Drug Development and Negative Clinical Trial Results

This May, Guest Editors Marc Humbert, MD, PhD, Director of the French Pulmonary Hypertension Reference Center, and Professor of Medicine at Paris-Saclay University, Le Kremlin-Bicêtre, France, and Mark Nicolls, MD, Professor of Medicine, Pulmonary, Allergy, and Critical Care Medicine at Stanford University School of Medicine in Stanford, California, held a discussion with Norman Stockbridge, MD, PhD, Director of the Division of Cardiology and Nephrology in the Office of Cardiology, Hematology, Endocrinology, and Nephrology at the Center for Drug Evaluation and Research, US Food and Drug Administration in Silver Spring, Maryland, and Roham Zamanian, MD, Associate Professor of Medicine and Director, Adult Pulmonary Hypertension Program at Stanford University in Stanford, California, on the topic of clinical trials, drug development, and publishing negative trial results.

Dr. Nicolls: Thank you all for being here today. Let me open the discussion. There have been several negative clinical trials that have been performed in the pulmonary arterial hypertension (PAH) space. I would like Roham to comment on how important he thinks it is to publish the results of negative trials. What can we learn from negative trials, and do you have any ideas about how we might develop leverage for getting the data out?

Dr. Zamanian: I think we should start by recognizing that we are discussing a rare disease field with a number of stakeholders: patients, patient advocates, clinicians, scientists, academicians, industry, regulators, clinical trialists, and even policy makers. Obviously, the concern is that there is a general bias against “negative” clinical trials, and those biases may be different across stakeholders and also impact them differently. I think maybe this issue is much more pronounced in a rare disease field where there is a limited number of subjects to study and tremendous competition for funding studies which are often costly. The bias not to publish negative trials is a tremendous loss for the community, especially with pulmonary hypertension (PH), where there are so few subjects and they’re very expensive to study in an efficient and appropriate manner.

The other thing I want to say, and probably this is not groundbreaking, is that a study can be deemed a negative trial when it either has constraints in its design or its implementation, or it does not appear to show what the investigators had hoped and had hypothesized that it would. Therefore, it’s brushed under the table, especially if reporting of the trial negatively impacts the financial wellbeing of a sponsor or the reputation of investigators.

Dr. Nicolls: Can you give some examples of things that we can learn from negative trials beyond the fact that the drug in question didn’t reach its primary endpoint?

Dr. Zamanian: I think we could learn either that a mechanism is not relevant to the disease, or that the disease doesn’t respond in the way that we thought it would. More importantly, we can learn a lot about trial design, from selection of endpoints, use of specific enrichment strategies, to trial conduct and challenges with subpopulation recruitment. All trials, positive or negative, can be tremendously informative. To be able to perform a “postmortem” as to why a study is negative is crucial, and it could move the field forward, so we need to overcome the misconception that a negative trial is a “failed” experience.

Dr. Nicolls: Dr. Stockbridge, maybe I can ask you to jump in on this point. I don’t know if you have an opinion on publishing negative trials from your vantage point; it’s not really what you’re most involved with, but do you have any comments on anything Roham said?

Dr. Stockbridge: We’re talking here about nontrivial trials. I don’t think that anybody cares quite so much about the first in-man and Phase 2 exploratory studies, but trials that actually had a reasonable shot at establishing effectiveness. It’s important to note that a healthy clinical trial therapeutic area development ecosystem has to have trials that fail. If you win on every trial, if that’s all that ever happened, then you’re not doing enough trials. It’s an important aspect that things do fail, and people need to understand something about what happens there.

One aspect of this is whether the investigators going into a trial have negotiated the freedom to publish regardless of the outcome. I urge clinical trialists to make sure that they retain the right to publish. You don’t want the company constraining that; even if they have some input on it, they should not constrain it.

The other aspect of this is that I think patients who invest their time and energy and risk in participating in these trials don’t generally think they’re doing it to support some company. They generally think they’re doing it to support medical knowledge in some area. If we don’t publish those studies and make use of what they’ve invested, I don’t think we’re doing what we’re supposed to with respect to them.

