# Trends-in-Medicine

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# Quick Pulse



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## FDA Advisory Committee Recommends Approval of New Rheumatoid Arthritis Therapy

Rockville, MD
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The FDA's Arthritis Advisory Committee voted unanimously to recommend approval of Bristol-Myers Squibb's Orencia (abatacept), a first-in-class T-cell co-stimulation modulator, for the treatment of moderate-to-severe active rheumatoid arthritis. Panel members were concerned about an increased risk of serious infections and the potential risk of malignancy, but they were sufficiently impressed with the company's proposed risk management program to give Orencia a thumbs-up, saying the benefits outweigh the risks.

If the FDA approves Orencia, it will compete with TNF inhibitors – Amgen's Enbrel (etanercept), Johnson & Johnson's Remicade (infliximab), and Abbott's Humira (adalimumab). Orencia interrupts the inflammatory process by selectively modulating one of two signals needed for full T-cell activation, therefore slowing the body's response to inflammation. Activated T-cells control the autoimmune response that leads to joint inflammation and deterioration as well as the disability often associated with rheumatoid arthritis.

Bristol-Myers Squibb is seeking FDA approval to market Orencia to adult patients with moderate-to-severe rheumatoid arthritis who have had an inadequate response to one or more DMARD, such as methotrexate and TNF blockers. The company is asking for the indications to include:

- Reducing signs and symptoms, including major clinical response.
- Inhibiting the progression of structural damage, and improving physical function.
- Use in combination with methotrexate or other non-biologic DMARD therapy.

### The Company Perspective

A company official told the committee that Orencia's clinical benefits include:

- Improvement in patients' signs and symptoms.
- Improvement in physical function.
- Improvement in overall quality of life.
- Halting of damage progression.

Placebo-controlled studies included 1,955 patients, representing 1,688 person-years of exposure. Of these, 1,330 patients were in studies ≥1 year. In addition, 2,339 patients participated in open-label, uncontrolled studies, and 2,688 patients were in combined double-blind and open-label studies, representing 3,827 person-years of exposure. Orencia was given in doses of 10mg/kg, 2 mg/kg, and 0.5mg/kg. The efficacy data presented showed improvement in physical function.

**Substantial Clinical Responses at 1 Year**
***(in Patients with Inadequate Response to Methotrexate)***

| Measurement | Orencia n=424 | Placebo n=214 |
|---|---|---|
| Major clinical response | 14% | 1.9% |
| **Patients with joint counts of zero** | | |
| No swollen joints | 18% | 4.2% |
| No tender joints | 16% | 3.8% |

**Clinically Important Improvement in Physical Function**

| Patient population | Decrease in mHAQ ≥0.3 | | |
|---|---|---|---|
| | 1 year | 2 years | 3 years |
| **All patients (n=84)** | | | |
| Number of patients | 84 | 73 | 64 |
| % responders | 55% | 53% | 53% |
| **Responders (with discontinuations considered non-responders) (n=84)** | | | |
| % response | 55% | 46% | 42% |
| **mHAQ responders at 1 year (n=46)** | | | |
| % response | --- | 67% | 57% |

The company presented efficacy data indicating that the drug met all primary and key secondary outcomes, including a consistent effect on ACR20, ACR50, and ACR70, with inhibition of structural damage, and improvement in physical function and quality of life and major reductions in disease activity. On safety, officials claimed that the frequency of malignancies was similar to placebo and to the U.S. general population overall and for major categories, such as skin, solid, and hematologic cancers. The incidence of lymphoma and lung cancers were reported to be greater than in the U.S. general population but within reported ranges for RA patients, and virally-associated malignancies were uncommon. The company insisted that the totality of evidence does not suggest an increased malignancy risk with Orencia. Rather, the major identified risk with Orencia is infection, and officials said that Orencia showed a frequency slightly increased (1%) rate of serious infection; but the type, duration, treatment, and outcome were similar to placebo.

