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ALNY - 2017 RNAi Roundtable: Revusiran investigation results

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OVERVIEW:

ALNY provided an update on Revusiran investigation results.

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PRESENTATION

Operator

Thank you, ladies and gentlemen for joining today's RNAi Roundtable. We will be conducting a web-based question-and-answer session during the webcast. (Operator Instructions)

I would now like to turn the call over to Josh Brodsky, for opening remarks. Josh, you may proceed.

Joshua Brodsky

Good afternoon, everyone. Thanks for joining us for today RNAi Roundtable to discuss the results from our investigation into the mortality imbalance observed in the ENDEAVOUR Phase III study with revusiran.

I am Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alnylam. With me today are John Maraganore, our CEO; and Akshay Vaishnaw, Executive Vice President of R&D. In addition, John West, Senior Director of Clinical Research; and [Erina Constin], Associate Director of Clinical Research are here and available for Q&A.

Before I turn the call over to John, I just want to make a few comments. Today's RNAi Roundtable is part of a series of roundtables that we're hosting this summer and early fall. Today's event will end at around 1:30 p.m. Eastern Time. John will moderate a Q&A session at the conclusion of the presentation. (Operator Instructions)

Finally, as a reminder, we will be making forward-looking statements, and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And with that, I will turn it over to John.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Thanks, Josh, and good afternoon, everyone. We're pleased to host today's RNAi Roundtable on the findings from our investigation of the mortality imbalance in the ENDEAVOUR Phase III study with revusiran.

As you know, revusiran was previously in development for the treatment of hATTR amyloidosis with cardiomyopathy. As a reminder, revusiran was a first-generation GalNAc-conjugate investigational RNAi therapeutic that used so-called STC chemistry. This is a delivery approach that is distinct from all other molecules that are in pipeline, including patisiran and our ESC GalNAc-conjugate RNAi therapeutic programs.

Revusiran was being studied in hATTR cardiomyopathy patients in a Phase II open-label extension, or OLE study, of approximately 20 patients, and in the ENDEAVOUR Phase III study, a randomized double-blind placebo-controlled study of approximately 200 patients. Revusiran was also being studied in a small open-label study in 12 patients with hATTR amyloidosis with disease progression following orthotopic liver transplantation.

Now in September of 2016, reports of peripheral neuropathy and elevated blood lactate levels in the Phase II OLE study led Alnylam, in the interest of patient safety, to ask the ENDEAVOUR Data Monitoring Committee, or DMC, to conduct an unblinded safety review of ENDEAVOUR. The DMC met on October 4, 2016, and informed the company that while there was no conclusive evidence for a safety signal with regards to peripheral neuropathy or lactic acidosis, there was a mortality imbalance against revusiran and further dosing in the study should stop.

Indeed, we then learned that of the total of 18 deaths in the 2:1 randomized study in the database, on October 4, that 16 had occurred in the revusiran arm, and only 2 in the placebo arm. With 18 deaths overall, a balanced distribution, given the 2:1 randomization, would have been 12:6. The mortality difference that was observed was statistically significant, and we made a decision to stop all further development of revusiran on October 5.

Following secession of dosing, Alnylam modified the ENDEAVOUR protocol to enable continued patient follow-up for a period of least 3 months. We also launched an extensive investigation, the results of which were reviewed and discussed with global regulatory authorities, ENDEAVOUR instigators and independent academic cardiology and neurology experts and will now be discussed with you on the call.

Akshay will take you through these results in just a minute in much greater detail, but we conclude the following -- we can conclude the following from our investigation. First, the majority of deaths were adjudicated as cardiovascular, primarily heart failure, as expected in the study population of heart failure patients. Mortality on the revusiran arm occurred predominantly in older patients with more advanced disease. That is to say, the older, sicker patients, were those that died. A broad range of potential hypothesis were investigated to establish causality. There was no overall baseline imbalance, although there was a greater number of older patients in the revusiran arm. There was no clinical evidence for revusiran-mediated cardiotoxicity, and there was no evidence of a PK- or PD-related effect of revusiran. While our investigation cannot fully exclude a possible drug or drug disease-related cause, there was some evidence for imbalance due to a lower-than-expected mortality rate in the placebo arm at the time of study discontinuation.

Regarding the original peripheral neuropathy findings in the Phase II OLE study, adverse events in this category occurred in 20% of revusiran and 12% of placebo patients. While this is also consistent with the underlying disease, a potential role for revusiran cannot be excluded. So where we go for here -- from here? For starters, we remain committed to the potential for RNAi therapeutics and hATTR cardiomyopathy and believe that the ENDEAVOUR findings will ultimately strengthen our efforts by informing future studies with patisiran and ALN-TTRsc02 in this indication.

We're very (inaudible) about the impact of patisiran from our APOLLO study, including in patients with cardiomyopathy, where we remain encouraged about the potential for a positive overall result. In addition, we have generated many lessons learned that will inform the conduct of future studies we aim to pursue in the hATTR cardiomyopathy setting, including with ALN-TTRsc02.

