J.P. Morgan Biotechnology Conference Call Series
BioMarin (BMRN)

CEO Jean-Jacques Bienaime & Head of R&D Hank Fuchs

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Moderator: Cory Kasimov
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Cory Kasimov: Great. Thank you, Maddie and good afternoon everyone. My name is Cory Kasimov, Senior Biotech Analyst at JP Morgan, and I'm here with Matthew Holt from our team. Thanks for joining us for the latest installment of our 2019 Spring Biotech Conference Call series where today, it's our pleasure to

be joined by J.J. Bienaime, the CEO of BioMarin; Hank Fuchs, the Head of R&D; as well as Traci McCarty from IR. So thank you all very much for participating today. We really do appreciate you taking the time.

Our standard format for this call, following some opening comments from J.J., we'll jump into Q&A where we'll cover the recent valrox update, as well as a couple of other assets from both the clinical and commercial portfolios. And we'll also of course spend some time discussing some broader strategic topics.

There is a lot to cover, but as usual, you can feel free to email us additional questions throughout the call, and we'll get to as many as we can time permitting.

So with that out of the way, let me turn things over to J.J. to set the stage for us with some opening comments about BioMarin. J.J.?

Jean-Jacques Bienaime: Thank you, Cory. We appreciate the opportunity to speak with you today. And as most of you know, BioMarin is a 21-year-old company with seven approved products that we expect would generate about $1.7 billion in revenue this year, and around $2 billion in 2020.

Each of our product is not just the best or first product for their indication, they are the only product for their indication. So BioMarin is known for making breakthrough advances for patients with very difficult to treat rare disorders.

As demonstrated with PALYNZIQ for PKU, we have the capabilities to provide highly innovative products to much larger patient populations where therapies are either non-existent, or deficient.

So our most recent success in Hemophilia A with valrox positions us to bring our eighth product to the market. The results of our Phase 3 pivotal clinical trials for anticipated approval, and our Phase 2 subjects were treated three years ago with a single dose of valrox to put our strategy to pursue expedited review.

To remind you, the phase 3 interim analysis met the pre-specified criteria for an accelerated filing, and we intend to pursue that track as quickly as possible.

Now the Phase 2 study after three consecutive years and one dose of valrox, the annualized bleeding rate was less than one. And over 3,000 Factor VIII infusions were spared for those patients that were in the study.

Our subjects typically require prophylactic therapy or Factor VIII three times per week. So each patient had over 400 Factor VIII infusions eliminated since being treated with valrox in 2016.

This data, coupled with the overwhelming and enthusiastic response and feedback we received from the hemophilia community have invigorated our focus on accelerated approval in the very near term followed by full approval thereafter.

We have been very encouraged by QOL feedback since the updates, including results from a recent survey of 25 Hemophilia A prescribers who collectively treat 3,000 Hemophilia A patients, adult patients in the U.S. and Europe.

For example, physician survey expects to treat about 28% of the patients on average with valrox by the second year of the valrox launch. That estimate increases to 39% of the gene therapy eligible patients by year five of launch.

And just as a reminder, we anticipate that the initial size of our market target is on 30,000 patients worldwide to 39% of their gene therapy patients at year five would mean that would have treated by then potentially, we could, around 12,000 patients, which is very significant considering the cost of therapy today.

So the most frequent driver physicians cite for the adoption of valrox gene therapy was a reduction in IV infusion burden, the curative potential for some patients, and better quality of life for most of them.

These results are all post our May 28 data update, the marketing research results. So we are very pleased with the increasing enthusiasm from the hemophilia community for the product profile of valrox, and with the Wall Street is beginning to appreciate the groundbreaking advances we have made with valrox, and expect enthusiasm to increase as we move closer to potential approval.

Next steps will include meeting with health authorities in the U.S. and Europe in the coming weeks as we pursue expedited review of valrox. And we would keep you informed of our progress.

Turning briefly to other categories for the remainder of 2019. We also expect to complete the full phase 3 enrollment of the valrox pivotal study in the third quarter of this year which would serve as a basis of a potential for approval.

And now, to Vosoritide, we are making great progress with the zero to five year old study. The first cohort of two to five year old had been fully enrolled, and we expect cohort two which includes six months to two years old to be enrolled by year end.

So currently, we expect to have the global Phase 3 results by the end of this year. There is tremendous enthusiasm and unmet need in this patient population. And importantly, we feel the program is largely derisked from a safety and efficacy perspective which is very encouraging as we look towards Phase 3 results at the end of the year.

R&D Day is also coming later this year. We look forward to reviewing what the R&D group is focused on, including our next potential gene therapy product, BMN 307 for the treatment of Phenlyketonuria PKU. The IND or CTA for BMN 307 is anticipated in the third quarter of this year, and will benefit from commercial scale material from first patients in through potential launch, which distinguishes from competition here.

And not to be forgotten, our commercial-based business is expected to generate around $1.7 billion in 2019, and around $2 billion in 2020. We are fortunate to have the global footprint in place in over 70 countries around the world as we contemplate our next potential product approvals and launches in Hemophilia A and Achondroplasia in the not too distant future.

