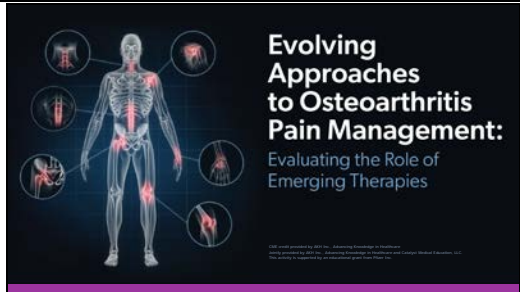
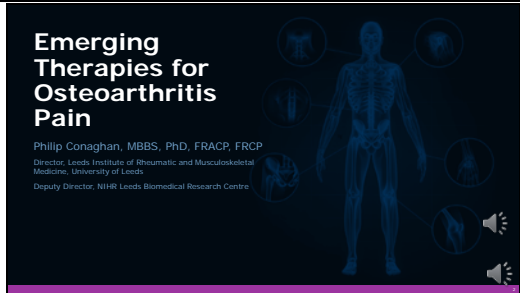
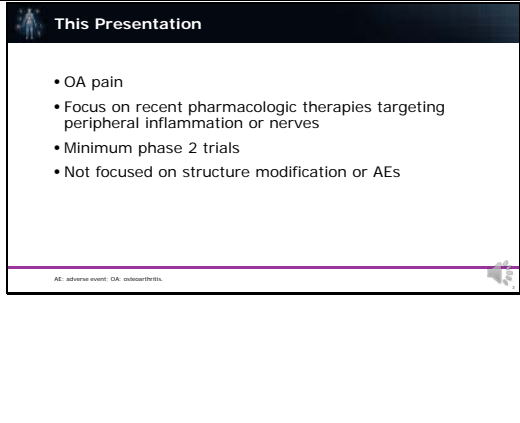
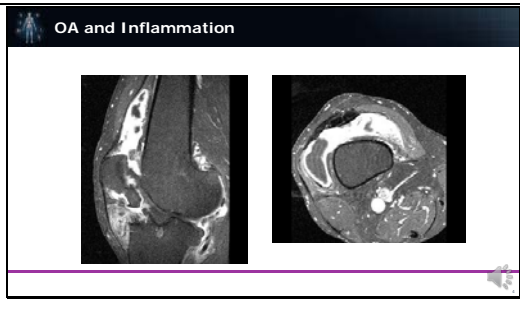
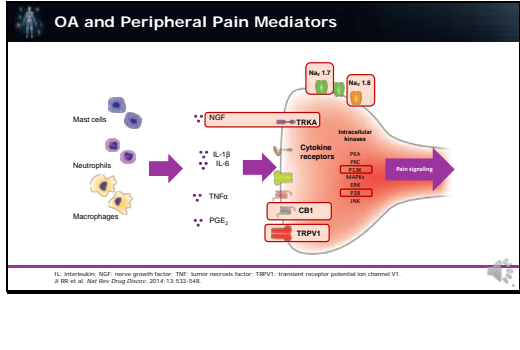



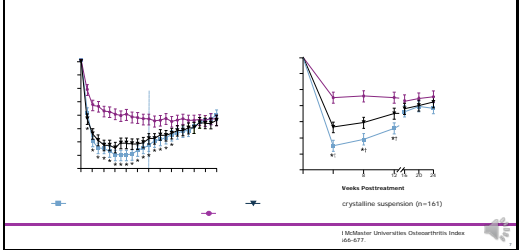
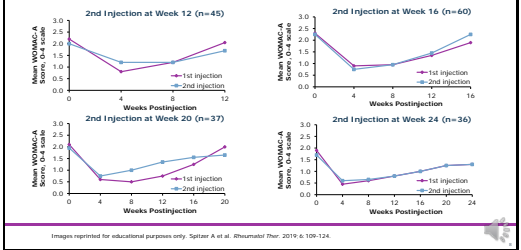
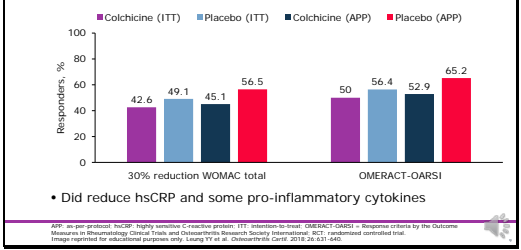
Evolving Approaches to Osteoarthritis Pain Management: Evaluating the Role of Emerging Therapies

Emerging Therapies for Osteoarthritis Pain

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2		<p>Hello. My name is Philip Conaghan.</p> <p>And I'm a rheumatologist and academic from the University of Leeds in the North of England. I'm going to be talking to you about some therapies that are being developed for osteoarthritis pain.</p>
3		<p>So this presentation will focus, as I said, on osteoarthritis pain, rather than structure modification. And I'm going to be looking at relatively recent literature on therapies coming through drug development pathways. And it just so happens that they tend to be focused on either inflammation, or on nerves themselves.</p> <p>I've only included in this discussion today phase II trials. So you have to have at least got that far. And I've not talked a lot about adverse events, because we have limited time today.</p>
4		<p>Now it's not surprising to most people that inflammation is very common in osteoarthritis. And depending on what sensitive modality you use, whether it be ultrasound, MRI, or MRI with contrast agent, you can see inflammation in the knee, in anywhere from 80 to 95 percent of patients. So we know synovitis and effusion is very common in osteoarthritis, especially in more advanced structural disease.</p>
5		<p>But in the last 10 to 15 years, we've also understood more about peripheral nociceptive pain, and about the mediators that are important in these pain pathways, of which perhaps primarily, inflammatory cytokines, which we're all familiar with, prostacyclins, but also nerve growth factor, or NGF. And I'll come back to these later on.</p> <p>So both inflammation and peripheral nociceptive pain are intimately connected. And they're also</p>

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6	 <p>Treating Inflammation</p>	<p>offering us understanding of how these factors bind to their receptors on peripheral nerves.</p> <p>So what's been going on with treating--</p>
7	 <p>Triamcinolone Extended Release</p> <p>Weeks Posttreatment crystalline suspension (n=161)</p>	<p>--inflammation? Well, we've had intraarticular steroid injections for a very long time in treating osteoarthritis pain. Some more recent trials involved a slow release microsphere that releases corticosteroid, in this case triamcinolone, slowly in the joint environment. And this study showed, when compared with a regular triamcinolone injection, or against placebo, that there was benefit from the new therapy out beyond 12 weeks, although 12 weeks was the primary endpoint. And then, when we used the WOMAC-A or the WOMAC pain subscale that many of you will be familiar with, there was differentiation from regular triamcinolone when using the extended release. And that was maintained out to 12 weeks. So new formulations of old drugs.</p>