Now, before turning it over to Akshay, I do want to thank all the patients, families, caregivers and investigators and study site staff who participated in the revusiran studies. In addition, I also want to thank the members of Alnylam's revusiran development and investigation teams for their tireless work on this very important program.

so with that, I'd like to now turn it over to Akshay to review the results of our investigation. Akshay?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Thanks, John, and hello, everyone. The presentation from this point forward will be divided into 3 main sections. First, I'll give a brief description of hATTR amyloidosis, in particular, the cardiomyopathy -- cardiomyopathic from of the disease for which revusiran was being developed, and I'll describe important design and baseline features for the ENDEAVOUR Phase III study. Then I'll get into a series of analysis performed to understand the cause of the observed mortality imbalance. I'll talk about key findings from the study and any conclusions we can draw from these findings. Finally, I'll wrap up with implications for our TTR programs, patisiran and ALN-TTRsc02, and the rest of the platform comprising our ESC-GalNAc-conjugates.

Starting with an overview of hATTR amyloidosis. As you know, this is a disease we've been studying at Alnylam for quite some time now. It's a multisystem orphan disease, caused by TTR amyloid deposits that build up in the nerves, the gut and the heart, which ultimately cause damage

to these tissues. On one side of the phenotypic spectrum, patients present with a polyneuropathy, on the other side, patients present with cardiomyopathy. However, most patients have some form of mixed presentation of the 2 phenotypes, with symptoms characteristic of both types of disease. In fact, as many as 50% of hereditary ATTR amyloidosis patients with cardiomyopathy also have some symptoms of peripheral neuropathy. Peripheral neuropathy has been seen in a wide range of mutations, including V122i and has also being seen in wild-type ATTR. Hereditary ATTR amyloidosis with cardiomyopathy results in heart failure and ultimately, death in most patients. There are no approved therapies, and the [indiscernible] who have very high morbidity and mortality, with a short-medium survival of about 2.5 years.

Turning to Slide 12, the design of the Phase III ENDEAVOUR study is shown here. We had planned to enroll about 200 patients and ultimately enrolled 206. The key inclusion criteria, as shown in the box on the left, and include documented presence of a TTR mutation, amyloid deposits on biopsy, history of heart failure determined by NYHA Class and evidence of cardiac amyloid involvement. Patients were randomized 2:1 revusiran to placebo. Revusiran was dosed at 500 milligrams daily for the first 5 days, and then weekly versus placebo. The endpoint structure is shown on the right, with co-primary endpoints of 6-minute walk distance and TTR knockdown, which would clear out at 18 months. And accordingly, I want to note that median follow-up on the study at the time of dosing cessation was only about 6 months, and as such, the primary endpoint could not be read. Accordingly, there's no opportunity from our ENDEAVOUR results to make any conclusions on efficacy or benefit risk.

Subsequent to the termination of dosing in the revusiran studies, the ENDEAVOUR protocol was modified to collecting important safety data at 3 time points: that is immediately after dosing cessation; at a modified early termination visit and after 30 and 90 days of follow-up post last dose.

Slide 14 highlights the baseline demographics of the ENDEAVOUR study population. The first thing to note is that the overall population, as expected, was older, with a mean age of 68 to 69, and was predominantly male. The study population had a range of mutations, with the most common, as expected, being the V122I mutation. The vast majority of patients have symptomatic or advanced heart failure, being in NYHA class 2 or 3 categories. Emphasizing the multi-system nature of the disease, almost half of the patients had some degree of co-existent polyneuropathy with PND scores of 1 or 2. You also see the baseline results from the 6-minute walk distance and estimated glomerular filtration rate, or eGFR, both of which underscored the degree of morbidity in the study population. Overall, the 2 groups, revusiran versus placebo, generally, balanced with regard to the range of baseline demographic factors, although, there were more patients, aged more than 75 years of age, in the revusiran arm, a point, which we'll come back to, in just a minute.

Looking in more detail at disease severity at baseline, note that heart failure biomarkers, such as BMP and troponin and echo parameters, such as longitudinal strain and cardiac output, all support the fact that patients had significant and advanced heart failure study entry. Again, however, these parameters appear generally balanced in the 2 arms in this randomized study.

And with that background, let me now review the primary data that led to our decision to discontinue revusiran development last autumn. The Kaplan–Meier curve, shown here on Slide 16, illustrate the mortality imbalance in ENDEAVOUR, with follow-up out to November 4, 2016, or 30 days after the last dose. At this time, there were 18 deaths on revusiran, 2 more than in October, when dosing was discontinued, and 2 on placebo. This difference between groups is statistically significant with a p-value of 0.04 against revusiran. As we've previously stated, the majority of the deaths were cardiovascular in nature, primarily heart failure. Given the nature of the disease, this was not unexpected.

With that, now let's focus on the patients in the revusiran arm who died. The baseline characteristics of these 18 patients are shown here, relative to the 122 who were alive at that time. You can see highlights in the blue box that those who died in the revusiran arm were older and sicker, with more underlying cardiac disease relative to those who survived. So for those who died, the median age was 77, and importantly, more than half of those who died, were 75 years of age or older. 2/3 of the patients who died have NYHA class 3 heart (inaudible) 1/4 of patients who were alive. And consistent with cardiac decline, they also had lower renal function and higher NB, BNP and troponin 1 values, all of which indicate that they're the most advanced of populations enrolled in the study.

These deaths in a sick at-risk population are consistent with the natural history of disease. Furthermore, this may internally explain why at the time of dosing discontinuation, each death was considered unrelated to study drug by the blinded treating physician.

Let me now turn to our investigation into the mortality imbalance in ENDEAVOUR. We focused on analyzing data from 2 key time points, the first being approximately 30 days after termination of dosing to evaluate if the potential toxicity directly relates to the drug, and the second, examining

data through the end of follow-up, which was conducted in late March, allowing evaluation of potential carryover effects. Throughout our investigation, we have sought input and discussed or asked expectations about data with experts in the cardiovascular community, neuropathy and neurology community and hATTR amyloidosis experts. We've also had multiple interactions with the FDA and other regulators, who have given us valuable feedback on -- in our investigating plans as well as resulting data.

