**Episode 66 Transcript: *Fenebrutinib in PPMS: Insights from ACTRIMS Forum 2026***

In this episode, fenebrutinib PPMS trial leads Prof. Amit Bar-Or (University of Pennsylvania) and Dr. Stephen Hauser (University of California San Francisco) discuss newly presented Phase 3 data on fenebrutinib in primary progressive multiple sclerosis (PPMS), shared at ACTRIMS Forum 2026. The conversation explores the scientific rationale for BTK inhibition, the key findings from the FENtrepid trial, and what the results may mean for people living with progressive MS. Listen to the full episode here.



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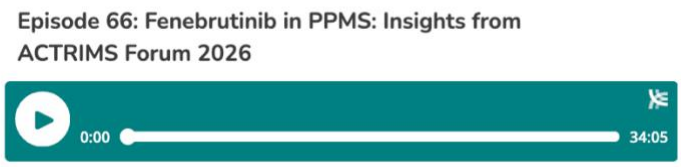


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Amit Bar-Ohr
Hi, my name is Amit Bar-Or. I'm a neurologist and neuroimmunologist at the University of Pennsylvania.

Stephen Hauser
And I'm Stephen Hauser, also a neurologist and neuroimmunologist at the University of California, San Francisco.

Brett Drummond

And I'm Brett Drummond. You're listening to the ECTRIMS podcast, the official podcast from the European Committee for Treatment and Research in Multiple Sclerosis.

Welcome to this special episode. Just moments ago, new clinical trial results for fenebrutinib in primary progressive MS were presented at ACTRIMS Forum 2026. We've had a brief press release pointing to positive outcomes, but today is the first time we're seeing the full in-depth data, and that's where this episode comes in. BTK inhibitors have been one of the most closely watched therapeutic areas in MS, with huge interest around their potential to target disease activity in a new way.

In this exclusive episode, we're joined by two of the trial leads, Amit and Stephen, to unpack what these findings really mean. What stood out in the data, how to interpret the results, and where could this take the MS treatment landscape next? Let's get into it. Amit, Stephen, thanks for joining me.

Brett Drummond
So I think before we get into the trial itself and there's a lot to unpack from what we've just heard, let's just talk really briefly about the use of BTKis in MS. They're relatively new in terms of the field. There's been a few that have been investigated, but what's the rationale for why we're interested in using these class of molecules in the treatment of multiple sclerosis?

Amit Bar-Ohr
So Brett, we now think of MS involving two different processes that can contribute to injury to the central nervous system. One involves immune cells in the periphery that through their interactions may mobilize and traffic to cause infiltration and injury that is perivascular and associated with the acute inflammatory relapse biology, if you like. And those interactions almost certainly include important B cell, T cell, and possibly myeloid interactions in the periphery.

The other issue, though, is that there's within the CNS compartmentalization of processes that almost certainly include some inflammation. Some of the cells from the periphery tend to set up shop in the CNS, principally B cells, and their presence may contribute. But also, importantly, activated glial cells in the chronic state are now thought to be very relevant for the non-relapsing progressive aspect of MS. It turns out that BTK is a molecule that is upregulated during the activation of several cells of the immune system, particularly B cells and myeloid cells, which in the central nervous system include the microglial cells. And inhibition of BTK therefore leads to decreased activation and in fact a shift in the response profile of B cells, myeloid cells in the periphery and compartmentalized B cells presumably and microglia within the CNS. We've been able to achieve pretty good control of relapsing disease biology, but much less so of course in terms of progressive biology.

And wouldn't it be great if a single treatment could target both the peripheral mechanisms involved in relapse disease as well as the CNS compartmentalized ones involved in progressive disease. And the BTK inhibition, particularly by CNS penetrant BTKis has been an exciting area for us to pursue with that goal in mind.

Stephen Hauser
I agree completely, Amit. And in fact, if one were to dream of a perfect cell target for people with chronic MS, it would be very hard to do better than a BTK inhibitor. Given what you've said about the critical importance of B cells in relapsing and also to some degree in progressive biology and the very evident importance of pro-inflammatory microglia in the central nervous system that are likely culprits in progressive biology unrelated to focal new inflammation.

