Clinical Trial FAQs

If you were a participant in the trial, you will receive a letter from your enrollment site about a week after the results are announced. It will include information about what medication you were taking during the trial and other information that may be helpful in making decisions about your care.

Here is a comprehensive list of questions about the trial that we anticipate you might have, along with the answers. Please feel free to print this document and bring it to your/your child's doctor when you discuss your/your child's treatment. If you have additional questions, please contact our help center at support@marfan.org.

TRIAL BASICS

What did the trial study?
The trial studied two drugs, atenolol and losartan, at specific doses, to see if they slow aortic growth in people with Marfan syndrome. It also looked for, and compared, any side effects that occurred when a person took either drug.

What is atenolol?
Atenolol is a medication often used to treat high blood pressure. It is in a class of drugs called beta blockers. It has been used by most physicians at the FDA recommended dose for hypertension to treat people with Marfan syndrome because lowering blood pressure may slow down how fast the aorta grows.

What is losartan?
Losartan is another medication used to treat high blood pressure. It is in a class of drugs called angiotensin receptor blockers (ARBs). Based on research done in Marfan mice, it is believed that losartan may help manage Marfan syndrome not only by lowering blood pressure, but also in a different way.

Who was in the trial?
The trial included individuals with Marfan syndrome who were between the ages of 6 months and 25 years, had not had aortic surgery, were not pregnant, and had aortic enlargement that was beyond what is considered normal for their body size (Z-score of 3 or above).

What did the trial results show?
The results showed that use of losartan, at up to the FDA recommended dose, was associated with a significant reduction in aortic root Z-score (a measure of deviation from normal) over time. Atenolol, at a dose well above the FDA recommended dose that is not normally prescribed to patients, was associated with a comparable reduction in aortic root Z-score. Prior studies have shown a progressive increase in aortic root Z-score in children and young adults with Marfan syndrome who received no treatment or who received more typical (lower) doses of atenolol. This is a new finding for losartan and confirms that adequate dosing of atenolol (titrated to hemodynamic effect) can have a significant impact on the aorta. Both of these results are providing important information to our community. In addition, response to therapy was greater in younger age groups, with the greatest benefit in the youngest children. This could change the management of younger patients as some doctors and parents have been hesitant to start medication in young children with Marfan syndrome.

Are these trial results similar to the research studies conducted in mice?
Scientists study new treatment options in animal models first. Clinical trials are necessary to test if humans will respond similarly or differently. It is very hard to directly translate mouse studies to people. For example, the doses of atenolol and losartan in the mouse model studies are hard to compare to those in the humans. Mice metabolize drugs differently than humans do. In mouse studies, the doses of losartan and atenolol, standardized to body weight, were 40-60 times higher than the doses employed in this trial. In the mouse model study, losartan was shown to prevent abnormal aortic enlargement while atenolol led to a significant but relative decrease in abnormal aortic growth. The comparable effects of these drugs in this trial might relate to the differences in dosing, although this needs to be addressed in future studies.

Do the trial results indicate that losartan is not effective in reducing aortic enlargement?
The trial showed that both losartan, at up to the FDA recommended dose for hypertension, and atenolol, at a dose well above the FDA recommended dose, associate with a reduction in aortic root Z-score in patients with Marfan syndrome over time, suggesting that body growth is outpacing aortic growth. This suggests that people with Marfan syndrome now have two good choices, but that additional attention needs to be paid to drug dosing.

MEDICATION DOSE QUESTIONS

Are there any specific guidelines on medications and dosages recommended for Marfan patients now that the trial is over?
At this point in time, there are no new medication guidelines. This trial's results provide us with some important information, that both atenolol and losartan are options for preventing aortic growth in Marfan syndrome at specific dosages. However, we need to wait for the results of other studies to determine more specific guidelines. At this time, we would recommend that you speak with your physician to determine the best treatment plan for your specific situation.

What was the atenolol dose used in the trial?
Atenolol was started at an initial dose of 0.5 mg/kg/day and increased to a maximum dose of 4 mg/kg/day, not to exceed 250 mg. Each patient's heart rate was monitored and, when there was a 20% decrease in heart rate during a 24 hour period, that indicated that the appropriate dose was reached. This is referred to as "titration to a hemodynamic effect." As a result, the average atenolol dose was above the FDA recommended dose for hypertension, and the maximal dose in the trial was up to twice the FDA's recommended dose.

