Trends-in-Medicine

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by Lynne Peterson

SUMMARY

♦ **Rheumatoid arthritis:** Bristol-Myers Squibb's Orencia is picking up market share among the currently approved TNF inhibitors. Rituxan use is holding steady. Of the many new agents on the horizon, rheumatologists are most interested in Roche/Chugai's Actemra because it has a new method of action (anti-IL-6), but they predicted Johnson & Johnson's golimumab will be popular with patients because it is once-monthly. The real excitement is over oral small molecules, though they are somewhat further away, there is no clear leader yet, and several have failed.

♦ **Gout:** Doctors were impressed with the efficacy of Savient Pharmaceuticals' Puricase for treatment-failure gout and predicted it would have high usage, but questions were raised about its safety and about antibody formation, suggesting the regulatory hurdle may be high.

♦ **Osteoarthritis and pain:** Pfizer's tanezumab looks very promising not only for osteoarthritis but also for many other pain-related conditions.

♦ **Osteoporosis:** Rheumatologists predicted an important role for Amgen's denosumab, saying the twice-yearly subcutaneous injections are not a barrier to use.

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The current economic crisis was on the minds of rheumatologists attending their annual meeting, but their real attention was on the wide range of new treatments on the horizon for rheumatic diseases, from rheumatoid arthritis and osteoarthritis to osteoporosis, fibromyalgia, gout, pain, and systemic lupus erythematosus (SLE).

The economy has not caused patients to cut back on their prescription drug use – yet. Insurance copayments have been going up, and that trend is expected to continue, but pharmaceutical companies have set up programs to help patients with those copayments, which has mitigated that potential problem. A rheumatologist said, "Fifteen to 20% of patients wouldn't be on a biologic without those programs." A West Coast rheumatologist commented, "The economy is just beginning to have an effect. The market for rheumatic disease drugs should grow, but the economy may not let it. If the new oral agents are less expensive, that would really help. Pills are generally more acceptable (to patients)." A South Carolina doctor said, "The economy has not had much effect on patient drug use yet because most patients have a drug benefit. But pre-certification is harder…There is talk that the carriers will move biologics to a 20%-30% copay tier, and we are starting to talk to Congress that this would not be in patients' best interest…And we are seeing an economic effect on patients because there has been an increase in patients not showing up for appointments."

Insurance companies also are affecting the choice of biologic in rheumatoid arthritis. Many carriers have established a preferred TNF inhibitor that a patient must fail before trying another biologic. However, doctors said that this hasn't been a problem, and they can usually get another TNF inhibitor approved with some extra paperwork.

Yet, even in this environment biotech companies and pharmas are helping the ACR encourage research through the ACR's non-profit Research and Education Foundation (REF) and its $30 million national *Within Our Reach: Finding a Cure for Rheumatoid Arthritis* campaign. The money that the ACR raises in this campaign goes to two-year research grants in basic research, translational research, clinical practice issues, novel clinical trials, and collaborative research projects.

FIBROMYALGIA

About 2% of Americans are estimated to have fibromyalgia, with about 1 million diagnosed. The incidence is almost 7-times more common in women than men. It is a difficult condition for patients, both in terms of diagnosis and treatment. Fibromyalgia is a syndrome characterized by a variety of symptoms, including widespread soft tissue pain and muscular pain, a decreased pain threshold (tender

points), fatigue, disturbed sleep, anxiety or depression, irritable bowel syndrome, Raynaud's, headache, and paresthesias.

Fibromyalgia Symptoms

Symptom	% of fibromyalgia patients with this symptom
Pain	97%
Fatigue	91%
Poor sleep	90%
Depressive symptoms	67%
Difficulty concentrating	36%

PFIZER's esreboxetine

Esreboxetine is a more selective isomer of Edronax (racemic reboxetine, which is approved in Europe) for fibromyalgia. Esreboxetine is a QD drug in Phase III development, and it has a different pharmacologic approach from Pfizer's Lyrica (pregabalin), which is already FDA-approved for fibromyalgia, and it is more selective than Forest Laboratories/ Cypress Biosciences' milnacipran, which is awaiting FDA approval, but which has been delayed – for reasons the company has not disclosed.

The two areas of fibromyalgia that Pfizer wants to target with esreboxetine are: difficulty in concentration (described as an unmet need) and fatigue. A Pfizer official said, "Difficulty in concentration is an unmet need…and that is where we will focus along with impact on fatigue."

8-Week Results of Esreboxetine Phase II Study 1034

Measurement	Placebo n=133	Esreboxetine n=134	p-value
Pain reduction by NRS score	- 1.0	- 1.6	<0.01
Improvement in function by FIQ score	- 8.1	- 15.6	<0.01
Improvement in fatigue	- 2.8	- 6.4	<0.01
Patient global impression much/very much improved	23.4%	42.6%	<0.01
Patient global impression very much improved	3.8%	17.1%	<0.01
30% responders	22.6%	37.6%	0.004
50% responders	8.3%	18.1%	0.01
Adverse events			
Any adverse event	57%	72%	---
Withdrawals due to adverse events	3.0%	8.2%	---
Serious adverse events	0.7%	0.7%	---
Constipation	5.3%	19.4%	---
Insomnia	3.8%	17.9%	---
Dry mouth	2.3%	16.4%	---
Headache	3.8%	14.2%	---
Nausea	3.0%	9.0%	---
Blood pressure effects at 8 weeks			
Systolic blood pressure	Up 0.4 mmHg	Up 0.1 mmHg	---
Diastolic blood pressure	Up 0.6 mmHg	Up 0.2 mmHg	---
Sitting heart rate	Up 0.3 bpm	Up 0.9 bpm	---

At ACR, 8-week results of the esreboxetine dose-escalation, Phase II Study 1034 were presented. The efficacy looked reasonable, but several side effects will be watched in Phase III including: CV safety (especially heart rate) and anti-cholinergic-like effects such as constipation and urinary retention. Ken Verburg PhD, development head for pain therapeutics at Pfizer, said his company is waiting to see how the heart rate "plays out in Phase III." He also said, "Fibromyalgia may not be what we target down the road…It (tanezumab) may be more targeted to specific subgroups, based on phenotype studies." Phase III data are expected in 2009, with a possible FDA submission in 2011-2012.

GOUT

REGENERON's Acrylase (rilonacept), an anti-IL-1

Rilonacept has the same net effect on the IL-1 receptor as Amgen's Kineret (anakinra), but its method of action is slightly different. A Regeneron official said the "efficacy might be the same." Regeneron is recruiting sites at ACR for its Phase III trial of rilonacept in gout, Study IL1T-GA-0814, and they hope to start enrolling patients by the end of the year. All the details on the trial have not been finalized, but this is a randomized, multicenter, active-controlled trial of subcutaneous rilonacept + oral indomethacin vs. rilonacept alone vs. placebo + oral indomethacin.

SAVIENT PHARMACEUTICALS' Puricase (pegloticase) – effective but safety questions

No new drug has been approved by the FDA to treat gout in more than 40 years. Dr. John Sundy of Duke University – which holds patents on pegloticase and licensed it to Savient – estimated that there are 2-3 million Americans with gout, and ≥50,000 of these have treatment failure gout (TFG). Savient is developing Puricase as an orphan drug under a Special Protocol Assessment (SPA) with the FDA. The company is expected to file this soon with the FDA – without waiting for the results of an ongoing re-treatment study.

Rheumatologists are excited about Puricase. One commented, "That is the best drug I've seen. It usually takes 2-3 years to get rid of tophus. This works in 2-3 months. It doesn't work for everyone, but we've never seen anything like it."

However, data presented at ACR raised questions about the approvability of Puricase. There did not appear to be any question that the drug, which is administered by IV infusion over two hours, works in nearly half the patients, but there were 3 deaths on drug and eight Puricase patients with cardiovascular side effects vs. no deaths and 1 cardiovascular side effect with placebo. Thus, it may be difficult for the FDA to approve this drug, despite the SPA. Given the potential risk of off-label use, approval would appear to need a strong risk management program, and there were no indications that the company plans to submit a riskMAP with its application. Remember, the FDA cannot impose a riskMAP, it can only approve or reject a plan proposed by a company.

Company officials pointed out that the randomization was 4:1 of drug to control, which makes the cardiovascular side effects less unbalanced. But the number of events could still be construed by regulators as a potential signal requiring additional study or requiring restrictions on use.

Then, there is the problem of antibodies. Patients develop antibodies to Puricase rather quickly and significantly. This raises questions about how long patients could take the drug if it were approved. Asked how to deal with the antibody issue, Dr. Sundy said, "I believe we can answer that from the open-label extension study (ongoing)…We think antibody formation is a relatively early event…This (Puricase) is going to be a foreign protein in all patients…I can only speculate on the duration of treatment because we have not had an opportunity to follow patients on long-term therapy. We have to follow them in the extension study. We have some re-treatment protocols underway." The chief medical officer of Savient pointed out that all patients with a high antibody titer and a correlated loss of activity saw this happen by Month 4, "If patients don't have a high titer by then, they won't develop it out to 18 months…There was a single patient with a high titer and no loss of activity…so you can simply measure the serum urate…Antibodies are an explanation for why we don't have 100% response." Dr. Michael Becker of the University of Chicago agreed that measuring antibodies isn't necessary. He said all doctors have to do is measure plasma urate to identify patients likely to have inactivating antibodies.