Dr. Nicolls: That’s a great point. Building on that question, can you use your imagination to think of any kind of leverage that might be exerted in the future to compel companies to release the information? Roham and I are actually involved in a situation like this, so we would love to publish the results of our negative trial and dig into the data. I think Roham was interested in
Dr Stockbridge: I think it’s too late when the trial’s over. After you sign the contract, it’s too late. The place to be working on this kind of problem is setting up groups that have a strong enough presence in the field that companies are likely to come to them to get a trial done. Then you’re in the driver’s seat. You have some ability, at that point, to negotiate how the contract is written, to ensure that you’ve got access to the data, and some privileges with regard to publishing no matter how it comes out. If you wait until it’s over, you’re going to have a hard time.

Dr Nicolls: Because not everyone is in the luxurious position of having that kind of international reputation, and sometimes these companies are one-off companies that may not come back with another PH drug, I think something that anybody could do, any investigator-initiated proposal, would be to start at the contracting process before the trial. I think that could be a good takeaway point from this discussion.

Dr Zamanian: At the World Symposium on PH in 2018 in Nice, France, Dr Stockbridge and I and others, including Lewis Rubin, were on the same task force, and from that section came the recommendation that you develop a process for reporting negative clinical trials, you make it a contractual obligation upfront and utilize the leverage of international experts who carry a lot of weight in that process. The second part to that is that you may also need to develop an independent and self-funded core, whether that resides as part of the data safety monitoring board or the steering/adjudication committee or an analytic core committee that would carry out and report on analyses, so that you’re not depending on the industry for providing statistical support. Tie that in with some sort of a mandatory publication timeline which balances the need to report on a study with the industry need to absorb the findings—I would suggest something like a publication embargo period of maybe 6 months so that the impact of the data on the company may be minimized. Really, the stockholders will know by 6 months after the study whether the study was negative or positive.

Dr Nicolls: That’s great. I think maybe we should move onto another subject. I’ll invite Marc Humbert to introduce any topics he’d like to discuss.

Dr Humbert: I wanted to focus a little bit on Phase 2 studies in PAH because we usually have different endpoints in Phase 2 and Phase 3 clinical trials, and the negative trials give us different messages. I was thinking that the relatively small Phase 2 studies, in which primary endpoints are usually pulmonary vascular resistance (PVR) measurements obtained by invasive right-heart catheterization, should always be presented in great detail with careful presentation of individual data, not only because we want to have a complete analysis of the active compound results, but also because of the importance of the results observed in the placebo arm, or the control group. I wonder whether either Dr Zamanian or Dr Stockbridge would like to comment on the possibility of having a single control group for several active drugs tested in order to expose fewer patients to a placebo, especially when data obtained by right-heart catheterization are needed.

Dr Zamanian: I don’t know if I have an answer, and I would love to hear Dr Stockbridge’s opinion on this. Several of us have discussed the idea of using a master protocol in early phase development as a platform for what you’ve just said, Marc. The idea is to test multiple drugs more efficiently and allow for a single placebo arm that would be used for a single control arm and others which are the intervention/therapeutic arms. This would allow a more efficient drug development program and allow for some degree of adaptation, utilizing biomarkers or maybe some phenotype information.

The difficulty with the idea of the master protocol is, I think, a problem for academicians. I think when it comes to the biopharma companies, they may view it as competing with each other. I would love to hear Dr Stockbridge’s thoughts about utilizing that in the setting of a master protocol.

Dr Stockbridge: We’re certainly on record as having advocated for people to do that as a way to get efficient Phase 2 studies done. I think the reason why it doesn’t happen is because nobody knows how, or nobody knows what to do to organize such a study. I think the problem has been getting companies that are not anxious to share and not anxious to even be perceived as helping to move the field, move their colleagues along, move their competitors along. It’s hard to bring them to the table. They need to be more or less at the same stage because the first company doesn’t have a lot of incentive to help drag the rest of the community along. This does need to be organized, I think, at the academic consortia level or some international funding agency or something, and then you’re going to have to sell it to the companies.

