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QURE.OQ - uniQure N.V. - Special Call

EVENT DATE/TIME: DECEMBER 21, 2020 / 1:30PM GMT

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PRESENTATION

Maria E. Cantor - *uniQure N.V. - Chief Communications Officer*

Good morning, and thank you for joining us. This morning, uniQure announced that its hemophilia B gene therapy program has been placed on clinical hold by the U.S. Food and Drug Administration, pending review of a serious adverse event. This SAE is associated with the preliminary diagnosis of a form of liver cancer in one patient in the HOPE-B clinical trial being studied in adult patients with severe and moderately severe hemophilia B.

Joining me for this investor event and webcast are Mat Kapusta, our Chief Executive Officer; Dr. Ricardo Dolmetsch, our President of Research and Development; Eileen Sawyer, our Vice President of Global Medical Affairs; Dr. David Cooper, our Vice President of Clinical Development; Dr. Steven Pipe, Professor of Pediatrics and Pathology and the Pediatric Medical Director of the Hemophilia and Coagulation Disorders Program at the University of Michigan and the Principal Investigator of the HOPE-B pivotal trial of EtranaDez; and Dr. Graham Foster, Professor of Hepatology at Queen Mary University in London and Lead of the U.K. National Health Service for Elimination of HCV.

Please note that we will be making forward-looking statements during this investor call. All statements, other than statements of historical fact, are forward-looking statements. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this conference call. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the factors described under the heading Risk Factors in uniQure's quarterly report on Form 10-Q filed on October 27, 2020, and other securities filings. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future.

Now let me introduce Matt Kapusta, uniQure's CEO.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Thank you, Maria, and good morning, everyone. A deep commitment to patients has guided uniQure for more than 20 years as we pursue highly innovative treatments with the potential to transform lives. Today is no different. The safety of our patients who place their trust in us will always be our utmost priority, and we are committed to open and transparent communication to the patient communities we serve. As announced in our press release this morning, our hemophilia B gene therapy program was placed on clinical hold by the FDA following the submission of a safety report regarding the finding of a liver lesion suspected to be hepatocellular carcinoma, or HCC, which is a form of liver cancer in one patient in our HOPE-B study. We are focused on ensuring this patient receives the best care possible.

It is important to note that, at this time, we do not know if this event is related to EtranaDez, and we will be conducting a rigorous investigation to collect more information. Over the last 20 years, uniQure has administered its gene therapies to more than 100 patients, including 67 patients with hemophilia B, with some patients treated more than 10 years ago, and no reports of HCC prior to this event. We are also not aware of any of the reported cases of HCC in other AAV gene therapy studies.

The patient in the HOPE-B study that was affected has multiple risk factors for HCC, including a 25-year history of hepatitis C, hepatitis B, nonalcoholic fatty liver disease and advanced age. We have conducted extensive preclinical and nonclinical studies of EtranaDez and our other gene therapy candidates in hundreds of animals and have not observed any cases of HCC. uniQure has also conducted numerous AAV integration studies, including the assessment of patient liver biopsies from our clinical study in acute intermittent porphyria. These studies have demonstrated a low risk of random integration and no integration in hotspots or sites associated with tumorigenesis. AAVs are naturally occurring and affect a significant fraction of the human population and are not thought to be pathogenic. Additionally, vectors incorporated in gene therapies are modified to remove the genetic material required for directing cellular integration.

Before I hand the call over to Dr. Ricardo Dolmetsch, our President of R&D, I'd like to reinforce that patient well-being will always be uniQure's top priority, and we are committed to working with the FDA and our advisers to gather more information. We are taking this matter very seriously and our clinical and medical teams have already prepared a detailed investigational plan, which Ricardo will describe shortly. With respect to the findings from this investigation, we pledge to be transparent with our stakeholders, most importantly, the patient communities who we serve.

Regarding the HOPE-B clinical study, patient dosing was completed in March 2020, and we have no plans to enroll or treat additional patients. All patients enrolled in these studies will continue to be followed by their care providers without any impact from the clinical hold. Currently, we do not expect an impact on the completion of the clinical trial or regulatory submission time lines for EtranaDez.

Now let me call -- turn the call over to Ricardo.