8	 <p>Triamcinolone Extended Release Phase 3b Repeat Dose Trial</p> <p>2nd Injection at Week 12 (n=45) 2nd Injection at Week 16 (n=60) 2nd Injection at Week 20 (n=37) 2nd Injection at Week 24 (n=36)</p> <p>Images reprinted for educational purposes only. Spitzer A et al. <i>Rheumatol Ther</i>. 2016; 6:109-124.</p>	<p>I've thrown in this trial, because I think it's probably interesting. We've all heard the story that injections lose their efficacy over time. Difficult to know what time span that's over. But in this repeat dose study, using the extended release triamcinolone, you can see whether you've got your second injection at week 12, 16, 20, or 24, that there was equivalent analgesic response. So we need to understand more about that old issue of whether people lose response over time.</p>
9	 <p>Colchicine in Knee OA (COLKOA) RCT</p> <p>30% reduction WOMAC total OMERACT-OARSI</p> <p>• Did reduce hsCRP and some pro-inflammatory cytokines</p> <p>APP: all-<i>per-protocol</i>; hsCRP: highly sensitive C-reactive protein; ITT: intention-to-treat; OMERACT-OARSI = Response criteria by the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International; RCT: randomized controlled trial. Image reprinted for educational purposes only. Leung YY et al. <i>Osteoarthritis Cartilage</i>. 2016; 24:331-340.</p>	<p>I've put in this study on colchicine, because we know that at least later in osteoarthritis, that there is crystals present. And one German study demonstrated crystals in the cartilage of almost 100 percent of people with late-stage disease. So it's interesting to now have a therapy that might treat crystal-induced inflammation was useful. This was a nice randomized control trial done by a group in Singapore. And they showed, effectively, that there was no benefit from colchicine in this group selected for osteoarthritis in the knee. So</p>

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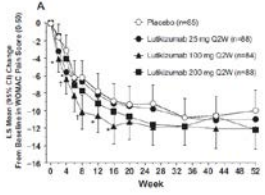
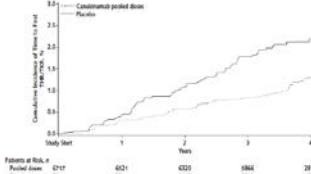
		<p>unfortunately, no benefit demonstrated there, although there was some benefit in reducing highly sensitive CRP and some pro-inflammatory cytokines.</p>
10	<p>HERO: A Placebo-Controlled RCT</p> <p>Hydroxychloroquine Effectiveness at Reducing the symptoms of hand osteoarthritis (HERO)</p> <p>People with painful (VAS ≥4/10) radiographic hand OA</p> <p>Usual hand OA medication + hydroxychloroquine</p> <p>Usual hand OA medication + placebo</p> <p>6 months 6 months</p> <p>Primary outcome: Reduced pain?</p> <p>Sustained reduction in pain? Reduced structural progression?</p> <p>Baseline Ultrasound Sub-study</p> <p><small>VAS: visual analog scale. Conaghan PG et al. Trials. 2013; 14:64. Slide courtesy of Vericus Arthritis. http://www.vericusarthritis.com</small></p>	<p>We conducted a trial in Leeds, looking at hydroxychloroquine, which anecdotally has been used for hand osteoarthritis pain for many years. And we did a large randomized control trial where we added hydroxychloroquine to people's usual analgesic medications. We had a six-month pain primary outcome, and a six-month further, or 12-month x-ray outcome.</p>