And Bruton's tyrosine kinase inhibitors, as Amit has said, focus their activity on the activation process of B cells and microglia in the nervous system, the two cells that I think one would most like to have control over.

And the FENtrepid trial illustrates that this approach could be extraordinarily helpful, not only in controlling relapses, but controlling the progressive neurodegenerative component of disease that is the most important problem in 2026.

Brett Drummond
Yeah, and so obviously, I think there's, for all of the reasons that you've both just described, a lot of interest and a lot of hope for what BTKis might deliver. I think you've both also really importantly mentioned the difficulties that we've had targeting progressive biology in people living with MS. Now the FENtrepid trial, which is the trial where the results have just been discussed at the ACTRIMS Forum was in a cohort of people with primary progressive MS. I want to spend a little bit of time talking about the trial design behind that, because I think it was interesting that this trial was set up as a non-inferiority trial with an active comparator, which is something that we're seeing more and more of in MS trials. Can you talk us through exactly how the FENtrepid trial was set up and why decisions were made to use that sort of trial design?

Amit Bar-Ohr
Yeah, so I think the FENtrepid trial to many of us is viewed as a pretty brave trial pitting a BTK inhibitor against ocrelizumab, which is, as you know, the currently only approved treatment for primary progressive MS and one that has been viewed as a high efficacy treatment in our field. And so FENtrepid is a phase three multi-center study. It was a randomized clinical trial that recruited patients with primary progressive MS. Their ages were between 18 and 65 and an EDSS that was at least moderate from 3 to 6.5. It was a randomization of one-to-one, either to fenebrutinib, which is taken as a 200-milligram tablet twice a day, or ocrelizumab at the standard therapeutic dose, and it was double-dummy in its design. And in essence, the study had to have people in for at least 120 weeks each, but also somewhat more than 480 events of the primary outcome in order to power the study for likely non-inferiority primary outcome measure. And the C-CDP-12, which is the composite confirmed disability progression at 12 weeks, is made up of three different elements that form the primary outcome. And the individual could meet that primary outcome by meeting either of those three, one of which was the CDP-12 week of the EDSS, with the usual one point or more change for EDSS is less than 5.5 and 0.5 point change in the EDSS of greater than 5.5 range. The other way to meet the primary endpoint would be 20 % or more increase in the timed 25 foot walk. And the third one would be a 20 % or greater increase in the nine-hole peg test test. And so as you pointed out, this was an active comparator against ocrelizumab and was designed as a non-inferiority study.

Stephen Hauser
Yes, and for those of us who don't often think of non-inferiority studies, these are studies where testing against a placebo or a therapy that barely works is either impractical or in this case, perhaps even unethical.

And it is a study that is designed around creating a confidence interval that falls below the margin of what would be a clinically significant difference in the standard therapy, ocrelizumab. To be certain that the results that we see preserve the standard treatments effectiveness. And as we'll hear as we go forward, ocrelizumab was effective, we think, in this study. But more important, fenebrutinib actually by some secondary measures did a little bit better. And even on the primary measure did a little bit better numerically.

Very important, I think especially when we begin to examine the data in greater detail and recognize that this effectiveness of fenebrutinib is also present and in fact powerfully present in patients with less evidence of inflammation during the course of the study.

Amit Bar-Ohr
Yeah, that's exactly right, Stephen. And in fact, in terms of the entry baseline characteristics, the groups ended up being very well balanced overall, including in terms of the proportion with the presence of GAD lesions at baseline as a measure of focal inflammatory disease. And they were low in both groups, about 10,

11 percent. So this was a population of patients with primary progressive MS with very little focal inflammatory disease activity at study entry. And as you pointed out, in terms of the primary outcome, there appeared to be a separation between the trajectories of confirmed composite disability progression between the two arms already at week 24 that persisted throughout and that the curve for fenebrutinib nominally was always favorable to the ocrelizumab, which resulted in about a 12 % risk reduction in terms of the hazard ratio. And as you pointed out, the statistics here allow for the confidence interval of the hazard ratio to go on both sides of unity, which in a superior trial, superiority trial would be viewed as non-significant, but there's a limit to how high above unity it can go. And indeed, the result of this study had the upper limit of the confidence interval well within the range of what would qualify for non-inferiority of fenebrutinib versus ocrelizumab.