Results were presented from two 6-month, randomized, double-blind, multicenter, placebo-controlled, Phase III trials – GOUT-1 and GOUT-2 – of IV Puricase vs. placebo in 212 patients (randomized 4:1 to Puricase) with TFG. The two trials had identical designs and were conducted simultaneously. Dr. Sundy, who presented a pooled analysis of these two trials, said the key findings of the analysis were:

- About 40% of patients had a biochemical response to Puricase.
- There was an early indication of a reduction in the number of gout flares.

6-Month Results of Phase III GOUT-1 and GOUT-2 Trials

Measurement	Puricase 8 mg Q2W n=90	Puricase 8 mg Q4W n=89	Placebo n=46
Withdrawals for adverse events	15 patients	16 patients	1 patient
Completers	59 patients	59 patients	39 patients
Primary endpoint: Plasma urate <6.0 mg/dL 80% of the time during Months 3 and 6 (*ITT analysis*)	GOUT-1: ~ 42% (p<0.001) GOUT-2: ~ 36% (p=0.044)	GOUT-1: ~ 18% (p<0.001) GOUT-2: ~ 49% (p<0.001)	0
Plasma urate response (per protocol analysis)	GOUT-1: ~ 64% (p<0.001) GOUT-2: ~ 53% (p=0.044)	GOUT-1: ~ 30% (p=0.014) GOUT-2: ~ 63% (p<0.001)	0
Secondary endpoints in pooled analysis			
Tophus complete response	40.4% (p=0.004)	21.2% (p=0.0499)	3.7%
Gout flare burden – Months 1-3	2.3 (p<0.05)	2.7 (p<0.05)	1.2
Gout flare burden – Months 4-6	0.8 (p<0.05)	1.5 (p=Nss)	1.3
Tender joint count	- 7.4 (p=0.008)	- 6.1 (p=0.024)	- 1.2
Quality of life by SF-36 – physical component	+ 4.38 (p<0.009)	+ 4.94 (p<0.009)	- 0.3
Quality of life by SF-36 – mental component	+ 2.13 (Nss)	+ 0.08 (p=Nss)	+ 2.36
Quality of life by SF-36 – arthritis specific health index	+ 16.5 (p=0.003)	+ 15.03 (p=0.003)	+ 0.93
Safety			
Died	2 patients	1 patient	0 **
Any adverse event	94%	100%	95%
Serious adverse event	24%	23%	12%
Severe adverse event	39%	48%	28%
Treatment discontinued due to adverse event	19 patients	20 patients	2 patients
Adverse events			
Gout flares	77%	83%	81%
Infusion reactions	26%	41%	5%
URTI	5%	5%	21%
Nausea	12%	7%	2%
Cardiovascular serious adverse events	8 patients *	0	---
Anti-pegloticase positive	89%		0

*** 2 cardiac arrests (death), 2 congestive heart failure exacerbations (1 death), 2 dysrhythmia, 1 MI, 1 angina (All patients who didn't die continued in the study)**

**** 1 placebo patient died of multi-organ failure before being dosed.**

- In terms of clinical improvement, tophus size was reduced, and patients experienced an improvement in quality of life, disability, and the number of tender joints. He said, "What we are seeing is patients who are responders having dramatic improvement – a marked reduction in pain and in the ability to get around. I don't want to oversell this…but it is hard to explain what this treatment means to patients."
- The most common side effect was gout flare, which improved with time.
- Infusion reactions "seem related to antibody formation."
- Cardiovascular side effects were more frequent with Puricase. There were 8 patients with CV side effects vs. 0 with placebo. Dr. Sundy suggested the CV adverse events might be "related to underlying comorbidities," but a doctor in the audience questioned that statement since presumably the placebo patients had the same comorbidities.
- Patients died from CV events on Puricase, which takes on additional meaning given the higher incidence of CV side effects with Puricase. In the double-blind phase of the trial, 3 patients on Puricase died, all from cardiovascular causes – 2 at the Q2W dose and 1 at the Q4W dose. Two of these were sudden deaths, presumed to be cardiac arrest "with no sign of coronary artery disease." Another patient reportedly "had concealed the presence of pretty profound congestive heart failure," had an exacerbation, and died. One patient died in the placebo arm, but that was before receiving any placebo dose. Dr. Sundy said, "There is no evidence that these are drug-related at this point, but we need to keep following patients."
- Most patients (89%) developed antibodies to Puricase in just six months, and the antibody titer was significantly associated with plasma urate non-responder status as well as a higher incidence of injection reactions. This raises questions about how long patients could take Puricase.

A 12-month, open-label, extension study is continuing, and Dr. Sundy said 96% of patients chose to continue therapy, and almost all chose to be in an active treatment group rather than observation.

TAKEDA's Uloric (febuxostat)

The FDA's Arthritis Advisory Committee will consider febuxostat on November 24, 2008. At ACR, Dr. Becker presented the results of a 2,269-patient, multicenter, double-blind trial of daily febuxostat. The trial was designed to have at least 35% of patients with mild or moderate renal impairment. Low dose febuxostat (40 mg) was non-inferior to allopurinol, and high dose febuxostat (80 mg) was superior to allopurinol.

Febuxostat Results in Gout

Measurement	Febuxostat 40 mg n=767	Febuxostat 80 mg n=766	Allopurinol 200/300 mg n=756
Primary endpoint: sUA <6.0 at final visit (by ITT)	45% *	67% *	42%
Secondary endpoint: sUA <6.0 in patients with mild/ moderate renal impairment	50% †	72% **	42%
Adverse events			
Discontinued	16%	21%	18%
Discontinued due to adverse event	6%	8%	8%
Any adverse event	57%	54%	57%
Infections	9%	7%	8%
Serious adverse events	3%	4%	4%
Deaths	1 non-cardiac	1 non-cardiac	3 (two cardiovascular)

*** met criteria for non-inferiority vs. allopurinol † p=0.021 vs. allopurinol**
**** p<0.001 vs. 40 mg and vs. allopurinol**

OSTEOARTHRITIS (OA)

Pain control in OA is an unmet need. Dr. Nancy Lane of the University of California, Davis, said, "Chronic joint pain is the reason patients come to physicians…They hurt, so they come to the physician. And today we have very few effective medications. OA patients take analgesics, NSAIDs, occasional injections of corticosteroids, or hyaluronic, or they take narcotic analgesics to try to reduce the pain, but the efficacy of those agents is not good, and they have toxicity. We really need to focus a little more on pain (relief)."

PFIZER's tanezumab

Phase II data on this humanized anti-nerve growth factor look promising, and Pfizer has decided to begin a Phase III trial by the end of 2008 or in early 2009. Dr. Lane, the principal investigator, said, "Preclinical studies showed it is quite effective in reducing chronic pain models. A Phase I in OA of the knee was presented three years ago at ACR, showing that patients had rapid reduction in pain and no untold side effects."

The Phase II trial was a 444-patient, 16-week, randomized, placebo-controlled, parallel-arm, double-blind, multiple-dose study. It looked at the safety and tolerability of two administrations of tanezumab, one at baseline and one at Day 56. Patients were then followed to Day 112. Several doses were tested: 10, 25, 50, 100, and 200 µg. Dr. Lane said there was "a pretty nice dose response curve. After the first dose, all doses were different from placebo…There was a placebo response, but this treatment quickly and continually separated itself from placebo at almost every dose." She said that more than one dose will be taken into Phase III.

The two primary endpoints were knee pain with walking and patient global assessment of response to therapy, and both endpoints were met (p<0.005). Patients were also rated on the

16-Week Results of Phase II Tanezumab Trial in Osteoarthritis of the Knee

Measurement	Placebo n=74	Tanezumab Q8W 10 µg/kg n=74	25 µg/kg n=74	50 µg/kg n=74	100 µg/kg n=74	200 µg/kg n=74
Primary endpoint #1: Walking knee pain (by VAS)	- 15.5	- 32.1 *	- 36.0 *	- 31.0 *	- 42.5 *	- 45.2 *
Primary endpoint #2: Subject global assessment of response to therapy (change)	+ 9.2	+ 16.3	+ 23.6	+ 17.5	+ 23.7	+ 21.0
WOMAC physical function – change from baseline	- 15.9	- 28.5	- 29.9	- 31.6	- 41.1	- 44.2
WOMAC pain – change from baseline	- 17.5	- 28.8	- 31.9	- 29.2	- 40.7	- 44.8
WOMAC stiffness – change from baseline	- 17.8	- 31.6	- 33.9	- 36.7	- 42.9	- 48.1
Met OMERACT-OARSI criteria	43.8%	74.3% **	84.0% **	75.0% **	93.2% **	93.1% **
Adverse events						
Treatment-related adverse events	8.1%	14.9%	17.6%	10.8%	28.4%	35.1%
Any serious adverse event	1.4%	2.7%	0	2.7%	0	2.7%
Discontinued due to adverse events	0	8.1%	1.4%	5.4%	4.1%	10.8%
Paresthesia	2.7%	5.4%	5.4%	1.4%	10.8%	10.8%
Allodynia	0	0	0	0	1.4%	1.4%
Dysesthesia	0	0	0	0	1.4%	1.4%
Headache	N/A	8.9%				
Upper respiratory tract infection	N/A	7.3%				

* p<0.0001 ** p<0.001

WOMAC and OMERACT-OARSI scales, and tanezumab patients were significantly better.

Asked if there is any rebound when tanezumab is stopped, Dr. Lane said that in the patients she treated in the study there was no rebound, "It took quite a while (for patients to return to baseline). In my groups it was six months before their pain came up to baseline…Patients were really quite happy with it."