As part of that investigation into the cause of the mortality imbalance, we explored 4 underlying hypotheses: one, whether there was imbalance -- there was a baseline imbalance in the randomization that led to the outcome; two, whether there was underlying clinical evidence of cardiotoxicity from revusiran; three, whether there was an issue with regard to the pharmacokinetics of revusiran or TTR knowdown that caused the mortality imbalance; and lastly, whether the mortality imbalance may have resulted from a lower-than-expected mortality rate in the placebo group at the timing of discontinuation.

Let's turn now to these hypotheses one at a time. With regard to hypothesis 1, and as shown earlier, the 2 groups were generally balanced at baseline. However, there was an imbalance in the number of patients aged of 75 or older in the revusiran arm. And, as noted earlier, the majority of patients who died were 75 years of age or older. Nevertheless, results from the multi-variant analysis suggested that the difference in age does not fully explain the mortality imbalance. Whilst the greater number of patients age more than 75 was probably a disadvantage for the revusiran arm, we can't pin that down as a definitive explanation for the imbalance.

Moving on to hypothesis 2, cardiotoxicity. Our key findings are summarized here. There was no clinical evidence of direct revusiran-related cardiotoxicity. If the drug was cardiotoxic, then a worsening over time would be anticipated in the revusiran arm versus placebo for heart failure biomarkers, anchor parameters and CV hospitalizations. We looked at all of these parameters, however, and they were similar in both groups in progression over time. Lastly, we also looked for signs of drug toxicity by analyzing lactate levels in mitochondrial utlrastructure [ph] on tissue biopsy. Lactate levels were comparable between the groups, and they were no signs of mitochondrial toxicity which, if present, might have led to cardiotoxicity.

So with that, let's now go into detail with the data.

As shown on Slide 24, we analyzed several important echo parameters and cardiac biomarkers. This is a match pair analysis of patients in placebo and revusiran arms, where we've taken patients at baseline and looked at that month 3 and 6 values.

As you can quickly see, there really no substantiative differences over time between groups, and the change in parameters, whether it's ejection fraction, longitudinal strain, BNP or troponin 1 -- troponin I, all of which are important (inaudible) in heart failure and are similar over time.

For example, if revusiran was cardiotoxic, you would have expected to see a greater change in biomarkers such as for BNP or troponin over time as compared with, obviously, in the placebo arm. This lack of a difference between the treatment arms with these cardiographic measures and biomarkers suggest that there was no direct revusiran-related cardiotoxicity.

The lack of clinical evidence indicative cardiotoxicity is further corroborated by the hospitalization data shown on these next 2 slides. We showed time to first CV or heart failure hospitalizations in the 2-study groups at 30 days post dosing and the last follow-up visit. These plots have been of great interest to our cardiology experts who have expected -- who had expected to see a significant separation between revusiran and placebo arms, if revusiran was cardiotoxic. First, on the table above, you can see that the number of patients with at least 1 CV or heart failure hospitalization was similar between the 2 groups. The bottom of this slide, you can see the KM curves or time to first CV or heart failure hospitalization for the 2 groups. In these clause, there is no significant separation between placebo and active arms. Regarding times first heart failure hospitalization, that may appear to be a separation of 6 to 9 months, the defect here has to reflect a slowdown in the placebo event rate rather than any fundamental change in the revusiran arm. Indeed when we look at these Kaplan–Meier curves during the study, you can see more clearly that they are in fact, no differences between the revusiran and placebo curves. The lack of difference in CV and heart failure hospitalizations is contrary to what is expected when there's a mortality imbalance and heart failure is the predominant cause of death. In fact, based on prior heart failure trials, as discussed with our cardiac expert panel, a separation in mortality could -- mortality curves would amplify and generally associated with needing bigger separation in cam curves for time to first CV and heart failure hospitalizations. But the similar rates in hospitalization in revusiran and placebo

subjects, points against a cardiotoxic effect of the drug and further raises the possibility that the mortality imbalance, there would have been a chance finding in what ultimately was a small heart failure study. We'll discuss this lateral possibility further in just a minute.

Turning to Slide 27. We also looked at whether there was evidence of mitochondrial toxicity leading to lactate elevations. The panel shows that comparing groups, we did not see any difference in lactate elevations between drug and placebo arms that might suggest potential revusiran-related lactic acidosis. Whilst not shown here, there was also no evidence of a difference in the anon gap between revusiran and placebo arms. We then looked at biopsies from skin, nerve and muscle tissues from 14 patients by light microscopy and electron microscopy and still no evidence of drug-related mitochondrial toxicity. In fact, the findings are generally in line with both amyloid neuropathy and amyloid myopathy.

Let's then move on to hypothesis 3, examining PK or PD-related toxicity. To summarize the findings, revusiran plasma concentrations and TTR knockdown were similar in patients who died versus those that were alive to suggest that either of these factors -- that suggest that neither of these factors contributed to the mortality imbalance.

Furthermore, we did exploratory imaging, looking at technician scanning and cardiac MRI, to see whether reabsorption or redistribution of amyloid from the heart subsequent to TTR knockdown there contributed to mortality. But once again, our analysis indicated that this was not a close to factor.

