, not really what we wanted to see. We want to get somebody improved and keep them there. We didn't want to have to wait for them to have deterioration to retreat them, but payer requests or payer rules, et cetera, mandated that we had to do it in this particular fashion with this dosing cycle.

A dosing paradigm was designed where the patient was loaded over four weeks and then administered efgartigimod every two weeks, and we found that the degree of improvement was quite similar, the number of patients in terms of achieving minimal symptom expression, a subset of the MG-ADL score in those individuals who achieve either a zero or one, implying that there's no clinical disease, were quite similar. The adverse event profiles were similar with upper respiratory tract infection, urinary tract infection, mild headache, et cetera. This was done during COVID, so we saw COVID infections both and no new safety signals were seen, but clearly, the patients achieved stability, maintained stability over this dosing cycle and did quite well, and the degree of improvement was quite similar as we found in the original ADAPT trial.

The next study I want to talk to is one by Tuan Vu at Florida, looking at the long-term subcutaneous administration of efgartigimod in generalized myasthenia gravis. The original efgartigimod trial was intravenously, weekly times four, as I said. Here, it was administered subcutaneously on a very similar cycle, every four weeks and observed, and there was a non-inferiority trial originally that demonstrated no difference. This long-term safety trial demonstrated that patients had very similar adverse event profiles to the original inferiority trial, that adverse events were quite similar with injection site reactions being most common. There were no discontinuations of the drug due to these injection site reactions, and the degree of MG-ADL improvement was quite similar to the IV in the previous non-inferiority trial, more than a four-point change at week four, following the first cycle. This response in the ADL score was consistent, it was repeatable with each dosing cycle.

More than half, 55% of patients, achieved minimal symptom expression, an ADL score of zero or one at any point in time across nine cycles of administration, and improvements in quality of life were quite similar and patients tolerated this drug quite well. We feel it works as well and is a patient choice whether one receives intravenous or subcutaneous administration. The next trial I want to talk about is one by Mahuwala and their team, looking at the effects of rozanolixizumab, or rozi as we call it, in terms of control of ocular symptoms. One sees in the top bar the various dosing, because this was a two-dose trial versus placebo, that similar improvements were seen when given active drug and these improvements outweighed those seen with placebo, whether it was double vision, whether it was ptosis, both in the ADL as well as in the QMG score, and then a patient-reported outcome measure specifically dealing with double vision in end ptosis. In all instances, very favorable responses were seen in the ocular domains with this FCR inhibitor, rozanolixizumab.

The next trial that we're going to talk about was a switch trial, where we took patients from intravenous complement inhibitors, targeting complement protein C5, and switched them to subcutaneous zilucoplan. This study was led by Miriam Freimer at Ohio State University. In general, comparing all of the IV patients following their switch to sub-Q, there was additional improvement in the symptom scores, ADL, QMG, et cetera. Notably, those individuals on eculizumab didn't have much additional improvement, if at all, when they were switched to zilucoplan, but those on ravulizumab had considerable improvement. One would suggest that, if your patient is not up to perfect snuff with ravulizumab, a switch to zilucoplan may give them the additional benefit of the drug.

Looking at outcome measures related to global satisfaction, effectiveness, convenience, all favored the subcutaneous administration relative to intravenous administration, and our own experience, we find that the elderly population actually prefers IV over sub-Q, because they go to the infusion center and it's a social event to meet with their friends that they see every period, depending upon what their dosing interval is. Our younger people, the business individual are the ones who are favoring, the student, are favoring subcutaneous administration, because of convenience. Again, it becomes, really, patient choice. The Spotlight Registry was a real-world effectiveness study of ravulizumab, and looking at various outcome measures before the initiation of C5 inhibitor and then what their last score was on ravulizumab. Some of these individuals were those who are on eculizumab who then transitioned over to ravulizumab. One sees from this table where we have the ravulizumab -only group from nothing, to those who are on standard of care to eculuzimab to ravulizumab.