11	<p>HERO Primary Outcome: Hand Pain</p> <p>Overall hand pain (0-10 max)</p> <p>Months Follow-up: M0, M3, M6, M12</p> <p>Legend: HCO (red line), Placebo (blue line)</p> <p>Difference: -0.16 95% CI (-0.72, 0.41) P = .584</p> <p>Difference: 0.24 95% CI (-0.30, 0.79) P = .381</p> <p>Difference: 0.14 95% CI (-0.44, 0.72) P = .639</p>	<p>Unfortunately, again, no difference clearly in pain outcomes at six months with the hydroxychloroquine, and no benefit, also--</p>
12	<p>HERO: Response by Ultrasound Synovitis</p> <p>Positive Greyscale Synovitis (n=134)</p> <p>Overall hand pain (0-10 max)</p> <p>Months Follow-up: M0, M3, M6, M12</p> <p>Legend: HCO (red line), Placebo (blue line)</p>	<p>--with the x-ray outcomes at 12 months. We also looked to see if the amount of inflammation at baseline predicted your response, and used ultrasound in a subset of patients in this study. But neither greyscale synovitis, nor positive power Doppler devote more vascular aspect of synovitis, was associated with response. So disappointing lack of benefit from hydroxychloroquine.</p>
13	<p>PROMOTE: Methotrexate in Knee OA RCT</p> <p>Multicenter (15 UK sites), randomized, double-blind, placebo-controlled trial</p> <p>160 people with symptomatic and radiographic knee OA</p> <p>Methotrexate + ongoing usual care</p> <p>Placebo + ongoing usual care</p> <p>6 months (24 weeks) 6 months (24 weeks)</p> <p>Primary outcome: Reduced pain?</p> <p>Secondary outcomes: Improved function? Structural changes?</p> <p><small>MTX: methotrexate. Conaghan PG et al. SAGE 2019. Oral presentation. Slide courtesy of Vericus Arthritis. http://www.vericusarthritis.com</small></p>	<p>We also have done a large randomized control trial across multiple UK sites using methotrexate added to usual care for knee osteoarthritis. So again, concept here is treating inflammation to reduce pain. And the primary outcome here was pain at six months. And we also looked at synovial volume to see if that was the mechanism by which methotrexate may be affected pain.</p>
14	<p>PROMOTE Primary Outcome: Overall Knee Pain</p> <p>Overall Knee Pain (over the last week, NRS)</p> <p>Months Follow-up: M0, M3, M6, M9, M12</p> <p>Legend: MTX (red line), Placebo (blue line)</p> <p>Diff: 0.41 95% CI 0.17 to 1.07 P = .001</p> <p>Diff: 0.53 95% CI 0.19 to 1.00 P = .001</p> <p>Diff: 0.71 95% CI 0.37 to 1.05 P = .001</p> <p>Diff: 0.71 95% CI 0.37 to 1.05 P = .001</p> <p><small>NRS: numerical rating scale. Image reprinted for educational purposes only. Conaghan PG et al. SAGE 2019. Oral presentation.</small></p>	<p>What we showed at six months was a significant difference in pain in the methotrexate treated arm. Now this was using VIS pain scale—sorry, an NRS pain scale. And the amount of difference there is probably clinically meaningful.</p>

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<p>15</p>	<p>PROMOTE: Secondary Outcomes</p> <p>Images reprinted for educational purposes only. Conaghan PG et al. OARSI 2019. Oral presentation.</p>	<p>In terms of the secondary outcomes, the WOMAC pain did not show the benefit that we saw in the numeric ratings scale pain. But the stiffness and function subscales of WOMAC did show quite significant differences at six months. So there does appear to be a benefit from methotrexate, although it wasn't consistent across the two pain outcomes here.</p>