Brett Drummond
So think if we start to unpack those, the trial results in a bit of detail, because that's obviously what people are really interested in and what has just come out in the presentation. You talk about the composite test and you had the three different measures here that you were looking at. Can you go through the results seen across all of those composite measures and was there any difference in terms of which ones seemed to be contributing more or seemed to be having more of an effect with the fenebrutinib?

Stephen Hauser
Yes, well, as was stated earlier, the primary endpoint was the composite CDP, which is comprised of the EDSS, 25-foot walk and nine-hole peg test. And that was numerically favoring that. And that study, sorry, the composite score successfully demonstrated non-inferiority, as we said before, numerically favoring the fenebrutinib arm. But the most favorable data when the components of the composite were examined individually turned out to be the nine-hole PEG test and then the EDSS and not the 25-foot walk.

And if we had used the composite CDP that had been used for the ocrelizumab hand study, the O-HAND study, which was comprised of the composite of the EDSS and 9-hole PEG test, one would have had a more than 20 % reduction in composite CDP favoring fenebrutinib.

Another interesting point for people often is how different subgroups behave with respect to the primary endpoint. And here, essentially, all point estimates of subgroups were left of unity, meaning a hazard ratio of less than 1.0, favoring fenebrutnib versus the ocrelizumab. There were no particular differences whether you were younger or older than 55, nor whether your EDSS was five or less versus five or greater, the one point estimate that was right of unity actually related to the presence or absence of GAD lesions at baseline. And so the group that had the GAD lesions present at baseline, which only comprised, as we mentioned, about 10 to 11 percent, and hence was a smaller group and therefore a much larger confidence interval, was the one that crossed unity. But the one with the absence of GAD lesions, the larger segment of the population, actually had a favorable hazard ratio. Again, reinforcing the point, that the treatment effect that we're seeing her for fenebrutinib is likely to be playing out on the non-relapsing biology of MS, the progressive biology.

Stephen Hauser
I think that's important point, Amit. I always do cross trial comparisons with trepidation.
But it's worth looking at the baseline characteristics of the 2017 ORATORIO primary progressive MS trial with ocrelizumab and contrast it to FENtrepid. And the population in the original ocrelizumab trial had, as Amit said, more gadolinium enhancing lesions at baseline, a longer disease duration, and yet similar EDSS character as in the study being reported out today. So in some respects, the baseline characteristics suggest that the population studied in the FENtrepid was a more progressive, more neurodegenerative and less inflammatory population.

And that combined with the data showing efficacy favoring fenebrutinib in the population of patients without gadolinium enhancement at baseline argues for an effect that is due at least in part on microglia and

innate immune mechanisms. And I think that's enormously exciting for patients with primary progressive MS who may have had more chronic disease and less inflammation yet accumulating disability.

Amit Bar-Ohr
Exactly.

Brett Drummond
And I'm really glad that you brought up looking at this subgroup analysis and seeing, you know, whether there was a difference across any of those, because I think we've certainly seen in trials recently that, you know, there may be more of a mixed effect, but when you narrow it down to certain groups, you can see that effect amplified. And I thought it was quite noticeable in these trial results that that wasn't necessary, that across all, you know, this benefit was observed across all cohorts.

I'm interested to know from a personal perspective, did that surprise you at all? And just to follow on, I guess, from comments that you've made explaining that already, do you think that speaks to the strength of the cohort selection in this trial in terms of how well-defined you think this population was as a progressive cohort?