**Improvement in Quality of Life (SF-36) Score at 1 Year**
***(in Patients with Inadequate Response to Methotrexate)***

| Physical and Mental Component Summary, Quality of Life at 1 year | | | |
|---|---|---|---|
| **Mean change from baseline** | **Orencia n=417** | **Placebo n=207** | **p-value** |
| Physical component summary | 9.1 | 5.0 | <.001 |
| Mental component summary | 6.3 | 4.7 | <.05 |
| Physical function | 8.0 | 4.5 | <.001 |
| Role – physical | 9.4 | 5.7 | <.001 |
| Bodily pain | 11.6 | 6.9 | <.001 |
| General health | 6.5 | 4.2 | <.001 |
| Vitality | 8.1 | 4.7 | <.001 |
| Social function | 8.4 | 5.3 | <.001 |
| Role – emotional | 8.8 | 5.5 | <.01 |
| Mental health | 6.3 | 4.2 | <.01 |

The company proposed a 5,000 patient pharmacovigilance plan, including:

- Enhanced data collection for clinical and spontaneous reports, including special event forms and phone contact.
- Long-term clinical study extensions up to five years.
- A pregnancy registry.
- Large observational safety studies.

***FDA panel members had a variety of questions for the company presenters, including:***

**Subgroups.** Several panel members expressed concern that the drug would be given to patient populations in which it hasn't been adequately tested, such as children, pregnant women, and the very elderly.

- **Elderly**. A Bristol-Myers Squibb spokesman responded, "In the over-65 population we noted a significant difference – more malignancies and infections. These were predominantly bacterial, respiratory tract, and tissue-type infections. The malignancies were scattered, with the exception of four with lung cancer…However, we saw consistent efficacy in the elderly, and patients greater than age 65 had a significant decrease in symptoms along with the rest of the population."
- **Children**. A company speaker said that the company has just completed enrollment in a juvenile RA study.
- **Pregnancy**. A Bristol-Myers Squibb physician was asked to talk about a study of Orencia in pregnant rodents, and she said that pups from dams dosed with Orencia were evaluated at 16 weeks and assessed for the presence of autoimmunity. She reported, "We found 3-fold clinical exposure had no effect. At 11-fold clinical exposure, we found a 9-fold increase in the mean T-cell-dependent antibody response and inflammation of thyroid in one female rat out of 10 males and 10 females. There was no effect on any of the other organs. So, based on the weight of data here, we conclude that the risk to human progeny…is low."

**Additional studies.** One panel member observed that the company's planned observational studies would be powered at lower levels than the efficacy studies (80% compared to 95%).

**Non-U.S. data.** A panel member asked about trial results in areas outside the U.S., particularly in South America, where efficacy data appeared skewed, with a surprising number of placebo patients responding favorably.

**Multiple sclerosis (MS).** A panel member commented, "You made a brief foray into MS with confusing results, in which the low dose group had a substantial number of lesions, and the higher dose group had fewer than the placebo. Are you confident the drug can be given for patients with MS?" A company speaker responded, "We are not advocating the use of abatacept in patients with MS. We're not investigating it for that indication here today." However, when pressed, he said that the drug's proposed label would not caution specifically against giving the drug to MS patients. Instead, the proposed label would say that patients with a history of an autoimmune disease would have to use caution. A Bristol-Myers Squibb physician said, "We have no intention of encouraging the use of abatacept in patients with MS."