<p>16</p>	<p>PROMOTE: Imaging Substudy</p> <ul style="list-style-type: none"> 96 patients (62%) had analyzable MRI data at baseline and 80 patients (52%) at 6 months No change in total synovial volume observed Baseline synovitis group not linked to MTX effectiveness ($P = .565$) <p>MRI: magnetic resonance imaging Images reprinted for educational purposes only. Conaghan PG et al. OARSI 2019. Oral presentation.</p>	<p>And synovial volume was not different across the six months of the study between the two arms. And when we looked at whether we had a low degree or a high degree of synovitis at baseline, that also didn't predict response. So if methotrexate effect does not appear to be related at least to reducing synovial volume. Of course, there are many other effects on inflammatory markers that we may not have measured with synovial volume alone.</p>
<p>17</p>	<p>Adalimumab in Hand OA: HUMOR Trial</p> <ul style="list-style-type: none"> American College of Rheumatology criteria for hand OA Hand pain $\geq 5/10$ ≥ 1 x-ray erosive joint, synovitis on MRI Randomized to placebo (25 patients) or adalimumab 40 mg SC (18 patients) twice weekly for 12 weeks, 8-week washout crossover design, follow for 12 weeks Primary outcome: change in VAS hand pain over 12 weeks Structural outcomes: HOAMRIS synovitis, bone marrow lesions <p>HOAMRIS: hand OA MRI score. SC, subcutaneous. Aitken D et al. Osteoarthritis Cartilage 2018;26:880-887.</p>	<p>There's been a number of trials looking at the role of TNF inhibitors, which have been fantastically successful at reducing synovial volume in rheumatoid arthritis. Most of those trials have been negative. And this is a more recent trial in hand osteoarthritis, which involved a double blind crossover design with washout in between, and patients treated for 12 weeks in each component of the trial. The primary outcome was change in a visual analogue score hand pain over a three-month period.</p>
<p>18</p>	<p>Adalimumab in Hand OA: HUMOR Trial (cont)</p> <ul style="list-style-type: none"> No change in AUSCAN, HOAMRIS features <p>Australian/Canadian Hand OA Study Images reprinted for educational purposes only. Aitken D et al. Osteoarthritis Cartilage 2018;26:880-887.</p>	<p>And what this showed, unfortunately again, was no change in AUSCAN, which is a pain and function patient reported outcome, nor in the HOAMRIS MRI score for features. So what we see there on the VAS pain, the primary endpoint that there was no benefit. So like other TNF trials, we're not seeing a benefit from TNF inhibitors in osteoarthritis pain.</p>
<p>19</p>	<p>Anti-IL-1α and -β With Lutikizumab: ILLUSTRATE-K Trial Design</p> <p>Screening: Clinical examination, ultrasound, X-ray</p> <p>Week 0: MRI</p> <p>Week 16: Primary Endpoints: WOMAC pain, MRI endpoints (pain, Effusion volume, Synovial membrane thickness, WOMRIS synovitis/effusion)</p> <p>Week 26: X-ray for JSN MRI</p> <p>Week 52: Patients enrolled: n=85 (Group 1), n=89 (Group 2)</p> <p>Standard of care: Acetaminophen or ibuprofen rescue</p> <p>200 mg joint space narrowing. Q2W, every 2 weeks. WOMRIS, Whole-Organ Magnetic Resonance Imaging Score. Fouchardier M et al. Arthritis Rheumatism 2019;71:1056-1068</p>	<p>More recently, people restudied the benefit, potential benefits of interleukin-1 antagonism. And we know interleukin-1 is very integral to a lot of the pathological processes going on in the osteoarthritis joint. And this was a large randomized trial of a molecule that inhibited both IL-1 alpha and beta, called Lutikizumab. And the study was called the ILLUSTRATE-K Trial.</p>