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Thanks, Matt, and good morning. As Matt stated, patient safety will always be our top priority. As soon as we were notified of the serious adverse event, we conducted an initial investigation and contacted the site and the medical care team to understand the facts and ensure that the patient was receiving the best possible care. We informed the FDA in mid-December and the agency issued a clinical hold in the middle of last week. We will work closely with the FDA and with outside scientific advisers to conduct a thorough investigation into the cause of this event. We're working hard to conduct our investigation as rapidly as possible and hope to provide some updates early next year. I want to reiterate at this time that we don't have adequate data to determine whether there is a causal relationship between the EtranaDez and HCC. Hepatocellular carcinoma has a complex etiology, and this patient had several risk factors that could have predisposed him to HCC regardless of his treatment with EtranaDez.

So let me now provide the details of this case as we have communicated to the health authorities. So a patient in the HOPE-B clinical trial had a liver lesion, suspected to be a hepatocellular carcinoma. The lesion was initially detected during an ultrasound conducted as part of the routine study assessment at 1 year post dosing. A needle biopsy was conducted, which confirmed the presence of cells that express the markers for HCC. The patient also had a routine assessment of alfa-fetoprotein that was within the normal range. Complete surgical resection of the lesion is scheduled

for this week and will allow for confirmation of the preliminary diagnosis that was made following the needle biopsy. Tissue will be sent for analysis, which will provide information about any potential contribution of the gene therapy to the development of HCC.

The investigations that we plan will be comprehensive. So histology will be conducted on the resected tissue to confirm the diagnosis of HCC. The number of vector genomes in the tumor and in the healthy tissue will be measured to determine if the tumor is, in fact, infected with EtranaDez. Genomic DNA will be isolated from the tumor and from healthy tissue. LAM-PCR and next-generation sequencing will be used to determine if the vector DNA has integrated into the genome of the tumor. The total number of integrations and the specific integration events will be compared between the tumor and healthy tissue. If vector DNA has integrated into the genome, we will determine if the integration events affect the expression of any tumor suppressors or oncogenes. We will use PCR and next-generation sequencing to determine if there has been a clonal expansion of any integration event. And finally, we will use whole genome sequencing to identify any mutations that could drive the proliferation in the tumor tissue independently of EtranaDez. These studies will help us determine if EtranaDez contributed to the development of HCC in this patient.

As we stated previously, no other events of HCC have been detected in any of uniQure's trials or the preclinical toxicology studies. All patients in the HOPE-B study are screened regularly with AFB and abdominal ultrasound as part of the clinical trial assessment and this will continue, and we plan to follow all patients for 5 years. We will share the results of our investigation in a timely manner with regulators and with the medical and scientific community when we have more results.

So now let me turn it back to Matt. Matt?

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Thank you, Ricardo. I'd like to introduce Professor Steven Pipe, a clinical investigator in our Phase IIb study of EtranaDez and the principal investigator of the HOPE-B pivotal study. Dr. Pipe, thank you for being with us to provide your perspective on the safety event in the HOPE-B study and risk-benefit considerations for patients.

Steven W. Pipe

Thank you, and good morning. And I appreciate the opportunity to provide a commentary on this event. I can speak today as a clinical investigator, but also as a clinician. As a clinical investigator studying gene therapy for hemophilia, we've been informed by preclinical studies with AAV-mediated liver-directed gene therapy over more than 2 decades, including extensive safety evaluations, and these have identified that this platform has a sufficient risk-benefit to move into the clinical trials. When determining what participants will be included in the early studies, it was decided across multiple gene therapy clinical trial programs that we should not exclude patients with a history of hepatitis B and C and HIV, provided they had no evidence of active hep B, had eradicated their hepatitis C with current state-of-the-art antiviral therapies and had well-controlled HIV. However, all the programs still have exclusion criteria based on some assessment of liver health so as to exclude participants who would be seen as having an unacceptable degree of cirrhosis or liver fibrosis where the risk-benefit evaluation would be deemed unfavorable. So this is an assessment of potential impact on the efficacy for a therapy that targets the hepatocyte, but it's also because such participants risk significant liver adverse events.

As some programs have advanced our gene therapy programs, observations in some subjects have identified additional risk factors for adverse events. For example, some anti-HIV medications have contributed to liver toxicity and some trials have elected to either exclude subjects with HIV altogether or to evaluate them in separate clinical trials. These strategies allow for a proper evaluation of risk-benefit across all potential patient populations. Now the occurrence of hepatocellular carcinoma in this gentleman in the HOPE-B trial is a watershed moment for all liver-directed gene therapy for hemophilia. I'll explain that further in a minute.