**Overview of Patients with Adverse Events**
***(double-blind, controlled study periods)***

| Measurement | Orencia n=1,955 | Placebo n=989 |
|---|---|---|
| **Adverse events** | | |
| Total | 88.8% | 84.8% |
| Discontinuation due to adverse events | 5.5% | 3.9% |
| Deaths | 0.5% | 0.6% |
| Headache | 18.2% | 12.6% |
| Nasopharyngitis | 11.5% | 9.1% |
| Dizziness | 9.4% | 7.0% |
| Hypertension | 6.6% | 4.3% |
| Dyspepsia | 6.4% | 4.2% |
| **Serious adverse events** | | |
| Total | 13.6% | 12.3% |
| Musculoskeletal and connective tissue disorders | 3.0% | 3.7% |
| Infections and infestations | 3.0% | 1.9% |
| Injury, poisoning, and procedural complications | 1.5% | 0.7% |
| Neoplasms – benign, malignant, and unspecified | 1.4% | 1.1% |
| Gastrointestinal disorders | 1.2% | 1.3% |
| Nervous system disorders | 1.0% | 1.4% |
| Cardiac disorders | 0.9% | 1.7% |
| **Most common infections** | | |
| Total | 53.8% | 48.3% |
| Upper respiratory tract infection | 12.7% | 12.0% |
| Nasopharyngitis | 11.5% | 9.1% |
| Sinusitis | 6.4% | 6.9% |
| Urinary tract infection | 5.8% | 4.6% |
| Flu | 5.7% | 5.3% |
| Bronchitis | 5.2% | 4.6% |
| **Serious infections** | | |
| Total | 3.0% | 1.9% |
| Pneumonia | 0.5% | 0.5% |
| Cellulitis | 0.3% | 0.2% |
| Urinary tract infection | 0.2% | 0.1% |
| Bronchitis | 0.2% | 0% |
| Diverticulitis | 0.2% | 0% |
| Pyelonephritis acute | 0.2% | 0% |
| Sepsis | <0.1% | 0.3% |

**Psoriasis.** Asked about using the drug for people with psoriasis, a Bristol-Myers Squibb physician said, "We intend to encourage physicians to prescribe on label. Psoriasis is off-label."

**Hypersensitivity.** A company speaker said, "We evaluated infusive reactions as to pre-specified adverse events – infusion reactions that occurred within one hour." Almost 9% of patients on abatacept had adverse events compared to 5.6% on placebo. Adverse events were predominantly dizziness, elevated blood pressure, and rash. Four patients experienced hypersensitivity reactions that occurred in the first hour, two were hypersensitive, one was drug hypersensitive, and one was hypertensive. All four discontinued the drug.

## THE FDA PERSPECTIVE

The FDA staff presentation concluded that use of Orencia results in:

- Improvement in signs and symptoms.
- Improvement of physical function.
- Inhibition of radiographic progression.

*On safety, an FDA official said:*

➢ **Serious infections.** The data showed a higher rate of serious infections in patients treated with Orencia, especially in patients receiving concomitant TNF blockers.

➢ **Cancer.** Overall malignancy rates were not substantially different between Orencia- and placebo-treated patients (1.5% vs. 1.1%). However, Orencia-treated patients were found to have had more cases of ***lung*** cancer, with the rate of lymphomas higher than expected compared to the general U.S. population. There were eight cases of lung cancer in patients receiving Orencia. Pre-clinical studies demonstrated an increased rate of mammary tumors and lymphomas in mice that was believed to be secondary to Orencia-induced chronic immunosuppression.

➢ **Infusion-related reactions.** These were observed, including hypersensitivity reactions and **two** cases of anaphylaxis.

➢ **Chronic obstructive pulmonary disease (COPD).** Patients with COPD treated with Orencia had a higher incidence of adverse events and more serious adverse events, particularly respiratory disorders.

➢ **Combination therapy.** An FDA official said that 204 patients received Orencia with a concomitant RA biologic therapy during the double-blind period, representing 173 person-years of exposure. Patients receiving abatacept and RA therapy experienced more serious adverse events and adverse events than those on placebo."

➢ **Deaths.** There were 26 total deaths. An analysis of the individual deaths didn't suggest a safety signal for any single type of adverse event. Eight of the 16 Orencia deaths occurred during a study that permitted enrollment of patients with co-morbidities.