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		<p>And you can see here, in this ascending dose trial, that there were three different doses of drug, reasonable number of patients, and co-primary endpoints of pain at week 16, and inflammatory MRI endpoints at week 20.</p>
<p>20</p>	<p>Anti-IL-1α and -β With Lutikizumab: ILLUSTRATE-K Trial Results: Pain</p>  <p><small>clinical purposes only. Fleischman BM et al. Arthritis Rheumatol. 2019;71:1056-1069.</small></p>	<p>But no benefit from—in terms of the structural inflammatory endpoints either.</p>
<p>21</p>	<p>Canakinumab and Joint Replacement</p>  <ul style="list-style-type: none"> • Exploratory analysis of a large randomized trial • In the pooled canakinumab groups, compared with placebo, incidence rates for THR/TKR were 0.31 and 0.54 events per 100 person-years (HR, 0.58 [95% CI, 0.42 to 0.80]; $P = .001$), respectively <p><small>HR, hazard ratio; THR, total hip replacement; TKR, total knee replacement. Image reprinted for educational purposes only. Schreier M et al. Ann Intern Med. 2020. doi:10.1126/aim.2020.0527.</small></p>	<p>However, recently, we've reported data from a large canakinumab study. Now canakinumab is another anti-IL-1 monoclonal antibody. And this trial was not primarily an osteoarthritis trial, but a trial in patients selected for cardiovascular risk, people who'd had a previous myocardial infarction, and a mildly elevated, at least highly sensitive CRP. This trial was all about trying to understand if treating with canakinumab would reduce cardiovascular endpoints.</p> <p>However, when we looked at the secondary and adverse events here, what we saw was, in those treated with canakinumab, that the incident rates for total hip replacement and total knee replacement were reduced up to 40 percent over the roughly three and a half years that this trial ran over.</p> <p>So this is very interesting, because previously, IL-1 trials have not shown a benefit. And yet here in a group selected for a systemic inflammatory component, with large numbers treated three-monthly, over a long period of time, there does seem to be a benefit. So this opens new questions for us about IL-1 and its role in osteoarthritis, and the potential role of inhibiting it.</p>

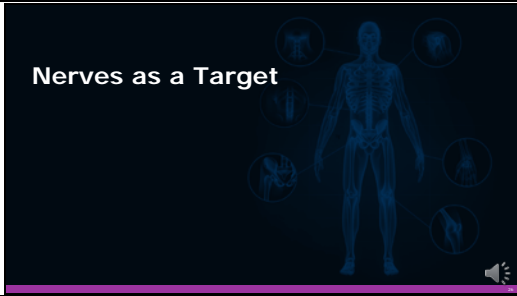
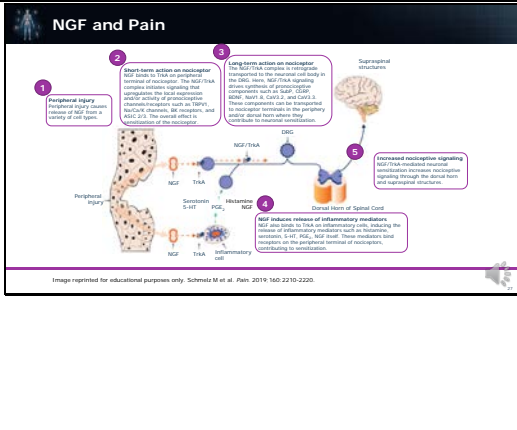
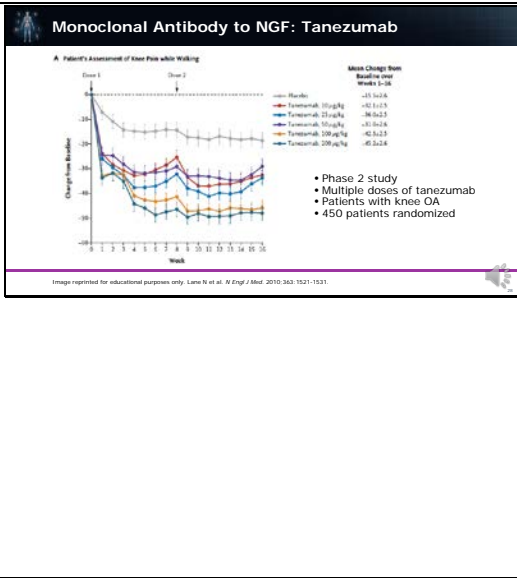
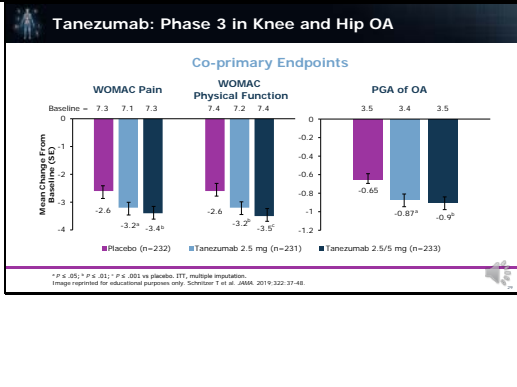
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<p>22</p>	<h3>Wnt Signaling Pathway in OA</h3> <p>Image reprinted for educational purposes only. Lorenz RJ, Monteggia S. <i>Rheumatol Ther</i>. 2020;7:259-270.</p>	<p>Wnt signaling is another integral part of healthy joint, cartilage bone structural maintenance. And the Wnt pathway plays a pleiotropic role here. And we know that when the Wnt signaling is disordered, we can see cartilage degradation, bone remodeling, and inflammation</p>