Let's now look at the data in more detail. The plot on Slide 31, this shows TTR knockdown in those who were alive in red and those who died in blue. You can see that the mean knockdown was 89% to 92% in the 2 groups, with individual maximum knockdown of 99%. It's readily apparent here that there was, therefore, no difference in TTR knockdown in those who died versus those who survived.

Turning to cardiac TTR imaging results on Slide 32. Here you can see data from technician scanning on the left and cardiac MRI analysis on the right. Whilst these 2 methods were exploratory, it nevertheless, failed to show any significant differences between revusiran and placebo groups in terms of an increase or decrease in cardiac amyloid load. In fact, the 2 groups have randomly distributed in both panels, and so the base do not suggest that the PD effects of the drug contributed to mortality. At the same time, we wouldn't have expected to see significant difference in the cardiac amyloid burden with just 6 months of dosing. So this is also not a relevant measure for potential clinical activity at this time point. Regardless, there was no evidence here to suggest reabsorption or redistribution of cardiac TTR at this early time point as a contributor to the mortality imbalance.

In the absence of any evidence implicating significant baseline imbalances, cardiotoxicity, or PK/PD toxicity has contributed to the mortality imbalance. The last hypothesis, we explored, was that the imbalance may simply reflect a lower-than-expected mortality in the placebo group at the time of study discontinuation. The results of our examination of this hypothesis are as follows: even though the mortality rate in the placebo arm does appear to be lower than expected based on comparison to natural history and subgroup analysis by age. In addition, and as noted earlier, the similarity of cardiovascular and heart failure hospitalization between treatment arms is inconsistent with the drug-related mortality imbalance. Finally, as a small study with a small placebo group, we need to acknowledge that there is an increased risk of a chance imbalance.

Let's start by looking at natural history. Slide 35 shows the risk-stratified mortality in the ENDEAVOUR study compared to natural history. Let me at the outset emphasize that this type of comparison between studies always has many caveats and one cannot make definitive conclusion. However, we're comparing ENDEAVOUR data to the best published data available. So we'd caution, and let's look at the data. The Mayo Clinic published a risk-stratified mortality analysis in Journal of Clinical Cardiology in 2016, where a population of patients with wild-type TTR amyloidosis were risk-stratified based on baseline biomarker levels, that is whether they had elevated troponin, anti-proBNP or both. These are standard risk stratification parameters and being useful in delineating high-risk groups in other heart failure settings, including AL cardiac amyloidosis. In the left-hand panel, we can see the overall mortality in the Mayo study, based on the absence of any risk factor or the presence of one or both risk factors. You can readily see that patients with elevated levels of both risk factors, designated 2 above, have a markedly worse prognosis compared with patients with only one or no risk factors.

Now to the right of the Mayo data, we placed the data with the same risk stratifications for revusiran treated patients in the middle and placebo-treated patients at the far right. While we always have to be careful about making indirect comparisons from one trial set to another, I think you can see in general that the Kaplan–Meier mortality curves on a risk-stratified basis in the revusiran arm are somewhat similar to what was expected based

on the Mayo population based (inaudible) neurologic study. In contrast, the placebo arm with small numbers, looks to have a somewhat lower-than-expected rate of mortality. Specifically, if one looks at the 2 above group in the placebo arm with a net of 15 in blue, there was surprisingly no death in this highest risk group. This suggests that the survival in the placebo arm patients may have been better-than-expected at the time of discontinuation and, as a result, contributed to the appearance of a mortality imbalance between the 2 study arms.

What happens when we examine the mortality at early versus late time points? Here on slide 36, one can see K end curves for mortality, 30 days post last dose on the left, and at the end of the study, on the right. The left-hand panel shows that at the time the study was discontinued, there was a mortality imbalance for the revusiran curve declining, with the placebo curve seemingly relatively flat. After further follow-up, which we see on the right, the revusiran mortality curve maintains an essentially constant decline, but in fact, the placebo curve has now started declining at an accelerated pace and narrows the gap. Indeed, at the end of study timepoint, there were 23 deaths in the revusiran arm and 7 deaths in the placebo arm, which is closer to a balanced distribution. In other words, they were a number of deaths that occurred in the placebo arm in extended follow-up, and ultimately, the separation between the 2 arms diminishes and loses statistical significance.

Finally, we examine all-cause mortality and CV hospitalization as stratified by age, specifically patients with less than 75 years of baseline and those who were above 75.

Looking at the left-hand set of panels, on Slide 37, we see mortality and CV hospitalizations in those under 75 years of age. One can see that they track closely together in both placebo and revusiran-treated patients.

On the right, we see mortality and CV hospitalization for those over 75. As expected, the rate of hospitalization is greater in the older subgroup than in those under 75 and is similar in the placebo and revusiran-treated patients. But paradoxically, in the mortality analysis in patients 75 or older, shown on the top right, of the revusiran group declines consistent with the rate of hospitalizations, we see no death in the placebo group. So again, these analyses suggest that the lower-than-expected rate of mortality in the older subgroup placebo-treated patients may have contributed to the mortality imbalance in ENDEAVOUR.

So turning to Slide 38, we can sum up the results of our investigations as follows. First, based on characteristics, we're generally well-balanced between study groups, although there were more patients 75 years of age or older in the revusiran arm. There was no clinical evidence of revusiran-related cardiotoxicity and no evidence of a PK or PD-related toxicity from drug-related TTR knockdown or mobilization of cardiac amyloid.