OSTEOPOROSIS

A concern was raised at ACR that future federally-mandated decreases in reimbursement for DXA (dual-energy x-ray absorptiometry) scans could lead to increased hip fractures among senior citizens. Researchers used the Nationwide Inpatient Sample, which is derived from a random sampling of U.S. community hospitals, to look at inpatient hospitalizations between 1998 and 2005 for non-traumatic hip fractures in patients age ≥50. They found 5.2 million cases that met this criteria, with 76% occurring in women.

Yet, the overall prevalence of hip fracture hospitalizations decreased per 100,000 patients from 428 in 1998 to 328.1 in 2005 – almost a 23% decline. In women, prevalence rate per 100,000 patients was essentially consistent from 1988 to 1996 and then began a steep decline from 635.9 in 1996 to 437.3 in 2004. The researchers noted that the decline in fractures correlated with the approval of bisphosphonates for osteoporosis and federal legislation (the "Bone Mass Measurement Act") mandating osteoporosis screening benefits for women. The researchers said they are worried that decreasing payments for DXA will lead to decreased use of the scans for screening and assessment possibly reversing this decline.

AMGEN's denosumab

New data from the DECIDE trial comparing denosumab to oral alendronate (Merck's Fosamax) were presented at ACR. Dr. Chad Deal of the Cleveland Clinic emphasized that DECIDE is not a fracture trial; the fracture data from the FREEDOM trial were presented in September 2008 at the American Society for Bone and Mineral Research (ASBMR) meeting.

Dr. Deal insisted that denosumab, administered subcutaneously once every six months, is more effective and safer than Fosamax, and rheumatologists appeared convinced. The 1,189-patient, randomized DECIDE trial showed that the markers of bone turnover were reduced faster and to a greater extent with denosumab than Fosamax, with safety similar to placebo. Adverse events were similar between denosumab and weekly Fosamax.

Denosumab has a relatively short half-life vs. the bisphosphonates; therefore, unlike Fosamax which has a long residual effect in bones, tanezumab has a quicker onset and off-set. Denosumab also has a different method of action from Fosamax, and it is given much less frequently, which Dr. Deal said "could have important indications for compliance." He added that there has not been any osteonecrosis of the jaw (ONJ) with denosumab, at least so far.

Doctors questioned at ACR were optimistic about denosumab and agreed it will have a role. Dr. Iain McInnes from the University of Glasgow, U.K., called denosumab "beautiful biology," adding that this work suggests that "ultimately, you may break RA (rheumatoid arthritis) down into different parts and treat the different parts." A West Coast doctor said, "Patients will accept it, even with the subcutaneous injections.

1-Year Results in Denosumab DECIDE Trial

Measurement	Denosumab 60 mg Q6M n=594	Fosamax 70 mg QW n=595	p-value	Relative treatment difference
Change in BMD from baseline at Month 12				
Total hip	3.5%	2.6%	<0.0001	38%
Lumbar spine	5.3%	4.2%	<0.0001	26%
Femoral neck	2.4%	1.8%	0.0002	33%
Trochanter	4.5%	3.4%	<0.0001	29%
Distal 1/3 of radius	1.1%	0.6%	0.0002	83%
Other findings				
Gain >3% BMD at total hip	62%	39%	<0.0001	---
Gain >3% BMD at spine	77%	65%	<0.0001	---
Suppression of serum type 1 C-telopeptide from baseline at Month 1	- 89%	- 61%	<0.0001	---
Suppression of serum type 1 C-telopeptide from baseline at Month 12	- 74%	- 76%	Nss, 0.5	---
Procollagen type 1 N-propeptide level at Month 1	- 26%	- 11%	<0.0001	---
Procollagen type 1 N-propeptide level at Month 12	- 72%	- 65%	<0.0001	---
Anti-denosumab antibodies	0	0	---	---

Some patients have trouble accepting Forteo (Lilly, teriparatide), but that is given daily, and no one (no insurance) is paying for something so expensive. Denosumab is not daily, and the way it works is light years above bisphosphonates, so it will be easier to convince patients this is the thing to do." Another rheumatologist said, "Once every six months administration is very good. There is a comfort level with subcutaneous injection, and there is a possible reimbursement advantage if it is administered in the doctor's office."

RHEUMATOID ARTHRITIS (RA)

A huge number of RA patients are not getting treatment, but rheumatologists do not see any huge increase in the number of patients in treatment until there are easier and safer agents available. The introduction of oral agents is likely to expand the market, but safety remains an issue.

Myocardial infarction (MI)

U.K. researchers looked at a 7-million patient U.K. database, identifying 34,364 RA patients and 103,089 matched controls, finding that MI occurred much more frequently in RA patients: a rate of 6.49 per 1,000 person-years in RA patients vs. 2.96 per 1,000 person-years in the control. An analysis of the 996 cases of MI in the RA patients found that 73% had been on a DMARD or prednisolone in the 2 months prior to the MI. The data may be able to be used to judge the safety of new RA therapies, though that was not the purpose of this study.

- Hydroxychloroquine, methotrexate, and sulphasalazine were all protective against MI (p=0.03, 0.03, 0.004, respectively).
- Prednisolone increased the risk of MI (p<0.001).

Cardiovascular disease (CVD)

Dutch researchers, comparing the CARRÉ trial in RA patients to a non-RA population in the HOORN study, found that RA is an independent risk factor for CVD (3.30 per 100 person-years vs. 1.51 per 100 person-years).

RHEUMATOID ARTHRITIS: BIOLOGICS

What is the outlook for the currently approved biologics in RA? Doctors questioned at the meeting predicted that over the next 6-12 months – without the introduction of newer agents – Bristol-Myers Squibb's Orencia (certolizumab) and Abbott's Humira (adalimumab) will gain share, while both Johnson & Johnson's Remicade (infliximab) and, to a lesser extent, Amgen's Enbrel (etanercept) will lose share.

Outlook for Use of Current Biologics in RA

Biologic	Now	In 6-12 months
Abbott's Humira	25%	29%
Amgen's Enbrel	35%	32%
Bristol-Myers Squibb's Orencia	7%	11%
Genentech's Rituxan (rituxumab)	3%	3%
Johnson & Johnson's Remicade	30%	25%

How will the current biologics be affected by the introduction of new biologics? Many of the doctors questioned at the meeting said they just don't know enough yet about the new options to figure out where they will fit in their practice. However, most predicted that Johnson & Johnson's golimumab would be popular with patients because it is given once-monthly, and they expect it to take share mostly from Humira, but it would also affect Enbrel. And some doctors said they will approach the newer agents cautiously, waiting six months or so to be sure that it performs well in clinical practice.

Rheumatologist comments included:

- *Washington:* "Golimumab won't affect Remicade because Remicade is an infusion…Humira burns more than Enbrel, so golimumab will replace Humira."
- *California:* "There is no evidence that one TNF inhibitor works better than another. Cimzia (UCB, certolizumab) and golimumab are me-too agents. Golimumab is just a subcutaneous Remicade…And the question is if it is better or worse to have a long-acting drug because you are stuck with it if a patient gets an infection…Actemra (Roche/Chugai, tocilizumab) is the most interesting because it has a different mechanism of action (anti-IL-6), but I'll still wait at least six months before prescribing it."
- *South Carolina:* "Actemra seems to work. It will make a run at Remicade – if there are no unexpected or excessive side effects…And Actemra could expand the market a little because of its different method of action. Otherwise, the new agents will just cut up the pie…Golimumab's once-monthly dosing is an advantage, but it doesn't look to me as good as the others (TNF inhibitors). It looks like a weak sister. But patient demand will drive use, and J&J has been good to me (with Remicade), so maybe I'll try golimumab faster than I tried Humira…Humira may be the current TNF inhibitor hurt the most by the new agents because there is a sense, whether it is true or not, that Enbrel has fewer side effects – cancer, tuberculosis, infections – than all the others currently used…In a year or two we may figure out which agent is best for which patient."

A study by Spanish researchers found that TNF inhibitors do not increase the risk of cancer in patients with rheumatoid disease. The researchers used a Spanish registry, BIOBADASER, which records adverse events with all rheumatic disease in that country, going back to 2001, for 100 centers. Historically, two kinds of cancer are elevated in patients with rheumatoid diseases: hematologic (lymphomas and leukemias) and lung cancer. Dr. Loreto Carmona said that the cancer incidence rate was higher in patients ***not exposed*** to TNF inhibitors than in the exposed patients, but after adjusting for age and disease activity, there was no protective effect of TNF either.

BRISTOL-MYERS SQUIBB's Orencia (abatacept)

- A double-blind, randomized, placebo-controlled, Phase IIa trial in 68 patients with active RA looked at different dosing approaches with Orencia. It found that weekly subcutaneous injections of a flat dose of 125 mg were well tolerated and similar in efficacy and safety to an IV dose of ~10 mg.
- A long-term extension study found Orencia safety and efficacy remained consistent out to four years, with no unique or unexpected adverse events.
- Three studies are ongoing testing subcutaneous dosing of Orencia, which currently is FDA-approved only in IV formulation. A researcher said patients would start with an IV load but would start subcutaneous injections that same day, taking them weekly thereafter. The subcutaneous studies are expected to be completed in 2009, with the biggest of these most likely to be presented at the European League Against Rheumatism (EULAR) meeting in 2010 or at ACR in 2010.

GENENTECH's Rituxan (rituxumab) – a B-cell depleting monoclonal antibody

Genentech has a humanized version of Rituxan in development – ocrelizumab – and the company is taking ocrelizumab and not Rituxan forward in multiple sclerosis, but in RA, there was no discussion at ACR about shifting from Rituxan to ocrelizumab, even in clinical trials.