This community still lives with the legacy of the tragedy of hepatitis B, C and HIV from contaminated factor products from the late '70s and early '80s. And in regard to hepatitis C specifically, whereas we've embraced innovations of antiviral therapies, we've learned that even eradication of hepatitis C with these therapies does not eliminate the risk for hepatocellular carcinoma. You'll hear more from Dr. Foster, I'm sure, on this point. But general population study suggest the 2% to 3% rate of development of hepatocellular carcinoma over a 30-year span. Similar studies in the hemophilia population also suggest a rate that's in agreement with that risk. And this risk can certainly be increased with either more advanced

cirrhosis or failure to eradicate the hep C with antiviral therapies, but it doesn't eliminate the risk. Recent data also suggest that other forms of acquired liver pathology, such as nonalcoholic fatty liver disease, can also contribute to the hepatocellular risk.

I chair the Medical and Scientific Advisory Council to National Hemophilia Foundation, and we've made recommendations to our Hemophilia Treatment Centers and to patients to maintain diligence to evaluate and screen for hepatocellular carcinoma among those with long-standing histories of hepatitis C because of this remaining risk. So we've included patients who carry this remaining small risk within investigational gene therapy trials because we've made an assessment that the risk balanced against the potential benefits to them from an efficacious gene transduction remained favorable. As an investigator, I've had discussions on this point with all the candidates who've come to consider participating in investigational gene therapy. We have discussion that those with a history of hepatitis C that despite eradication of hep C, their risk for hepatocellular carcinoma remains. And I then share what we've known to this point that nothing has yet been identified to indicate that receiving AAV gene therapy to the liver would increase that background risk. Nevertheless, at a, say, 3% risk there's always been some certitude that the clinical trial subjects from this group could develop hepatocellular carcinoma within a trial, particularly as we increase participation to larger numbers of participants.

So why do I consider this current event a watershed moment? We first need to ensure that the medical team has the opportunity to deliver the patient the best surgical care. But then the obligation of the investigative team is to conduct the analysis that Ricardo outlined to determine if there's any evidence that the AAV gene therapy contributed to its development. This will then allow continued evaluation of not only the risk-benefit assessment of specific risk groups, but also this particular clinical trial program and perhaps the entire platform of AAV-mediated liver-directed gene therapy for hemophilia as well as other disorders. And if necessary, risk mitigation can be considered in specific clinical groups. Now as a clinician, I have risk-benefit discussions with patients every day. That's how we choose together from among a number of existing approved therapies. Those discussions are individual, and they're not the same for every patient. There's a similar process for investigational clinical trials. Depending on the evaluation of the potential benefit for their clinical situation, a patient may be willing to embrace a certain degree of risk. Now this discussion is difficult when you're trying to weigh previously unknown but possible risk. So we will have an opportunity to now have better informed discussions with our patients and potential clinical trial candidates based on what we learned from this case.

So I'll be happy to take any questions in this regard at the end. Thank you.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Okay. Thank you, Dr. Pipe. Now I'd like to introduce Dr. Graham Foster, a Professor of Hepatology at Queen Mary University in London, United Kingdom, who will provide perspective on liver cancer, specifically HCC. Dr. Foster?

Graham Foster

Thank you very much indeed, and thank you for inviting me along this morning. I want to preface my remarks by making it clear that at this stage, we don't know the etiology of this lesion. I don't, for 1 moment, want to suggest that there could not be an association with the gene therapy, but I do think it's important that the risk is put in the perspective. We've been treating patients with hepatitis C now with all oral antiviral agents for many years. It's very clear that in some patients with cirrhosis, the cancer risk remains even after viral clearance. We're seeing patients who are treated, the liver histologically appears to improve, but we believe the cancer risk continues.

What is more disconcerting are a series of observations, anecdotal at the moment, and the risk is not yet clear, in that some patients even without cirrhosis are developing liver malignancies after hepatitis C has been cleared. We know the risk in cirrhotic patients is around 2% per year post viral clearance. That by the way compares to a risk of 5% in patients with ongoing viremia. We don't yet know the risk in people who do not have cirrhosis. We believe it is low. We're not sure how low, and we're not sure who is at greatest risk. What we are beginning to see is some stratification of risk factor. It's very clear that male patients are at greater risk. It's very clear that patients with most fibrosis are at increased risk and the fibrosis risk increases such that when you have cirrhosis, the risk is very high. It's clear that previous exposure to hepatitis B increases the risk, and some viral genotype, particularly genotype 3, increases the risk.