So we are very busy indeed. So thank you for your attention. And I would turn the call back to Cory.

Cory Kasimov: All right, great. Well, I think you answered all of my questions with your opening comments. We can probably make this pretty quick.

All right, no, kidding. So let's obviously start with valrox, which has been in the spotlight here over the last few weeks with the multiple updates you had. And let's begin with that three-year update.

To start with you, J.J., and Hank, feel free to chime in. But just your key takeaways and from that three year update and how this informs your views on the product's durability?

Jean-Jacques Bienaime: The key update I think was as good as we were expecting, if not better, because now we have shown durability - I think Hank can elaborate, but that our hypothesis of the circular DNA which would result in stabilizations of the Factor VIII levels seems to be in a sense the beginning of proving this is happening with this data.

We believe based on the modeling that we've done on this data that the durability of effect in terms of control of bleeding rate is at least eight years, if not more, which would be a tremendous benefit for the patients, and actually allow us to have time to potentially re-treat them with a new vector that we are developing and there will be more information at our R&D Day. But I think we are very, very pleased with the three year update on the Phase 2 data.

And also the bleeding control at three year was as good, if not better than year one and two.

Cory Kasimov: Okay. Hank, anything to add there and kind of the insight you have now into that potential mechanism behind the possible tapering the Factor VIII levels?

Hank Fuchs: Well, a couple of things I'd say. First of all, there's been some attention today to variability of the Factor VIII expression, which is not particularly new.

But what's striking to me, what's not very variable is the reduction in the annualized bleeding rate. So in the year three, it was 0.7 annualized bleeds per year. And in the accelerated approval cohort, it dropped like a stone to like a ABR of 1.5 in just the first six months, and I'd expect it to drop even

further with time as people get re-acclimated to life without - with better hemostatic efficacy. So I was really pleased to see how well controlled bleeding is in both studies.

And then we presented at ASGCT some data on - that you obtain from humans treated with valrox. And we're able to examine cells from the peripheral blood to document vector persistence and characterize that the vector basically persists.

And so that prognosis quite well for persistence of vector in the liver where it's been documented pre-clinically that transgene turnover in the liver in dogs is relatively slow, and it's been documented with Factor IX in humans over now up to eight years that liver cell turnover is relatively slow.

So we approached doctors about considerations like durability, every day that goes by is another day of durability. And I think we've already cleared the bar for a lot of doctors interested in getting patients on valrox. And the additional information that we generated about the slowdown of the loss of vector in subsequent years is also very reassuring to clinicians.

Cory Kasimov: Okay. So then before moving on to the Phase 3 study, how should we be thinking about future updates for the phase one-two? Is this something you're going to continue to present on an annual basis as you've done in the past once these patients get to year four, year five, or that's kind of still TBD?

Hank Fuchs: I think that's kind of TBD. But I think it's also worth remembering that between now and then, there are other material things going on like what's the timing of the accelerated approval application, how's that review is going. And I think that that will be more relevant than presenting updates.

Cory Kasimov: Okay.

Jean-Jacques Bienaime: And the product might be on the market, or about to be on the market by the time we hit the year four. So commercial considerations will become more important than continuing to update on Phase 2 data.

Cory Kasimov: So turning to that first look you've provided for the Phase 3 study, it seems like it's the bigger source of controversy for some on the street. What do you make of - or what are your high level takeaways and how do you compare these results or is it worth comparing these results to what you generated in the Phase 1/2?

Hank Fuchs: Well, first of all, I think it's pretty good that we actually met the accelerated approval criteria in only 20 patients. That's a relatively small sample size to have accomplished what we've set out to accomplish which is to show that a meaningful proportion of patients had a very meaningful Factor VIII response. And so that's a particularly joyous outcome of the accelerated - of the interim analysis.

I think also the fact that with the ABR reduction looked as good as it did was also very encouraging. And the fact finally that there appears to be a nice correlation between vector expression and bleed control as we showed with both of the data.

I think it's going to give the agency a lot of comfort about accelerated approval because their standard is robust evidence on the surrogate Factor VIII, and that surrogate is reasonably likely to predict the clinical outcome. So we're really checking all the boxes in the Phase 3 interim analysis.

Cory Kasimov: Okay. And then how should we be thinking about the non-responders that were in the Phase 3 study? How concerning is this? And what do you think are the reason behind it?

Hank Fuchs: We had seven patients in the first study, and now we've got 17 patients that we're talking about. I think when you go into larger numbers, you get a larger sense of a distribution of the population.

I don't know that 3 out of 17 is necessarily different than what we have seen in the prior statistical trial for data as time goes by to have a better and better understanding.

But I'll remind people that when we set out on this journey, we would have considered it heroic to get 80% of the patients above 5%. And we've achieved way beyond that.

Now obviously, we like to treat 100% of the patients. It's very hard to come up with drugs that are effective at 100% of patients, but that doesn't mean that we won't try.

Jean-Jacques Bienaime: And actually, there is only one that was really a non-responder. There were two that Factor VIII levels didn't go very high, but we understand that their bleeding is under control. Is that correct, Hank?