Was the atenolol dose that was tested higher than what is commonly prescribed for patients with Marfan syndrome?
Yes, the amount of atenolol commonly prescribed by physicians for Marfan patients ranges from 1-2 mg/kg/day, up to 100 mg/day, which is the FDA recommended dose. The dose of atenolol used in the trial was as much as 4 mg/kg/day, not to exceed 250 mg/day. Each patient was given the maximally tolerated atenolol dose within these guidelines in attempt to maintain a 20% decrease in heart rate for a 24 hour period.

Why wasn't the common dose of atenolol used?
In clinical practice, most pediatric patients receive a dose of atenolol in the 1-2mg/kg/day range, with adults commonly receiving up to 100mg/day. A common titration method is to try to keep the heart rate less than 100 with submaximal exercise, such as running up and down a few flights of steps. However, higher dosing is sometimes used in desperate circumstances. Given a prime focus on safety, one incentive to allow for more liberal dosing in this trial was to provide physicians with sufficient flexibility to adapt dosing if a worrisome rate of aortic enlargement was observed in a given individual. In the trial, however, the new titration method that had not previously been employed in Marfan syndrome resulted in atypically high dosing of atenolol in many study participants irrespective of their aortic growth pattern. The trial investigators also wanted to compare losartan's effect to maximally tolerated doses of atenolol. Therefore, this trial represented an opportunity for the trial investigators do to a very comprehensive study on atenolol as well as losartan. It is possible that higher doses of losartan, another ARB, or combination therapy might be better than atenolol alone; however, the study investigators did not feel they could recruit enough patients to test all of these possibilities. Additionally, they did not feel they would be able to test higher doses of losartan than recommended by the FDA, without strong evidence that standard doses would be beneficial in this setting. Research studies have to be carefully and responsibly designed, keeping all issues, including safety, in mind while attempting to answer as many questions as possible. We should be thankful for the careful consideration of all factors by the trial investigators that made this trial successful.

Should I/my child be on a higher dose of atenolol?
This is a discussion you should have with your/your child's cardiologist (heart doctor). Only your doctor knows your specific medical history. The trial showed that a high dose of atenolol can associate with a decrease in Z-score, the body size-indexed aortic dimension over time, in people with Marfan syndrome and was generally well tolerated. You should talk to your doctor about the option of trying higher doses of atenolol and should inform your doctor about any side effects that you experience.

What was the losartan dose used in the trial?
Losartan was started at an initial dose of 0.4 mg/kg/day and was increased based on weight to a maximum dose up to 1.4 mg/kg/day, not to exceed 100 mg, as currently recommended by the FDA for the treatment of hypertension.

Should I/my child be taking losartan or atenolol?
This is a discussion you should have with your/your child's cardiologist (heart doctor). Only your doctor knows your specific medical history. The trial suggested that both losartan and atenolol reduce the body size-indexed aortic dimension in people with Marfan syndrome.

How do I know if the dose of losartan I/my child is on is an effective dose?
This is a discussion you should have with your/your child's cardiologist (heart doctor). The dose that was used in the trial was 1.4mg/kg/day, which is the FDA-recommended dose for hypertension. Further studies need to be done to determine if higher doses of losartan could be useful. Higher doses of losartan or other angiotensin receptor blockers are routinely used for other medical conditions and have been shown to be well tolerated. You should always inform your doctor about any side effects that you experience.

How do I know if the dose of atenolol I/my child is on is an effective dose?
This is a discussion you should have with your/your child's cardiologist (heart doctor). In theory, the novel titration method for atenolol that was used in this trial might be considered in clinical practice. You/your child could slowly be given more of the drug until you reach the optimal dose you can tolerate given your body mass that stabilizes aortic growth. You should always inform your doctor about any side effects that you experience.

Should I take both a beta blocker and losartan?
This specific trial did not study combination therapy (taking atenolol and losartan at the same time). However, a number of smaller studies have reported a significant reduction in aortic growth rate in people taking both losartan and atenolol, compared to those taking more typical doses of atenolol alone. Additional trials taking place outside of the U.S. are studying combination therapy. This is an option that you should discuss with your/your child's doctor.