Dr Humbert: It’s really interesting. I think that patients should be really strong advocates for that in close partnership with other stakeholders. Maybe the academicians, as Roham said, should try to develop such master protocols and persuade the National Institutes of Health (NIH) or some European funding agencies to support this. Of course, it’s difficult to organize, but I think it would be very good to do it as soon as possible, or at least try to, because a big disappointment for me is to see multiple, very small Phase 2 studies with invasive measures first presented as negative on press release, but with no data whatsoever presented to the community. I feel that it’s a big waste, and I think it’s not really ethical to keep these data hidden somewhere.

Dr Nicolls: I agree. We’re about halfway through our time here, so Marc, I have three different ideas for the next discus-
sion. One is, I’ll always remember being at a meeting with Norman Stockbridge and talking about the utility of using the 6-minute walk distance.

Another subject is the challenges of add-on (ie, adjuvant) therapy in the 21st century, when we add in a new potentially disease-modifying therapy on top of maximal vasodilation. It can be very, very challenging to get a readout; even though it might be an important therapy, the ability to detect change in a rare disease is challenging.

The third topic is, is there a value in developing endotypes for a rare disease, like looking for responder subsets in an already rare disease?

What do you think would be the most interesting one for us to discuss?

Dr Humbert: I think the patients would like to hear from experts about the typical classical endpoint like 6-minute walk distance, and then we can touch on the other subjects. I would like to discuss a little more the 6-minute walk distance as a Phase 3 endpoint, either on its own or as part of a composite endpoint.

Dr Nicolls: Can I ask it in the form of a controversial question? Basically, some believe that the 6-minute walk distance is an overly crude measure of determining whether a drug is useful. The Food and Drug Administration (FDA) has historically been very much in favor of using this benchmark, and it’s time-honored and useful. It’s certainly usable. Why don’t I ask Roham to go first?

Roham, what is your view of the 33-m idea, and what do you think about where we are as a field with regard to endpoints?

Dr Zamanian: I’m not sure if I specifically should comment on the 6-minute walk, but generally, I think one of the challenges we currently have with endpoints is that it can be difficult to show a treatment effect. Let’s assume that’s about 6-minute walk distance. We now have the largest number of patients in therapies that are on at least dual therapy from a vasodilator perspective. Most of the current trials enroll new patients on these therapies with New York Heart Class 2 or early Class 3 symptoms.

I think, from a 6-minute walk distance perspective, it may be valid to say that we’re challenged, because of existing success with vasodilator therapies, to show a treatment effect going forward. On the other end of it, I guess, if you accept that argument and you move toward clinical worsening, whether just purely mortality or a composite endpoint, those studies become extremely difficult and expensive to perform in our rare disease population. I think that challenge that I see is not entirely just the 6-minute walk.

I would love to hear Dr Stockbridge’s opinion on what the future would be. Mark, I think you and I have been involved with a number of studies, both academic and some early-phase industry, where I think that the fact that we have these patients, even those on intravenous therapies, who are maximally vasodilated, makes it increasingly difficult to pick up a signal of a 6-minute walk distance change with the number of patients we keep enrolling into these Phase 2 studies, which is about 100 to 150 patients.

Dr Nicolls: Before I turn it over to Dr Stockbridge, do you want to just quickly comment on this 33-m cutoff? Because you’ll recall that there are some trials that have moved forward to Phase 3 with a 10-m walk difference, which turned out to be—I think Phase 3 was terminated. Do you think that’s reasonable, or do you think that’s unreasonable?

Dr Zamanian: I think some of those decisions are based around the appetite for risk and what investigators or decision makers of those studies will accept as a potential “signal” without meeting this sort of a bright-line rule of a P value of .05. I believe Steve Mathai’s publication is a study that shows the minimum important difference for a 6-minute walk distance in a connective tissue disease population is around 33 m.

I know Marc and others have published also on what’s appropriate and meaningful change in 6-minute walk distance. I think those decisions might be both a scientific and a business interpretation of the data in early phase studies.