Hank Fuchs: Yes.

Jean-Jacques Bienaime: For perspective, as Hank said, there are very, very few drugs that are working 100% of the patients if any. And one should ask the same question about HEMLIBRA recently launched by specific antibody where in

the pivotal trial about 40% of the patients still had bleeding episodes. It appears to be higher than our "non-responders".

Cory Kasimov: Good point. Do you have information on those non-responders at this point in terms of the immune response they had and whether prophylactic steroids may or may not have had an impact there?

Hank Fuchs: Immune response data looks pretty clean. So there doesn't appear to be a correlation between detectable immunity to the capsid, or the transgene product that is correlating with Factor VIII expression or transaminitis.

So whatever mechanism that's causing transaminitis in the context of valrox appears to be different than the immune mediated mechanisms which have held other back in prior trials.

Cory Kasimov: Okay. So then with ISTH a little under a month away, what should we be looking for in the data that's to be presented that you haven't - that hasn't already been toplined?

Hank Fuchs: I don't think anything materially significant would be at ISTH. I think that at the medical conference, or scientific conference, people have an interest is deeper dive types of issues, but I don't think it will meaningfully change the overall story.

Cory Kasimov: All right. And then you've talked about it already, both this decision on filing for the accelerated pathway that's coming up here in the near term, and you just need to meet with regulators first.

Given the recent updates, what is the latest on the regulatory outlook? And maybe what are the key factors that are remaining if there are any remaining

that will influence your decision to file through these pathways? Has that decision been made already?

Hank Fuchs: Well, I think that decision has been fundamentally made in the sense that we've had a lot of interactions with the FDA and the EMA prior to looking at the data. And in those lots of interactions, we've had ample time to examine every single possibility. And health authorities are really good at that by the way. They're very professional. They're reviewing data, and they are very good at asking questions that might not be answered in the context of the study.

And what's happened since we've looked at data is that we've been very careful to go back and tick and tie to make sure the data do really meet everything that we've spoken about in terms of being required for accelerated approval.

And so I think of the coming meetings with health authorities has worked pro forma. That's not to say that - anything can happen. But there is nothing that's been identified that represents kind of loose end that's not been tied up.

But one major outstanding area is having the completed the PPQ campaigns. We need to now finish the product characterization work and some initial stability work on the material that came out of the PPQ campaign.

But the campaign performed substantially well overall. The expectation is the material that we produced in the PPQ will be sufficiently similar to the material that was produced in the clinical trial that there should be no impediments on that front as well.

Cory Kasimov: Okay. So then assuming these regulatory meetings go as anticipated, how long do you expect it would take to put the regulatory packages together to collect or what's left with the CMC database that you're just talking about? Like what's a reasonable turnaround time?

Hank Fuchs: Well, that depends on very specific and concrete feedback that we get from that in terms of what timestamp data cutoff do they want.

So we have that eight patients for example that was outside of the interim analysis cohort. Now, we know that patient data. Does the FDA want that with database, or are they willing to put those patients on the side? So it's little details like that that can sometimes affect weeks, or months or so to figure out the exact date of filing.

So we haven't really communicated a specific date on which we intend to file by partly out of respect to having the conversations with the health authorities in terms of content submissions.

Cory Kasimov: Okay. Are you able to say whether or not you're having these meetings with health authorities prior to ISTH, or it would be after that?

Hank Fuchs: I think we said that, yes.

Cory Kasimov: Okay.

Hank Fuchs: Prior to ISTH.

Cory Kasimov: Okay. And then how are you thinking about the timing for the Phase 3 study? So potentially thinking down the line towards full approval? I know your guidance is to - and you would just reiterate it, to complete approval of that

study in the third quarter. But then what length of follow up should we expect in the full study results, and how important do you think these will ultimately be for the eventual like, commercial outlook for the product?

Hank Fuchs: Well, first of all, in regard to the timeline, the complete enrollment, we've been guiding to the third quarter. Since the data came out, we've done a little bit of pulse check with our steering committee and with a lot of the investigators who have patients who are lined up and ready to go. And the feedback we've gotten is all systems are go. And so investigator enthusiasm is high.

From a patient perspective, we have a run-in study to, if you will, warehouse patients prior to entry into the confirmatory study. And that we have 96 remaining slots as of our last communication about enrollment for the pivotal confirmatory portion of the trial.

We have way more than that in terms of patients pre-identified and investigated for enrollment really on us about - well, you've got to create a waiting list, somebody drops out, I want first slot. And so we ended up creating a very large waiting list. So we have a pretty decent insurance policy for enrollment.

The endpoint is 52 weeks. So if we are successful with completing enrollment in the third quarter of '19, 52 weeks later weeks later will be the third quarter of '20. Give us some time to clean the data, analyze the data. And shortly after that, we'll see the results of a full 52 week analysis primary endpoint ABR comparing pre-treatment run-in to post-gene transfer.

