Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Tafamidis (PF-06291826)

Protocol Number: B3461045

Dates of Study: 13 June 2016 to 23 November 2023

Title of this Study: Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy

[A Phase 3 Multicenter, Open-Label Study to Evaluate the Safety of Daily Oral Dosing of Tafamidis Meglumine (PF-06291826-83) 20 mg or 80 mg (or Tafamidis [PF-06291826-00] 61 mg) in Subjects Diagnosed With Transthyretin Cardiomyopathy (ATTR-CM)]

Date(s) of this Report: 21 November 2024

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is transthyretin amyloid cardiomyopathy?

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of heart disease that is caused by a certain kind of protein building up in the heart muscle. This protein is called transthyretin, or "TTR". TTR is normally made by your liver and carries things like hormones and Vitamin A (retinol) throughout your body. In a person with ATTR-CM, the TTR breaks apart, misfolds and clumps together in fibers called "amyloid" fibers. These amyloid fibers build up in the heart muscle and cause it to become stiff, eventually resulting in heart failure.

What is Tafamidis (PF-06291826)?

Tafamidis (tuh-fuh-mi-dis) is also known as tafamidis meglumine or by the brand names Vyndaqel® and Vyndamax®. Tafamidis is taken by mouth and works by keeping the TTR protein from breaking apart and forming into amyloid fibers. Researchers think that tafamidis slows down the buildup of amyloid fibers in different organs of the body, including the heart. This may help slow down the rate at which the disease gets worse over time. Tafamidis is approved to be used in many countries for the treatment of ATTR-CM (amyloid fiber build-up in heart muscle) and transthyretin amyloid polyneuropathy (ATTR-PN Stage I, which is amyloid fiber build-up in nerves).

What was the purpose of this study?

This study was a 60-month extension of the B3461028 "ATTR-ACT" study, which evaluated the treatment of participants with ATTR-CM with tafamidis for 30 months. The main purpose of the current study was to learn about the long-term safety of tafamidis for the treatment of ATTR-CM.

This study was later modified to include an additional group (cohort) of participants who had ATTR-CM but had not participated initially in the B3461028 study. The purpose of this additional cohort was to give these participants access to tafamidis for ATTR-CM for up to 60 months before it was locally available by prescription.

Researchers wanted to know:

What effect did long-term treatment with tafamidis have on participants with ATTR-CM?

What medical problems did participants have during the study?

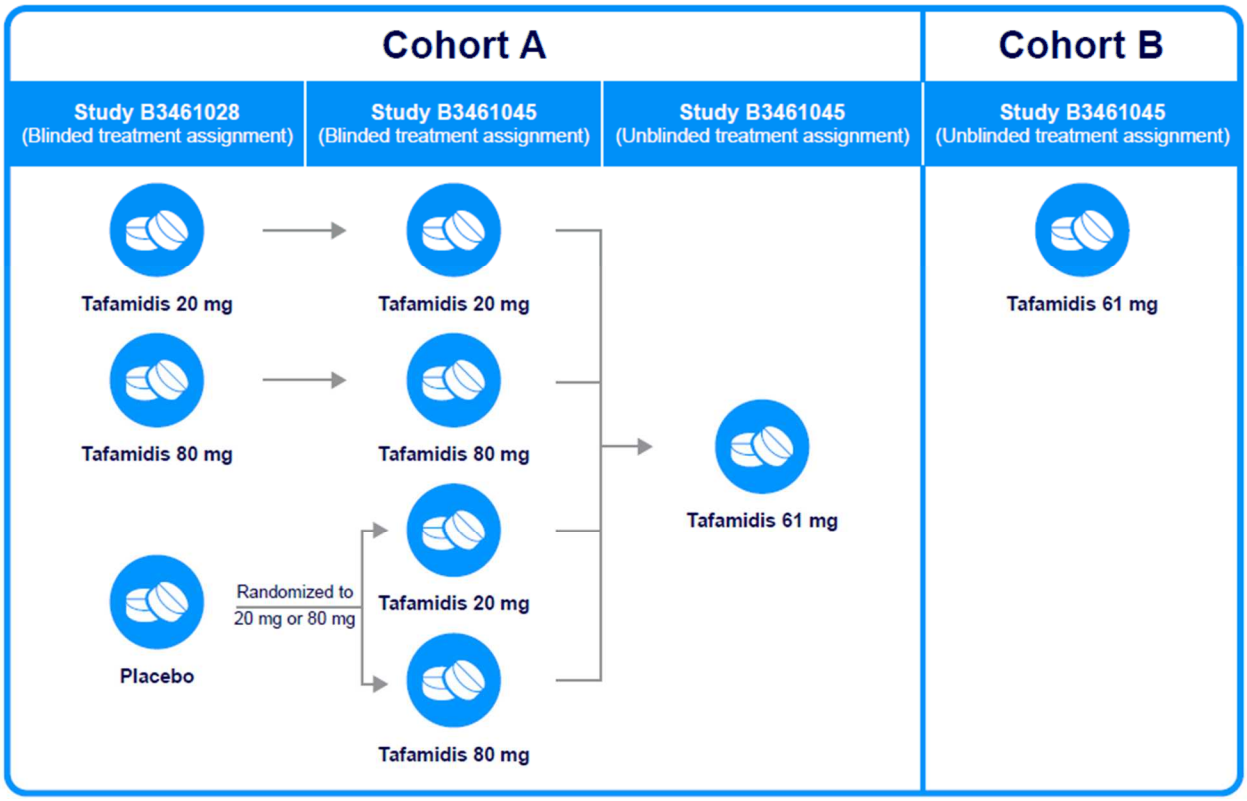
What happened during the study?