Finally, there was some evidence of lower-than-expected mortality in the placebo-treated patients at the time of study discontinuation. Of course, we always need to caveat these statements by noting that we can never fully dismiss the potential drug-related effect since it's impossible to prove the negative.

So what are the implications of these revusiran results for future studies in hATTR cardiomyopathy? First, we remain very committed to patients with this disease and aim to develop RNAi therapeutics for the treatment of patients with hATTR cardiomyopathy in the future. In this regard, data from the ENDEAVOUR study will inform a number of aspects of optimal study design for other TTR programs such as ALN-TTRsc02. Specifically, in their results of inclusion/exclusion criteria, sample size, randomization and the study duration.

With our patisiran program, our APOLLO Phase III trial will provide additional insights as approximately 50% of patients came on to the study with cardiomyopathy. Here, we were reassured by the experience of our Phase II OLE study where over 1/3 of patients had cardiac involvement, and we've seen encouraging evidence for tolerability and stability in cardiac measures. We're also reassured that of the 27 enrolled in our original Phase II OLE study with patisiran, 25 remained on study with approximately 3 to 3.5 years of continued dosing. In addition, the APOLLO DMC has met on multiple occasions since October 2016 to review unblinded Phase II results and have recommended study continuation without modification. Of course, APOLLO remains on track to read out in just a few weeks in mid-to-late September.

For ALN-TTRsc02, the learnings from ENDEAVOUR are important, and we intend to transition the program into Phase III in 2018. ALN-TTRsc02 has encouraging potential to be a small volume subcutaneous self-administered agent, given once quarterly or even potentially semiannually for the full range of hATTR mutation and amyloidosis manifestations, including neuropathy and cardiomyopathy.

In closing, let's now turn to a brief discussion of broader platform implications of the revusiran findings.

As a reminder, Alnylam is leveraging a modular and highly reproducive approach to the development of innovative medicines. This approach has led to the development of 8 clinical stage programs in our pipeline today, including our most advanced programs, patisiran, which is nearing its Phase III readout; and fitusiran, which recently entered Phase III. In addition, we'll also be starting Phase III development later this year in our givosiran program in acute hepatic porphyrias, and our partners at The Medicines Company have guided that they intend to start a Phase III program for inclisiran for the treatment of hypercholesterolemia later this year as well.

If we now analyze the totality of safety across our RNAi platform beyond revusiran, remain very encouraged. Today -- day-to-day is comprised of well over 1,000 individuals with over 3 years of exposure. The main platform related to safety signals comprise injection site reactions or ISRs and a low instance of generally mild asymptomatic and reversible transamination changes. To date, we've not seen the type of safety signals observed in ENDEAVOUR across the rest of our RNAi platform.

We can also take strong encouragement from the results from the results of the ORION-1 Phase II study of inclisiran in patients with atherosclerotic cardiovascular disease. As you know, we and our partners at The Medicines Company, are advancing inclisiran, an investigational RNAi therapeutic for the treatment of hypercholesteremia. Back in March, Medco presented complete data from the ORION-1 Phase II study with inclisiran, which in turn, in addition to the (inaudible) rather, showed a very encouraging safety profile for the drug. Notably, this 500-patient study is the largest randomized placebo-controlled clinical trial for investigational RNAi therapeutic to date, and we've been very encouraged by the safety findings. These included a low incidence of SAEs, which were balanced between the placebo and drug arms with no dose-dependent trend. The overall incidence of treatment emergent adverse events was also similar in patients randomized to placebo and patients randomized to inclisiran. Injection site reactions associated with inclisiran were infrequent, mild to moderate and transient, and there were no drug-related elevations in liver enzymes. This is a very encouraging result in a high-risk cardiovascular population in a placebo-controlled study that is over twice the size of ENDEAVOUR.

More broadly, what about ENDEAVOUR and safety across the platform? The central tenet in drug safety is of course drug exposure. We have to think about the exposure of revusiran relative to the other pipeline programs. So the bar chart on the left of Slide 44 shows you the annual exposure to revusiran where in the first year, patients were being exposed to 28 grams to achieve the needed pharmacologic effects. In sharp contrast, the remainder of our pipeline programs which utilize either LNP or ESC GalNAc-conjugate delivery technology require (inaudible) low annual dose levels in terms of the overall drug exposure relative to revusiran.

Looking at this in a different way, one year of exposure to revusiran is equivalent to 70 years of patisiran, or 140 years of ALN-TTRsc02 to achieve the same level of overall drug exposure.

So from an exposure viewpoint, we're very comfortable that the other pipeline programs after revusiran are associated with significantly lower exposures, plus that even if the revusiran results were related somehow to drug exposure, we would not expect a broader safety implications.

This is best exemplified by our ALN-TTRsc02 program. Just last week at our patisiran RNAi Roundtable, we shared updated Phase I data from 80 subjects in this program. As you can appreciate on this plot on Slide 45, single subcutaneous doses of ALN-TTRsc02 resulted in highly potent and durable knockdown of serum TTR. Even a dose as low as 5 milligrams provided a 50% lowering of serum TTR that lasted about 90 days. And then a dose of 25 or 50 milligrams resulted in approximately 80% level of TTR knockdown comparable to patisiran with a durability that supports a low-volume subcutaneous once-quarterly, possibly semi-annual dose regimen.