Rituxan works in RA, but doctors are reserving it for a niche group of patients (<5%). There was no real discussion of progressive multifocal leukoencephalopathy (PML) with Rituxan and no evidence of any real concern among these doctors about Rituxan and PML, perhaps because PML is a rare but known occurrence in rheumatoid diseases *(See page 15)*. A doctor commented, "Rheumatologists are hesitant to use Rituxan because of possible long-term B-cell depletion. It really works, though…Rituxan won't go first-line because of the PML risk; PML will be in the back of your mind."

Dr. Philip Mease of Seattle Rheumatology Associates presented the results of the open-label portion of the SUNRISE trial of Rituxan in RA, looking at 1 course vs. 2 courses of Rituxan over one year. He emphasized that the trial was not an effort to assess what the optimal time is for individual patients to get re-treatment; it was a fixed re-treatment period recommended by the FDA (Q6M). The study found that patients who received two courses of Rituxan have improved clinical efficacy at 48 weeks vs. patients who received just one course of therapy. Patients who responded to the first course of Rituxan and were not re-treated had 2- to 4-fold greater risk of loss of response. Patients who had an ACR response at Week 24 were 60% more likely to have an

48-Week Results of Rituxan Re-treatment in SUNRISE Trial

Measurement	Rituxan re-treatment	Placebo re-treatment	p-value
Primary endpoint: ACR20	45%	54%	0.0195
ACR50	26%	29%	Nss
ACR70	13%	14%	Nss, 0.70
DAS28	- 1.5	- 1.9	0.0058
Safety			
Any adverse event	76.8%	70.6%	---
Serious adverse events	7.1%	6.9%	---
Infections	38.1%	37.5%	---
Serious infections	1.9%	2.2%	---
Deaths	0	1 *	--

* Considered not related.

ACR response at Week 28 (odds ratio 4.52). Likewise, patients with a DAS28 response at Week 24 had a greater response at Week 48 than non-responders at Week 24.

Thus, it would appear that patients who respond to Rituxan probably should keep taking it, and those who don't have a good initial response may not benefit from further treatments. Dr. Mease advised, "Patients not re-treated with Rituxan began to have a rise in CRP and sed (sedimentation) rate at Week 32, while those re-treated maintained a low sed rate…so we should think about re-treating patients just prior to disease flare or lab parameters suggesting disease flare."

Asked if there are patients who may not need re-treatment, Dr. Mease said he was not suggesting that patients with an ACR70 should necessarily be re-treated at Week 24, "We saw quite a number of patients who have extended response to the agent …This was not an attempt to identify individual patients…If you have a patient with a high degree of response...you could say, 'If we don't re-treat you at this time, you may be in the 30% group that may maintain'…This data would suggest if you don't have a response in the first course, that the odds are very much stacked against you for a response in subsequent courses…So, for the practicing clinician, it will depend on what other options are available to a patient...If there is no other option, there is a chance they may respond to a subsequent course."

JOHNSON & JOHNSON's golimumab, a TNF inhibitor

Golimumab is no different from other TNF inhibitors in terms of safety or efficacy, according to experts, company officials, and rheumatologists. As an investigator said, "It's not safer, and it's not worse." Another investigator said, "We are in the NSAID era – where there are only small differences in the agents." A third expert said, "Nothing sets golimumab apart, but it is once monthly, and patients will want that."

The company reportedly will launch the product with a pre-filled syringe, and J&J is working on an autoinjector that it plans to introduce later.

The only things that really set golimumab apart are:

1. **Monthly dosing.** This is a big deal. It may be of more importance to patients than some rheumatologists think.
2. **Administration.** Golimumab will be available both IV and subcutaneous. The other TNF inhibitors are either IV or subcutaneous.
3. **Data.** J&J will have some data that the other TNF companies don't have – like the anemia raising data. Probably this is a class effect, but only J&J has the data. For instance, there are data on golimumab and anemia, and the only prospective, double-blind study of a TNF inhibitor in TNF failures is with golimumab.

A J&J official added, "The initial response to golimumab is the same as with Cimzia, and payors are starting to cut coverage if there is no response by Week 12, so the fast response may be an advantage.

J&J submitted both 50 mg QM and 100 mg QM to the FDA. There is no difference between the 50 mg and 100 mg doses in terms of efficacy, so why did the 100 mg get submitted? Two possible reasons:

1. **Marketing.** If patients don't do well on 50 mg QM, instead of going to 50 mg Q2W, they can try 100 mg QM, keeping the once-monthly aura intact. Remember that when Humira launched as a once-every-two-weeks drug, some patients failed and had to go to weekly, which hurt Abbott's early marketing message somewhat. J&J may be trying to avoid repeating that.
2. **TNF failures.** In patients who have failed one or more other TNF inhibitors, it appears the 100 mg QM dose may be more effective than the 50 mg QM dose.

Can J&J sell golimumab? Doctors questioned at the meeting said yes, because they have a good relationship with most rheumatologists through Remicade, which has made money

Results of GO-FORWARD Trial

Measurement	MTX n=133	Golimumab 100 mg n=133	MTX + 50 mg golimumab n=89	MTX + 100 mg golimumab n=89
Discontinuations	7.5%	6.8%	2.2%	6.9%
Discontinuations for lack of efficacy	1.5%	0.8%	0	0
Discontinuations for adverse events	4.5%	4.5%	2.2%	5.6%
Efficacy				
ACR20 at Week 14	33.1%	44.4%	55.1% (p<0.001)	56.2% (p<0.001)
ACR20 at Week 24	27.8%	35.3%	59.6%	59.6%
ACR50	13.5%	19.5%	37.1%	32.6%
ACR70	5.3%	11.3%	20.2% *	14.6% *
DAS28	42.1%	51.9%	71.9%	76.4%
DAS28 remission	6.0%	12.0%	20.2%	22.5%
Safety				
Any adverse event	67.7%	68.2%	68.2%	68.2%
Malignancies	1	4 patients		
Serious adverse events	3.8%	9.4%		
Serious infections	0.8%	3.1%		
Injection site reactions	3.0%	4.7%		
Antibodies to golimumab	---	2.1%		

* p<0.05

for many rheumatologists. And doctors said patients will drive use – the monthly dosing will have appeal. They also predicted that golimumab would take market share from other injectables – mostly from Humira, but perhaps also some from Enbrel – and very little from Remicade because, they explained, infusion patients will remain infusion patients.

Dr. Edward Keystone of Mt. Sinai Hospital in Toronto presented the results of the randomized, multicenter, double-blind, placebo-controlled, Phase II GO-FORWARD study comparing methotrexate monotherapy vs. golimumab monotherapy Q4W vs. the combination of methotrexate + golimumab (at 2 different doses, both Q4W). He concluded: "Golimumab at 50 mg and 100 mg + methotrexate were significantly superior to placebo. Golimumab alone was generally not significantly better than methotrexate alone.

A poster by Canadian researchers looked at hemoglobin levels and golimumab, and it appears that golimumab boosts hemoglobin slightly – a positive finding in these patients. A researcher said, "I have a lot of 9-9.5 g/dL patients, and I give this, and the hemoglobin goes to 10. There is no need to transfuse just for hemoglobin with patients at 9-9.5. So, you treat their disease and their hemoglobin." The increase reportedly occurs within a couple of months.

Is this unique to golimumab? The researcher said, "My gut feeling, without data, is that other TNF inhibitors also increase hemoglobin, but that hasn't been shown."

ROCHE/CHUGAI's Actemra (tocilizumab), an anti-IL-6

This is the new RA agent in which rheumatologists said they are most interested, and that is because it is a new method of action. They predicted it would take some market share from Enbrel, Humira, and Remicade. The doses submitted to the FDA were 8 mg/kg Q4W for adults and 8 mg/kg Q2W for children.

FDA approval has been delayed perhaps 6 months, causing a "negative halo" to develop around this drug, and a key opinion leader is recommending that Roche conduct an education campaign to overcome this. Sources said the problem is not just an additional manufacturing site that needs approval but is a "manufacturing process issue" with the FDA. And one knowledgeable source said the FDA is asking for additional animal model studies. Roche officials said the drug sold in the U.S. will be manufactured in Japan.

The safety issues with Actemra are:

- **Infection.**
- **Serious infections.**
- **Liver enzyme elevations.** There have been no serious hepatic events reported, but ALT will need to be monitored as with the methotrexate guidelines. A source said that Actemra doesn't damage the liver but that it did block liver repair.
- **Lipid elevations.** These were described as treatable with statins, and there has been no cardiovascular signal. A Roche researcher said, "There is no early evidence these elevations will translate into excess cardiovascular events …If the ALT is ≥3xULN, the drug is interrupted, not stopped."
- **Transient decrease in neutrophil count.** This can translate into neutropenia, but it has not been associated with febrile neutropenia or serious infections.
- **Bowel perforations.** There have been a number of bowel perforations in Actemra patients, but it is not clear how significant this issue is. A source said these occurred early but haven't been seen recently.

Roche presented a lot of data on Actemra at ACR, including the results of the RADIATE, AMBITION, LITHE, and Japanese juvenile idiopathic arthritis (JIA) studies.

RADIATE. The results of this randomized, double-blind, placebo-controlled, international, 499-patient study found that Actemra + methotrexate is superior to methotrexate alone in TNF failures. Asked about the side effects, the investigator said, "Most were not sustained. That's what let them stay in the study. LFT elevations were nearly all self-limiting. Essentially, they were transient."