How was the study done?

Researchers tested tafamidis on a group of study participants to learn about the safety of taking tafamidis long-term to treat ATTR-CM. Participants in the study received tafamidis once daily in addition to the standard of care treatment for heart failure. This is a medicine to reduce water build-up in the body ("diuretic" medication).

Participants were assigned to treatment as shown in Figure 1. For part of the study, participants and researchers did not know which treatment each participant received. This is called "blinded" treatment. For part of the study, participants and researchers knew which treatment each participant was taking. This means they were "unblinded" and the study became "open label".

Figure 1. Study Treatment

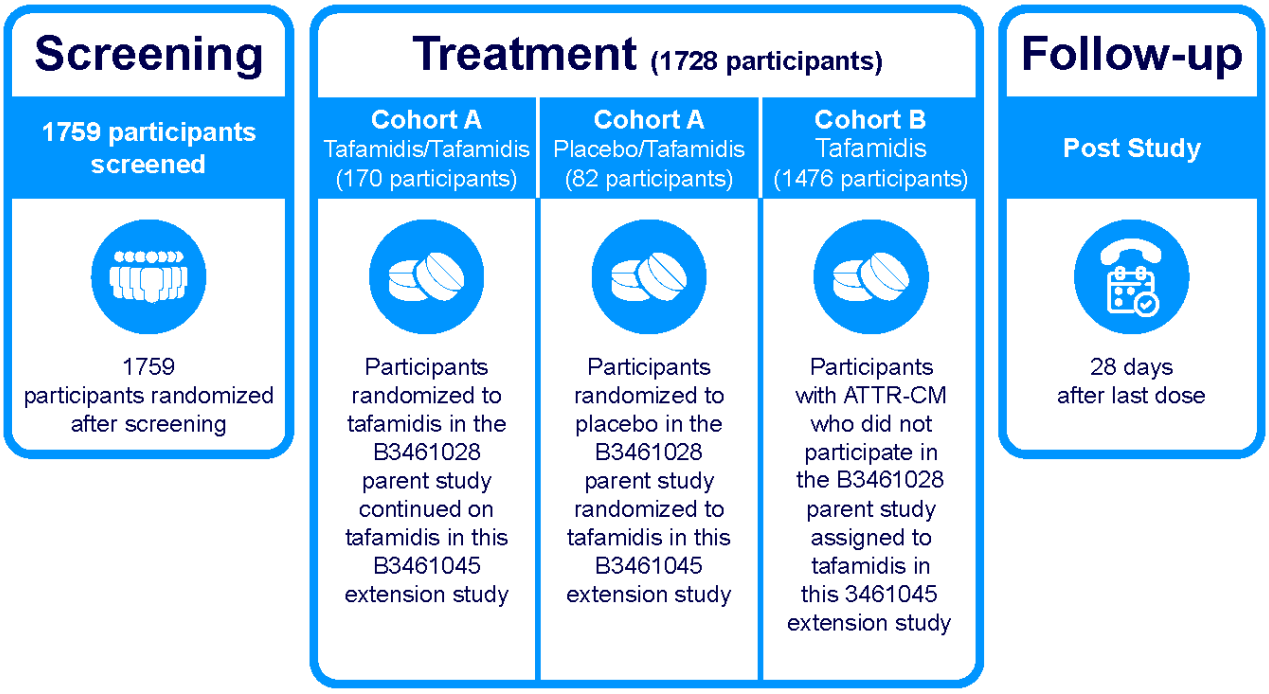


Placebo was given in the B3461028 study but not in the B3461045 study. A placebo does not have any medicine in it, but it looks just like the study medication.
Participants were assigned to tafamidis 80 mg in regions where tafamidis 61 mg was unavailable.