In addition to potency and durability of knockdown, the safety results from this study have been very encouraging as well. There were no SAEs, no discontinuation due to AEs or AEs were mild and moderate in severity and there were no clinically significant changes in the batch parameters, ECG or physical exam. As we have guided, we plan to meet with regulators following the APOLLO Phase III readout with patisiran to solidify our plan for late stage clinical development with TTRsc02 where we expect to start Phase III in 2018.

So finally, to summarize, we observed an imbalance in mortality in the revusiran arm relative to the placebo arm in the ENDEAVOUR Phase III trial, which led to our discontinuation of the program. We developed an extensive investigational plan that was reviewed with regulators, investigators and other experts with whom we've discussed all the data highlighted today. The majority of deaths were determined to be cardiovascular in

nature, primarily heart failure, which would be expected with this disease. Our key findings were, first, there was no baseline imbalance with the exception that there were more patients greater than 75 years of age in the revusiran arm. Second, we saw no clinical evidence of revusiran-related cardiotoxicity. Third, no evidence of PK or PD-related cardiotoxicity was identified. And finally, there were some evidence suggesting that the imbalance we observed may have been due to a lower-than-expected mortality event rate in the placebo group at the time of the study discontinuation.

That said, we must acknowledge that the results of the investigation did not fully exclude the possibility of drug effect or drug disease interaction as it is simply impossible to prove the negative.

Looking ahead, we plan to publish these and other results from ENDEAVOUR in peer review meetings and publications. In the meantime, we'll continue to advance patisiran and ALN-TTRsc02 for patients with hATTR amyloidosis, including cardiomyopathy, and we'll continue to advance on many ESC GalNAc-conjugate programs where safety remains encouraging.

In closing, we want to thank all the patients, caregivers, investigators, especially the Phase II OLE investigators and the Phase III investigators and the site staff who all participated in the various revusiran studies, especially the ENDEAVOUR study. The outcome of the ENDEAVOUR study was disappointing for patients, patients' families, investigators, and Alnylam alike. But we remain committed to finding novel, safe and effective therapies for all patients with ATTR amyloidosis and the learnings discussed today will help us make those medicine a reality for patients afflicted with this terrible disease.

And with that, we can now move to the Q&A.

QUESTIONS AND ANSWERS

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Well, thanks, Akshay. And obviously, we did have a number of questions that came in the call. We went through a lot of data. And obviously, usually, when you go through a lot of data, there are questions that emerge. So let's go through some of them. Let's see here. There were a couple of questions around TTR mobilization from the heart as one of the hypothesis. You showed some data on that. But maybe you can expound on those data a little bit more to help educate people why we can rule that out at this time.

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. Thanks, John. That's obviously an important hypothesis that TTR supression could have led to mobilization of TTR from the heart. And that may in turn have had impact on cardiac rhythm or cardiac function that could have led to mortality. Now, as we saw, there was no difference in the extent of TTR knockdown between those who survived and those that died on study, so that tends to argue against TTR knockdown being a factor instrumentally in the mortality imbalance. And then we used 2 exploratory techniques, technician scanning and cardiac MRI, both of which attempt to quantify cardiac load in the heart. And essentially, we don't see any significant changes in cardiac load, revusiran versus placebo. And the changes that we did see and the degrees of increase or decrease that we did see, seemed randomly assorted between placebo and revusiran. And so all of those techniques are exploratory. I think, along with the TTR knockdown data in those alive versus those who died, we can say that it's unlikely that TTR knockdown and mobilizations are factor in the death that occurred here.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Okay. Good. Thank you. Another question is when we talked about the exposure differences between revusiran and the other programs in our pipeline, patisiran, the ESE GalNAc-conjugate, how do we know that we investigated -- fully investigated the higher exposure as a potential cause for revusiran in the ENDEAVOUR study?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Well, we note that -- so it's not on a mass basis, we give -- or when revusiran was active, we would give 500 milligrams daily for the first 5 days and then once weekly. And that is 28 grams per annum, and that is the significant multiple of any of the other pipeline programs that we examine. And so we can draw a direct comparison between revusiran and patisiran, which is patisiran, of course, is active also in the TTR space as we know, and we're giving 0.3 milligram per kilogram, which is about 21 milligrams in a 70-kilo individual. And in any given year, a year of patisiran is about [170th] of the mass of a year of revusiran. And we know that. We've administered patisiran for multiple years. And seemingly so far, with encouraging safety data. And in the phase of (inaudible) for example, there have been 27 patients -- 25 of whom have had over 3 years of therapy now. So I think with that, things bode well for patisiran and the other pipeline programs, and we look forward to the TTR data from patisiran in September.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes. And I would just add that obviously, the investigation of revusiran in the study, the absence of any evidence -- clinical evidence of cardiotoxicity as well as drug [mediate] effect is in fact what we did, and we didn't see any evidence for those type of features in the study.

Okay. Next question is were the older patients concentrated in a smaller number of sites? Do we know that answer? I don't...

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

I don't know that. John, do you know if they were randomly distributed, or do they come from...

John Vest

No, I don't think we've looked at the data in that way. We should look at that. I think it'd be worthwhile looking at that.

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Okay, I think (inaudible), there was that imbalance in those over 75.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes. that our another quick question is are muscle biopsies with muscle biopsies cardiac tissue.