24-Week Results of RADIATE Trial

Measurement	MTX + Actemra 4 mg/kg n=161	MTX + Actemra 8 mg/kg n=170	MTX alone n=158
Completers	87%	85%	79%
Primary endpoint: ACR20	30.4% *	50.0% *	10.1%
ACR50	16.8% *	28.8% *	3.8%
ACR70	5.0%	12.4% **	1.3%
DAS28 remission (<2.6)	7.8%	30.1%	1.6%
ACR20 based on prior TNF inhibitor inadequate response (IR)			
IR to 1 TNF inhibitor	34.6%	48.9%	10.5%
IR to 2 TNF inhibitors	28.3%	50.0%	10.9%
IR to 3 TNF inhibitors	22.2%	53.8%	5.6%
Adverse events			
Serious adverse events	7.4%	6.3%	11.3%
Adverse events leading to discontinuation	6.1%	5.7%	5.0%
LDL elevated	15.3%	12.0%	3.8%
HDL elevated	13.5%	16.6%	3.8%

* p<0.0001 vs. MTX ** p<0.001 vs. MTX

AMBITION. This randomized, double-blind, placebo-controlled, 673-patient, international, Phase III study found monotherapy with Actemra 8 mg/kg met the criteria for non-inferiority to methotrexate – and even proved superior – in moderate-to-severe RA. Actemra worked fast (by 2 weeks) across all outcome measures. Hemoglobin also increased rapidly and then stabilized out to six months with Actemra, while MTX had little effect on hemoglobin.

In a post hoc analysis, investigators looked at patients who were truly MTX naïve vs. MTX-experienced patients, and they found the response was about the same. Another post hoc analysis looked at the effect of disease duration, and not sparingly that found more effect with Actemra in patients with longer duration of disease at baseline. Dr. Joel Kremer of Albany Medical College said, "The effect did not reach plateau until about Week 28 and then appeared to be sustained. Methotrexate is a pretty good drug, but this drug does somewhat better."

LITHE. This two-year, randomized, double-blind, placebo-controlled, international study showed Actemra significantly inhibited the progression of structural joint damage in RA patients.

1-Year Results of LITHE Trial

Measurement	MTX + Actemra 4 mg/kg n=401	MTX + Actemra 8 mg/kg n=401	MTX alone n=394
Completers	86%	86%	85%
Change in Genant-modified Sharp score	0.3 (p<0.001)	0.3 (p<0.001)	1.1
No progression of either joint erosion or joint space narrowing by Genant-modified Sharp score	80.5% **	84.5% **	67.2%
1-year results			
ACR20	47%	56% *	25%
ACR50	29%	36% *	10%
ACR70	16%	20% *	4%
DAS28 remission (<2.6)	30.2% *	47.2% *	7.9%
Erosion score	0.21 **	0.17 **	0.71
Joint space narrowing score	0.13 †	0.12 †	0.42
Adverse events			
Infections and infestations	2.5%	3.0%	1.5%
Neoplasms	2.5%	0.3%	0.3%
GI	0.5%	0.8%	0.5%
Cardiac	0.3%	0.8%	0.3%

* p<0.0001 ** p<0.001 † p<0.01

Juvenile idiopathic arthritis (JIA). A Japanese study found that Actemra, which is already approved in Japan, is effective in JIA. Dr. Shumpei Yokota of Yokahama City University, Japan, reported on an 84-week study of 128 JIA patients in which the efficacy of Actemra (8 mg/kg IV every two weeks) looked very good. There were a lot of serious adverse events (37.5%) – including 2 deaths – but Dr. Yokota insisted that these events occurred because these are very sick children, not because of the drug, and other experts agreed with him. A European trial of Actemra in JIA is underway.

TRUBION/WYETH's TRU-015, an anti-CD-20

The results from a Phase II re-treatment study using 800 mg IV were presented at ACR, and this showed that infusion reactions were low and decreased with time. A Wyeth-run trial (Study 2203) is ongoing using 2 doses administered at Month 0, Month 3, Month 6, and every six months thereafter. A Trubion researcher said a subcutaneous formulation "is a possibility," but he wouldn't say if that is in development yet. At EULAR 2009, the results of another Phase II re-treatment study may be presented. These are the only trials ongoing, a Trubion official said, though the company is considering a study in multiple sclerosis.

UCB's Cimzia (certolizomab)

Cimzia is currently under review by the FDA. It is expected to be labeled for use once every 2-4 weeks (allowing either Q2W or Q4W dosing). Sources at ACR said there may be a substantial delay in approval of Cimzia, perhaps another 8-14 months. The issue appears to be an FDA demand for additional data on the pre-filled syringe prior to approval. One source said, "The FDA appears to have put its foot down, saying it doesn't want two different dosing configurations on the market at the same time (a vial and a pre-filled syringe)." Another source said the problem is the viscosity of the drug in the syringe, which has been associated with some leakage.

With these pre-filled syringes, patients will have to give themselves 2 injections for once-monthly dosing since each syringe is only 200 mg (1 cc). UCB reportedly is working on a 400 mg syringe, but the problem with that is the volume required.

Reportedly, UCB has been asked to do another study with pre-filled syringes in Crohn's to validate the syringes. UCB has also been less than clear on the PDUFA date, but it may have been October 6, 2008.

Dr. Roy Fleischmann of the University of Texas Southwestern Medical Center in Dallas said one of the advantages of Cimzia is that doctors will be able to make a go/no-go decision quickly because of the rapid onset of action of this agent, "By Week 12-16 you know if it works…Cimzia really works quickly – faster than all the (currently approved) TNF inhibitors. It takes a year for maximum benefit with the other TNF inhibitors." And, he noted, it doesn't burn as much upon injection, so patients may find it more tolerable. He added, "I'll probably use Cimzia first (when it is approved), but I'm not going to not use the other (TNF inhibitors)."

RHEUMATOID ARTHRITIS: ORAL SMALL MOLECULES

Which oral agent is the most exciting? A researcher for one product (Rigel) cited Pfizer's CP-690,550. Other rheumatologists questioned at the meeting generally said it is too soon to differentiate them, but they are excited about oral agents. A Washington doctor said, "We are all waiting for the small molecules. They will be a major breakthrough. They could be cheaper, and eventually they will go generic. The safety is not overly concerning."

Asked how these oral small molecules are likely to be used when approved, an expert said, "Right now, we are looking to add an oral small molecule to methotrexate to work in non-responders to biologics or as an alternative to a biologic. The question is whether they are as effective as monotherapy as they are in combination with methotrexate. I'm not looking at these to be a replacement for methotrexate…Safety is not likely to be a big advantage with the oral small molecules. They have a different toxicity profile, but they have toxicity. All the orals have some adverse events associated with them." A South Carolina doctor said, "I would use an oral small molecule before methotrexate or a biologic. Methotrexate is not a good drug. It may be more comfortable, more familiar, but it is horrible…The concept of the oral small molecules is good, but they will be more toxic than patients and doctors expect. The pathways being blocked are too broad. If there are too many side effects, there will be resistance to prescribing them. I'd rather be the guy in three years who said he didn't prescribe something when it is withdrawn. That is why I am not focused on the orals – because of the side effects."

RIGEL's R-788 – a Syk inhibitor

Dr. Michael Weinblatt of Brigham & Women's Hospital presented Phase II data that showed good efficacy for the 100 mg dose but which raised significant safety questions.

In Phase I studies, R-788 was associated with a reversible reduction in neutrophil count, mild transaminase elevations, mild elevations in blood pressure, and occasional GI toxicity. All of these remain a problem in Phase II. Dr. Weinblatt said, "The adverse events were absolutely predictable based on the pharmacology…We predicted GI intolerability, elevated liver enzymes, and neutropenia would be the most common, and that was the case."

- **GI side effects.** Dr. Weinblatt said, "The 150 mg dose had a significant increase in GI toxicity, primarily diarrhea in 40% of patients."
- **Systolic blood pressure** increases of 4-7 mmHg, which returned to baseline 2-4 weeks after drug discontinuation. Investigator-reported hypertension was 6% at 100 mg BID and 4% at 150 mg BID. Dr. Weinblatt said this was a predictable off-target side effect, given the VEGF-related mechanism of action, adding, "Now, we have to study whether lower doses achieve similar efficacy with fewer side effects."
- **Neutropenia.** Of the 15 patients who had dose reductions, 13 were for neutropenia. The 150 mg BID patients who developed neutropenia had their dose cut to 100 mg BID, and Dr. Weinblatt said that did not appear to affect the efficacy of the drug.
- **Liver enzyme elevations.** In an LFT study, 30 patients had ALT 3xULN, and eight patients had ALT 5xULN. Five of these patients had hepatic events, but all had something that might explain this.

This 189-patient, Phase IIa safety study was conducted in the U.S. and Mexico, and a post hoc interaction study by country found differences in response, with Mexican patients having a stronger response to R-788. However, the delta between drug and placebo was the same for both countries. Dr. Weinblatt had no explanation for why the Mexicans were better responders since they found no differences in patient demographics, background MTX use, serological status, etc.

Patients who responded to R-788 had a rapid response. And the investigators identified two biomarkers of R-788 response: IL-6 and MMP-3. Dr. Weinblatt said, "There was a significant reduction in both biomarkers within the first week of doses at the two highest doses tested (100 mg BID and 150 mg BID) vs. placebo or low dose (50 mg BID)…The drug worked very quickly. We saw clinical responses as early as one week…The molecule worked early and persisted over 12 weeks."