Dr Stockbridge: First of all, I need to respond to this notion that we’ve promoted the 6-minute walk. We have not. Somewhere along the line, somebody came in and asked if it was acceptable, and we said, “I guess so.” Because it was successful, other people followed suit. At no point did we allege that this was the best, or the only, or anything more than an acceptable way to demonstrate the benefit.

There is another thing that’s kind of interesting here, and I don’t think there’s anything written about it from a regulator—some of this obviously took place while someone other than me was a division director.

If you were to come in today with a more common disease and say, “I want to do a 6-minute walk,” we would tell you that it’s fine, but you need to show us an effect that a patient has some opportunity to perceive. We never did that with PAH. We didn’t do that initially, with the first few drugs, and we didn’t start incorporating it until we were beginning to get asked about the effects on the order of 10 m. I think the 6-minute walk effects that have been seen with vasodilator therapy have been tiny, have been miniscule.

What I am sure of is that, because we didn’t ask for big effects, we got a fair amount of drug development done here, an opportunity to look for things that were perhaps more clinically meaningful—disease progression kinds of endpoints, hospitalization endpoints—and I think we created some interest that will now drive the field more toward disease-modifying kinds of therapy. We probably wouldn’t be where we are if we had taken the classic approach of insisting that an effect be demonstrated that was actually clinically irrelevant.

Dr Nicolls: That’s a really fascinating discussion. The way that I was understanding it was that the FDA looked at the 6-minute walk distance as the “gold standard” for large trials. That was my bias. That’s what I’ve always thought.

Dr Stockbridge: Never happened.
Dr Nicolls: Interesting. I’m just curious whether or not Roham or Marc was laboring under that misunderstanding as well, if you thought that the FDA thought that the 6-minute walk distance was the “gold standard” for the field.

Dr Humbert: Yes, I think we have understood that the message that the 6-minute walk distance was quite a pragmatic way to favor drug development in a feasible fashion in rare conditions like PH, and we recognize that it has been extremely helpful. That’s something we appreciate very much.

The problem we face right now is, what can we offer as an alternative that will support drug development and innovation efficiently? When we develop clinical trials, we often discuss composite endpoints such as “time to clinical worsening” or “time to treatment failure,” etc. To be frank, it has a negative aspect in the wording, while walk distance is expressed as improvements, which is more positive. I think that we all wish to develop a more positive endpoint of “clinical improvement,” but it is quite challenging, and we often end up with a combination of parameters which usually includes walk distance improvements and biomarkers which have no direct consequences for the patient. I must say that I think a lot about endpoints, and I try to find the best way to develop a drug efficiently for my patients. I must confess that, in the last 20 years, the walk distance has treated us quite well and that other endpoints are more complex to use.

I think the walk distance was a good endpoint for early drug development in PAH and chronic thromboembolic PH (CTEPH). For future drug development, we will have to consider using modern technology, maybe actigraphy exercise recording, etc. I know that the agencies are quite open to these kinds of endpoints. We are very far from Phase 3 clinical trials with a positive endpoint on actigraphy in PH, but I hope it will come one day.

Something I wanted to discuss, because Roham said it twice, is the concept of “maximum vasodilator therapy.” I would rather say “combination therapy” because I am not sure it should be labeled as “maximum.” I would rather say that it’s the current standard of care. Right now, we have lots of patients on double or triple combination therapy who still present with very high pulmonary artery pressure, very high PVR, exercise limitation, and a lot of room for improvement in terms of hemodynamics and other clinical endpoints. Rather than saying that they are on “maximum vasodilator therapy,” I prefer to state that they receive “double” or “triple combination therapy.” Indeed, the word “maximum” corresponds to our current knowledge, but hopefully we will have more to offer sooner or later. Recently, we have seen some quite interesting results suggesting that you may be able to decrease pulmonary artery pressure on top of what we currently consider as “maximum” vasodilator therapy, corresponding to “double” or “triple” combination of vasodilators. Maybe we should think outside the box a little bit and consider that we will be able to add a treatment targeting other mechanisms on top of the current standard of care, leading to meaningful decreases in pulmonary pressure and resistance.