<p>23</p>	<h3>Loxecivint: Phase 2a: Study Design</h3> <p>Primary objective: Change from baseline in WOMAC Pain at week 13 Clinical assessments: WOMAC Function, Pain: Patient and MD Global Assessment: SF-36 Imaging: Fixed flexion knee X-ray with QuAP™ positioner Safety assessments: AEs, vital signs, physical examination, laboratory panels</p> <p>SF-36: 36-Item Short-Form Survey Image reprinted for educational purposes only. Yucht Y et al. <i>WOCJ</i> 2018. Oral presentation O14.</p>	<p>So there's now a small molecule Wnt inhibitor called Loxecivint. And Loxecivint has been trialed and is in a trial program at present. And this is some data from the Phase 2A study, as you'd expect, an ascending dose study, with a primary outcome of WOMAC pain. This is by intraarticular injection in knee osteoarthritis.</p>
<p>24</p>	<h3>Loxecivint Phase 2a: WOMAC Pain</h3> <p>Image reprinted for educational purposes only. Yucht Y et al. <i>Arthritis Rheumatol</i>. 2020 May 20. [Epub ahead of print].</p>	<p>And what you can see here in the intention to treat cohort, there wasn't a clear benefit of any dose. But when they looked at a unilateral symptomatic group, and that was a predefined outcome, or in a unilateral symptomatic group who didn't have widespread pain, there was, indeed, a significant benefit for the 0.07 milligram dose.</p> <p>And this shows us that, in the last few years, we've also started to understand more about how to do osteoarthritis pain trials. Because one of the big problems is differentiating any active therapy from placebo, because placebo response can be quite high. And we know that looking at groups with unilateral pain, especially without widespread body pain, improve the responsiveness of these studies. So interesting signal on pain coming out of that Phase 2A study</p>
<p>25</p>	<h3>Loxecivint Phase 2b</h3> <p>FAS: Full Analysis Set; PGA: Patient Global Assessment Image reprinted for educational purposes only. Yucht Y et al. <i>ACR</i> 2018. Poster L03.</p>	<p>In the Phase 2B study, we also see some separation for the 0.07 milligram for the pain numeric rating scale outcome, and also for the patient global outcome. So interesting early signals. And Loxecivint is now moved into a Phase 3 program.</p>

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<p>26</p>	 <p>Nerves as a Target</p>	<p>So moving on from treating various parts of inflammation pathway, what about things targeting nerves?</p>
<p>27</p>	 <p>NGF and Pain</p>	<p>So I've mentioned nerve growth factor and its important role in pain. And this is from a NICE review, looking at NGF and its multiple roles in this pathway. It binds to TrkA or the tropomyosin receptor kinase A, and stimulates a cascade of events involving the dorsal root ganglion, and the dorsal horn of the spinal cord, basically increasing nociceptor signaling to the brain.</p> <p>It's also involved in release of inflammatory mediators, locally. So NGF has quite a complex role in the pain pathway.</p>