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. No, the muscle biopsies were peripheral, skeletal muscle, and obviously, doing a cardiac biopsy is a significant procedure and has a 1% mortality rate in and of itself. And I think, in this study, it would not have been advisable. But doing skeletal muscle biopsies can be very informative when it comes to cases like this where you invest getting potential drug toxicity, and I think we're happy to report that we didn't see any evidence of mitochondrial changes on light microscopy or EM.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Okay. So a more technical question. I'm not sure we have the answer to this. But given the sample size, what is the probability that random chance could lead to a better survival in the placebo arm? Was this calculated?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. We would need to go back and look at that.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes, okay. So that -- a very good question, but I don't think that specific question was addressed. Another question here on the note around peripheral neuropathy. Question is were those rates statistically significant between the placebo arm and the revusiran arm in the study?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes, we haven't formally tested that, but one of the things that I do want to highlight is that the primary focus of the study was the cardiomyopathy. and the site -- the sites involved investigates with cardiologists. And so no formal neurological assessments were done here. And we note that at baseline, you know, about half the patients have significant PND scores. So when these peripheral neuropathy age were reported, it could -- we have to be cautious how we interpret the data because there was no formal neurological assessment. And so I think we want to be careful how much we attribute to those data but the data on what we report today.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Okay. A question on TTRsc02 and the development plan. Question is, will we be taking it into hATTR cardiomyopathy? And if so, how will we mitigate the risk of a mortality imbalance and are thinking about the design of say, like that.

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. I think, obviously, we're grateful for the participation of the various investigators and patients in our various revusiran studies, especially the ENDEAVOUR study, of course, in the Phase II OLE. Those studies have been highly informative, and I think what they've hold us is firstly, we can accrue studies in the hATTR amyloidosis space in patients with cardiomyopathy. I think we can have the ambition to actually do larger studies, and of course, larger studies give more definitive statistics and reduce the chance of the types of recurrences we are discussing today. Secondly, I think the whole issue of what's the right threshold in terms of how sick the patient can be before they're allowed into studies with experimental agencies is important. And in the case of cardiomyopathy, I think that the case we made that perhaps these studies in future should be focused on New York Heart Association Class 1 and Class 2 patients. I think the randomization scheme can revisited. And of course, having 1:1 randomization would tend to guard against these kinds of effects along with an increased sample size. And we've also learned a lot about biomarkers and the predictive power of biomarkers in terms of how sick patients are at baseline and what the likely outcomes will be. And that can also help to stratify these patients between. So these are, of course, very important learnings. And again, I emphasize how grateful we are to patients who investigated and helped us with these learnings. And we will cycle the means to our future studies with ALN-TTRsc02, which will go into the cardiomyopathy space and the neuropathy space.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

And I think, obviously, one of the benefits of potentially excluding patients with more advanced heart failure using biomarkers and Class 3 association designation might also be that we're going to get patients earlier in their disease course where they can benefit -- stand to benefit better by -- with a drug like this. And I think one of the anxieties we always had about the study was will we be capturing patients too late in their disease course to make a difference? And clearly, we can bias it for the earlier stage by excluding those very high morbid patients.

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

And indeed, as one talks to investigators and folks dealing with this disease, it's clear that they're beginning to recognize patients at earlier and earlier stages of disease. But I think evidently feasible.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes, good. Okay. A number of questions that have just come in. So given what we've seen from the follow-up data, how will we think about 6-minute walk distance as a primary efficacy endpoint in the future Phase III trials? Do we think differently about that now? And I think the question really is around the fact that there really was a significant number of deaths in CV hospitalizations. Is that -- do we have a different view on those type of endpoints compared to a 6-minute walk distance endpoint.

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. I think although the primary endpoint -- the co-primary endpoints in the ENDEAVOUR study of 6-minute walk and TTR knockdown, the CV hospitalization will (inaudible) always going to be important in the overall analysis of the study. (inaudible) secondary. So there's no question of that. But I think, having this data set in hand now, we can clearly run power calculations from a variety of endpoints. And I think we can acknowledge that obviously, deaths in CV hospitalization are very, very important points. The most important point, that functionally, 6-minute walk distance still continues to be an important endpoint because after all, on a day-to-day basis, that is a large part of qualify of life. So we have the information now. I think we can go and run the power calculations and determine what the best way to move forward (inaudible) to an other products.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

So we covered it in the presentation, but I just want to come back to it. One of the questions here from the audience is, what evidence suggests that there was no imbalance in lactic acidosis between revusiran and placebo? Do you want to go cover that again real quickly?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes, we did look at lactate level upon cessation of the study that lactate levels weren't measured during the study. And the distribution that we saw between active and placebo was similar and we even looked for lactate levels and associations with various outcomes, and we don't see any relationships there between the various outcomes in the study in lactate levels. And I think perhaps most importantly is that if we looked in an unbiased way during the study as the study was running and patients were being dosed. An indirect way to look for evidence of lactic acidosis is to do anion gap analysis. And we -- as we examined those data in trial study, we saw no separation between revusiran versus placebo. And I think that is quite reassuring as well.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Okay. That's very good. Again, a lot more questions here. So question is, I just spent a lot of time looking through the data. Were there things you saw in ENDEAVOUR that gave you confidence that patisiran by also knocking down TTR, could have efficacy in the cardiac subgroup in APOLLO? And any changes to your view that knocking down TTR to slow the progression of disease in the case of the cardiomyopathy overall?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. I mean, I think, first and foremost, safety. And the safety (inaudible) ENDEAVOUR teach us that whether due to events in the placebo rate, as we've discussed today, or other factors, the fact that for patisiran, in patients that have New York Heart Association 1 or 2 disease that have been dosed for 3 years or longer and the encouraging safety profile that we've seen without adverse cardiac outcomes or mortality outcomes, that's very encouraging. So I think we can test the hypothesis. Secondly, we've seen a stabilization of biomarkers as opposed to a deterioration in