We have been very pessimistic in recent years, certainly too pessimistic. I remember at the 2018 6th World Symposium on PH in Nice, there was a trend to say that all the Phase 2 studies had failed and that it will be difficult to develop something meaningful rapidly. Indeed, it’s very difficult to develop new agents in the field, but when you try to understand the true mechanisms at play in PAH, maybe novel pathways which are critical in at least a subset of patients, there is certainly room for significant improvement in our patients because many are very limited in terms of exercise capacity and still have hemodynamic compromise. I think we have to be positive thinkers and try hard to develop drugs which should be efficacious on top of what we have.

Dr Zamanian: I quite agree with what you’re saying, Marc. I guess my intent wasn’t to say that those are maximized; I think my intent was to reflect that, maybe more than ever, there are now patients who are on dual or triple therapy. As Mark and I are dealing with in an NIH study, there are some clinical trial subjects who now are on dual or triple therapy and have lower PVR than anticipated, meaning that the power calculations that were used to estimate the impact of the therapy on PVR as an endpoint are inaccurate. I completely agree about this notion that we need to keep going because there are patients who have very, very severe disease despite current therapy.

Before we leave the endpoint discussion, can I just ask—there are a number of colleagues who have been working on patient-related outcomes (PROs) and health-related quality of life tools, and we’re very aware of a wonderful meeting sponsored by the FDA. In terms of hearing the voices of the patients and using PROs as primary endpoints of clinical trials, I wonder if both Dr Stockbridge and Dr Humbert could speak to that and how we would envision PROs as maybe even primary endpoints of Phase 2 studies.

Dr Stockbridge: There’s no problem from my perspective in having a PRO as the basis for approval. If patients say they feel better on some instrument, that’s got to be at least as good as 10 m on a 6-minute walk, but it has the same potential problem that, if you’ve enrolled 800 or even 100 people in a study and show a small effect that appears to be about the same in everybody, that effect will be perceptible to no one. You’ve got to deal with that if we’re going to move into therapies that have more clinical impact than the ones we have now. You ought to want them to show effects that individual patients are apt to perceive. This isn’t an issue with hospitalization. I don’t care if it’s 1/10 of a percent, statistically significant 1/10 of a percent change in hospitalization, but PROs ought to be perceptible to patients.

Dr Humbert: These are very interesting comments. I am very much in favor of PROs, but what Norman just said is very important. The instruments should be of good quality; the effect should be sizeable and meaningful. At the end of the day, I feel that the instruments we use right now with the drugs we currently develop show marginal effects.
This might not be the case for all the pulmonary hypertensive diseases. For example, CTEPH patients treated successfully with surgery or angioplasty will show large improvements in terms of PROs. That’s another field, but I think it demonstrates that PROs could be a primary endpoint to demonstrate efficacy of novel agents, but the size of the effect has to be as large in order to convince the community, which is not always the case with drugs we have developed recently; but I remain optimistic that it will come one day.

Dr Nicolls: That’s great. Maybe we have time for one or two more subjects. I see that Dr Stockbridge represents cardiology, hematology, endocrinology, and nephrology. Thinking just on the first one, cardiology, there are conditions where you need to layer on drugs, established standard-of-care drugs, but in diseases that may have a log order more patients than we have currently in PAH. This brings us to the challenge of adding adjuvants to the standard of care, potentially disease-modifying adjuvants. There are many different ways that you could take this question, Dr Stockbridge. I’m going to let you take it wherever you would like to.

There is maybe a useful oversimplification in PH—you can reasonably disagree with this statement; I’m not intending it to be dogmatic. Right now, when we give vasodilators, we are treating potentially a symptom and not a pathogenic driver of disease, yet our way forward in the field of actually treating disease—causing factors, such as metabolic changes or inflammatory changes, is extremely difficult because our readout is primarily based on what we think are PVR and things that are already being addressed by the symptom-driven therapy. With the hat that you wear, do you have any ideas for us about how we proceed with adjuvant therapies?