Participants were to be treated for up to 60 months or until the treatment becomes available in their country.

Figure 2 shows what happened during the study.

Figure 2. Study Design



a Of the 1733 participants who were randomized after screening, 1728 participants were treated, and 5 participants were not treated.

Where did this study take place?

The Sponsor ran this study at 57 locations in 17 countries.

When did this study take place?

It began on 13 June 2016 and ended on 23 November 2023.

Who participated in this study?

The study included participants who were diagnosed with ATTR-CM.

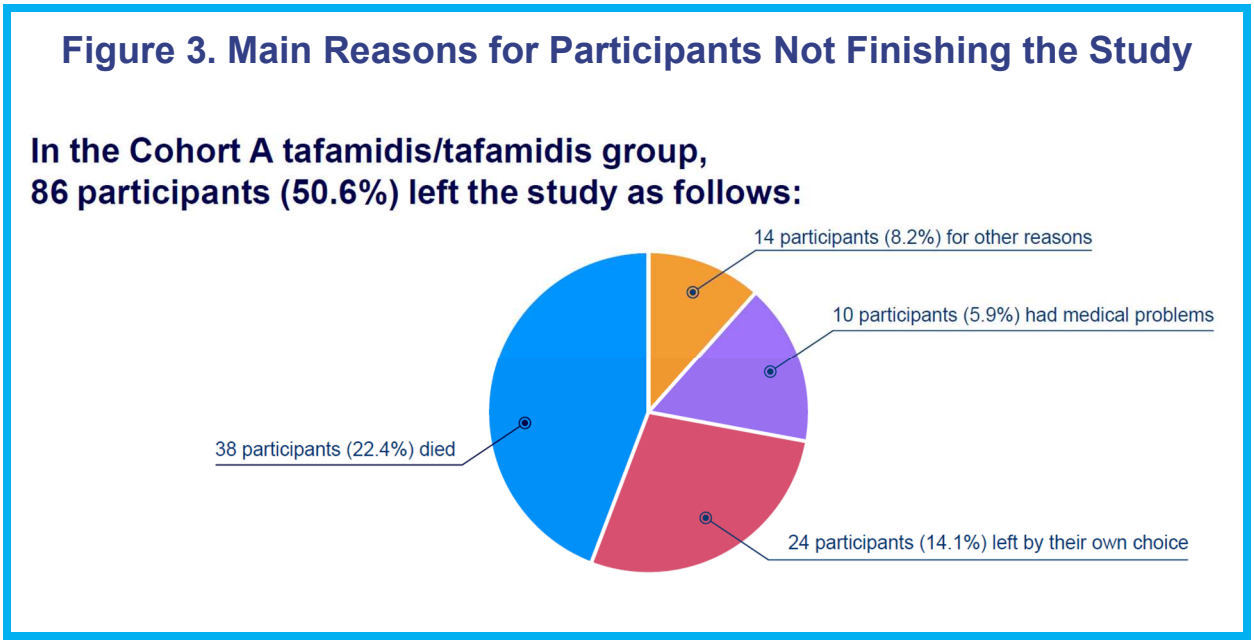
- A total of 1542 men participated including:
  - 157 men in the Cohort A tafamidis/tafamidis group
  - 74 men in the Cohort A placebo/tafamidis group

