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Tribulations of trials for antibacterial drugs: interview with Mark Leuchtenberger and Scott Hopkins

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Mark Leuchtenberger and Scott Hopkins work for Rib-X. Rib-X Pharmaceuticals is a Connecticut-based pharmaceutical company committed to developing a broad spectrum of antibiotics through a combination of computational analysis, medicinal chemistry, microbiology and biochemistry. Chief executive officer of Rib-X Mark Leuchtenberger and chief medical officer Scott Hopkins spoke with Laura Harvey at *Clinical Investigation* on some of the key issues facing the pharmaceutical industry for clinical trials in this arena.

Q Thank you for agreeing to speak with *Clinical Investigation* today. What would you say were the most pertinent outcomes in light of the recent US FDA re-evaluation of non-inferiority trials as a means of assessing drug efficacy for bacterial diseases?

Mark Leuchtenberger: Well, in terms of my nonmedical opinion, I think it's important to differentiate between (what the FDA has done in terms of) the self-limiting infections such as, say bronchitis, where the FDA appears to want superiority trials, and the serious, complicated infections, whether it's skin infections, intra-abdominal infections or pneumonia where they have reaffirmed non-inferiority but have changed the end points that have been used in the past, and are moving to what they call more objective end points. I don't know if you agree with that differentiation Scott?
Scott Hopkins: Well, I think that's exactly right, they have drawn a line in the sand between the self-limited infections, which often don't even need antibiotics to effect a cure, and those where antibiotics are life-saving or certainly prevent a lot of serious morbidity, and the result of that I think is to reassess the clinical trial end points that have been used in the past to assess drug efficacy. Where the FDA has come down has been to seek after what they are calling objective end points, and also to change the timing of those observations, those end point observations, to earlier in the course of therapy.

Now I think we should note right off the bat that Europe and perhaps the rest of the world don't seem to be going along at all with the FDA change in thinking regarding primary end points and there has been a recent regulatory document from the EMA on skin infections [1] that reaffirms as the primary clinical trial end point the traditional clinical global assessment of outcome at some point shortly after the end of therapy. So we've really got a divergence between the USA and the rest of the world here.

Q Do you think that divergence in opinion will have a negative impact on drug development?

SH: Well, so far it appears that the FDA and EMA are talking to each other and have reached agreement, at least in terms of complicated skin or acute bacterial skin and skin-structure infections as the FDA is calling it now, to let a single trial have two primary

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end points, one which is analysed according to how the FDA would like things analyzed and another primary end point analysed in the way that the EMA would like it to be done, with two separate statistical analysis plans to go along with that. So as long as that can be done I think we will be able to work things out. If and when we get to the point where you can't satisfy both parties with a single set of trials, because of trial logistics or complications or too many additional observations being added into the trials, then we will have some decisions to make.

Q Is this approach going to be logistically much more complicated as well as expensive? Can you think of another way a compromise could be reached that would simplify things from an industry point of view?

SH: The compromise in the past between FDA and EMA and other parties was the international harmonization effort called International Conference on Harmonisation. That really was a very difficult effort that went on over a number of years to harmonize preclinical development and clinical trial practices, involved input from all the major markets, and was really quite successful up until the time the FDA began to re-evaluate end points in anti-infective trials.

ML: I would take issue with the concept that this approach is going to be much more expensive, I don't think we agree with that. It would be more expensive if we were doing a redundant trial, but what we're talking about is two parallel statistical plans which of course will make the statistical consulting firms happy! But in the context of a trial that could be tens of millions or US$20–30 million for a Phase III trial on one of these indications, you know, this is a very small, single-digit amount of millions on top so I would take issue with the idea that it is going to be a real, large cost to companies, it is just one more layer of complexity we have to accept while these things are in question.

SH: I would certainly agree with that, at least in terms of acute bacterial skin infections, I think that we have been able to work it out for that indication, and it represents an incremental addition in complexity and cost, but not a deal breaker by any means.

Q Do you think then it will make the trial process, if not a lot more expensive then potentially slower to implement, especially given the choices facing companies at the moment in terms of how to approach trial analysis?