<p>28</p>	 <p>Monoclonal Antibody to NGF: Tanezumab</p>	<p>I think everybody was very excited ten years ago, when Nancy Lane and colleagues produced this data in New England Journal of Medicine, in a dose ascending study of tanezumab, one of the first monoclonal antibodies to NGF, and showing very much a dose response to NGF, given intravenously. So this was very exciting data. But subsequently, there were problems of rapidly progressive osteoarthritis, and I'll come back to that topic, with these drugs. And then, problems of potential sympathetic nerve toxicity, which indeed did not turn out to be a problem. But these things were the cause of holes in the program.</p> <p>We've now seen the Phase 3 program going ahead well.</p>
<p>29</p>	 <p>Tanezumab: Phase 3 in Knee and Hip OA</p>	<p>And the results of two large Phase 3 trials have been published. This is one of those Phase 3 trials. And you can see, now, the bar in these trials has been lifted in that we're looking at co-primary endpoints of pain, function, and patient global assessment of osteoarthritis. And in these studies, tanezumab at 2.5 milligrams in sub-cut injection. This was done twice, over a 16-week period, or 2.5 milligrams at first injection, increasing to five milligrams at eight weeks.</p>

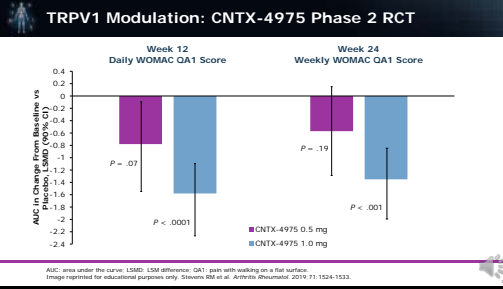

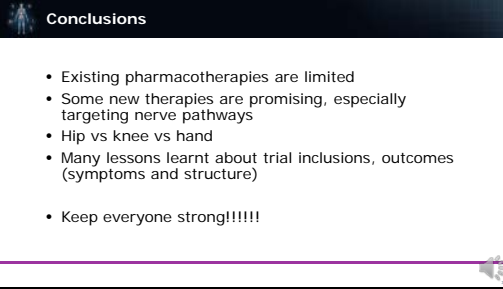

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		<p>You can see the statistically significant benefits of tanezumab for both doses at 16 weeks. So good evidence that the sub-cut drug is showing positive benefits on people's pain, function, and global assessment.</p>
30	<p>Tanezumab: Phase 3 in Knee and Hip OA (cont)</p> <p>Co-primary Endpoints</p> <p>Baseline = 6.59 6.7 6.6 (WOMAC Pain); 6.67 6.77 6.76 (WOMAC Physical Function); 3.55 3.61 3.56 (PGA of OA)</p> <p>LSM (SD) Change From Baseline</p> <p>Placebo (n=282) Tanezumab 2.5 mg (n=283) Tanezumab 5 mg (n=284)</p> <p>* P < .01; ** P < .001 vs placebo, ITT, multiple imputation. Image reprinted for educational purposes only. Bierbaum F et al. Ann Rheum Dis. 2020;79:800-810.</p>	<p>This was the second Phase 3 paper published just recently. And again, here we see tanezumab versus placebo. Tanezumab given in three doses of 2.5 milligrams, or three doses of five milligrams. And we see, again, statistically significant benefits for pain and function, although the 2.5 milligram tanezumab did not achieve the patient global benefit, though the five milligram dose did. So it looks like we have something that might come soon, in terms of pain relief--</p>
31	<p>The Efficacy, Tolerability, and Joint Safety of Fasinumab in Osteoarthritis Pain: A Phase IIb/III Trial</p> <p>Mean [SD] Change from Baseline</p> <p>Time (weeks)</p> <p>No. of patients: Placebo (n=80), Fasinumab 1 mg (n=80), Fasinumab 2 mg (n=80), Fasinumab 4 mg (n=80), Fasinumab 8 mg (n=80)</p> <p>Image reprinted for educational purposes only. Guo F, et al. Arthritis Rheumatism. 2020;72(11):1634-1644.</p>	<p>--using antibodies to monoclonal, sorry, monoclonal antibodies to nerve growth factor. And there are other such monoclonal antibodies. This is fasinumab, an IgG4 monoclonal antibody to NGF. And this was a Phase 2B trial. You can see dose-ascending trial. And again, statistically significant benefits of fasinumab, although perhaps not a clear dose response here, definite response across all doses. So looks like a class of drugs that look very promising for pain relief, at least in short trials.</p>