biomarkers. If you look in the ENDEAVOUR study, and we obviously move through the data quickly, but folks can look at the slide, you will see biomarkers go up very quickly. And even the 0 to 6-month timeframe, you see significant deterioration in biomarkers like BNP and troponin, which have important agnostic powers in this disease. And so the fact that we've stabilize them in the Phase II OLE study, I think, is encouraging. Now it's only in the fullness of time with the APOLLO data that we'll be able to speak definitively on that point as well as other cardiac outcomes, such as (inaudible) and other parameters. But I think we should be encouraged by that, and of course, the safety with patisiran.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Okay. Another question here. Based on the baseline characteristics on Slide 14, it looks like there may have been a slight imbalance on polyneuropathy visibility scores, PND scores, with lower scores in the placebo arm. And the question is, does anything in your investigation suggest that this might have been a contributing factor to the mortality imbalance?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

I'm sorry, can you repeat that? Oh, the slight imbalances in PND scores?

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes. The placebo patients had lower PND scores. They had less neuropathy. And did that...

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. I mean, I think, first of all, that speaks to the polyneuropathy disability scores, and so how it directly relates to the cardiomyopathy aspects is hard to comment on. The other thing, I would say, is that rather than this imbalance, what the question in some sense is emphasizing is these are fake complicated patients. They carry many morbidities, all of which can influence an outcome like mortality and can influence the skewing in mortality of the type that we saw. Another factor that I think in future studies we'd be looking very carefully at is to make sure there's baseline stratification for other concomitant cardiac risk factors -- diabetes, hypertension, ischemic heart disease -- and you can imagine a population like this carries a significant amount of that. So I think the question is right that other factors need to be borne in mind as we examine the causes for this mortality imbalance.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes. Question here. How sick is the cardiac subgroup in APOLLO relative to ENDEAVOUR?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. Speaking to our earlier point about perhaps studies should be restricted to Class 1 and 2 New York Heart Association both in the Phase II of label extension study for patisiran and the Phase III study, that's squarely where the patients are. We don't allow admission or inclusion of New York Health Association Class 3. And the baseline biomarker comparison also shows that they're an earlier less-sick population. And so I think that's for the good in terms of testing the hypothesis.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

That's good. Question here. Did the FDA have any input in the halt in the trial?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

No. We confirmed with the Data Monitoring Committee October 4, October 5, and they gave clear evidence, or rather they gave the clear instruction that risk benefit was not further supported. And we ran the Kaplan-Meier analysis. They looked back, confirmed that there was a clear separation on mortality with the p-value that we've noted. And at that point, we felt it was important to respect our patients' safety first and foremost, elected to stop the study and then informed the FDA, and they have been supportive of our decisions.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes, good. I think we have time for one last question, Akshay. It's a question on the competitive landscape. So many (inaudible) seem to think that demonstrating modality of inotersen, which is the Ionis' drug, might be simpler for neuropathic patient versus IV dosing? What is your opinion on this? And are you hearing opposing views from neurologists that you have spoken to?

Akshay K. Vaishnaw - *Alnylam Pharmaceuticals, Inc. - EVP of Research & Development*

Yes. I mean, I think the, first and foremost, amongst neurologists, and I think I was (inaudible). And at least to date, from what we've seen of the safety data reported for inotersen, there are a number of factors that I think describe it and that others want to understand more. I think we've heard about the thrombocytopenia issue, we've heard about renal impact of the drug and there are other aspects, I'm sure, that we will be -- hope to understand. When we look at patisiran so far, we have the Phase II label extension data going out in [1 to 3 years] in that Phase II cohort. They have looked really quite encouraging. And the fact that the Data Monitoring Committee for the Phase III study have met recurrently both before and after the ENDEAVOUR event and elected to continue the study (inaudible) is also an encouraging finding. So we're hopeful for the safety of patisiran, and we hope that it can improve upon the profile that it appears to offer. Now beyond that, for the efficacy, I think we have clear efficacy data in hand, at least from a single arm open-label Phase II study, and our TTR knockdown is greater for patisiran versus what appears to be the case for inotersen. And so I think our anticipation would be that we hope to win on that as well. And so by both parameters, the investigators were saying that they're going to be important rather than (inaudible) administration, I think we're going to have a competitive and hopefully best-in-class agent.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Yes. Good. Well, we look forward to data from patisiran later in September. Okay. With that let me turn it over to Josh. Josh.

Joshua Brodsky

All right. Thanks, John and thanks, Akshay. This concludes our RNAi Roundtable for today. The replay and slides will be posted on the Alnylam website later today at alnylam.com/capella with the transcript to follow shortly thereafter. We look forward to your participation on Wednesday, August 23, at 3:30 p.m. Eastern Time as we discuss the latest in platform advances with RNAi therapeutics and in the weeks that follow to discuss additional programs from Alnylam's pipeline of investigational RNAi therapeutics. For more details, please visit www.alnylam.com/capella. Thanks, everybody. Have a great day.

John M. Maraganore - *Alnylam Pharmaceuticals, Inc. - CEO & Executive Director*

Thanks, everybody. Bye bye.

Operator

Ladies and gentlemen, thank you for participating in today's conference. This does conclude the program and you may all disconnect. Everyone, have a wonderful day.