Appendix D. Rheumatologist discussions

Rheumatologist interview I

We recently spoke with a rheumatologist with decades of experience who is a professor of medicine and rheumatology at a major academic institution on the West Coast. The rheumatologist sees approximately 40 patients monthly with RA and is very familiar with the biologic therapies and the JAK inhibitors for rheumatic diseases. Below are notes from the conversation and **not** a transcript.

Berenberg Capital Markets (BCM) question: Can you describe the type of practice you run, and whether the patients you typically treat are new onset RA or established RA patients?

Rheumatologist: The expert runs a community-based rheumatology practice. Sometimes patients are referred from their primary care physicians with new onset RA or they see the expert directly. Most patients the expert treats have established RA. Some patients have been seeing the expert for decades and are well controlled.

BCM question: Describe your treat-to-target strategy.

Rheumatologist: Historically, the expert would start the patient on methotrexate (MTX), then typically add on an anti-TNF biologic, with the preference being etanercept (Enbrel, Amgen). The expert incorporated the use of JAK inhibitors (JAKi) since their introduction into the treatment paradigm 10 years ago. The expert reports that patients have had very good experience with JAKi, mostly tofacitinib (Xeljanz, Pfizer), though also some with baricitinib (Olumiant, Incyte/Eli Lilly). If the patient does not respond to Enbrel, then the expert would try a different anti-TNF or possibly another mechanism, including a JAKi. The expert rarely administers rituximab.

BCM question: How persistent is the treatment efficacy with the biologics and the anti-TNFs specifically?

Rheumatologist: Very good. The expert reports some patients have been taking anti-TNFs since the first was approved more than 20 years ago. Specifically, the expert has had patients on Enbrel for decades who remain stable.

BCM question: How big a factor are comorbidities for your patients, particularly with the biologics and JAKi?

Rheumatologist: It depends. The expert makes sure the patients do not have tuberculosis, and also considers contraindications, though for the most part, comorbidities have not been a limiting factor in prescribing biologics (mostly anti-TNFs, and mostly Enbrel) or JAKi (mostly Xeljanz).

BCM question: How would you describe the unmet medical need in RA?

Rheumatologist: The expert describes the treatment options for RA as being very good. Most of the expert's patients are really happy.

BCM question: What is your view on MTX tapering?

Rheumatologist: The expert has a few patients on Enbrel who do not take MTX. Some patients will not take MTX. Either way, the expert tends to lower MTX over time, though not completely halt it. If patients are very far along in their disease, the expert tends to halt MTX.

BCM question: Having long-term experience with Xeljanz, and with two additional JAKi on the market, including one first-gen JAKi, baricitinib, and one next-gen JAKi, upadacitinib, what are your opinions on the class for RA?

Rheumatologist: The expert helped AbbVie prepare for the FDA meeting ahead of the approval of Rinvoq (upadacitinib), and as the expert mentioned, patients are having a very good experience with the JAKi. To the extent that insurance will cover the drugs, the expert offers them to patients ahead of anti-TNFs. Patients tend to prefer a pill to an injection.

BCM question: The efficacy appears to be as robust as the biologics, though there have been safety concerns raised by the FDA. What is your view on this aspect of the JAKi?

Rheumatologist: The JAKs are so interesting because, with them interacting with so many different cells, we would have expected there to be major issues. That simply has not been the expert's experience. The expert did not report a serious adverse event among their patients treated with the JAKi.

BCM question: Do you intend to actively switch patients stable on biologics to JAKi?

Rheumatologist: This would not be the expert's preference. Patients with RA do very well on their drugs and it takes them a while to fall off of them, or to switch.

BCM question: The next-gen JAKi upadacitinib (Rinvoq) and filgotinib (Phase III in the U.S., submitted in the EU) are selective JAKi with higher relative specificity for JAK1 vs. the first-gen JAKi. At ACR2019, the debate over JAK specificity continues in terms of onset of action, magnitude of efficacy, and safety. Where do you stand on this?

Rheumatologist: The expert does not think JAK1 specificity matters for RA and probably not for PsA either. Perhaps for other rheumatic diseases it could make a difference, however. The expert adds that the JAKs all end up on the same cell surfaces and transcription in the nucleus tends to be the same. Is it possible the onset of action could be a bit quicker for the next-gen JAKi? Sure. But the onset with tofacitinib and baricitinib is amazing. So the expert does not see onset as being a differentiator. Where the expert sees an opportunity perhaps is with tolerance; what if a patient is on tofacitinib and then stops responding to it? Or perhaps the patient is on upadacitinib and stops responding to it? Then perhaps the expert would switch patients between the first-gen and next-gen JAKi. However, the expert admits it is simply too soon to know for sure where the first-gen and next-gen compare to each other on the aforementioned measures; the expert wants to see more data and see how the patients respond to the JAKi before making a final determination.