How serious is the side effect problem? Rigel researchers said the company (1) has a follow-on compound, but the status is

12-Week Results of R-788 in RA

Measurement	Placebo n=46	R-788 50 mg BID n=46	R-788 100 mg BID n=49	R-788 150 mg BID n=47
Discontinuations *	23%	14% (Nss)		
Primary endpoint: ACR20	38%	32%	65% *	72% ‡
ACR50	19%	17%	49% †	50% ‡
ARC70	4%	2%	33% ‡	40% ‡
DAS28 remission	8%	16%	26% **	49% ‡
Safety				
Adverse events leading to withdrawal	Anorexia, nausea, dizziness, RA flare	Neutropenia	RA flare, varicella, hypertension	Pneumonia, dizziness, UTI, dehydration, gastritis, vaginal bleeding
Drug reduction	0	0	10%	32%
Diarrhea	13%	11%	15%	45%
Dizziness	2%	4%	8%	11%
Hypertension	0	0	6%	4%
Neutropenia	N/A	15%		

* p=0.008 ** p=0.036 † p=0.002 ‡ p<0.001

very early, and (2) is investigating what is causing the side effects. One said, "We know (R-788) is not 100% selective against just Syk." She cited 4 other actions that could account for the side effects:

1. **FLT-3.**
2. **VEGFR-2.** A researcher said this is thought to be the most likely cause. She noted, "R-788 is not as potent against this as against FLT-3. The blood pressure side effect may be related to this. Sutent had it with its VEGFR-2, and there is an increase in blood pressure in 30% of patients. For us, that is an off-target effect. (With follow-on compounds) we are trying to get rid of the VEGFR-2 activity and retain the other activity."
3. **JAK-3.**
4. **RET kinase.** The researcher said, "This is problematic for us because it causes malformation in kidney formation, so it (R-788) would have a pregnancy exclusion (contraindication). We are trying to get rid of RET also."

The follow-on compound is still in preclinical development. A researcher said, "We are looking at the (Pfizer) torcetrapib animal model to see if we can determine for sure if VEGFR-2 (is the culprit)."

The side effects with R-788 also may be unique to RA, the Rigel researcher said.

The 400-patient, Phase IIb trial, which is underway, is testing 100 mg BID and 150 mg QD. This reportedly is ahead of schedule on enrollment and could finish in 3Q09, with data ***possibly*** at ACR 2009. Dr. Weinblatt said if the results of this trial are good, a trial vs. methotrexate should be considered, but he warned that this would be a high bar because methotrexate is well tolerated, very good, and inexpensive, "To replace methotrexate, you (a drug) would have to be really good – and that is what we need."

PFIZER's CP-690,550 – a Janus Kinase (JAK) inhibitor

There were several presentations on "CP" at ACR. Older DMARDs have a delta vs. placebo of ~20 points on ACR20, and biologics have a delta of ~30 points. In comparison, the efficacy of CP looked comparable or slightly less than biologics. The questions about this agent are (1) the side effects, which were significant, and the (2) rebound (more than baseline) that occurs upon discontinuation. Lipids (both HDL and LDL) are increased dose-dependently, but a researcher said there have been no cardiovascular effects from this. Dr. Ethan Weiner, development head for inflammation therapeutics at Pfizer, said, "We believe the adverse events are manageable." Another source said, "There is slower efficacy but it still gets there. Over time, it ratchets up, especially at 24 months."

Pfizer plans to start the Phase III program in 1H09. The Phase III trial will be a one-year study, but two-year major clinical response will be monitored. The company plans a two-tier filing "to get it on the market earlier."

Pfizer has an extensive worldwide Phase II program designed to guide the Phase III RA program, and the company expects to have an end-of-Phase II meeting with the FDA in December 2008. An official said, "We hope to use it after any DMARD failure, and if the Phase III is spectacular, we might ask for first-line before methotrexate. We would probably have to do a head-to-head study vs. methotrexate to do that, and we have no plans for that study right now." In addition, transplant studies are ongoing, and the company has started psoriasis studies (both topical and oral).

The plan has been to study CP as both monotherapy and in combination with methotrexate. Dr. Weiner said, Pfizer intends to "vet this with regulatory authorities in the U.S., Europe, and Japan pretty much at the same time for a global simultaneous filing…The Phase III requirements will come out of those discussions, but we anticipate having a large cohort and filing in 2010-2012." Until those discussions are completed, he said Pfizer won't know what monitoring and testing requirements will need to be a part of the Phase III trials.

Asked about the role of JAK-3, a researcher said, "We didn't think that JAK-1 and JAK-2 were important at first, but other JAK inhibitors have efficacy without JAK-3. We thought our spectacular data were due to JAK-3, and we were trying to avoid JAK-1."

Asked about QD dosing, the researcher said, "We are still teasing that out. It may be we will do QD for convenience, not because we think it is better, though it may be."

The infection rate was described as comparable to TNF inhibitors.

Study 1025. In a 12-week interim analysis of the dose-ranging Study A3921025 comparing CP (from 1 mg BID to 20 mg QD) added to methotrexate vs. placebo, all doses except the 1 mg BID were significantly better than placebo. The efficacy generally improved with higher doses, and the onset of efficacy was as early as 2 weeks, peaked at 8 weeks, and was maintained at 12 weeks. The study was conducted primarily in North America, Europe, and Latin America, and there was a smaller placebo response in North America but no other significant geographic patterns of response. The analysis presented at ACR was intent-to-treat by last observation carried forward (LOCF), but Dr. Weiner said an analysis using baseline carried forward (BCF) "looked very similar."

The side effects of note were:

- Urinary tract infections – the most common drug-related adverse event.
- Diarrhea – the second most frequently reported adverse event.
- Neutrophil decrease.

12-Week Interim Results of CP-690,550 in Phase II Study in RA

Measurement	1 mg BID n=71	3 mg BID n=68	5 mg BID n=71	10 mg BID n=75	15 mg BID n=75	20 mg QD n=80	Placebo n=69
Primary endpoint: ACR20	~ 49%	~ 58% *	~ 60% *	~ 59% *	~ 58% *	~ 59% *	~ 38%
Secondary endpoint #1: ACR50	~ 23%	~ 30%	~ 35% *	~ 30% *	~ 46% **	~ 35% *	~ 17%
Secondary endpoint #2: ACR70	~ 6%	~ 22% *	~ 18% *	~ 15%	~ 26% *	~ 25% *	~ 5%
Safety							
Discontinued	14.1%	13.2%	18.3%	12%	16%	15%	20.3%
Discontinued for adverse events	4.2%	1.5%	1.4%	5.3%	6.7%	5.0%	4.3%
Serious adverse events	0	1 pneumonia 1 urinary tract infection	1 pneumonia	1 respiratory tract infection	0	1 pneumonia	0
Serious infections	0	2 patients	1 patient	1 patient	0	1 patient	0
Headache	4.2%	2.9%	0	2.7%	5.3%	12.5%	1.4%
AST ≥3xULN	0	0	0	1% (1 patient)	3% (2 patients)	3% (2 patients)	0
ALT >3xULN	0	0	0	1% (1 patient)	5% (4 patients)	1% (1 patient)	2% (1 patient)
HDL change (mg/dL) †	+ 2.22	+ 3.6	+ 6.11	+ 2.71	+ 4.74	+ 5.78	- 1.32
LDL change (mg/dL) †	+ 6.31	+ 8.14	+ 12.97	+ 16.17	+ 15.23	+ 9.61	- 5.15
Mean hemoglobin change	+ 0.02 g/dL	+ 0.11 g/dL *	+ 0.14 g/dL *	- 0.14 g/dL	- 0.40 g/dL	- 0.12 g/dL	- 0.18 g/dL
Severe anemia	3 patients	2 patients	1 patient	5 patients	6 patients	2 patients	2 patients
Neutropenia (ANC <1000 k/µL)	1 patient	0	0	0	2 patients	0	0

† all drug doses were statistically significant vs. placebo * p≤0.05 ** p≤0.0001

- Lipid increases (both HDL and LDL) – Investigators were encouraged to treat cholesterol levels as they wanted, and when treated levels reportedly responded as expected.
- Hemoglobin decrease at higher doses.
- Liver enzyme elevations.

Study 1024. An interim analysis of the open-label, long-term, multicenter Study A3921024 was also presented at ACR, combining extensions of Studies 1025 and 1019. Data were available for 129 patients, of which 40 patients had completed 6 months on study. Researchers concluded that the 5 mg BID dose was well tolerated and efficacious over a median of 109 days, with DAS28 similar in all patients at 6 months, regardless of prior study experience. Mean laboratory values remained within normal limits at 6 months. No patient required discontinuation due to individual changes in laboratory values.

Adverse Events with CP-690,550 in Phase II Study in RA

Measurement	Mild	Moderate	Severe	Total
Adverse events	93 events	64 events	3 events *	160 events
Infections	13 events	19 events	0	32 events

* MI, RA, acne

Asked about other indications for CP, Dr. Weiner said, "In Phase II (there are trials ongoing in) psoriasis (oral and topical), inflammatory bowel disease (ulcerative colitis and Crohn's disease), and solid organ transplant (starting with kidney transplant), which is the most advanced program behind RA."

Asked about the lab abnormalities, a Pfizer official said there were no ALT elevations >3xULN plus bilirubin elevations 2xULN, which is the definition of Hy's Rule. There were some elevations of 1.4xULN or 1.5xULN, but he did not know if that was in patients with elevated ALT. Dr. Weiner said, "You see neutrophils decrease in the first few weeks, and then they seem to stabilize. LFTs generally showed a similar pattern."