Amit Bar-Ohr
Well, I certainly was pleased with the findings. I'm not sure, surprised, just because certainly we were hopeful and went into this with a rationale that we described at the beginning. And I think that the population selection we've been learning repeatedly is critical for trial outcomes. If you don't have the disease biology of interest that's going to sufficiently play out in the group in your control arm, you're not going to be able to see a benefit of your active intervention. And so we learn about the importance of the populations. We learn about the importance of the selection of the outcome measures. We talked about different elements of the composite confirmed disability progression outcome. And I think that part of our reality is that there's luck involved. But I think we're trying as a field to do better and better. And this is an example of a trial where we were able to demonstrate the non-inferiorityin part based on the population selected and perhaps even in part in spite of the outcome measure perhaps not being the best outcome measure for this population.

Stephen Hauser
Yes, I agree. And I think it was fortuitous that we had a somewhat less active population, at least by history, in this study compared with some of the other earlier ones, because it permitted us, in retrospect, to examine progressive biology independent of focal inflammation more closely.

Brett Drummond
Moving on from the trial results, I think it's important in a discussion of BTKis to talk about safety and adverse events. This is obviously something that we've seen played out across a number of the trials of BTKis in MS populations. Can you talk to us about what safety issues, adverse events were found in the FENtrepid trial?

Amit Bar-Ohr
Sure. So overall, there were similar proportions of patients who experienced any type of adverse event, and there were no differences in serious adverse event frequencies. There were more adverse events that led to withdrawal in the fenebrutinib arm compared to ocrelizumab, and almost all of those were because of elevations in liver enzymes, which you can talk a little bit more in detail about. And there was also an imbalance in the fatalities, with seven fatalities in the fenebrutinib arm and one fatality on the ocrelizumab arm, which I think is important for us to also delve into. I can start commenting perhaps about the liver enzymes, Stephen, if you want to follow on to, yeah. So the liver enzyme elevation, which of course we've

now recognized as an issue in the context of at least some, if not most of the BTK inhibitors, born out, not surprisingly, in the fenebrutinib trial as well.

There were about 13 % of individuals in the fenebrutinib arm who had some liver enzyme elevation of three-fold greater than upper limit normal as compared to about 3 % in the ocrelizumab arm. There were relatively few who had elevations that were much higher and those that were above 20 times upper limit normal occurred only in 0.6 % of the fenebrutinib arm and 0.2 % of ocrelizumab, so very low proportions. There were no confirmed Hy's law cases in either arm.

There were two individuals who qualified for what's called biochemical Hy's law in the fenebrutinib arm and one in the ocrelizumab arm. And biochemical Hy's law is when you have an elevation of greater than three times upper limit normal of the liver enzymes with at least a two-fold elevation of bilirubin. And it is a biochemical Hy's law as opposed to a confirmed Hy's law if there are alternate explanations. And in all cases, there were indeedalternate explanations for these liver enzyme and bilirubin abnormalities. And then it's noteworthy that the ALT elevations were predominantly within the first 20 weeks of treatment, and they were essentially all reversible and came down quite quickly when drug was discontinued.

Stephen Hauser
So maybe I would add a few points stepping back a little bit and trying to put these changes in context. Like with anti-CD20 monoclonal antibodies as a class, I think that it is important to recognize that all BTKs are not bioidentical molecules. They are all different. Some bind covalently, some bind non-covalently.

But as kinase inhibitors, importantly, the selectivity of the BTK molecule is very important because there are off-target effects with many, particularly the first generation BTK molecules. I think what makes fenebrutinib and also remibrutinib more unique among the BTK inhibitors that are being tested in MS is that they are highly selective. Fenebrutinib is a non-covalent, so it's reversible, whereas remibrutinib is a covalent binder, as are the earlier BTKs, the evobrutinib and tolebrutinib tested in MS. And the LFT abnormalities appear to be present though, irrespective of the selectivity of the drug. It may be a class effect of the BTK. Why this is happening is not entirely clear. Is the abnormality and its early appearance due to BTK expressing Kupffer cells in the liver. Removed or inactivated, the signal will disappear. And a number of, most of the patients in the FENtrepid study were able to continue treatment despite the LFT transient change. So I think there's much to learn about the ALT and LFT abnormalities associated with BTK inhibitors. And there will probably be private lessons for each molecule along with public lessons for the class.