And I think that's going to be very helpful, not so much for physicians who understand already that Factor VIII is relevant, and for patients to understand

that ABR is relevant. And they've already seen enough data that have a lot of excitement about potential for ABR reduction.

I think it's going to be very helpful for payers because then they can put more in and they could put more quantitative belief behind the ABR reductions.

And you've got to remember also that with payers, statistical evidence of reductions and factor use are going to their money shot if you will. And so having more of that is just going to be more momentum to get payers behind us in terms of supporting adoption of valrox.

Cory Kasimov: Okay. All right, so then I wanted to ask on competition. How difficult do you think it's going to be for others to meet or potentially exceed the bar that valrox has set in terms of the clinical profile?

Hank Fuchs: Well, let me take it one by one in terms of who's in the clinic and who reports the initial data. And I think Sparks travels here are relatively well known, and they've had seven patients that have been treated with SPK-8011, two of whom lost vector attrition at their most recent doses and prior observation in IV steroids, and still weren't able to preserve vector from being lost.

They also talked about capsid specific immunity accompanying that vector loss. So they'll have to work around that.

The hypothesis is that an early dose of steroids is going to present what amounts to being viral hepatitis as a result of that capsid. And it remains to be seen if that could occur. It's going to be difficult I think for them unless they get a perfect outcome to even contemplate raising the dose because of that toxicity. It's pretty significant outcome.

So a lot of TBD on whether they can get to meaningful levels of vector expression and a meaningful traction of patients.

Jean-Jacques Bienaime: If I may, going back to the hurdle we've had, we have over 40% of patients that were over 40% of Factor VIII expression around six month using the chromogenic assay, which is about 60% of the one stage. They only have responses so far in one stag data. And their seven patients, even eliminating the two non-responders, which you should not, but let's - it would be very nice to them. I think they were around 35% or so one stage if I'm not mistaken.

Hank Fuchs: Yes.

Jean-Jacques Bienaime: So that would be around 20% chromogenic. Actually they're actually lower than that if you include the two non-responders. So that's way too far from the hurdle here. So it looks like they have a big challenge.

And on top of it, this is with non-commercial scale product and not making it in a commercial facility. Another hurdle.

Cory Kasimov: Okay ...

Jean-Jacques Bienaime: Because I just want to highlight that there is no company in the world so far that has reported any data with commercial product made in a commercial facility.

Hank Fuchs: And so similarly that's true for Sangamo who are off to a good start, but there's only two patients that we look forward to a major update where we'll see a little bit more length of exposure of the initial patients. They are where we were approximately three years ago and still in front of them. As J.J. just

mentioned it's the migration of the to-be-commercialized facility, and all of that entails.

And honestly, my hope is that having converted to full approval that that becomes a barrier to their entry in the sense of they'll have - the accelerated approval won't be available in that context, and therefore they'll have to do a larger and longer study to get on the market.

And given that at the time that they'll be considering launching that study, we'll have that much more valrox data, that much more durability, that much more sample size. It may be hard to imagine - it may be very difficult for them to enroll ...

Jean-Jacques Bienaime: Actually this is a very important point that Hank made. I want to make sure that you understand it that once a product has full approval for the indication, the accelerated approval pathway is no longer available.

Hank Fuchs: It's accelerated approval criteria is that there is unmet need. And if the need is being satisfied - you could find nooks and crannies with the patient population, people who are excluded from our trial. But then there's issues and risks associated with that. So I mean, is the whole thing going to depend on being able to treat HIV patients, et cetera. So being this far ahead in this context, there's a real advantage.

Cory Kasimov: Right, okay. Okay, that makes sense.

All right, so we'll come back and talk more about gene therapy and some bigger picture topics around it towards the end.

But in the interest of time, I want to move over, because lest we forget, you have another Phase 3 asset in Vosoritide. And so I want to make sure we get some questions in on these other programs.

So first of all, can you help set the stage for what to expect in the Phase 3 data readout later this year, and your overall confidence that the trial will read out positively given what you've presented to date?

Hank Fuchs: Yes, so the full trial is enrolled, and the last patient will be out in the fourth quarter, and we're working really hard to enable at least a look at top line data, did we meet, and were there any unexpected safety findings by the end of the year, or right at the beginning of the year.

The primary endpoint is that change from baseline from the - there's a run-in period during which untreated patients are measured longitudinally to determine their growth velocity, and then patients will be switched to either - they'll later be put on placebo, or on vosoritide. They'll be followed for a year.

And the comparison between vosoritide and placebo will be individual patients change from baseline during the run-in to their on study by AGV.

So there's power to detect what we've observed in our prior Phase 2 studies. And so as with valrox where we adequately powered the study, so to here, have we taken a lot of clinical trial risks out of the Phase 3 trial.

We've done a lot of additional analysis of the ongoing Phase 2 extension study. We reported out 42 months' worth of data at R&D Day. And one of the things that we wanted to make sure to debunk was how do we know that we didn't just get lucky and enroll some patients who were in between growth

spurts such that when they went on vosoritide, they were on a slow growth mode, they went on vosoritide, they were on slow growth mode. After they went on vosoritide, they had a little growth spurt. And that really wasn't for Vosoritide.