**Orencia Deaths**

| Cause | Orencia deaths n=10 (0.5%) | Placebo deaths n=6 (0.6%) |
|---|---|---|
| Cardiovascular disorders | 4 | 2 |
| Found dead at home | 3 | 1 |
| Malignancy | 2 | 1 |
| Infection | 1 | 2 |

## THE PANEL PERSPECTIVE

***The FDA posed several questions to the panel.***

**Question #1 – Efficacy:** *Please discuss the strength of evidence regarding the demonstration of efficacy of abatacept in the treatment of patients with rheumatoid arthritis.* **Unanimous in favor of proven efficacy.**

The panel agreed unanimously that Orencia showed efficacy for signs and symptoms as well as physical function.

*Panel chair to another panel member:* "Doctor...What can you say about the efficacy (of Orencia)?"

*Panel member:* "Well, I think it works." *(laughter)*

*Panel chair:* "Thank you, can we have the next question?"

**Radiographic progression.** There was some discussion about efficacy in radiographic progression, but panel members appeared satisfied with the answers from the FDA staff and the company speakers. A panel member said that one of the problems with radiographic progression is that no one knows for sure how the drug works.

*Panel chair:* "To what extent do you look at the total score as opposed to the individual components?"

*FDA official:* "So long as the effects are similar between the components, there's no reason it would lack the clinical benefits."

*Panel chair:* "And you're not concerned that this has only been demonstrated in one study?"

*FDA official:* "To get claims of efficacy, one usually needs reproduction of benefits in at least two trials. However, once we have evidence of efficacy in one area, when you look at other areas that are related, you don't necessarily require two studies. With respect to radiographic progression, with a single trial which is large and robust – and showing benefit – we do not always require a second study."

*Panel chair:* "Let's then break down the discussion into three areas: signs and symptoms, physical function, and radiographic progression. Does anyone have any concern on the efficacy of signs and symptoms?...(pause)…Apparently not. What about physical function?...(pause)…Apparently not. That leaves us with radiographic progression. Is anyone uncomfortable with the data?...(pause)…(One panel member) abstains…We're comfortable with signs and symptoms and with physical function. If there's any question, it's in the strength of the evidence of radiographic progression. The data exist in only one study."

**First- or second-line therapy.** The patient representative on the panel asked if the company is considering prescribing the drug only after failure with methotrexate or whether the company sees Orencia more as a first-line drug, and she expressed concern about what happens when Orencia is taken with other drugs. An FDA official agreed with the concern about combining Orencia with other drugs. A Bristol-Myers Squibb official responded, "Our clinical program is based on patients who have an inadequate response to existing therapy, so, in that sense, it would be for patients who don't respond to methotrexate or anti-TNF therapies…Abatacept should not be used in combination with biologic therapies at this point because it shows an increased risk of infections, and we haven't seen that, added to biologic, there is going to be consistent benefit."

**Duration of therapy.** There was a question about how physicians should use Orencia with their patients:

*Panel member:* "We were trying to get some guidance for a physician as to how long you keep giving the drug to a patient before you give up? Data suggest that you know after two months whether this is going to work or not."

*Bristol-Myers Squibb official:* "We don't have enough information at this time. I'd think a two or three month trial would be insufficient."

*A company consultant:* "It is a chronic disease, and not all patients respond the same. Say, with five infusions over 12 weeks – if you haven't had a response at that point, I'd move to a different therapy."

**Labeling.** There was a question about proposed labeling, which includes RA negative patients as well as RA positive patients. A panel member said, "It doesn't look as though enough negative patients were studied to make any conclusions at all. It doesn't look as if there are enough patients in that subgroup. One assumes that the results for the positive extend to the negative."

*Panel member:* "Can you separately say that the drug works for the negative patients when so few negative patients were looked at? If you say, in general, that it works for RA patients, then you don't have to insist on specific evidence for every subgroup. If you try to say it works for both the subgroups, then that group is small."

*Bristol-Myers Squibb official:* "We're not trying to say that it works in any one subgroup any more than another subgroup."