Amit Bar-Ohr
I think that's absolutely right. And it's interesting that, again, this is one of those adverse events that if only we knew who the relatively few were who were at risk, everybody else would be spared the risk. There are a lot of efforts ongoing to try to understand how to identify these individuals. As you point out, Stephen, the mechanism is really not that clear. And it's also interesting that it seems that if you don't experience the elevation over the initial period, you're not going to experience it with further exposure.

That hopefully will help us in terms of risk mitigation strategies when we see these agents approved.

Brett Drummond
Yeah, and do you have any, obviously we're recording this and this episode is obviously focused on fenebrutinib, but we're recording it on the backdrop of an FDA decision on tolebrutinib in non-active secondary progressive MS where they have chosen at this stage not to approve based on the risk of drug-induced liver injury. Do you have any feeling based on the results that you've seen out of this?

Obviously we can't predict what's going to happen from a regulatory perspective, but do you see differences in terms of that that may be more favourable for fenebrutinib?

Difficult question to answer, I know.

Amit Bar-Ohr
It's difficult to comment in terms of numerical comparisons of frequency. Certainly there have been differences in terms of patient year exposures that one would have to somehow adjust for. My sense is, and Stephen can comment, that there seems to be a lesser frequency with fenebrutinib of the particularly high LFT elevations and the concern over Hy's law type numbers.

To what extent is that because, know, tolebrutinib started after evobrutinib and then we learned and were more vigilant and decreased exposure? It's a fair question. But hopefully we'll learn as the phase three trial programs complete for fenebrutinib that the risk of more serious liver abnormalities is on the low side.

Stephen Hauser
I think that's correct. Everything is in the data. And the data will need to be examined for each individual trial with each molecule. Another point that the BTK inhibitors has already taught us and is teaching us more and more as data are examined and more trials become available is that we really develop roadmaps for disease. We learn so much about disease by the results of the clinical trials that then send us back to the laboratory armed with new questions and ideas. Thinking about the tolebrutinib trial,it has been very hard for us to identify a pathologic, immunologic or genetic biomarker that distinguishes SPMS from PPMS. It could be that the discordant data in PPMS and SPMS in tolebrutinib is due to something about the trial design or the population study.

But this could also bring us back to the laboratory to ask, are we certain that the driving pathologies, the driving immunology behind SPMS and PPMS are as similar as we thought?

Brett Drummond
Yeah, I think questions that we could probably spend a very long time talking about this and trying to unpack all of this and lessons learned. But did you want to comment, I know it came up briefly at the start of this in terms of the increased fatalities and how it was mentioned in the presentation as well. I think it's probably an important thing to comment on briefly around that coming out of the FENtrepid trial.

Amit Bar-Ohr
Yes, I think it is certainly important. The fatal events included one individual who died of COVID-19, very unfortunately not vaccinated against COVID-19 in the fenebrutinib arm, one episode of diabetic ketoacidosis with an insulin pump failure. So again, very unfortunate in the fenebrutinib arm. There was one fenebrutinib treated patient with a myocardial infarction. This individual had no other identified risk factors or any relevant family history that we knew of. One sudden death on fenebrutinib. This was an individual who did have a pre-existing cardiac arrhythmia. There was one completed suicide in the fenebrutinib arm. This was an individual who committed suicide 15 days into the trial. So again, hard to attribute to the drug. There was a suspected suicide. This is an individual in the fenebrutinib arm who had a history of generalized anxiety disorder. One pulmonary embolism in the fenebrutinib arm, an individual with a history of chronic cardiac failure and hypertension. And the fatality in the ocrelizumab arm was a lung cancer metastasis in an individual with known tobacco use. So, whenever there are fatalities and imbalance, we try hard to understand if there's a pattern involved. And there's certainly no obvious pattern. These are all causes of death that are considered relativelycommonly reported in the MS population. They're not above the level that is seen in epidemiological studies, although clearly within the study, there is an imbalance. For what it's worth, all the deaths were assessed by the investigators as unrelated to the study drug.