I had a call and a discussion on Friday with colleagues in Pakistan, where we're just setting up a large study. Their reports where they have genotype 3 is that 11% of their cirrhotic patients post treatment have developed tumors. That's the highest rate that we've seen, but it indicates what we're beginning to believe that different viral genotypes have very different effects on cancer rates. So what we know about this individual at the moment is that he had hepatitis C. We don't yet know the pretreatment, i.e., pre-hepatitis C treatment state of his liver fibrosis, nor do we yet know his viral genotype. We do know that he'd been exposed to hepatitis B, and we know that he was elderly. So from the get-go, this individual has 3 of my risk factors for liver cell cancer. Whether there is an added impact of gene therapy on this pre-existing risk is not something we can comment on with any accuracy at this time, but you've already heard the plans to evaluate and a very comprehensive survey to try and determine any potential risk.

So in my view, as a practicing hepatologist with 20 years in the hepatitis C field is that, in some ways, this is not a surprise, it's clearly an unfortunate and distressing event for all concerned, and we now need to continue the investigation to work out what are the associated factors, if any.

And I'll be happy to take questions at the end of the call.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Thank you, Dr. Foster. With this, operator, please open the line for analyst's questions.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from the line of Gbolahan Amusa from [Garda].

Gbolahan Amusa - *Chardan Capital Markets, LLC, Research Division - Director of Research & Head of Healthcare Research*

It's Gbolahan Amusa from Chardan. I just had a question about the patient's history and whether you can say if the patient had a prior abdominal ultrasound or other assessments that did not show the petrocelli AR carcinoma or it's just a suspicion of such. And then hopefully, this is related enough to be okay. But are there any net analysis being done across the liver-directed AAV space on the potential for liver cancers? Have you seen anything there as well?

Steven W. Pipe

So I can take the first question. So yes, the patient was assessed with a abdominal ultrasound before the study as well as AFP and there was no evidence of lesion or beyond, of course, lesions can only be detected when they're at around 2 centimeters. So we don't know for sure. But this was a new lesion. And yes.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

And Dr. Foster, do you want to answer the second question?

Graham Foster

Happy to. To the best of my knowledge, there have been no prior reports of liver malignancy associated with this form of gene therapy. So I believe that this is the index case, the first case of such.

Operator

Our next question comes from the line of Robyn Karnauskas from Truist Securities.

Unidentified Analyst

This is Min, on for Robin. I guess more can you just talk about the increased risk that patient may have when going from single lesion infected HCV to acquiring HPV or non-alcoholic liver disease? And then a little bit more into -- is that due to added stress and strain onto the hepatocyte or is it more like increased integration event? And I'm sorry, one last one. Does this patient also has AAV5? And what concurrent effect on AAV5 may then lead to integration of EtranaDez?

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Dr. Foster, do you want to answer that first part?

Graham Foster

Thank you for the question. I think we're moving into areas where our evidence and knowledge base is fairly limited. We don't know the etiology of the liver malignancy associated with hepatitis C infection. We, to the best of our knowledge, don't think that there is direct oncogenic damage from hepatitis C. There's a paper from our group just coming out, talking about genotype 3 increase directing with the anti-oncogene PKR, but that has no clinical correlates that we're aware of at this moment. So we're still only just beginning to understand how hepatitis B causes malignancy. And I think it would be speculative to talk about any possible interactions.

I think what we do know is that these factors are additive. And as you rightly say, a lot of our patients who have cleared hepatitis C go on to develop nonalcoholic steatohepatitis, they go on to develop, sadly, alcoholic liver disease. Important to make the point about non-alcoholic steatohepatitis, which is associated with liver malignancy without cirrhosis. And that clearly is a compounding factor. We don't yet know whether this individual will have evidence of steatohepatitis on his liver biopsy nor can I do anything other than speculate on any possible interactions. So sorry that I can't address in any accurate fashion, but I hope that gives you the context that we're looking at this in.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Yes. And in terms of the second question, the integration associated with AAV5 or other AAVs, for that matter, has been studied quite extensively by uniQure and other independent researchers. We -- I think some studies have suggested that the percentage or rate of integration can be as low as 0.1% of total AAV forms. We've studied this in hundreds, if not thousands of animals, and have never seen an event of HCC. In our acute intermittent porphyria study, we did collect liver biopsies. That was a study that was using AAV5 gene therapy. We did not see a high rate of integration. In fact, the risk of integration was low, and there was no integration in any hotspots or areas of oncogenesis. So as I said, this is something that we've explored significantly. But of course, we will explore it further as it relates to this particular patient.