**Question #2 – Safety:** *More serious infections have been observed in the abatacept-treated groups than in the control comparison groups. This was particularly notable for, but not limited to, patients who received concomitant TNF-antagonist agents.* **A concern, but not a big concern.**

A panel member asked about breaking down agents into non-biologic and biologic categories. He was specifically concerned with Sanofi-Aventis's antirheumatic drug Arava (leflunomide). An FDA official said, "We didn't break down the non-biologic DMARDs by mechanism. It's a good idea, but in practice it's hard to do."

**Question #3 – Infections and safety:** *The clinical development program incorporated an analysis of "Infections of Special Interest" which included fungal (e.g., aspergillosis), viral (e.g., herpes zoster), and bacterial infections (e.g., pneumonia and TB). Overall "Infections of Special Interest" were observed in 10% of abatacept-treated patients compared to 7% of control group patients, with the majority of the difference in the herpes and pneumonia categories. However, the total patient sample size and exposure duration (median 14 months) cannot rule out an abatacept-associated increase in the rate of uncommon opportunistic infections.*
**Acceptable company pharmacovigilance plan, though members wanted it larger.**

A few panel members would like to see larger numbers of patients enrolled in the pharmacovigilance studies, saying they are especially concerned about serious adverse events, especially lymphomas. The panel chair quoted from that day's ***Wall Street Journal*** article, which observed that the financial and medical industries are watching this week's FDA panels to gauge how careful they will be when dealing with safety issues. He told the panel that the proposed five-year pharmacovigilance programs are "extraordinary" and would not have been proposed five years ago. The chairman also voiced his pleasure at the proposed pharmacovigilance trials.

The panel expressed concern about infections with Orencia. A public health physician said that he was still worried about vulnerable people getting Orencia, "I'm not sure, given the pharmacovigilance plans…that we're really going to know the level of risk. I think there is a concern here that there is an excess of infection. I'm not sure it's different from anti-TNF agents or Anakinra (Amgen, kinaret)." The panel chair agreed, "Going from clinical trials to actual practice, to what extent we can extrapolate from trials to clinical practice is a concern…That is the natural queasiness that comes out from looking at data from a clinical trial and saying 'How can I use this when the drug comes out?'"

This discussion continued:

*FDA official:* "The sponsor has proposed pharmacovigilance studies. Are they suitable? Do you see other kinds of studies? For instance, observation of patients in clinical practice gives us one kind of information, but it can be difficult to draw conclusions with the absence of controlled studies…I think what we're discussing today is typical for many products we've brought before the committee for RA…It's really a question of how much concern the committee members have regarding adverse events such as frequency or seriousness compared to the magnitude of benefits that have been observed."

*Panel chair:* "We have pretty much accepted the efficacy of the drug. The issue is safety. I'm very comforted by the pharmacovigilance plan. I think it will solve problems. It will stress registries – *plural* – which can be drawn upon for patient enrollment. I think we can't always know what we don't know, but I'm certainly satisfied that there's a plan to at least monitor intensively and monitor what we don't know so we can understand where we are on this drug. I'm also satisfied with the data to date…I think that by using registries one begins to nibble away at the question of vulnerable populations. Each of those registries gives us another opportunity to walk around the elephant."

*Panel member (rheumatologist):* "I'm wondering if the number (of patients in the post-marketing studies) should be expanded."

*Panel member (public health physician):* "The problem is the clinical trial population isn't the same as the regular population…What I was going to ask the sponsor is, does the U.S. healthcare database have a Medicare representation to it?"

*Bristol-Myers Squibb consultant:* "It's the United Healthcare database, and it does include a proportion of people over 65. Since this is an infusion drug, it's reimbursed under Medicare…It's also not just one study. United Healthcare is a study which will accrue…We are also undertaking a registry study in which we will enroll 5,000 abatacept initiators and a comparison study of 15,000 patients, and those will be followed for five years."

*Panel member (biostatistician):* "But we're still going to be in the dark for several years on information."