Well, the way we debunk that is we look at early and earlier time points of run-in for these children and documented that there was in fact no sort of deceleration of growth prior to the initial study.

So that's given us even more confidence that the effect that we observed in the ongoing 205 study is attributed to Vosoritide and will be maintained.

And so we have a lot of confidence in the Phase 3. Obviously Phase 3 trials are Phase 3 trials, right? But we have a lot of confidence in the prospects or efficacy.

Durability is looking strong. That was encouraging safety data in children under five. So it's a strong component of the initial registration application. We fully enrolled the first cohort of those children who are between two and five years of age. We're underway in the second cohort of patients who are between six months and two years of age.

So the initial application will have a lot of safety data and a bare minimum in terms of very young children, which I think is going to be a great comfort to the FDA and to the EMA.

And finally, we've just completed the development of a natural history database, another key requirement from the FDA, with more contemporaneous and larger natural history database for comparison for that

long term efficacy to give more comfort that the treatment effect is as durable and meaningful.

So in the last few months since people have been asking us a lot of questions about vosoritide, we've really also made a lot of progress in being ready for the Phase 3 unblinding and subsequent filing.

Cory Kasimov: Okay. So then specifically within the trials, either the Phase 3 or before that, how is the product presentation in terms of needle size and dosing frequency been received by patients and physicians?

Hank Fuchs: Quite well. Compliance with the trial is really extraordinarily good.

I think some of the patients could make some device improvement suggestions which we were actually pretty prepared for. With PALYNZIQ, we started the program with - you had to withdraw your dose from a vial and administered by a syringe. And we switched over to a pre-filled syringe which is well-received. And we can imagine doing a similar thing post-approval, and that would offer I think patients improved convenience.

We use relatively narrow gates; needle, and the tolerability has been really quite good. So we're not sensing any problems right now with the dosage presentation. We have some ideas for how to make it even better in the future. But there's no urgent need to improve the product presentation as we sit here today.

Cory Kasimov: Okay. And so I guess as a segue from that, I wanted to ask about the competitive outlook. I think most people kind of turn their attention towards Ascendis. Maybe you see other competitive threats out there as well.

But specifically regarding Ascendis, what do you see is the key differences or maybe similarities, and how far ahead do you believe you are in terms of development?

Hank Fuchs: Well, I don't really see a whole lot of key differences between what I've read about Ascendis. I know they have their version of the story. But we don't really see a whole lot of hypertension. And we often don't see a lot of room for improvement in growth velocity since we're already near - relatively near normal. And we've shown that even if you give a higher dose of vosoritide, you don't get meaningful more growth out of it.

So it's not clear that there's an efficacy for a safety potential for advantage over with vosoritide. And given the number of years - I don't even know how many years ago it was that we did our healthy volunteer study, that they've done a single dose healthy volunteer study. And I think we did a multi-dose healthy volunteer study, I want to say seven years ago or something like that.

Now maybe they could pick up steam because we've kind of lit the pathway for them. But in the absence of a safety or and efficacy advantage, they're really down to a period of convenience advantage which is really pretty hypothetical in the sense that there have been products that have a proper dose than convenience advantage.

On one level, you ask a parent, would you rather inject your child once a week, or once a day. Of course they're going to say, weekly would be better than daily.

But you have it on the details here. When J.J. and I were in Genentech, we're developing a long acting form of Neutra Pigmentosa, the best idea in the world. It actually proved to be adequately efficacious. But it was a dud in the

marketplace because the injections were painful and it wasn't really knowable until it really got into the marketplace.

So it may be many years before we find out if there's even - if there is even really a competitive threat. And obviously during that time, we will be in regular contact with our patients and families in discerning what do they care the most about. And they may care about other things than just injection frequency.

Cory Kasimov: Okay.

Jean-Jacques Bienaime: And again, as Hank say, we have a close to no discontinuation of therapy in the current trial.

Cory Kasimov: Okay.

Jean-Jacques Bienaime: And also basically no significant hypertension had been observed in thousands of injections here in those patients.

And then finally, in addition to - Hank said it's kind of difficult to draw any comparison to Acendis because they have not treated one patient yet.

Cory Kasimov: Right.

Jean-Jacques Bienaime: As Hank said, they have not even treated one healthy volunteer with multiple injections. So there's very, very little data to hang your hat on.

Cory Kasimov: Okay. So last question I have on vosoritide before we move on is presumably you've been doing market research as you get closer to your Phase 3 data and

potential launch. What do you see as the overall commercial opportunity at this point?

Jean-Jacques Bienaime: For Vosoritide, I mean, they are about 100 thousand patients in, what we call a BioMarin world excluding India and China and most of Africa that are affected with Achondroplasia.

With Vosoritide, it's very likely to be only indicated for patients during the age of 18. So that's about 24, 25K addressable patients. So that's a pretty significant market. It's not ultra-rare. But so we believe we are equipped around the world to address this market. It will be bound of course on pricing. But even it gets simple - and I'm not giving you a price here, but even if it was $100,000 a year on average, I think it could be more than data depending on the data. That's a $2.5 billion of market here.