Operator

Our next question comes from the line of Paul Matteis from Stifel.

Paul Andrew Matteis - *Stifel, Nicolaus & Company, Incorporated, Research Division - Co-Head of the Biotech Team, MD & Senior Analyst*

Great. Specifically, what do you think FDA wants to see to resolve the hold? And if you show no evidence of integration, is that enough where everything is kind of back on track with no other discernible issues? And then what's the impact on the CSL deal? Have you talked to them, gotten any feedback? And what are the different sort of possibilities there as we resolve this?

Steven W. Pipe

So let me take the first part of that question. So we have had conversations with the FDA, and we're engaging in further conversations. I would say it's fair to say that we have pledged to this investigation. We don't know exactly what would be required to get us off hold. Yes.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Okay. With respect to the second question, the only contingency in the executed agreement with CSL relates to the clearance of antitrust review. And they are aware of this issue, and we will be working closely with them with respect to the investigation.

Paul Andrew Matteis - *Stifel, Nicolaus & Company, Incorporated, Research Division - Co-Head of the Biotech Team, MD & Senior Analyst*

Can I ask one follow-up. If you don't know exactly what FDA wants, what gave you guys the confidence this morning to reiterate that your regulatory filings were on track?

Steven W. Pipe

Well, I think that we do know what analyses is possible. So I think that we will conduct very thorough analyses of the potential for integration. The work that Ricardo outlined I think, will provide us a lot more information. I think that we've presented these plans to the agency. So they're aware of them. We'll have more conversations associated with the plans. But we do think that this is a thorough analysis that we believe will be completed early next year. So in that regard, because it won't impact the timing of the study and the patient follow-up of the study, today, we don't believe that this will impact our regulatory submissions, which are planned for next year.

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Yes. I can add a bit of that. So we think the investigation is going to take somewhere between 1 and 3 months, depending on exactly how things go. And we know that the last patient will be dosed in March and therefore, we will have a complete data set by then. And the -- our regulatory submissions are -- we've guided that they're going to be towards the second half of next year. So we think we can do the investigation in the time frame that would allow us to have no changes to our regulatory submission.

Operator

Our next question comes from the line of Joseph Schwartz from SVB Leerink.

Joseph Patrick Schwartz - *SVB Leerink LLC, Research Division - MD of Rare Diseases & Senior Research Analyst*

Do you have an estimate for the prevalence of the risk factors that this patient has like HPV, HCV and NAFLD? And how that compares the prevalence of those in the heme B patient population versus the general population?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Well, I think we have the most information about hep C. And that is around, at least in the U.S., it's on the order of around 10% of patients have hep C or have had hep C. I think the fraction of patients that have both hep C and hep B is significantly smaller than that, at least in our study. And I don't think we have good epidemiology around non-alcoholic fatty liver disease. So this patient, of course, had an unfortunate trifecta. I think, of course -- that, I think, is going to be relatively unlikely, but the most obvious risk factor here is hepatitis C.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Yes. I can tell you in our 67 patients that were included across the 3 studies that we have in our hemophilia B program, there's approximately 30 of them that had a history of hepatic C.

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Only 3 of them had hepatitis C and hepatitis B.

Operator

The next question now comes from the line of Joseph Thome from Cowen and Company .(Operator Instructions).

Joseph John-Charles Thome - *Cowen and Company, LLC, Research Division - VP of Healthcare*

I was wondering if you could just comment on sort of the advancement of the NAFLD in this patient, how severe that was? And when you look at the AE profile of this patient in the trial, were there any other liver enzyme elevations or anything that popped up after dosing?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

So there were no other signs. There were no liver enzyme elevations or anything else that would give us any sense that there was anything wrong. We don't know how advanced, and we will not know until we have a biopsy.

Operator

Our next question comes from the line of Madhu Kumar from Baird.

Madhu Sudhan Kumar - *Robert W. Baird & Co. Incorporated, Research Division - Senior Research Analyst*

My question is for the 2 physicians who joined in. In your experience with hemophilia patients who have had hepatitis C, how many instances of liver cancer have you observed among that population generally in your own clinical practices?