Brett Drummond
Thanks. Let's shift now to think about next steps. Obviously coming out of this, we've seen positive results. We've seen the data coming out of this. What do you both now see as next steps for fenebrutinib? Let's focus, I guess, on the progressive cohort of people living with MS. I know there will be results of fenebrutinib for relapsing remitting coming up at an upcoming conference, but so let's focus in that progressive cohort of people. What do you think the next steps are? Do you think this is something that we will see approved? And if so, how do you see it fitting in the clinical management of people with progressive MS?

Stephen Hauser
Let me start by saying that just to follow up on the earlier point that we learn more from our clinical trials or as much from our clinical trials as we do from all of our basic investigations, but it's when we bring the two together that progress truly happens.

We believe, I believe that progression is present from the beginning of MS in most or all patients from day one. There are multiple pathologies that are underlying progression. The importance of each underlying pathology may differ as the disease course becomes more chronic, but progression is a common feature to all types of MS. One result that I'll be especially interested in, will be the effects of fenebrutinib on progression independent of relapse activity in the relapsing MS population. So when these studies are unblinded later this year, we are going to see very interesting progression data that will connect what we know now about progression in primary progressive MS to progression in relapsing remitting and secondary progressive MS. So I think that's one very important area. These trials also will ask as many questions as they answer and exactly where will be the place for fenebrutinib in the armamentarium of patients with all forms of MS and especially...for today's discussion, patients with primary progressive MS, I think is the great question. In my opinion, the data on... In my opinion, the data favoring fenebrutinib in patients without disease activity and primary progressive MS seems powerful enough for this to become a most attractive option for patients with primary progressive MS.

Amit Bar-Ohr
I agree completely with Stephen and you can certainly turn the I into we on all counts.First, with this trial completing, we hope that it will translate into an approval for PPMS. And as Stephen said, I too am impressed that because of what we discussed previously, one can attribute the impact of fenebrutinib compared to ocrelizumab on non-relapsing disease biology, which really is the unmet need. And I think it would very much be an attractive option for PPMS patients once hopefully approved. And like Stephen, I also think that progressive disease biology is present throughout the broad clinical spectrum of MS. We've coined patients as having clinical courses based on what we see as their phenotype, but that's really not capturing the underlying biologies, both of which are present, don't transition from one to the other, relapsing remitting to secondary progressive, for example, rather they overlap likely by decades. And we still, think, for the most part have come to believe that the biology of primary progressive clinical phenotypes and secondary progressive clinical phenotypes is more similar than different, but there's a lot of heterogeneity across individuals. You could imagine, and especially if fenebrutinib emerges as having the impact we hope it will have also in relapsing disease activity, that this could be a very attractive, easy to take, well tolerated medication starting early on and throughout the spectrum of MS.

Brett Drummond
Yeah, I mean, very exciting times. Again, we could talk a lot about how this might be used in a relapsing and remitting population. Obviously, we've got the trial data for that, as you've said, coming out later in the year. So that's a discussion maybe to leave until we have those results at all. But what this might mean for treatment of progression-independent relapse activity, what this might mean for non-active secondary progressive MS, but a huge unmet need in primary progressive MS. I think it's a really exciting time. I thank you both for all of your hard work in making this trial a reality and for spending the time with us to share these results off the back of what's just been discussed at ACTRIMS Forum 2026. Big results for a patient

population in MS that are crying out for new treatment options. So thank you both very much for all of your hard work and for your time today.

And thanks everyone for listening. Once again, I'm Brett Drummond, host of this podcast episode and co-founder of MStranslate. The ECTRIMS podcast is produced and hosted in collaboration with two key partners, MStranslate, an independent resource center that aims to simplify the complex wealth of information about MS for the greater MS community. And the MS Journal, a peer-reviewed international journal that focuses on MS, neuromyelitis optica, and other related autoimmune diseases of the central nervous system.

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