32	<p>Tanezumab: Rapid Progression of OA</p> <p>Time to Event Analysis of Rapid Progression of OA (Older Phase 3 Program)</p> <p>Percent of Patients</p> <p>Time (Days)</p> <p>Tanezumab 2.5 mg NSAID p=0.002 Tanezumab 5 mg NSAID p=0.006 Tanezumab 10 mg NSAID vs. active comparator p=0.004 Tanezumab 2.5 mg NSAID vs. active comparator p=0.002</p> <p>NSAID: non-steroidal anti-inflammatory drug. Image reprinted for educational purposes only. Hochberg MC, et al. Arthritis Rheumatism. 2016;68:380-391.</p>	<p>However, we can't ignore the potential problem of what's been called rapidly progressive osteoarthritis. And this is data from earlier trials of tanezumab published a few years ago, showing that there does appear to be a dose response to tanezumab over time. And that that seems related, also, to concomitant use of anti-inflammatories. And certainly, using them all the time would not be wise, given this data.</p> <p>I think we've still got a lot to understand about rapidly progressive OA, because there seems to be two types. There seems to be a type 1, where there is progression of joint space loss, and then type 2, which is much more uncommon, which seems to be a more disruptive arthropathy. So lots more for us to understand about the potential toxicity of these drugs, and before they will be licensed.</p>

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33		<p>Other things targeting nerves, including the TRPV1 modulator. And TRPV1 has a long name, but probably best known to you as the capsaicin receptor. This is an intraarticular injection. And you can see here that, after a single injection in a Phase 2 study, at week 12 and maintaining out to week 24, there's a significant reduction in WOMAC pain. That's the WOMAC first question score there. And again, potential that modulating peripheral pain nociceptives can have beneficial results. So we're waiting on Phase 3 data from this drug.</p>
34		
35	 <ul style="list-style-type: none"> Existing pharmacotherapies are limited Some new therapies are promising, especially targeting nerve pathways Hip vs knee vs hand Many lessons learnt about trial inclusions, outcomes (symptoms and structure) Keep everyone strong!!!!!! 	<p>So putting that all together, we've really only got limited pain pharmacotherapies coming for osteoarthritis. But some of them look promising, perhaps more so those targeting the nerve pathways. I think we have to be careful about generalizing all these products to hip, knee, and hand osteoarthritis, as those diseases have different trajectories and more likely need different subsets to be treated.</p> <p>In the last decade, we've learned a lot about who we should put into pain trials, trying to remove people who've got lots of widespread pain, since it's difficult to see signals. And we're learning more about both symptoms and structure. In the meanwhile, as some of the previous speakers in this symposium have mentioned, it's important to focus on things that will help patients, including muscle strengthening, which helps everybody to reduce their joint pain.</p>
36		<p>And I'll finish there. And thanks very much for listening to me today.</p>