SH: So far in bacterial skin infections, I don't think it has made it significantly more complicated or made these trials significantly longer or more difficult to do. There are some new things that the FDA wants to see measured, so there's a learning curve among investigators and sponsors, but we have a trial ongoing right now where we have implemented all the things the FDA is looking at and our experience so far is that enrollment is what we expected and what we wanted and we are able to find investigators and train them up and get these trials going.

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ML: I think that it is important to focus on the choices made by companies right now, obviously without burnishing our own reputation, we feel very confident about the choice we made when we had our end of Phase II meeting in April a year ago. We were technically ready for Phase III, when the FDA announced their views about new end points in December after a 6-month period of introspection, and everyone had a choice, everyone who was Phase III ready, to either do what the FDA recommended, which was to validate the new end points against active comparators in a sort of Phase IIb trial, or essentially ignore that strong recommendation and go right to the Phase III. Some companies have chosen to do the latter. We are very comfortable and confident in that we have chosen to do the former, that is to validate these end points in a Phase IIb study. Our Phase IIb includes delafloxacin, vancomycin and linezolid treatment arms and is accruing very well. The physicians are excited, even the patients are excited about the measurements, and we are comfortable that we have done the right thing. I think you can contrast that with decisions others have taken to go onto Phase III without an effort to validate the end points in comparator studies, and we think there is a substantial risk being taken by companies choosing to take that path.

Q Do you mean by that that you think these companies risk misinterpreting trial data, or that there is a risk of unsafe/ineffective drugs could reach the market?

SH: Well, you might not get to the market if you don't really understand very well what you're measuring! You may end up in a situation in a Phase III trial where your drug looks worse, and maybe it was, maybe it wasn't.

ML: Or, even more dramatically, you miss a chance to maybe prove superiority. We saw in September, with ceftaroline, that their Phase III trials were approximately 100 patients shy of potentially showing superiority over vancomycin. With non-inferiority being the rule of the game, not every one is focusing on that, but it is very clear that vancomycin is showing erosion in terms of its efficacy due to resistance and there may be opportunity, as quoted by the committee members, to show superiority of a new agent over vancomycin in the next several years. Given the chance during analysis to pick the right time point to maximize your treatment versus the comparator, if you don't take that (chance), not only may you expose yourself to the downside of non-approval, you may miss the big upside of being able to compete for superiority.

Q In light of what you've just said, do you think flexibility is a key for those designing and running clinical trials in the current landscape?

ML: I'd say more than being flexible, being realistic is key. The FDA has come out very clearly with these new guidelines and you need to be realistic that those aren't going to change, so now, we're going to gather data that will allow us to have a very detailed dialogue and discussion and Scott will be leading that dialogue at the end of the year with the FDA, as he does with all of our FDA dialogues. For that we will have a very, very rich database, an unprecedented database. It was customary to do one observation per patient in the old world, and that was the global clinical assessment of cure at 10 or 14 days, or at some other time, and you get one data point per patient. By contrast, for the lesion-spread cessation end points, we're going to have ten observations per patient so it's really almost like an oncology Kaplan–Meier type of statistical power for patients, and, for example, if there's a time-to-event analysis that shows some interesting data or a particular time that is not the FDA's first hypothesis we believe we will have absolutely all the data necessary for Scott and his team to make that strong argument to the FDA. That's why we feel good about this, so it seems responsive rather than flexible, realistic of the fact that you had better bring data to the discussion rather than hand waving.

Q Moving on to the specific end points used in these types of trials, there has been some debate over the objectivity of clinician assessment and a re-evaluation of end points, what do you think a primary efficacy end point should reflect in an antibacterial drug trial? Do you have any ideas about how clinician-assessed end points could be chosen/structured such that they are less subjective?

ML: Scott has been at the very heart of this discussion (with the FDA) and so is in a great position to discuss subjective versus objective.