BCM question: Which JAKi would you use first?

Rheumatologist: To the expert, this decision is just like that for the anti-TNFs. The newest JAKi is Rinvoq, so the expert intends to start patients there. "Rheumatologists like to experiment." The expert adds that rheumatologists do not know exactly which patient will be responsive to which mechanism. Even the response to the various anti-TNFs differs. Within five years, the expert believes rheumatologists will be able to make more informed decisions, including from a precision medicine perspective, where the expert believes more information will be available for rheumatologists to determine which specific patient will respond to which specific mechanism.

BCM question: AbbVie has been a leader in inflammation for a long time. Same with Amgen. These are companies and representatives whom rheumatologists are comfortable speaking to and working with. Next year, possibly, Gilead will be a newcomer with next-gen JAKi filgotinib. They will send sales reps knocking on your door. Will you listen to them?

Rheumatologist: We will listen to everyone; rheumatologists are typically very polite. For Gilead it will be the same as the others who stop by, AbbVie, etc. These people can say whatever they want to say to rheumatologists; will what they say be true? Clinical trial patients are not rheumatologists' patients. So no matter what these people say to rheumatologists, we shall see. Tofacitinib has been very good; so has baricitinib. Upadacitinib looks very good, too. Filgotinib could also be good. The issue to remember is that these patients have the disease for 20-30 years, so we have to be really comfortable that patients can stay on the drug for a very long time. This experience with a drug takes some time.

BCM question: Filgotinib will be the fourth JAKi on the market. What place will it have in a rheumatologist's armamentarium for rheumatic diseases where it is approved?

Rheumatologist: A safe and effective drug will find market share. That's what happens. The expert is sure that Galapagos and Gilead will figure out a way to get filgotinib a place in the market. Perhaps the biggest help for them will be the move toward a more precision approach, which is something the expert believes will become more of a reality within the next five years.

BCM question: How do you view the JAKi opportunity in PsA?

Rheumatologist: In PsA, five years ago, the expert reports that rheumatologists were giving a lot of anti-TNFs. Today, the expert prefers the anti-IL-17s, as well as Stelara. The

expert believes that in PsA, the IL-17s are likely to be used ahead of the JAKi.

BCM question: What is the next step in RA and rheumatic diseases broadly from an innovative therapeutic perspective?

Rheumatologist: Right now, what we do is we treat our patients, we monitor for heart disease, we check for infections, we conduct blood tests, etc., but we really do not think about what is triggering the disease, RA, Lupus, Sjogren's, etc. Once we have a better understanding of the underlying causes of these diseases, the expert believes a more precision approach will result, which could help one or more drugs currently available. More importantly, this will lead to the creation of drugs that halt the rheumatic diseases, (i.e., which halt disease progression).

BCM question: If there was one abstract or trial data during a session that stood out to you from ACR2019, which one would it be?

Rheumatologist: Tofacitinib's Lupus data.

Rheumatologist interview II

We recently spoke with a rheumatologist who treats around 100 patients each month with RA at a private practice in the Northeast. The rheumatologist attended ACR2019, and attended several sessions focused on the JAKi. Below are notes from the conversation and **not** a transcript.

Berenberg Capital Markets (BCM) question: Describe your experience and your practice, including the types of RA patients who present at your practice.

Rheumatologist: The expert has been practicing for 12 years and describes the practice as being very busy. The expert sees patients at an inpatient facility at the university, including a wide variety of patients who may receive their initial RA diagnosis at the expert's practice. The extent of the disease is evaluated; the expert sees the entire spectrum from mild to severe. Typically there is swelling of the joints, especially the hands. The expert starts patients on anti-inflammatories, possibly also low-dose prednisone, and then sometimes starts with hydroxychloroquine or methotrexate (MTX). MTX is an old medicine, but a very good medicine. Unlike hydroxychloroquine, which could take months to work, MTX usually works in 2-3 weeks. The nice thing about MTX is that the expert can titrate the dose; for instance, the expert will start an RA patient on one dose, then have them come back in a month, check the liver enzymes, etc., and if the patient is doing better but could be even better, the expert will then raise the dosage. Once MTX is maximized, the rheumatologist then could move a patient onto leflunomide, which tends to be better tolerated than MTX and is taken once a day rather than once per week like MTX. After this, the discussion moves to the biologics. The expert describes the various benefits and risks of each choice to patients; typically, the expert will start the patient on an anti-TNF drug.

BCM question: Which anti-TNF do you prefer?