*Bristol-Myers Squibb speaker:* "We will be tracking discontinuations…Additionally, we won't wait until the end of the study to examine the frequency of events. We will compile the data annually."

*Panel member (public health physician):* "You're getting something like 2% (infections), or something like that. But the lymphoma incidence is four lymphomas through a couple of months ago. We're dealing with 20 cases of lymphoma over a few years. I hate to go back to the Cox-2 inhibitors…We recognize that 5,000 patients initiating abatacept is great, but perhaps thinking of expanding that number to survey a larger number of people on this treatment for cancer, especially. This is going to give you numbers that are too small…I think the only way to go is get bigger numbers. I'd urge 5,000 for lymphoma. For some of the malignancies here, that's still small."

*Panel member (non-voting pharmaceutical representative):* "I think this panel is on the rebound from the Cox-2 inhibitor experience. I think we have to recognize that this program, which I'm hearing, is really extraordinary, and probably a sign of the times as we move into trying to make our medicine safer and safer. But don't forget that all these things go into the cost of the drug, too. We have to think about how much we're willing to pay for how much risk we're willing to take."

*Panel member (public health physician):* "I think that common diseases that we anticipate are likely to be related (to the drug) are the ones we need to survey for. Lymphoma and serious adverse events are important here."

*Panel chair:* "No less a scientific journal than the ***Wall Street Journal*** said today, 'Industry is looking at how tough the FDA will be,' so the emphasis is clearly on the issue of safety…rather than efficacy."

*Panel member (non-voting pharmaceutical representative):* "You can see the trend toward more safety and vigilant efforts right now, and the company came forth with five-year plans to follow the safety which you wouldn't have seen five years ago. There is also a reality of how far we can go with these and make it viable for the company."

**Question #4 – Malignancy:** *Overall malignancy rates were not substantially different between abatacept- and placebo-treated patients (1.5% and 1.1%, respectively). However, more cases of lung cancer were observed in abatacept-treated patients than in the control group (4 versus 0). The rate of lymphomas was not increased in abatacept-treated patients compared to placebo-treated patients; however, for the complete safety dataset (controlled and uncontrolled periods), the rate of lymphoma in abatacept-treated patients was higher than expected based on the general U.S. population. In addition, an increase in the rate of lymphomas and mammary tumors was observed in the murine model, though not in non-human primates.* **A concern, but not a game-stopper.**

The panel chair said that this is obviously a concern, and noted that "whenever one perturbs the immune system, the law of unintended consequences comes in." Nothing else was said about this.

**Question #5 – Hypersensitivity:** *Hypersensitivity reactions have been observed, including a case of anaphylaxis.* **No red flag.**

The panel chair said, "I don't think we've seen anything of a magnitude that triggers a particular red flag on this."

**Question #6 – COPD:** *Patients with COPD treated with abatacept had a higher incidence of adverse events and serious adverse events, particularly respiratory disorders.* **Less of an issue than expected.**

The panel chair asked Bristol-Myers Squibb to elaborate on congestive heart failure (CHF). A company official responded, "In the overall safety database, there were 5.9% of patients in each group who had adverse heart-related events. (On COPD) If you look at the overall profile, you saw more respiratory-related events, and there were three serious adverse pulmonary events."

**Question #7 – Other areas of concern:** *Please discuss any other areas of safety concern.*

Panel members discussed:

➢ **Children and pregnancy.** An obstetrician said, "I think the study of children will be good. I'd also like to see a study of off-label use in children." Another panel member said, "I think a reasonable period of time following children of women who use this drug for five or even 10 years would identify any significant clinical events that would occur."

A company expert said women who get pregnant while taking the drug will be advised not to breast feed. This prompted a panel member to ask, "Why would you ever want to treat a pregnant woman with this? There are so many options available, why would you take the chance?" An FDA official added, "We could put language in the labeling that includes a range of no concern at all to extreme concern."