Asked about pricing, a Pfizer official said, "It is very early to make those decisions, but we do think we will come forward with a strong value proposition that payors will be interested in and be willing to reimburse the product."

Study 1013. This fixed-sequence, drug-drug interaction study in 12 RA patients found no issues with administering CP concomitantly with methotrexate. Methotrexate had no clinically relevant effect on the PK of CP. There was a 10% decrease in methotrexate exposure with the combined therapy, but it was determined not to be clinically important, and no dose adjustment appears required when CP-690,550 and methotrexate are co-administered. Treatment-related adverse events included dizziness, disorientation, headache, and hot flushes. Abnormal lab values were observed, but none were considered clinically significant. One patient discontinued CP690,550 after experiencing mild leg pain but resumed the drug the next day, and another patient stopped after a mild vasovagal episode but resumed treatment right away.

Dr. Kremer said the HDL and LDL increases tended to peak at Week 16, and the neutropenia appeared to peak by Week 12.

INCYTE

➢ INCB-018424 – a JAK-1/2 inhibitor

Unlike Pfizer's JAK inhibitor, this agent does not inhibit JAK-3 at clinical doses. Incyte officials suggested this is an advantage, speculating that it is JAK-3 inhibition which is associated with adverse events. An official said, "If you mutate JAK-3 in rodents or humans, you get SCID (absolutely immunocompromised)…There are no JAK-1 mutations in humans." He said different safety profiles may distinguish the JAK inhibitors, with INCB-018424 safer than Pfizer's JAK-3. However, that argument is not entirely convincing.

Is a JAK inhibitor safer than a TNF inhibitor? The Incyte source said, "We really need more patient data to answer that."

INCB-018424 is being investigated in Phase IIa trials in three disorders: as an oral in RA, as a topical in psoriasis, and as an oral in myeloproliferative disorders. The lead indication for which the company will seek approval is myeloproliferative disorders. An official said, "The goal in psoriasis is to get patients off steroids. Our trial is a dose-escalation study vs. a potent topical steroid, and we are looking at least as good as the topical steroid…It is possible INCB-018424 could work in other indications where high-dose topical steroids are used."

Dr. Larry Moreland of the University of Pittsburgh reported on a randomized, placebo-controlled, 28-day Phase IIa trial of INCB-018424 (Study INCB-18424-231) conducted in the U.S. and Poland. Cohort 1 (n=16) tested 15 mg BID, and Cohort 2 (n=50) tested 5 mg BID, 25 mg BID, and 50 mg QD. The 15 mg BID dose appears to be the dose going forward. Responses were seen as soon as 1 week; the QD dosing did not appear as effective as lower doses with BID dosing.

Patient pain assessment, HAQ, and Physician Global Assessment were better than placebo with all INCB-018424 doses except the lowest (5 mg BID) dose.

28-Day Results with INCB-018424 in RA

Measurement	INCB-018424	Placebo
ACR20	83% at 15 mg BID 50% at 25 mg BID 30% at 50 mg QD	75%
ACR50	58%	0
ACR70	33%	0
ACR90	17%	0
DAS28 <3.2	7 patients	0
DAS28 <2.6	4 patients	0
Mean DAS28	Down 2.70	N/A
Adverse events	51% *	56%
Serious infections	0	0

* One patient discontinued due to abdominal pain at 25 mg BID, one patient had transient Grade 3 neutropenia that improved with drug discontinuation, and one patient, with a history of recurrent ITP, had Grade 3 thrombocytopenia.

Adverse events included mild diarrhea, fever blister, and dry mouth. Neutrophil counts were reduced but stayed above the upper limit of normal. Dr. Moreland said, "This was expected and predicted based on the inhibition of IL-6 and was most likely caused by neutrophil marginalization." Even at the highest dose, neutrophil rates returned to normal within 24 hours after stopping the drug. There were "occasional" transient liver elevations, but no significant changes in lipid levels, though he said this still needs to be looked at further.

Dr. Moreland concluded: "(INCB-018424) is safe and well tolerated, with one patient with neutropenia and one thrombocytopenia. Clinical response is seen as early as one week after dosing…INCB-018424 has the potential to be as, or more, effective than currently available RA therapy, including injectable biologics." He said the 15 mg BID dose will be further evaluated in a Phase IIb trial.

➢ INCB-028050 – another JAK-1/2 inhibitor for RA

This JAK inhibitor is currently in Phase I in healthy volunteers.

RHEUMATOID ARTHRITIS: ORAL p38 MAPKINASE INHIBITORS

Pharmas may not have given up on p38 MAPK inhibitors entirely, and Bristol-Myers Squibb and Array Pharmaceuticals presented data at ACR on their p38s, but a Johnson & Johnson speaker made a compelling case that none of these is likely to work.

BRISTOL-MYERS SQUIBB's BMS-582949

Three studies (2 in healthy subjects and 1 in RA patients) were presented:

1. A double-blind, randomized, placebo-controlled trial in 48 healthy male subjects found no serious adverse events or discontinuations due to adverse events and a dose-response curve, suggesting a dose of ≥100 mg might be appropriate.
2. A randomized, placebo-controlled, ascending multiple dose (30 mg, 100 mg, 300 mg), double-blind trial of BMS-582949 in 33 RA patients on stable doses of methotrexate found the drug was relatively well tolerated. One placebo patient had a serious adverse event (atrial fibrillation), and there were no serious adverse events in the drug arms. Three patients – all in the 30 mg dose – discontinued vs. 3 patients with placebo. There was no drug interaction with methotrexate. Mild-to-moderate laboratory abnormalities were observed but without clinical symptoms. There was a non-significant trend to efficacy with the 300 mg dose. Adverse events included mild-to-moderate dizziness (15%), upper respiratory infection (4%), and moderate skin rash (4%).

3. An analysis of these patients plus another 40 healthy patients from a second study were analyzed together, looking at PK, PD, safety, and tolerability. C_{max} and AUC were both dose-related but less than dose proportional across the evaluated dose range. Median T_{max} was 1-3 hours, and mean half-life was 11-21 hours. The conclusion was that BMS-582949 is safe up to a dose of 600 mg for 28 days in healthy subjects.

JOHNSON & JOHNSON'S SCIO-469

Dr. Mark Genovese of Stanford presented the results of the failed 12-week, randomized, double-blind, placebo-controlled, Phase II trial of SCIO-469. He concluded, "There were no significant differences in ACR20 responses between the drug and placebo. Declines in CRP during early treatment did not persist through Week 12 and did not correlate with stable drug plasma levels. The 60 mg TID-IR dose showed a dose-limiting ALT elevation. There is a possible safety signal for rash. The transient effect on CRP suggests a complex relationship of p38α MAPK in inflammation…A biologic adaptation may be taking place in response to inhibition of this pathway."

Asked about pain relief, Dr. Genovese said, "We looked at pain scores…We did see a fairly consistent improvement in pain, though a mild one, and we didn't see a similar pattern with acute phase proteins."

Asked if these data are generalizable, Dr. Genovese said, "Obviously, it is a political hot potato…Upcoming articles in the next few months and an editorial may provide additional insight into the field."

12-Week Results of a Phase II Trial of SCIO-469

Measurement	SCIO-469			Placebo
	30 mg TID-IR n=75	60 mg TID-IR n=73	100 mg QD-ER n=78	n=76
Discontinuations *	37 patients	36 patients	34 patients	37 patients
Primary endpoint: ACR20 at Week 12	24%	23%	26%	33%
ACR50	9%	8%	8%	16%
DAS28	- 0.5	- 0.9	- 0.9	- 0.4
Swollen joint count	- 27%	- 18%	- 27%	- 26%
Tender joint count	- 38%	- 22%	- 32%	- 39%
CRP	+ 8%	- 3%	- 10%	- 1%
HAQ	- 0.02	- 0.13	- 0.17	- 0.19
Safety				
Adverse events	85%	82%	N/A	75%
Serious adverse events **	4%	5%	6%	0
Rash	14%	18%	10%	4%
Dizziness	3%	4%	6%	9%
ALT ≥3xULN	3 patients	5 patients	0	1 patient

* mostly adverse events and also patient decision to discontinue
** only 1 serious infection

PML IN RHEUMATIC DISEASES

A study by Cleveland Clinic researchers looked at all the cases of PML from 1998-2005 in the U.S. Nationwide Inpatient Sample database, which is a 20% sample of all hospital discharges, weighted to represent the entire U.S. inpatient population. Out of ~300 million hospital discharges, they identified 9,675 cases of PML or 3.2 per 100,000 patients. The incidence was lower in RA (0.4 per 100,000 patients) but elevated in lupus. In comparison, the estimated rate of PML with Biogen Idec/Elan's Tysabri (natalizumab) in multiple sclerosis is 100:100,000 patients (1:1000). They concluded that PML occurs rarely in patients with a rheumatic disease but that PML is probably under-diagnosed. However, they also concluded that SLE is associated with a "predisposition" to PML, so a "high index of suspicion" is needed in lupus.

PML Cases in the U.S.