Rheumatologist: Enbrel and Humira are both very good. Typically the expert will present both medications to an RA patient. Importantly, most health insurance will cover one or the other. If there is a history of uveitis or IBD, then Humira is the better choice. If the expert had to choose though, Humira would be the first choice, in part because of the payor access being broad, though also because of the many indications on the label. The expert adds that RA patients tend to develop other issues later on, like PsA, so this is something to consider. Sometimes, for Medicare patients, the expert will go with Remicade first then Simponi Aria; it can be easier from an access perspective. Simponi is a shorter infusion and patients seem to have fewer infusion reactions with it than they do with Remicade.

BCM question: When would you consider a JAK inhibitor (JAKi)?

Rheumatologist: The expert notes that the biologics and particularly the anti-TNFs have been the mainstay for more advanced disease patients; it has been this way for a while and is likely to remain this way for a long time; "we have the most experience with biologics." The expert adds that for access reasons, for most patients, they have to have been on MTX and the anti-TNFs before they could move on to something else, like a JAKi. Access is becoming a much bigger issue. For instance, the expert may want to put a patient on a JAKi (typically Xeljanz) but the insurance denies it. Further, the expert was not impressed by Xeljanz in the beginning; what opened the expert's mind over time was the rapid onset of action. The expert receives samples of Xeljanz so it is real easy to give the monthly sample

to a patient, let them come back in a month, and if it works, the patient will know by then. The issue then becomes coverage and the expert will then have to determine if insurance will cover it.

BCM question: If we put the payor considerations aside, would you consider prescribing a JAKi first-line for RA?

Rheumatologist: The JAKi are very efficacious, so a first-line consideration is reasonable to the expert. However, the expert is concerned about the side effects. There is more monitoring involved, including liver tests. In addition, some patients do not like to add to their existing pill burden; they may already be taking several pills and don't want to add another on top of this. Then there is the cholesterol issue with the JAKs; the expert would not put a patient with high cholesterol on a JAKi. Then the FDA of course is concerned about thrombosis risk, which is a concern for the expert, who notes that many people in the country who have RA could also have CVD risk. "It's not the older patients, those in their 70s or 80s who are the issue so much; it's those who are in their 50s and 60s who could be walking time bombs". Certainly, for some patients, after discussing the black box warning, they have decided they do not want a JAKi. This is not a majority of patients, though it does affect some decision making for patients. That noted, the patient over the age of 50 without comorbidities is actually a very good candidate for the JAKi.

BCM question: What would it take for you to become very comfortable with the JAKi?

Rheumatologist: More experience with them, particularly the new JAKi that have been added to the market over the prior year. Let's see what the record looks like in five years. The expert has experience with Xeljanz, though is still cautious.

BCM question: For the time being then, Xeljanz will be your go-to JAKi?

Rheumatologist: In the expert's practice, a lot of Xeljanz is used. The issue sometimes emerges for patients with the black box warning; some patients are concerned about the potential safety/tolerability issues. The expert tells us that while Xeljanz flies off the shelf, Olumiant just sits there.

BCM question: The debate continues regarding the importance of JAK specificity. What is your view?

Rheumatologist: Rheumatologists will look at some of the differences, for sure. With a pan-JAK like Xeljanz, would there be a better side effect profile or worse side effect profile compared to a selective-JAK like upadacitinib or filgotinib? Is there something about upadacitinib, something about filgotinib that rheumatologists have to worry about? Could the sperm counts become an issue, for instance, with filgotinib, in terms of signaling a risk of testicular cancer? This is something else we will have to evaluate with the selective-JAKs.

BCM question: Have you had experience with Rinvoq, or is it mostly Xeljanz?

Rheumatologist: So far, it's really just Xeljanz. Let's see what happens when the formularies change next year. This will be interesting. The expert has had a handful of patients on the newer JAKi. The arguments with the insurance companies are becoming very disruptive though; for instance, the expert had a patient on Enbrel for three years, and then the formularies changed and the insurance would not cover it; the patient switched to other treatments that were covered but did not work; this led to a 7-8 month battle for the expert to get the patient covered with Enbrel again. Eventually, this worked out, but the battles are getting more difficult and tiresome.

"How much of our day can we spend arguing with insurance companies?"

Furthermore, the expert believes Xeljanz is going to take a huge hit come January 1, and that the other JAKi will be challenged by actions taken by AbbVie. The expert reports that already at least one patient has had coverage of Xeljanz denied, with Rinvoq favored instead on the insurance formulary. This makes the expert nervous because if a patient is stable on Xeljanz, and has to switch to Rinvoq for insurance reasons, this could lead to problems akin to when the expert has had to switch patients from one anti-TNF to another anti-TNF.