Has combination therapy been studied?
Three prior studies compared the performance of conventional doses of atenolol alone to that of combined therapy with atenolol and losartan. All three reported a significant benefit of combined therapy. Two of the studies were quite small (17 and 28 participants) and focused on young children with extremely severe Marfan syndrome. These were not randomized trials; rather the investigators compared each child's performance on combination therapy to that previously observed on atenolol alone. The third trial was a relatively large (233 adults with Marfan syndrome), randomized and well-controlled study that showed a significant reduction in aortic root growth rate upon the addition of losartan to prior medical therapy (largely atenolol). These investigators also showed a reduction in the growth rate of the more distal ascending aorta in the losartan group among individuals who had already undergone aortic root surgery. Additional trials that include combination therapy are being performed in other countries, but we do not have the results yet.

How do I decide whether or not I/my child should be on a beta blocker or losartan?
It is important to discuss the choice of medications with your/your child's cardiologist (heart doctor). Only he or she knows your specific medical history, which can help to determine which drug may be better for you/your child. Variables such as whether or not you have asthma or plan to become pregnant in the near future can help determine which drug may make more sense for you.

Since losartan and atenolol are FDA-approved as a blood pressure medication, is there any harm in going on either drug?
As with any medication, it's important to talk to your doctor about your specific medical history and health status. Other factors may also be important. For example, losartan is not a good choice if you are pregnant or plan to become pregnant in the near future, as its use during pregnancy can be associated with birth defects. Caution is warranted with atenolol if there is a history of asthma or depression. Sometimes an individual has other medical issues, besides Marfan syndrome, that may impact which type of medication is right for them.

Were any significant side effects observed that would impact my decision to take losartan versus atenolol?
The trial results showed few side effects for either drug. The side effects that were experienced were manageable for patients taking either drug.

People who have taken losartan outside of the trial have told me that they found losartan to be more beneficial than the beta blocker they were on. Does losartan help some people more than a beta blocker?

There are some people who believe that losartan has been more effective for them. It's important to recognize that individual situations differ. You need to have all the facts in hand to make an informed decision. For example, what dose of losartan (or other angiotensin receptor blocker) are they on? This is an important question since some physicians are using a higher dose of losartan than was used in this trial or they are prescribing other medications in the same class. What dose of beta blocker were they on? Do they have another medical issue, such as asthma, that prevented them from taking a beta blocker? How old are they? Have they had aortic surgery? When they say "losartan has been more beneficial," what do they specifically mean? Did it decrease aortic growth rate to a greater extent or are they experiencing some other benefit not yet studied? How well documented were such perceived benefits?

I asked my doctor to put me on losartan and he/she suggested waiting until we know the results of the trial. Now that we have the results, what should I tell my doctor? How should I advocate for myself?
The results of the trial showed a comparable performance of atenolol and losartan at the doses utilized. You should talk to your doctor about your specific medical history and your specific goals in taking either medication. Depending on your specific situation, one drug may make more sense for you than the other.

IMPACT OF DRUGS ON TYPES OF PATIENTS

Does family history or severity of the case have any impact on the effectiveness of losartan or atenolol?
Family history and severity of the case did not seem to impact the effectiveness of either losartan or atenolol in the trial.

Does the age a person starts taking losartan or atenolol have any impact on the effectiveness?
The trial results did show an apparent increase in effectiveness when an individual was given the treatment at a younger age.

My doctor prescribed me/my child losartan outside of the trial. Given the results of the trial, should I be taking losartan?
This is something you should discuss with your/your child's doctor. Given the comparable results of the two medications, it is likely that many physicians will advocate continuation of a treatment that is giving good results. The results of the trial should stimulate discussions regarding drug dosing.

This trial looked at the impact of losartan on the aorta. Has losartan been studied in other body systems/other parts of the body?
Losartan is being studied in other parts of the body/body systems affected by Marfan syndrome. The Marfan Foundation funded an ancillary study (done using the trial population) that is looking at the effect of losartan on the musculoskeletal system. We do not have the results of this study yet, but we will inform the Marfan community of the results as soon as they are available. Given that only a small subset of trial participants were included in this ancillary study, additional studies may be needed to reach strong conclusions.

Can losartan prevent the need for aortic surgery in some people?
Given the young age of people in this trial, and its relatively short duration, it was not possible to address this issue in this study.