Cory Kasimov: Right.

Jean-Jacques Bienaime: If we're able to penetrate the whole market.

Cory Kasimov: Okay, all right. That's good color.

All right, so let's move on and talk a little about the commercial products where we come back and talk some bigger picture items.

So PALYNZIQ, we're roughly a year into this launch. So I'm curious to get your view on the kind of the current state of that launch and how it's progressed relative to your expectations.

Jean-Jacques Bienaime: Yes, I mean, we are extremely pleased with - it's really the U.S. launch so far. We just got approval in Europe. But we need reimbursement and all that in Europe before we had any experience there.

So based on the U.S. experience which is about a year old as you say - it's less than a year old, but really doing well - we're doing great.

We gave you some numbers when we were on Q1 conference call, and we are over 400 patients on conventional therapy already in the U.S. We're close to 150 that were in at that time. So we obviously are ahead of that now.

But more importantly I think what's important here is that we had some concerns a little bit, at least I did, a year ago before we launched regarding how the product would behave outside of the clinical trial in terms of the management of potential physiologic reaction in the first four to six months of treatment. And so far, this is really doing very, very well.

Yet, a few patients had some severe physiologic reactions. We knew how to manage it. We've prepared them. We've prepared the clinicians for that. Most of them are actually back on therapy.

And the feedback that we are getting from PKU centers and from patients is extremely positive. I mean, they are patients that are really saying this is life-changing therapy for them. And this is the best we could expect.

So the only thing with this product I want to remind you is that between the number of patients that are getting on a drug and on commercial therapy and the dollars generated, the revenue generated is lagged because in the first four to six months, the patients are taking a very low dose of the product and they

are not on a cruising speed in terms of the number of injections that they take and then the revenues they generate.

But we now have some patients on steady states. Some patients are generating about $200,000 a year of revenues, but still a minority. But they've got to keep growing.

And so there is a lag between the patient numbers and the dollars, but that will take care of itself over time.

Cory Kasimov: Okay. So J.J., you've previously suggested that you believe PALYNZIQ could ultimately be a billion dollar product. Would you say your first year market experience here gives you more or less confidence in that projection? It sounds based on your comments, like more.

Jean-Jacques Bienaime: I would say more.

But if you look at the market, this is right now initially adult PKU patients that's in Europe, we have patients 16 and older, so young adults and adults.

If you look at U.S. and Europe, Middle East, Africa, just that population using those criteria for eligibility, and looking at the patients that are in the clinics. So these are patients that are want this disease to be actively managed. We're talking about 10,000 patients, and that's not counting Latin America and Asia.

So let's say we can convince about 65% of them to be on the drug, that's about 6,500 patients. And again, that's not counting any out of the clinic patients in there, many of them, that would triple the numbers.

And let's take back of the envelope $150,000 per patient on average between U.S. and Europe, Middle East, that is $1 billion right there.

So what's going to be impacting the peak revenues of PALYNZIQ are actually our own efforts in gene therapy, BMN 307, how quickly we can get this product approved, and then that would obviously - in some patients, if they go to gene therapy, they won't be eligible for PALYNZIQ anymore.

Cory Kasimov: Okay. All right, we'll get to the gene therapy questions in just a second. Before I do, I wanted to just quickly ask a couple on Vimizim. This has obviously been BioMarin's best launch to date. How much more room is there for Vimizim to grow?

Jean-Jacques Bienaime: We believe that there is still many, many patients that are not - that some of them identified, some of them not quite yet identified. They are not on the drug. So there is definitely room to grow.

If you look at the Naglu experience, it's been on the market for, basically in the U.S. for 14 years and still growing. And so there is definitely room to grow is beyond where we are right now.

And I think Vimizim, assuming that the pricing doesn't deteriorate significantly within a few years is also another drug that could get close to a billion dollars in revenues.

Cory Kasimov: Okay.

Jean-Jacques Bienaime: And on that one, there is no - as far as we know, there is no significant competition in development at this point.

Cory Kasimov: Okay. And then the product has just approved in China. Do you see this as a real and potentially meaningful opportunity, or is it more just a headline for now?

Jean-Jacques Bienaime: Well, I mean, it's a real opportunity in the sense that they are - there is a significant number of MPS IV patients in China. The question is the ability to pay and ability to find these patients and get them on therapy. So that's something we are debugging right now.

The good news is that there is definitely willingness and that's recent from the Chinese government to want to address rare disorders. And that's why they approved - that's why they approved the Vimizim.

So the approval in terms to approve this drug is definitely there from the Chinese government. The issue is as you know is reimbursement and pricing. And that still needs to be debugged and we believe that we will be able to get some patient on therapy, some paying patient on therapy. But that would take some time. We have a very small organization there. But I think that's the very beginning of our efforts in China.

There's a lot of interest in China for valrox, a lot of interest, and Vosoritide. So I think having now our foot in the door, getting some experience, Vimizim is going to be helpful there.