BCM question: Should next-gen JAKi be placed ahead of first-gen JAKi and anti-TNFs?

Rheumatologist: The expert does not see anything remarkable about the next-gen JAKi to encourage use of them ahead of first-gen JAKi or anti-TNFs. That noted, the expert reports that JAKi are already being used ahead of biologics, and would expect the next-gen JAKi to

have a place ahead of biologics in some instances as well.

BCM question: What could help the next-gen JAKi from a clinician and payor perspective?

Rheumatologist: More indications. It does change things. If you could target a few different autoimmune diseases, this is more of an incentive for 1) the clinician to fight with the insurance company, which is a real burden, and 2) the insurance company to cover the medicine.

The expert offered two examples; first, Enbrel, which is not effective in IBD vs. Humira, which has multiple indications, including IBD and uveitis, which is a big reason the expert prefers Humira. Second, Cosentyx (anti-IL-17) tends to flare up IBD, which makes it less attractive in some instances. Thus, for any medicine that demonstrates efficacy across more conditions, the patient is more likely to improve at a systemic level, and if rheumatologists have more indications on the label, the insurance company is more likely to approve the medicine.

Moreover, what the Humira vs. Enbrel example demonstrates is that although the target cytokine is the same, the mechanism is different; one is effective in patients with different diseases compared to another. Thus, the expert would not assume that if one JAK works well in one area it will work well in another. The data has to prove out.

BCM question: Any final thoughts on the JAKi?

Rheumatologist: The JAKi are moving up in the ranks. Getting more indications will help the next-gen JAKi.

BCM question: We are not far away from having many biosimilars of Humira on the market. Given your comfort with Humira, how comfortable will you be with its biosimilars, particularly if one or all are preferred on formularies ahead of Humira?

Rheumatologist: Biosimilars make the expert nervous, primarily because of the expert's experience with anti-TNFs not all acting similarly. However, the expert points to the experience in Europe as providing some solace; "they've had a positive experience."

In the case of biosimilars (and even more broadly), the expert reports that discussions with colleagues will be key; the expert will want to understand the experience of other rheumatologists with a particular biosimilar. Even if it is just a handful of patients, rheumatologists will share notes; "we do this with complicated cases, all kinds of cases, in all the diseases we look at; we show each other what we've tried; word of mouth between colleagues is key."

BCM question: How will the payor considerations factor into the use of biosimilars?

Rheumatologist: This will be very important. The expert notes that use of Xeljanz has increased because of the generous programs that Pfizer has, particularly for Medicare patients. Moreover, the out-of-pocket expenses matter for patients, so if biosimilar makers can find a way to improve their standing on formularies, reduce the out-of-pocket expenses, and increase patient compliance, then rheumatologists will view biosimilars very favorably.

BCM question: ACR2019 was very broad and interesting as usual. Where did you focus your time?

Rheumatologist: The expert was very interested in the JAK inhibitors; the expert attended several JAKi sessions, mainly to learn more about the safety of the JAKi. Aside from RA (which the expert believes is less interesting, mainly because the expert's patients are doing so well), the expert was focused on what is coming out in Lupus and scleroderma, both which are much more difficult to treat than RA nowadays; for instance, the expert believes the prior decade has been a very good time to have RA; "we will eventually find something that will work for patients."

BCM question: What stood out in Lupus?

Rheumatologist: Xeljanz stood out. The expert has used Xeljanz off label in Lupus with positive results. The expert also reports using Orencia off label in Lupus; Orencia did not hit the primary endpoint in a study in Lupus; however, the expert reports good results for patients when the medication is covered by insurance. The coverage is the bigger problem for Orencia; it is hardly ever covered according to the expert, even where indications are on

label.

BCM question: Where do the IL-6s fit in rheumatic disease?

Rheumatologist: The expert would rather wait until later lines to turn to an IL-6.

BCM question: What comes to mind regarding Acthar?

Rheumatologist: It is not a novel mechanism; it is not adding something dramatically different, which therefore makes it very difficult for the expert to "stick up for this one" in what have become routine payor battles for coverage of medicines broadly. The expert also reports that Acthar's sales reps keep changing, which also adds to the difficulty regarding insurance coverage. To the extent that a rep sticks around long enough to work with the expert, the expert notes that the reps can be very helpful to get the drug covered. "It's just cheaper and easier to put a patient on low-dose prednisone."

BCM question: Where it is appropriate, in which patients do you go with Acthar?

Rheumatologist: The expert has used Acthar occasionally in refractory patients, typically those with myositis. This is a really difficult disease; the patient typically cannot move, cannot even get up from a chair. The expert reports some success with Acthar in these patients. The problem is that the drug is "ridiculously expensive and no one approves it."