One sees that very consistent response and improvement in the MG-ADL score, the percent of patients achieving minimal symptom expression much better than what they were prior to the initiation of a complement inhibitor. Again, I think we're finding that our targeted therapies, whether it's complement inhibition, neonatal FCRN inhibitor use do much better than what we've seen with our standard of care. Not to say that everybody will. Clearly, that there are those individuals who receive a drug. Some individuals clearly are not going to get better or have the degree of improvement we'd like, but in general, the majority of patients are going to do well.

Self-administration of rozanolixizumab was looked at by Vera Brill at Toronto, taking 62 patients and then administering this drug through a subcutaneous infusion. This is not an injection like efgartigimod, like zilucoplan. This is a 10 to 20-minute subcutaneous infusion through a pump. Patients were able to self-administer this, 100% success rate. One saw improvements at week seven that were sustained, much like the original trial. The rates of adverse events were quite similar, most commonly headache in 20% of the patients. None of these events were any different than what we're seeing in the original trial, but clearly, patients were capable of doing this themselves.

The next paper was by Antozzi et al, looking at the long-term efficacy and safety of nipocalimab, a neonatal FC receptor inhibitor, and looking at 137 patients over the long term, one sees that there was efficacy, the change of ADL from baseline that was quite acceptable. Safety was well-tolerated, no new safety signals were seen, and many of these drugs in this asset class are very similar. Some with headaches, some with urinary tract, upper respiratory tract infections, et cetera. There were no new signals at all. Sustained improvement was seen across the 72 weeks of observation. Let's switch gears and talk about some real-world data. The next trial we're going to speak about is by Vera Brill, again, from Toronto, looking at the efficacy of intravenous and subcutaneous efgartigimod in those patients who were antibody-negative to the acetylcholine receptor. We took a subset of those enrolled in the ADAPT plus study and the ADAPT sub-Q and sub-Q plus, studies and 56% of them did not have antibody to acetylcholine receptor.

Clinical meaningful improvement, that is a two-point change in the MG-ADL score, sustained for more than four weeks was seen in more than 75% of these individuals. Minimal symptom expression, MG-ADL score of zero-one in almost a quarter of these patients during the first cycle. This was reproducible, this was durable across all cycles of infusion that these folks received, or injection that these folks received. Very comparable results regardless of the administration of the product as well as how it compared to those who had antibody to the acetylcholine receptor. The next study we're going to look at is by Rup Tandan at the University of Vermont, who evaluated the impact of ravulizumab on hospitalization rates and patients with ACHR-positive generalized myasthenia gravis. Call your attention to the last two lines. Prior to initiating a complement inhibitor, either ravulizumab alone or those individuals on eculizumab that transitioned to ravulizumab, 71% in 52% of patients had MG crisis or exacerbation.

In contrast, the last line, we saw, once on complement therapy, no patient had a crisis or an exacerbation during the time of this evaluation. Hospitalization rates improved in numbers of patients, as you can see, were substantial, who had more than one hospitalization. More than nearly half the patients in these groups required more than one hospitalization prior to complement inhibition. Again, supporting the role of new targeted therapies and the overall improvement in the patient's wellbeing in terms of their myasthenia gravis. Narayanaswami, at Harvard, looked at the ability to reduce the dose of non-steroidal immune suppressant, drugs after the initiation of efgartigimod an FcRn inhibitor, and looked at the changes in mycophenolate, mofetil, and azathioprine after at least a year's use of efgartigimod. This was retrospective claims data analysis. Of course, it has its limitations, but there is no question, as you look at the table, that the dosing for each of these drugs was substantially reduced with time. One may argue that, "Why couldn't it be more than that?"

We know that, at least with standard of care administration, that reductions in dose must occur slowly for fear of exacerbation. With the addition of a new targeted therapy, can we go faster? We have no data, and my impression would be that, as we follow these patients even longer over time, these dose reductions would increase even further. There was another study, looking at the hospitalization exacerbation outcomes following efgartigimod by Smith and their team. They compared hospitalizations, exacerbations, crisis rates in the year prior to being treated with efgartigimod and following. Again, claims database, and with those caveats, one sees there's more than a 50% plus reduction in hospitalizations regardless of cost, 60% plus reduction. Those that were MG-specific, exacerbations were reduced by 68%, crises by 71% with the introduction of efgartigimod to the treatment program. The Myasthenia Gravis Foundation of America maintains a global registry, and this interesting study by Chowdhury looked for identifying factors that were associated with self-reported exacerbations.