Steven W. Pipe

Well, as a pediatric treater, this is outside of my care as we graduate those patients over to the adult clinics. It certainly has been seen in most -- particularly for most clinicians who have been caring for patients over this past 25 to 30-year span. It's enough of an ongoing risk, but that's why we've had the call for due diligence for all of the hemophilia treatment centers to continue their long-term follow-up and evaluations. But it's also -- it's enough of a risk that we have been pushing for years now to encourage patients to go through the full eradication with the antiviral therapies because we know that that's critical to having an impact on eliminating the risk for cirrhosis and then, accordingly, also hopefully reducing the risk for hepatocellular carcinoma as a follow-on.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Dr. Foster, do you have anything to add?

Graham Foster

I can certainly think of a handful of cases over the last few years. We would expect, of course, the hepatocellular carcinoma rate to lag about 4 to 5 years behind the cirrhosis rate, and we're expecting to see increasing numbers. So to directly answer your question, we're in the early phases of the cancer post hepatitis C epidemic, and we're certainly seeing a few coming through.

Operator

Our next question comes from the line of Suji Jeong from Jefferies.

Suji Jeong - *Jefferies LLC, Research Division - Equity Analyst*

Pre-integration, is that patient 2021, do you expect that you're going to have to get biopsy from other patients who received the drug?

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

No. At this stage right now, we only expect that we'll have to conduct this assessment in this particular patient.

Operator

And our next question comes from the line of Luca Issi from RBC Capital.

Luca Issi - *RBC Capital Markets, Research Division - Research Analyst*

Great. A quick question for Ricardo. Circling back on the prior discussion, can you expand a little bit more on the tests that you will do on the surgical piece? In your mind, what are the key tests that will definitively tell you whether the AE is gene therapy related or not?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Yes, that's a great question. So this is what we plan to do. We're going to look -- first of all, we just want to make sure that -- we want to know whether the tumor itself is infected. So we'll compare the number of vector genomes in the tumor relative to the healthy surrounding tissue. Assuming that the tumor is infected, then we will look for integration events -- actually, we'll look for integration events anyway in case somehow the episomal vector is at a very low level. And when we look for integration events, we'll essentially look at which genes are close to where there is an integration event, should there be integration events. If -- we will then determine if any of those genes have been implicated in liver cancer or any other kinds of cancer. Of course, just because there's an integration that is close to a gene, it doesn't necessarily mean that it's affecting its expression. So we will then do RNA seq to actually look at the expression of that gene to see if it's increased or decreased depending on whether it's an oncogene or a tumor suppressor. And then we would like to see what the driver mutations are in that specific tumor. And so to do that, we will do just whole genome sequencing of the tumor tissue to see what mutations that tumor might have. And then we think this will give us -- well, this will certainly give us a lot more information. To be clear, it may never be possible to completely discard some contribution of the gene therapy. But at the very least, we should be able to discard smoking gun, I would say. Was that helpful?

Luca Issi - *RBC Capital Markets, Research Division - Research Analyst*

Yes, very helpful.

Operator

Our next question comes from the line of Difei Yang from Mizuho Securities.

Difei Yang - *Mizuho Securities USA LLC, Research Division - Executive Director of Americas Research*

Just a quick one with regards to CSL agreement. If one of those events can trigger a termination of the agreement?

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Yes. I addressed this in one of the prior questions. The only outs, if you will, or contingencies relate to the clearance of the antitrust review. There are no other contractual outs associated with the closing of the transaction.

Operator

And our next question comes from the line of Joseph Schwartz from SVB Leerink.

Joseph Patrick Schwartz - *SVB Leerink LLC, Research Division - MD of Rare Diseases & Senior Research Analyst*

I was just wondering, how will this occurrence impact the timing or content of your pre-BLA meeting coming up?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Well, our pre-BLA meeting might have to be delayed a little bit until we have all the data. And certainly, we will have a discussion around this incident in the pre-BLA meeting because this, of course, will affect the risk-benefit of our therapy.

Joseph Patrick Schwartz - *SVB Leerink LLC, Research Division - MD of Rare Diseases & Senior Research Analyst*

Right. And then -- so specifically, relating to my prior question about the prevalence of these risk factors in the population, do you think you'll be able to get a sense from the agency whether it's possible to just ring-fence these very rare trifectas or something like that and still proceed forward with the filing? Do you think you'll be able to get any insight into how that kind of a concept might resonate with the agency?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Well, I think we will start by trying to determine if there's any additional risk conferred by the gene therapy. And if there is, then we will try to craft a risk-benefit profile such that there is more benefit than there's risk so it's appropriate for individual patients. And of course, we'll have a conversation about this with the FDA when it comes to the label.