Cory Kasimov: Okay. All right, great. So now, I want to circle back and talk a little bit more about gene therapy. And obviously we spent a lot of times talking about valrox and having a product that's well into Phase 3. And now, another that's on this way into the clinic with your PKU asset.

First broader question on gene therapies, how are you thinking about the ultimate potential and importance of this platform to BioMarin?

Jean-Jacques Bienaime: I mean, Hank you want to get started?

Hank Fuchs: Sure. One of the cool things about 307 and PKU gene therapies is that we're making in our commercial facility at commercial scale. So that's a huge competitive advantage.

J.J. was talking about how Spark's in the clinic for a while now in both Hem A and Hem B. We're not seeing commercial scale material from them.

And so you could imagine that the kinds of competitive leads that we can be generating simply because we'd have to go through a facility or a process, or scale switch puts us years ahead of anybody in every indication that we into so that's a key platform advantage I think that we have.

There are on the drawing board in the research labs, a lot of ideas for gene addition that we can do, that leverage our capsid, AAV5. And as we talked about on R&D Day, we've generated a lot of knowledge about novel capsids, capsids that are for example, have different tropism than just than the liver, or capsids that have lower preexisting immunity, or as we've talked about very recently capsids that don't cross-react with AAV5 such that they could be used to those after a patient has seen another AAV. So that could be an incredibly important strategic asset.

So there's a lot of stuff that's going on and very exciting. And stay tuned to R&D Day for updates.

Cory Kasimov: Okay. And then just from the manufacturing side of things, it sounds like for some time it's been a significant competitive advantage for you guys.

How flexible though is your facility if the methods of manufacturing gene and cell therapies over time evolved? Can you evolve along with them with this facility?

Hank Fuchs: I think we're going to be a driver of that evolution.

We have been working with the FDA for example on facility design before we put shovel in the ground. We've been already in discussions with them about a lot of facility testing that needs to be done.

The fact that we make clinical supply for our Phase 3 trial, I think speaks volumes about the team's ability to generate material. The fact that we're able to execute PPQ campaign.

We're pushing the pace here. The FDA is keen to collaborate with us as we're setting a lot of the standards that are going to end up mattering in the field.

Robert Baffi, who's our Head of Technical Operations, like J.J. and I were in Genentech in the early days, and then the same way that large scale, we call it, manufacturing of monoclonal antibodies became a real competitive advantage. And then they were the leaders in, we're sort of repeating that playbook here.

So the facility was designed specifically with the idea of having flexibility in mind through the use of a lot of disposable equipment through a ballroom configuration which enables people - equipment to move around quite readily.

The fact that we have our own filling capability - these are all flexibility available type of options.

Jean-Jacques Bienaime: And also if I may add, we - the current facility can only do sequential manufacturing of different gene therapy products. But we already have some plans and drawings ready for a second facility that we'll be able to potentially do parallel manufacturing of several different gene products at the same time. And that's our plan going forward.

Cory Kasimov: Okay. All right. So I guess one of the - I want to work in an email question here, because I had a question on your overall appetite and capacity for business development, or bringing other assets in house given how much we have going on.

And the email question is - that relates to with gene therapy, can you internally grow your capabilities or is it easier to use M&A to build a larger, more sustainable effort?

Jean-Jacques Bienaime: I'll start. I think we have already a lot of capabilities in house. Of course most of our experience is with AAV5, always the AAV in general, and with the baculovirus.

So indeed, there are some potential complementaries in terms of companies that might have experience with other expression platforms, or other kind of vectors. So that's why we are evaluating the universe here of possibilities. So it could be a combination of both.

Cory Kasimov: Okay.

Jean-Jacques Bienaime: That's just for gene therapy.

I mean, you want to add something to this, Hank, on gene therapy?

Hank Fuchs: I don't really know that I have much to add. I think we're - there's so many spaces to go into in the gene therapy landscape. As I've said before, novel capsids with novel serologic capsids, re-dosing kinds of considerations.

Sure, there's always something out there that you could buy to expand your capabilities. But I think we've got a nice little diversity here.

So I suppose if we saw something we love and we absolutely have to have, that would be a story potentially.

Cory Kasimov: Okay. And then on pricing front and gene therapy, while I assume it's a little too early to be speaking specifically to valrox, I'm curious though how the gene therapy pricing to date has come in relative to your expectations and maybe what BioMarin is doing at this point to kind of set the stage for your future approvals and your own maybe innovative pricing schemes?

Jean-Jacques Bienaime: Yes, so we are - in the past year, we've been in discussions with many, many payers around the world, mainly U.S. and Europe to better understand their needs. So we believe that they're interested in bleeding rates, interested in savings, Factor VIII injections, or savings - all the products injections. They're looking at the cost offsets, the cost of treating hemophilia patients. Hemophilia is very well established, high on their radar screen. And they understand the value of a product like valrox here.

I would say the very different indication, the price Novartis came up with SMA gene therapy, is according to our expectations. But I see the difference between us and SMA is that SMA, there is no really established standard of

care. There is standard of care for Hemophilia A. There's lots of pharmacoeconomic data.