The MGFA registry is a self-reported instrument, got almost 1,400 patients in the registry, they looked between the periods of 2013 and 2023, so a 10-year period, and then analyzed the self-reported data. What seemingly linked with an increased risk of exacerbation? Interestingly, the depressed individual, the anxious individual, individual living alone, those who are on corticosteroids and those who had higher MG-ADL scores seemingly had increased risk. In contrast, those who had a decreased risk for exacerbation or those who had ocular onset and symptomatology, who had non-steroidal immune suppressant use, and who had a time from diagnosis of at least two years.

Why these links? I'm not sure I can give you great answers for it. It's interesting, it's data that I think we need to follow up, but clearly, psychosocial and clinical baseline factors do play a role in at least allowing us to identify those who are at risk, perhaps to track them more closely. Ideally, perhaps with a wearable aid or something of that sort, but that's research for the future. We're going to speak about stem cell transplants in refractory MG and a long-term analysis. This involved 21 patients, it's a study by Beland and their team, and they followed them over six, seven years. They had disease for at least four years, had difficulty gaining control, and thus, were recommended for this form of therapy. Efficacy was impressive, almost 90% had marked improvement, remission without treatment, and we've not been able to reach those responses yet with any of our current trials. That's a huge plus, and as I said, the durability of remission was approaching seven years.

The problem was the toxicity, if you will, the deaths. While it provides durable improvement in remission in refractory myasthenia, there is substantial procedural risk for deaths too early in relation to the actual procedure. One has to think carefully about medically complex patients and whether this is something that one would want to consider in these individuals. I think there are newer therapies that are in the pipeline that could supplement this. I'm thinking of CAR-T primarily, that may be a reasonable alternative that might mitigate against the risk that we see with stem cell therapy, but the procedure

gave us an insight in terms of disease responsiveness and gives us clues on where we need to look in order to capture long-term improvement in these individuals. For that, the trial was a huge success in my mind and has opened the door for us to explore other avenues.

The next one I want to discuss is a clinical trial by Tuan Vu, talking about Descartes-08. It's a messenger RNA CAR-T program, totally different from DNA-based CAR-T, which is the common form of CAR-T initially developed for the treatment of malignancy. This uses messenger RNA, so very precise dosing can be administered, and 36 patients total, 31 were able to be evaluated. The outcome measure of interest was a five-point change in the myasthenia gravis composite score, and those receiving Descartes-08, twice those in the placebo, 67%. When we look at the ACHR-positive population, because this included other serologies, it was 64 versus 20%. These are substantial improvements, as you can see, in both the MGC, the ADL, et cetera. What's critically important is to recognize that the safety of this was very exciting to see. There was no cytokine release syndrome, there was no ICANS, the immune effector neurological abnormalities.

These two outcome or adverse events are commonly seen in those receiving DNA-based CAR-T. There were minor infusion reactions all resolving within 48 hours and no patient had any adverse event after month three of the program. Durability was in excess of a year in many of these patients. My own personal experiences, patients went 18 to 24 months with a clinical-free disease, and so it's a new exciting... The other potential of this form of therapy is that it's repeatable, and as the patient lost the response, because it's not ingrained into the genome at all, it's simply in the messenger RNA, so it has a finite life, and one can re-dose the individual, and patients have been re-dosed and have done quite well. The long-term efficacy of this trial was published on August 26th, 2025, and is there in print. This trial by Bin Najib and the team looked at the long-term use of eculizumab in refractory myasthenia gravis.

Again, as one sees that clear differences in the ADL, the QMG, the composite QO15, were measured. Only the ADL and QMG were statistically significant, and the other two were not. Different from some of the other trials, this was a meta-analysis of only four trials, and it reflects variability that I think we have to understand further. Is it the population that we're studying? Is there anything related to their prior treatment courses that may impact the results? I think, while this is a signal, it's telling us that we need to look deeper and look further, and with that, team [inaudible 00:34:09] are going to do so.