SH: This really highlights the difference in view between the FDA and EMA. The traditional way of global clinical assessment at the end of therapy, I think a lot of physicians would say that that does reflect how a patient feels and functions as well as measuring survival, and is not as subjective as some people at the FDA would say because it encompasses objective things like fever resolution, white count coming down, clearing of chest x-rays, and certainly the physician's interaction with the patient in terms of how they feel. On the other hand, from the FDA's view, if you don't have a numerical thing you've been able to measure, that anyone can measure such as temperature, lesion size in skin infections and how that has regressed over time, there is the feeling at the FDA that there is room for difference of opinion with different viewers, different physicians watching the same patient and arriving at different opinions of outcome. So that's kind of the crux of the difference between Europe and the FDA, and going down the FDA's line of thinking, one has to very carefully evaluate these new objective end points for really how well they correlate to how the patient is doing. And that's really what we're doing in our Phase II trial, is measuring a lot of different things, and measuring them very frequently, particularly early on in the course of therapy to get a good sense of which of these is best and which correlates best to how the patient is doing globally.

We will have that information for complicated skin/acute bacterial skin infections but it is likely that we will have to be doing some similar sort of work in other indications, which may behave very differently and obviously won't have things like a skin lesion to measure.

Q When designing the trials, what steps do you take to choose end points such that they reflect how the patient feels and functions but that also have (an element of) objectivity?

SH: For a particular type of infection, such as a skin infection, obviously there are things like the size of the lesion that are obvious. There are other things that are very pertinent to any infectious process like the temperature or the white blood count or other blood parameters for inflammation. Then there are things like the patient response, how does the patient feel and so forth, that you can also gather, so it's taking to some extent what you see in any infection and then customizing that to the particular indication. So for pneumonia, you might have other things like lung function parameters, chest x-rays and so forth that will be more specific to a lung infection.

Q You say how the patient feels, is that purely assessed by the clinician's interaction with the patient? What do you feel about patient-reported outcomes for these types of trials?

SH: Traditionally, one parameter that has been part of just about every infectious disease trial that I've been involved in, is the 'how do you feel?' the open-ended question that you ask the patient. But you can be more precise on that and let the patient make that judgment themselves rather than interact with the physician in a back and forth, and you can put scales to that that the patient marks off, from 1 to 10 and so forth and there are various ways of giving these assessments. What's interesting is how few of them, at least in the infectious disease world, have been validated over the years, and, in fact I think that is one of the real tasks for the industry and regulatory agencies in the coming years is to start validating some of these patient-oriented outcome assessments.

Q What is your opinion of patient-reported outcomes in the form of a pain scale or similar in infectious disease trials?

SH: Well, pain scales have been useful more for chronic situations, than they have in acute indications like antibacterial diseases. I think that something in terms of how the patient feels you often gather anyway, but pain is usually not a component, for example for serious pneumonia. Things like shortness of breath, and things that relate to lung function certainly are, but at any rate what we are talking about is a patient-experienced sort of end point and measuring that. There are various ways of doing that (such as) putting scales to how short of breath you feel and I think those can be helpful. On the other hand it can also be very useful to measure things like blood oxygenation, vital capacities and things like that, which the patient doesn't directly sense that are also very easy to measure, very precisely measured and very objective.

Q Why do you think patient-reported outcomes as you have just described haven't been quite so well utilized in these trials?

SH: They haven't been much used in the past because the primary end point has been the physicians' global clinical assessment of outcome – 'cure, improved or failed' – and that's been the primary focus of end points in the past and the secondary focus has been the microbiological end point, which is certainly more objective, so the patient-reported response has been subsumed within the clinician assessment. No clinician is going to call a patient a cure if the patient is still complaining of no improvement of the primary event, whether it was a pneumonia or a skin infection, so those patients in the past would have been called an improvement or even a failure at say time point X at the end of therapy. So patient-reported outcomes have always been captured in some sense, but I think the FDA believes there is room for taking those more directly out of the mouth of the patient and perhaps more objectively measured, whether it is a 1–10 scale of shortness of breath or cough or whatever parameter you are talking about that the patient fills out. They (the FDA) are worried about the physician being the intermediary for the data.

Q Do you think this is a legitimate worry?

ML: I would say they are not replacing clinicians global assessments with patient-reported outcomes, not at all, what they are doing is trying to replace them with what they call objective end points, like mortality or some sort of lesion-size measurement, such as lesion-spread cessation, or the percentage size of a lesion that has actually stopped growing. So it has very little at all in this new world to do with patient self-reported outcomes and much more to do with clinical signs and symptoms that the FDA believe can be objectively measured and that move away from the physicians' judgment.