Operator

(Operator Instructions) Our next question comes from the line of Vincent Chen from Bernstein.

Vincent Chen - *Sanford C. Bernstein & Co., LLC., Research Division - VP*

A couple for the physicians on the call. The first one is simply, I want to get your thoughts on what's the latest thinking in the field on the risk of hepatocellular carcinoma with AAV gene therapy and potential AAV integration? And how long after treatment would you expect to see HCC due to AAV gene therapy? My understanding is that some of the earlier papers linking some risk of AAV to HCC generally suggested it would be a fairly long time frame between the events. And the second is also for the physicians. What would you want to see in the assessment of this case to get comfortable that this is not a peer AAV related and to be fully comfortable recommending gene therapy?

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Dr. Pipe, do you want to start?

Steven W. Pipe

Sure. Yes. Those are great questions, of course. Keep in mind that there have been no observations in any preclinical models or in patients to study to this point in the context of AAV gene therapy. So what you're referring to as far as associations with AAV and previous cancers, this relates to a natural infection, which is potentially a completely different mechanism. So it's hard to sort of extrapolate from those observations. Nevertheless, since the earliest days of selecting this platform of treatment for patients, so AAV-mediated liver-directed gene therapy, this was a concern that has been put forward before the investigators who were developing these therapies and it's been a shared concern amongst the community. So we never moved forward in any clinical trials until we had felt satisfied with the risk-benefit analysis from the preclinical studies was sufficient that, that risk-benefit was sufficient to move forward into the early phase trials, and then from the phase -- early phase trials, where there was another assessment of the risk-benefit being favorable to move forward into the larger Phase III studies. So from what have we had available to us with AAV-mediated liver-directed gene therapy? We've had animal models miring, but particularly dog models. And those dogs have been followed all through their entire lifespan. They've been analyzed at end-of-life to show that they had integration events. Several publications have demonstrated that just in this past year. We have seen some evidence of what are called clonal expansion in those biopsy specimens from the -- liver pathology specimens from those animals. But no evidence of tumorigenesis in those animals. And these are animals who had gene therapy and were followed over more than 10 years across their lifespan.

We have gentlemen, hundreds now, across all the Phase I/II programs, some of whom have now been followed for 10 years, and they have the same, if you like, risk profile as the individuals in the HOPE-B trial, meaning those trials did not exclude patients who had hepatitis C as long as they have had properly treated and eradicated hepatitis C. And they had to meet certain standards of overall liver health, et cetera. So that is what has informed the Phase III trials that are now underway across a number of different programs.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Okay. Dr. Foster, do you want to provide your perspective there?

Graham Foster

I think it's a great question as to the timing. And you've just heard, we really don't have any information on timing of any potential link. I think it's instructive to look at the hepatitis B situation. This is an oncogenic virus. We know this causes cancer. Children pick it up very early, often at birth. They have a period of viral replication with billions of viruses in the liver with clonal integration and expansion in childhood, and most of those cancers develop 4, 5, 6, 7 decades later. So I would expect this to be a very, very protracted course. And I would predict that any changes would take decades to develop and that's based on the hepatitis B scenario.

I think the follow-up question that you were asking, how would we stratify our patients that I personally would use on a very individualized basis. We spend a lot of time in talking to people about risk-benefits of transplantation. I was a very big user of Interferon, which is a fairly toxic, unpleasant therapy. And in patients with hepatitis with no symptoms, that's a difficult discussion. So I'm sure we would want to have individualized discussions.

Steven W. Pipe

Yes, I'll just follow up on. I think the other question was here...

Operator

We need to go to the next party for a question. (Operator Instructions)

Maria E. Cantor - *uniQure N.V. - Chief Communications Officer*

That's Dr. Pipe. Would you please let Dr. Pipe continue?

Steven W. Pipe

That's okay. I was trying to address the point of questioner asked about when would I be satisfied with the information that's provided. Again, that's a risk-benefit analysis. uniQure was prepared for this moment, in my opinion, as I think all the programs are to react to such an adverse event, ensure the patient gets best care, but then also be prepared to know what samples are going to be needed, what studies are going to have to be done on those specimens, identifying the proper labs who can provide those investigations, and then almost certainly, those will be made available for the scientific and the patient community to review and then reach their own assessments informed from all of those studies. That's what we've been doing for the past 2 decades together as a community. We've been sharing this information together, and we've been prepared for these watershed moments so that we can come back to our patients and give them a proper risk-benefit analysis for investigational gene therapy and also, hopefully, still for approved therapies. So I think satisfied is a difficult word, but I have to say that I think we're all going to be better informed coming out of this investigation and will know best how to move forward from this moment.