We are very open to different payment capabilities around the world including pay for performance, pay over time, pay upfront we will be offering also. So options to the payers.

As you know, there's still legal and regulatory issues with pay for performance in the U.S. because of the Medicaid best price, which is still in place in the U.S. There's a lot of noise about potentially removing it, or excluding, "curative therapies" or gene therapies from the Medicaid best price, which hasn't happened yet.

So we'll be watching that space. Actually we'll be very - we are very interested in the Zolgensma launch too - because they're launching basically ahead, a year or so ahead of us, and to see what their experience with value-based agreements and how they manage around the different regulations and the regulators in the U.S.

Cory Kasimov: Okay. So another email question I want to work in, this is on Vosoritide. One, can you confirm if the product is just dosed in the evening? And if so, is there - when you think about from an Ascendis point of view, is there a concern the patients with Vosoritide get dosed at night and therefore don't see blood pressure changes, but Ascendis will expose its patients for days, so more chances to see blood pressure changes?

Hank Fuchs: I don't see a whole lot of blood pressure changes with Vosoritide. We measure blood pressure change in our Phase 1 healthy volunteers with peak dose studies, or with wide range doses in our clinical studies now. As J.J.

said, tens of thousands of injections. And we don't see symptomatic hypertension as a really meaningful issue.

Cory Kasimov: Okay. And so the exposure for period of days was the Ascendis program, would that potentially change anything do you think on that front, or was it - mechanistically there's nothing than you wouldn't be concerned about that either?

Hank Fuchs: Well, honestly, they didn't show biomarker data. The concept of Vosoritide is that it activates the receptor and causes inter-cellular accumulation and ultimately release of cyclic GMP that's signaling intermediate.

And so frankly, I think about it the other way I'm not convinced that they're actually going to deliver enough active ingredient to the growth play to affect growth. I worry less about the hypertension thing. If I were in their shoes, I worry a little less about the hypertension issue and a little bit more about the efficacy issue.

Cory Kasimov: Okay. All right, so the last question I have, and there are a couple of other email questions I might be able to work in.

But, maybe start with you, J.J., and Hank you feel free to chime in. Biomarin share price obviously has been stuck in a relatively narrow range for what seems like forever now for several years, which I assume is pretty frustrating for you?

What aspects of the BioMarin story do you believe are most underappreciated by investors at this time?

Jean-Jacques Bienaime: I think investors appreciate commercial product that have been launched in the past few years, have been on the market for a while. I think they underestimate potential of newer products like PALYNZIQ, like valrox, and like Vosoritide.

Already for valrox, there is clearly a disconnect between the physician and the patient community. The market research we have been doing and others have been doing, whereby even after the Phase 3 data here and the Phase 2-three update, there's major interest from patients and hematologists for other product. So it seems Wall Street is more conservative than the patients that would be receiving the drug and the doctor will be treating them.

But that would take care of itself over time. I don't know if a lot of investors have realized that PALYNZIQ will be a very, very large drug. But that would take time also. And I think there is underestimation of the potential of vosoritide too, and exaggeration of the competitive threats for all our products in development today.

Cory Kasimov: Okay. And since we have a couple of minute left, let me just squeeze in one or two more email questions.

How much manufacturing capacity will you have for valrox, or do you have for valrox now, and when you have it launched?

Jean-Jacques Bienaime: So we have about - we have capacity for about 4,000 patients per year right now with the existing facility. We could get to 5,000 relatively quickly and with a minor investment and additional equipment. So that's already - that would have to cover valrox and early BMN 307 for PKU.

So I would say we could pull the trigger on starting the construction of the second facility any day now. So let's wait a little bit, see how it goes in the next few months. But then that would allow us to have a major, major increase in capacity here.

And really, we are all - we're looking forward to the time when we are running out of the current facility capacity on patients per year.

Hank Fuchs: If I could just add something that sort tied to earlier question in terms of the gap.

And I think there's going to be a reasonable number of patients that are going to be willing to make the valrox treatment decision without necessarily checking in with the Wall Street analyst on efficacy data.

And I was really pleasantly surprised that one of the most bearish physicians that's out there the other day went on a call through sort of all of the concerns and considerations. And then at the end of all that, concluded well, about a third of my patients will be interested in valrox gene therapy in the first couple of years.

So even bearish people are recognizing the potential value for patients. There's a lot of - people have been waiting a long time to have access to gene therapy and hemophilia. But having something that gets across the finish line and has the increment nature of an approval is going to be very meaningful.

Cory Kasimov: Okay, all right. Well I think that is a good place to end it. We're right up the top of hour. I promised we wouldn't go longer, so we'll stop there. J.J., Hank, Traci as well, thank you all very much for making the time today. Very helpful and insightful conversation as usual. So thank you guys.

Jean-Jacques Bienaime: Okay, thank you Cory for bringing this together.

Cory Kasimov: Yes, we'll talk to you soon.

Jean-Jacques Bienaime: Okay, take care. Bye.

Coordinator: And that concludes today's conference. Thank you for your participation. You may disconnect at this time.

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