Dr Stockbridge: I’ll just mention that in the area of cardiovascular disease and heart failure, the advice we’ve routinely given is that, if you want to study a new drug, it needs to be on the background of standard of care that includes the other things you know are useful. That’s a little bit complicated in the PAH setting where there are a number of things you could be doing that are—I mean, it’s more like hypertension, right? You have drugs of different classes, and there may be some questions about which ones reasonably add to one another, but there’s also not the expectation that all of the classes get tested. Even there, I think we’re going to be forced out of the mode of insisting that new therapy be tested on top of other things. It becomes just infeasible. Even though mortality rates and morbidity rates may be very high still, it’s just taking bigger and longer studies as the incremental effects of 10% here and 15% there whittle down on the observed event rates and the trial. I think we’ve got to be open to the idea of studying these things in a setting where people agree that it’s okay not to be on some things you know work as well as plowing some new ground.

Dr Nicolls: That is a really interesting statement. I like it. I don’t think it would play well with a lot of people in the PAH clinical trials community, but from my perspective, it sounds interesting. Marc, can you comment?

Dr Humbert: I like the thinking behind the statement, and I have very little to add, but it remains challenging.

Dr Nicolls: Do you think it would be hard to adopt in our field?

Dr Humbert: Could be difficult, yes, because guidelines clearly advocate for combination vasodilator therapy in most PAH patients, and it may be challenging to delay use of combination drugs in symptomatic patients.

Dr Nicolls: Dr Stockbridge, do you see any examples of that happening in cardiology?

Dr Stockbridge: I think people are now just so stressed over the number of complementary therapies that need to be accommodated in this that they’re beginning now to talk about nonoptimized background seriously, but there’s no precedent for it, and we’ve set huge, decades’ worth of precedents that say, “We expect background therapy to be optimized.”

PAH may be, hopefully, on a different pathway. Although the effects seen with other drugs in this field have been small, the therapeutic area is ready for, and people are trying hard to find, the therapy that’s actually going to be disease modifying.

You couldn’t find a pulmonary-specific vasodilator. There wasn’t one. You had to deal with systemic vasodilators. If you can manage the toxicity associated with antiproliferative therapy, you can expect huge effects. Somebody who’s got a product in PAH with disease-modifying characteristics is going to be the background for everybody from that point on.

Dr Zamanian: Can I ask you quickly—Marc, you mentioned that this idea might not have traction in our field. Could you maybe outline what some of the challenges would be in implementing this approach in PH? If you were one of the opponents, what would you identify as these challenges that make it impossible?

Dr Humbert: Could you clarify—what was the idea that would be difficult to adopt?

Dr Nicolls: What we’re saying is, if we thought we had—let’s not use the word adjuvant. Let’s say a new disease-modifying drug that might have a long-lasting, positive vasodilator remodeling benefit beyond that of a standard, if there is such a thing as a standard vasodilator. Let’s just call it a generic vasodilator. The worldview of the field is that it’s widely accepted that whatever we do, we have to add it on top of standard of care. It’s written into our subconscious by now. Dr Stockbridge gave a very good, I think excellent, point that maybe it doesn’t have to be that way, yet I think that, if we were to introduce that idea, it would meet a lot of resistance. I think Roham was asking, do you agree, or why do you think there would be resistance? Where would it come from? What would it look like?
**Dr Humbert:** It would be challenging today to ask somebody to stop “gold standard” vasodilator therapy to be randomized to a new agent which might indeed be very efficacious. This approach will need to be very careful. However, I am quite positive that we are developing new drugs which are really fascinating because they deal with new relevant pathways. If some new drugs are working on top of double or triple combination therapy, my strong belief is that it would be interesting to approach future development in two ways. One way would be, if this drug is truly disease-modifying, to consider stopping this new drug and see what’s going on in the long run. The other way would be to consider stopping/titrating down the vasodilators that are known to be efficacious, in order to see whether they can be replaced by a new “gold standard.”

Right now, in some forms of severe asthma we have developed new quite efficacious drugs, and recent clinical trials have tested either stopping these new drugs and evaluating possible disease-modifying effects or decreasing the standard of care treatments while being treated with these new agents on their own.

**Dr Nicolls:** It looks like we’re back up against our time here, so I don’t think we’ll have time to get to that last question, but I think this has been a great discussion. Thank you all for participating.