Condition	Number of patients	% of PML cases
HIV	7,934	82.0%
Hematologic cancer	813	8.4%
SLE	43	0.44%
RA	24	0.25%
Other connective tissue disease	25	0.2%
Other	836	8.71%
Disease	**Number per 100,000 patients**	**Number per 100,000 patients (excluding HIV, cancer, and organ transplantation)**
SLE	4	4
RA	1	0.4
Other connective tissue disorders	5	2
Systemic vasculitis	0	0

PAIN MEDICATIONS

New drugs are needed for rheumatic pain, especially osteoarthritis. The chronic pain population continues to expand, and there is an unmet need.

Currently Available Therapeutic Drug Classes for Chronic Pain

Acute pain, musculoskeletal pain	Neuropathic pain
Acetaminophen	Antidepressants
NSAIDs	Anti-epileptics
Opiates	Topical capsaicin
Local anesthetics	Local anesthetics
Muscle relaxants	

PFIZER's tanezumab

Initially, tanezumab – a humanized igG2 monoclonal antibody (nerve growth factor, NGF) – is being developed as a slow (5-minute) IV push at a dose of ≤100 mg given once every 8 weeks, but Pfizer has bigger plans for indications other than osteoarthritis and for subcutaneous (SC) dosing. An RTU (ready-to-use) liquid formulation (sold in vials) has been developed that must be refrigerated, but a small IV/SC bioequivalent study is expected to begin later this year. Pfizer expects to submit a BLA for tanezumab to treat osteoarthritis in 2011 or 2012 as an IV, followed by the SC dosing in osteoarthritis (OA) and chronic pain.

In animals, anti-NGF treatment does not affect the acute pain sensation or neuron survival. A 26-week study in adult cynomolgous monkeys at doses up to 30 mg/kg/week showed no target organ toxicities.

So far >675 patients have been treated with at least 1 dose of tanezumab (~250 patients for ≥6 months and ~60 patients for ≥12 months). The Phase II osteoarthritis program is complete, and an open-label study with 50 µg/kg IV Q8W has been completed, with data likely to be presented early next year.

Other Phase II studies of tanezumab include:

- Chronic low back pain – complete
- Visceral pain:
  - Interstitial cystitis – enrollment ongoing
  - Endometriosis – to start 4Q08
  - Prostatitis – to start 1Q09
  - Metastatic bone pain – to start 1Q09
- Neuropathic pain – enrollment completed

In the Phase II study in osteoarthritis of the knee that was presented at ACR, five doses (10, 25, 50, 100, and 200 µg/kg) were administered every 8 weeks for 6 months in patients who were NSAID failures or candidates for more invasive therapies. Dr. Lane of UC-Davis noted that no patients stopped for neurological abnormalities such as paresthesia; all adverse events were transient.

The most frequent adverse events were: headache (8.9%), upper respiratory tract infections (7.3%), paresthesia (6.8%), hypoesthesia (5.7%), and arthralgia (5.7%). Infusion site reactions were rare (burning 0.5%, pain 0.5%). Only arthralgia and worsening diabetes led to withdrawal by more than one patient. One patient withdrew due to abnormal cutaneous sensation. The serious adverse events were all considered unrelated to the drug. There also were adverse events related to abnormal peripheral sensation, but they were described as

12-Week and 16-Week Results in Phase II Trial of Tanezumab in OA

Measurement	Placebo	Tanezumab				
		10 µg/kg	25 µg/kg	50 µg/kg	100 µg/kg	200 µg/kg
WOMAC pain scale change at Week 12	- 16.5	- 34.0 *	- 36.7 *	- 31.7*	- 44.0 *	- 47.0 *
WOMAC pain scale change at Week 16	- 17.5	- 28.8 ‡	- 31.9 ‡	- 29.2 ‡	- 40.7 *	- 44.8
WOMAC function scale change at Week 12	- 15.0	- 32.5 *	- 34.7 *	- 33.2 *	- 43.7 *	- 46.5 *
WOMAC function scale change at Week 16	- 15.9	- 28.5 ‡	- 29.9 ‡	- 31.6 *	- 41.1 *	- 44.2 *
Stiffness change at Week 12	- 17.8	- 38.0 *	- 38.9 *	- 37.7 *	- 45.6 *	- 50.3 *
Stiffness change at Week 16	-17.8	- 31.6 ‡	- 33.9 *	- 36.7 *	- 42.9 *	- 48.1 *
30% pain responders	~ 35%	~ 70% *	~ 69% **	~ 70% *	~ 87% *	~ 88% *
50% pain responders	~ 25%	~ 57% ‡	~ 60% **	~ 56% ‡	~ 77% *	~ 78% *
90% pain responders	~ 4%	~ 15% **	~ 28% ‡	~ 17% **	~ 31% *	~ 34% *
Safety						
Adverse events	55%	69%	66%	60%	69%	78%
Drug-related adverse events	8%	21%				
Withdrawal due to adverse events	0	8%	1%	5%	4%	11%
Serious adverse events	1%	3%	0	3%	0	3%
Adverse events related to abnormal peripheral sensation	2.7%	5.4%	5.4%	5.4%	17.6%	16.2%
Allodynia	0	0	0	0	1.4%	1.4%
Dysesthesia	0	0	0	0	1.4%	1.4%
Hyperesthesia	0	0	0	4.1%	5.4%	5.4%
Paresthesia	2.7%	5.4%	5.4%	1.4%	10.8%	10.8%
Hypoesthesia	0	1.4%	9.5%	2.7%	6.8%	8.1%

* p≤0.001 ** p≤0.05 ‡ p≤0.01

mild-to-moderate, occurring early, and being transient:

- Allodynia – clothing/touch evoke pain sensation.
- Dysesthesia – sensitivity to touch and clothing or sun-burn/hot sensation.
- Paresthesia – tingling, pricking, or pins and needles sensation.
- Hyperesthesia – high/low sensitivity to touch, pain, or other sensory stimuli.

Asked about the peripheral edema (up to 11%) reported earlier this year, Pfizer's Dr. Verburg said, "We will look at that more carefully to see if that plays out in Phase III."

For the Phase III trials, Dr. Verburg said, "WOMAC (pain, function, and global assessment) will be the primary efficacy endpoint, per our discussions with the FDA."

Asked about the outlook for an injectable pain medication in OA, another Pfizer official said, "There is a large population of moderate-to-severe pain patients not receiving adequate pain relief…In the U.S. and Europe, there are 10 million OA patients in that moderate-to-severe category, and about 25% of those are in the severe category, so I think there is a significant unmet need…And remember this is not a typical infusion like with the biologics (for RA). It is a five-minute push, but we are quickly following with a subcutaneous injection that will let patients self-inject at home."

Asked if there are any theoretical issues that need to be watched in Phase III, Dr. Verburg said, "We are focused on a couple of theoretical adverse events – predominantly in peripheral neurons and sympathetic neurons…It is very hard to identify structural damage to neurons, especially sensory neurons. Hence, a nerve conduction velocity study…but then we are going beyond that with some tests of autonomic function density and nerve density in the skin. We think that will teach us a lot…One aspect we can't control but are mindful of rare patients who suffer from an injury – for example, auto accidents with peripheral trauma. We will be curious to see the prognosis of those patients and if we can detect any changes in their recovery and the recovery of their peripheral sensory function."

Asked if a bioequivalence study is all that will be needed for the subcutaneous formulation, Dr. Verburg said, "No…We did a bridging study in cynomolgous monkeys, and what we found so far is encouraging – no local irritation or particular pain. The (subcutaneous) bioequivalence is fairly similar to the IV. That is good, so it means we won't have to use a much higher dose or more frequency than with IV…But does that hold in humans? We have to go further and study and evaluate the subcutaneous (formulation) in an OA population. We don't have to repeat the entire IV program in terms of efficacy and safety…but we need to do some bridging in an OA population…It will be a lot smaller but larger than one study."

Asked why Pfizer didn't choose an indication with a lower bar than OA, Dr. Verburg said the program was inherited from Rinat Laboratories, which had chosen OA, "If we had started from scratch, we might have chosen a slightly different approach."

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

GENENTECH's Rituxan (rituxumab)

From data presented at ACR, Rituxan does ***not*** appear to work in lupus, but that also does not appear to be discouraging rheumatologists from prescribing it. Dr. Joan Merrill of Oklahoma, medical director of the Lupus Foundation of America, presented the results of the 52-week, double-blind, multicenter, Phase II/III EXPLORER study of Rituxan vs. placebo in moderate-to-severe SLE. Rituxan missed the primary endpoint and all secondary endpoints.

A pre-specified subgroup analysis by ethnicity showed that African-Americans and Hispanics did have a significant response to Rituxan, but that was because the placebo patients did worse than expected, not because Rituxan was doing better. Dr. Merrill said, "The major take-home message is: There is no evidence base to support the efficacy of Rituxan (in SLE)."

Dr. Merrill asked the audience how many of them have used Rituxan in a lupus patient, and quite a number of doctors raised their hand. Then, she asked how many will no longer use Rituxan in lupus patients, and only a couple of doctors raised their hand.

Pfizer Pain Portfolio

Preclinical	Phase I	Phase II	Phase III	Phase IIIb
4 compounds	PF-3558157 – PED7 inhibitor	PF-4480682 – PDE5i + α2δ	Tanezumab – anti-NGF Mab	Lyrica – post-operative pain
	PF-4191834 – 5-LO inhibitor	PH-797804 – p38 kinase inhibitor	Esreboxetine – NRI	Celebrex – gout
	PF-3864086 – TRPV1 antagonist	PF-4136309 – CCR2 antagonist		Lyrica – fibromyalgia (Europe)
	PF-4457845 – FAAH inhibitor	ADL-5859 – DOR agonist		
	ADL-5747 – DOR agonist			

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