I've already had aortic surgery. Would I benefit from taking losartan?
In Marfan syndrome, aortic enlargement is usually confined to the aortic root, but may extend to more distal segments of the ascending aorta (further away from the heart). One study completed in the Netherlands (the study was called COMPARE) included patients who had undergone aortic root surgery. Among the subset of patients who had already received aortic root replacement, the dilation rate of the more distal ascending aorta was significantly lower in patients treated with losartan plus prior medical therapy (largely atenolol), when compared to those people not receiving losartan.

The clinical trial focused on children and young adults. Can we make any assumptions about adults from this trial?
This trial focused on patients aged 6 months to 25 years. The COMPARE study in the Netherlands did show a benefit of adding losartan to prior medical therapy (largely atenolol) in adults with Marfan syndrome. There are other studies being done throughout the world; some of those studies are also looking at the impact of losartan in adults with Marfan syndrome. These studies will better help us to determine the effectiveness of losartan in the adult Marfan population.

Why weren't adults included in this trial?
Each study has limitations regarding the number of patients that they can expect to recruit and the particular expertise of the participating study sites. This study, funded by the Pediatric Heart Network of the National Heart, Lung, and Blood Institute, focused on children and young adults with Marfan syndrome. Other studies are specifically focusing on adults with Marfan syndrome.

PHN TRIAL RESULTS COMPARED TO OTHER STUDIES

What were the differences between this trial and the study that looked at a small population of severely affected children that was previously published in the New England Journal of Medicine?
The previously published study in the New England Journal did not directly compare atenolol and losartan. All participants in that study were treated with losartan in addition to continuation of their prior medication (largely atenolol). The study population was significantly younger overall and only included individuals with very severe and rapidly progressing aortic root enlargement. Comparison was made between the performance of the aorta before and after the addition of losartan for each participant. While, on average, there was about a ten-fold reduction in the aortic root growth rate after the addition of losartan, the study was quite small.

I've heard there are other losartan trials taking place in other countries. What are the results of those trials and how do they compare to the US trial?
Three prior studies compared the performance of conventional doses of atenolol alone to that of combined therapy with atenolol and losartan. All three reported a significant benefit of combined therapy. Two of the studies were quite small (17 and 28 participants) and focused on young children with extremely severe Marfan syndrome. These were not randomized trials; rather the investigators compared each child's performance on combination therapy to that previously observed on atenolol alone. The third trial was a relatively large (233 adults with Marfan syndrome), randomized, and well-controlled study that showed a significant reduction in aortic root growth rate upon the addition of losartan to prior medical therapy (largely atenolol). These investigators also showed a reduction in the growth rate of the more distal ascending aorta (further away from the heart) in the losartan group among individuals who had already undergone aortic root surgery. Additional trials that include combination therapy are being performed in other countries, but we do not have the results yet. A fourth small study showed that use of losartan alone in children who had not received prior medical therapy led to a significant decline in aortic root growth rate. Additional studies with various study designs are underway. The important point is that, while each clinical trial tests a specific hypothesis (e.g., is this dose of this drug as good or better than that dose of that drug), an iterative process of learning, modification, and testing is generally required to appreciate a treatment's full potential. Once all of the studies are completed, The Marfan Foundation is supporting an effort to combine all available data for further analyses (a so-called meta-analysis). This will likely provide additional information.

FUTURE PLANS

Are there plans for other clinical trials for medications for Marfan syndrome?
There will definitely be other clinical trials in the future that will likely include modifications of current study designs (such as higher doses or other medications in the same classes). Other classes of drugs that target different molecular events are already being studied in animal models with very positive results. Based on the experience with this trial, some future trials may not need to be as large or as long.

What next?
We keep learning. Any good research study both answers questions and creates new ones. We now believe that there are two medications that show promise for people with Marfan syndrome, atenolol and losartan. This is good news. It is very important to have more than one option for patients because not everyone can tolerate a specific drug. Meanwhile, research continues. Other studies are being done on losartan. The meta-analysis looking at the data from all the losartan trials will be conducted and we are studying other new drug treatments in animal models. Many drug companies have watched and admired the Marfan community for their enthusiastic participation, the professionalism and commitment of the physicians and researchers, and the key support that The Marfan Foundation has provided. As a result, there have already been many shared ideas regarding additional drugs to test and even inquiries about the logistics of launching the next trial.