SH: I think if they are uncomfortable with the physician making an assessment that is semi-objective or subjective it would be curious that they would then rely more upon the patient assessment for things that are due to acute, rapidly treated situations like infections. That is very different from (for example,) arthritis (or chronic pain in any other indication).

Q What steps do you think government could take to incentivise pharmaceutical companies to invest/develop more into infectious disease therapy?

ML: I think that we can look back and question the amount of time it has taken for things to happen for these revisions, now that the playing field is clear and the rules of the game are clear for some indications I think we (industry) are in a much better position than this time last year with the FDA's announcement that they have rejected 50 years of guidance and no clear prospects of any set of near-term resolutions. Well, the resolution happened in September, and they confirmed that by approving the drug ceftaroline based on the new end points. In terms of incentives I think the regulatory bodies have probably done what they can do. I think other governmental bodies can do a lot to encourage the development and approval of novel antibiotics and there are various legislative proposals in front of the US congress. I can't speak for the EU at this point, but one example in the USA is G.A.I.N.,

which is an act that is proposed to lengthen the patent-expiration time for novel antibiotics, and essentially to give this field a boost in terms of protection and encourage people, encourage companies, to make the investment, so that there is a longer period of time, essentially an orphan-drug type of protection for antibiotics. I think that would be a huge help if that ever did pass in encouraging people to make the investment because, lets face it, the antibiotic world goes in cycles, there's a crisis right now with deadly Gram-negatives, and methicillin-resistant *Staphylococcus aureus* (MRSA) is not going away. Approximately 10 years ago there were large pharmaceutical companies moving out of antibiotics, but there's now a changing of the guard and new players in the market, and any support that government bodies could give, not regulatory but government bodies, I think would be very timely.

Q Do you think the increasing dialogue between bodies in the past year has helped the situation and that this should be maintained in order to facilitate drug development and approval in the future?

ML: Scott, you've been part of the dialogue more than I have, I think that our first experience, not to get too granular, with the FDA in the April meeting last year, coming 2 weeks after they removed the old guidance was a very positive meeting because we sat down and talked. Scott led that discussion, and then the next sort of peak after that for us was the 2–3 August public workshop in Washington where Scott was the only industry person invited, you could argue that there could have been more but Scott had a relationship with the FDA that made them comfortable that he would be constructive as opposed to angry(!), and that certainly was validated. And so I think we have to understand that that dialogue is crucial, and the presentations we and others made led to the guideline announcements in September, so there is a dialogue and it has been productive.

Q So do you think that it would be helpful to maintain that dialogue going forwards?

ML: Yes, to keep it away from stone-throwing and keep it constructive!

Q What changes are you seeing now and foresee in the future in the antibacterial drugs arena?

ML: I think the last thing to say is that what we're seeing in terms of the development discussions we are having is that there is a changing of the guard underway, with respect to leadership in antibiotic development among large pharmaceutical companies, some of the traditional players are, not falling by the wayside, but de-emphasizing, but then other companies that really are at this point unknown to the outside world in terms of their interest in antibiotics are moving very consciously and rapidly to try and build a position, so I think 'watch this antibiotic space' is a useful (message) for people who want to understand that (the current situation), because, in the next 6–12 months people may see some moves by companies that are could be surprising, both in terms of those exiting and those entering.

SH: One point I would add to that is that the discussion so far has been more or less in the context of MRSA but we are now experiencing a very serious Gram-negative resistance problem and the discussion around how to deal with end points and clinical trials in serious Gram-negative infections may be a little bit different. So I think that the companies that are in the Gram-negative arena will be having a lot of these same sorts of discussions with regulatory bodiess we have seen with the MRSA-oriented discussions.

Financial & competing interests disclosure

Mark Leuchtenberger and Scott Hopkins work for and own shares in Rib-X Pharmaceuticals, Inc. Mark Leuchtenberger previously worked for Targanta Therapeutics. Scott Hopkins previously worked for Pfizer. They have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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