Let's talk about some clinical pearls. We look at the FcRn, we look at complement, we'll speak about that in a minute, but do we target downstream or do we target upstream? Our downstream therapeutics include the FcRn inhibitors, include the complement inhibitors, and they clearly have advantages. This may become monotonous, because they're quite similar. We see rapid, we see sustained improvements in virtually all of our outcome measures that we use, and their safety profile is very narrow and very acceptable for these drugs. There are differences with each product in terms of which adverse event may be a little more frequent than another, but in general, they're quite similar. Long-term disease control can be maintained and has been demonstrated for nearly 50 weeks in open-label extension trials, but the drug has to be repeated over and over, and the same holds true for whether it's nipocalimab, the two dosing paradigms of efgartigimod, and rozanolixizumab.

With efgartigimod, fixed dosing versus biweekly dosing produce similar effects. Sub-Q formulation, durable symptom response, much like the IV counterpart, and there are reductions in hospitalizations, exacerbations, et cetera, and we see this across the board. Rozanolixizumab, the data presented at AAN, tells us that ocular symptoms are quite responsive to these compounds or to this compound in particular, and I would suggest that probably to all the compounds. That self-administration, even though it's an infusion, a subcutaneous short-infusion, can be done by the patient. Self-administration is

feasible, well-tolerated, and safety is maintained. In terms of the complement inhibitors, ravu has demonstrated as that durable improvements in MG-ADL and the outcome scores of the myasthenia gravis post-intervention analysis are durable and can be maintained. Hospitalization rates fall, particularly in the biologic naive patients, and post-treatment admissions are mostly unrelated to MG with no reported crises, exacerbations.

With ecu, meta-analysis confirms its efficacy in refractory myasthenia with consistent improvements in the ADL and the MgC, as well as quality of life. Zilucoplan demonstrates improvement across all subdomains, the ocular, the bulbar, respiratory, et cetera, with high patient satisfaction. Each of these classes of drugs were targeting downstream, and as I said, rapid, sustained improvement with very narrow adverse event profiles. Cell-based and immunomodulatory therapies, here, we're targeting upstream, and so we expect that the onset of effect is going to be more delayed. We would like to see, and I think we are seeing, very good efficacy with these therapeutics, but it's different from the two that we've spoken about, because durability will be much longer. We're going to see longer time before we have to retreat. Clearly, with autologous stem cell transplant, nearly seven years in remission with Descartes-08 RNA-based CAR-T targeting the B cell maturation antigen. We're seeing efficacy that approaches two years before we need to retreat.

I think those are going to be the key differences, and we're going to have to then decide, "How do we rank these? Where do we place these in our therapeutic armamentarium? Do we use one group to initiate treatment and come along with something that's going to be much longer-lasting, less frequently dosed, for instance?" We'll see that in terms of other B cell inhibitors that are coming and will be approved, hopefully, in the next several months, by the end of 2025, that target B cell and B cell antibodies. Real-world treatment patterns, we said typically are used later in the treatment course. I don't think that's really the clinician's choice. I think that's been imposed upon the clinicians by a variety of health ministries and payers, because they work so quickly, because they have therapeutic adverse event profiles. Many of us would like to see them used earlier in the course of disease.

Cost is the elephant in the room, however, and that has to be taken into account. Clearly, health disparity across the world is huge for these expensive therapies, so while they have distinct advantages from a societal perspective, we still have a lot to work out. The MGFA registry analysis was an interesting one, and what are the risks for exacerbation and symptom worsening? Generalized disease, anxiety and depression, the use of corticosteroids, living alone, raising interesting questions that I think need to be developed further. Protective factors include the use of non-steroidal immune suppressants, plasma exchange, an older age, et cetera. I don't think we have good answers for the reasons why, and as I said, it's a call to arms to explore this further as we go. Well, I would like to thank you for your attention, I hope this was of benefit to you, and everyone, have a good day. Thank you again.