Operator

Our next question comes from the line of Paul Matteis from Stifel.

Paul Andrew Matteis - *Stifel, Nicolaus & Company, Incorporated, Research Division - Co-Head of the Biotech Team, MD & Senior Analyst*

I just want to clarify one CSL thing and one clinical thing really quickly. The CSL deal, so Matt, it sounds like you're saying that the CSL deal will close unless there's a hang up in the antitrust side. Is that right? They don't have an out or anything like that? And then on the clinical side, can you just clarify this patient -- it sounds like this patient did not have cirrhosis? So does that change your thinking on the degree to which hep C and hep B induced risk of HCC? Or is that not the right way to think about it?

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Yes, I'll answer the first one and then hand it over to Dr. Foster on the second one. Yes, I'll repeat it again. There is no out or contingency in the agreement in order to close the transaction other than the antitrust clearance. So that's as clear as I can be.

Paul Andrew Matteis - *Stifel, Nicolaus & Company, Incorporated, Research Division - Co-Head of the Biotech Team, MD & Senior Analyst*

Yes. No, very definitive.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

And then Dr. Foster, do you want to answer the second one?

Graham Foster

Yes. Thank you. We know prior to gene therapy, this patient did not have cirrhosis. What we do not know at the moment and are trying to find out is what level of fibrosis he had prior to eliminating his hepatitis C, and certainly, we've seen cirrhosis following viral clearance. So to directly answer the question is to whether he did have cirrhosis or advanced fibrosis prior to gene therapy.

Your question as to how that would influence my thinking is that the more fibrosis he had, the more likely, I would think, hepatitis C played a role. We also need to clarify the viral genotype. If it was genotype 3, that would increase my suspicion that hepatitis C was a major etiological factor.

Operator

Our next question comes from the line of Kristen Kluska from Cantor Fitzgerald.

Kristen Brianne Kluska - *Cantor Fitzgerald & Co., Research Division - Analyst*

My question is, if the AAV was integrating? I wanted to ask if there are any other clinical observations or perhaps any red flags that you might expect to see from these patients during their multiple follow-up visits?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Well, we can't really measure integration unless we have a liver biopsy. So -- and we don't expect to see anything related to integration in anything that we can measure routinely in the clinic. So I guess the answer to that is no. We -- integration is something that is sort of a molecular event and does require a sample of the cells. Now in terms of what we expect to see in these patients going forward. So far, the therapy has been very well tolerated, and we have seen very few adverse events of any sort that we reported earlier.

Operator

(Operator Instructions) And our next question comes from the line of Difei Yang from Mizuho Securities.

Difei Yang - *Mizuho Securities USA LLC, Research Division - Executive Director of Americas Research*

Just to circle back on this one patient, would you walk us through how many follow-ups he had leading up to this 1 year event -- year 1 event? And then because of this event, would you plan to change the protocol on monitoring other patients?

Ricardo Dolmetsch - *uniQure N.V. - President of Research & Development*

Yes. So we are doing abdominal ultrasounds every year and AFP measurements every 6 months, which is what this patient had, and it was in one of these abdominal ultrasounds that the lesion was identified. It was identified at a relatively early stage, so it can be resected. It's fully reflected. We will discuss with regulators whether it's necessary for us to change that schedule of assessments. And the schedule of assessments that we have is what has been recommended as the standard of care.

Operator

There are no further questions at this time. Please continue.

Matthew Craig Kapusta - *uniQure N.V. - CEO, CFO & Executive Director*

Okay. Thank you, operator. As I mentioned earlier, deep commitment to patients and their safety is guiding uniQure over a long history. We've been pioneers in the field of gene therapy for more than 2 decades. Developing safe and effective treatments with the potential to transform patients' lives remains our mission. Patient safety and open transparent communication to the patient communities who place their trust in us is our top priority and always will be. We're fully committed to working with the health authorities and will be completely responsive to their quests. I'd like to thank Dr. Pipe and Dr. Foster for being with us on this call. And I want to thank the dozens of patients, their families and their physicians who've been part of our clinical trials for their trust in us and their dedication to pursuing new treatment options. Thank you all for attending the call, and we look forward to providing further updates early next year.