➢ **Immunosuppression.** A rheumatologist panel member talked about the unintended consequences of immunosuppression, "This drug is a terrific drug for RA…There will be a slight increase in infections, viral infections. The problem comes when you look at the development of the immunorepertoire in the fetus…What then happens to the child as it ages? Is it more likely to develop Type 1 diabetes as the most likely event and is the risk of that…understandable? Can we study it? Should we study it? What standards should we hold the sponsor to in a standard that is perhaps predictable based on known immunologic concepts? This is the first of the costimulation factors coming through, and there will be more."

**Question #8 – The vote:** *In view of all the data available for the safety and efficacy of abatacept, do the benefits outweigh the known and potential risks?* **YES, unanimously.**

Among panel comments on this vote were:

- "The efficacy of this compound is quite well established. We've tried to find the right bar or level of safety oversight, and I think we've done a pretty good job of it so far, but my sense is the benefits certainly outweigh the potential risks of the drug."
- "There is clear-cut efficacy, and the safety profile is similar to the other TNF inhibitors. I'd be in favor of saying that this would have greater efficacy than problems with safety."

- "Not only are we dealing with a new compound, but we may be talking about a new day regarding collaboration between the industry and FDA."
- "I would encourage following babies and fetuses, including outcomes that might not be attributable right now to autoimmunity."
- "I think potential risks are very high, but with the evidence we currently see, it seems consistent with other drugs."
- *Non-voting pharmaceutical representative:* "I think the panel has come to the right conclusion. I think the pharmacovigilance plan is going to approach the standard and is going to make drugs more expensive."
- *Panel chair:* "The pharmacovigilance program is handed up to us rather than mandated to them. This is an excellent example of what could be done and what should be done."
- "The company said it would not do any advertising for one year, and that's the strongest thing (message) from the Cox-2 meeting."

**Question #9 – Additional advice:** *In addition to assessing ACR20, 50, and 70 responses, the sponsor collected data on the percent of patients achieving low disease activity, as assessed by the DAS-defined remission (DAS <2.6). Since DAS is a composite of tender joints, swollen joints, pain, and acute phase reactants, it is possible to achieve a DAS below 2.6 but still have multiple tender and/or swollen joints.*

**a.** *Does assessing the proportion of patients achieving low disease activity provide important information of a nature that is not adequately assessed by analyzing the proportions of patients achieving high levels of improvement (e.g. ACR70 or major clinical response)? If so, please discuss the nature of difference in the information.*

**b.** *If assessing the proportion of patients achieving low disease activity does provide important additional information, please comment on which measures are suitable or optimal to identify low disease activity. Please consider in particular:*

- *DAS-defined remission (DAS <2.6.)*
- *DAS <2.6 plus no more than 1 tender joint.*
- *DAS <2.6 plus no more than 1 tender or 1 swollen joint.*

Panel member comments included:

- "The concept here is a valuable one. We not only want patients to improve by a certain amount, but you want them to reach a point that makes them happier. The idea of getting to a certain point of low disease activity was a very appealing idea. It dovetails the idea of partial remission in cancer." However, this panel member said he favors the current way of scoring the ACR20 and would not be in favor of using any algorithm-based scores, especially in terms of endpoints.
- Another panelist had no comments on the specifics, but she said she would favor keeping the ACR20, etc., as major variable outcomes in studies.
- "It seems almost silly defining a remission as having a tender joint. It seems to me a remission is no joints that are inflamed, however we define that."
- *Panel chair:* "What in part these measures reflect is our frustration at being able to define when the patient has received the best outcome."
- "If we're really trying to achieve remission, we probably need some thought about carving up duration of disease in the context of these data sets, whatever they might be."
- *FDA official:* "We're not talking about remission here…Our question really isn't about that. But there has been some discussion about reporting something beyond improvement in labels."
- "I guess the short version is, sure, why not? I wouldn't use the DAS version…What is the distinction between major clinical response and low disease activity? The lay public or clinician may not fathom that at all."

♦