- 1311 men in the Cohort B tafamidis group

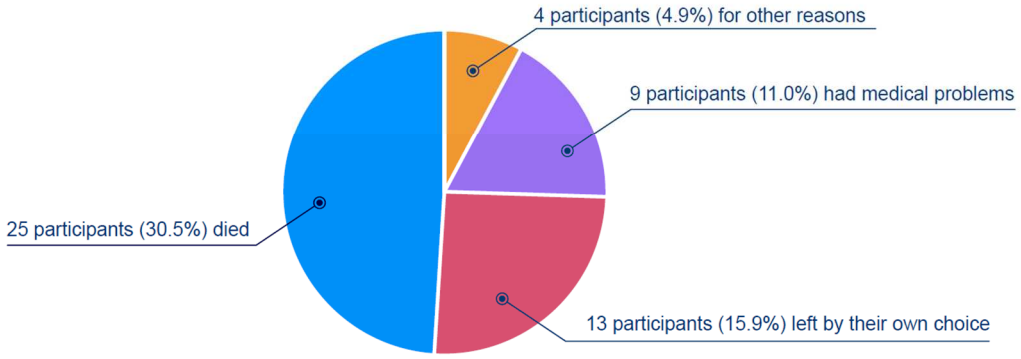
- A total of 186 women participated including:
  - 13 women in the Cohort A tafamidis/tafamidis group
  - 8 women in the Cohort A placebo/tafamidis group
  - 165 women in the Cohort B tafamidis group
- All participants were between the ages of 32 and 96 years
  - The average age was 76.5 years

Of the 1728 participants who started the study treatment, 1103 finished the study treatment. A total of 625 participants did not finish the study. The most common reasons for not finishing the study are shown in Figure 3.

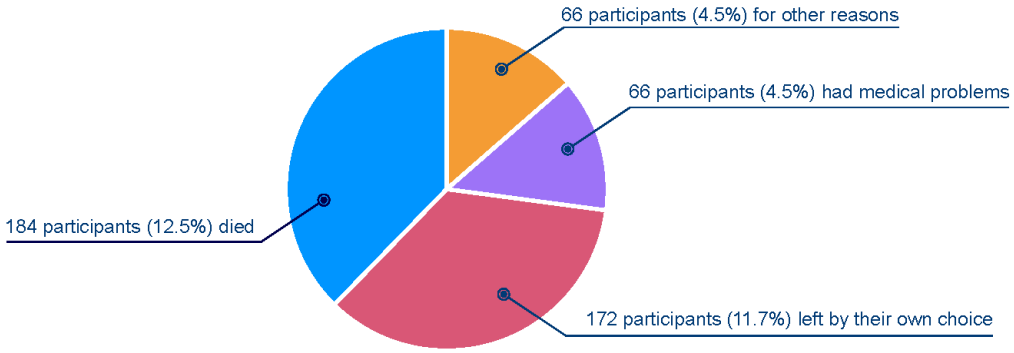
Figure 3. Main Reasons for Participants Not Finishing the Study



In the Cohort A placebo/tafamidis group,
51 participants (62.2%) left the study as follows:



In the Cohort B tafamidis group,
488 participants (33.1%) left the study as follows:



Note: Percentages may not always add up to the percentage of participants who discontinued in each cohort due to rounding.

How long did the study last?

Study participants were in the study for up to 5 years (60 months). The entire study took about 7.5 years (90 months) to complete.

When the study ended in November 2023, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

What effect did long-term treatment with tafamidis have on participants with ATTR-CM?

To answer this question, the researchers looked at how many participants died, or had a heart transplant, or had a device implanted in their body to mechanically help their heart work. Researchers looked at the results for all the participants of the B3461045 study and the earlier B3461028 study combined together.

- Of the 264 participants in the Cohort A tafamidis/tafamidis group, 132 participants (50.0%) died, 10 participants (3.8%) had a heart transplant, and 2 participants (0.8%) had a device implanted in their body to mechanically help their heart work.
- Of the 177 participants in the Cohort A placebo/tafamidis group, 120 participants (67.8%) died, 6 participants (3.4%) had a heart transplant, and no participant had a device implanted in their body to mechanically help their heart work.
- Of the 1476 participants in Cohort B, 336 participants (22.8%) died, 7 participants (0.5%) had a heart transplant, and 2 participants (0.1%) had a device implanted in their body to mechanically help their heart work.

Based on these results, the researchers have decided that the results are not likely the result of chance. Taking tafamidis may help to reduce the risk of death in participants with ATTR-CM.

This does not mean that everyone in this study had these results. Other studies may produce different results, as well. These are just some of the main findings of the study.

Medical problems throughout the study are discussed in the next section of this document.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

A total of 1541 out of 1728 participants (89.2%) had at least 1 medical problem during the study. Medical problems were seen in:

- 168 participants (98.8%) in the Cohort A tafamidis/tafamidis group
- 79 participants (96.3%) in the Cohort A placebo/tafamidis group
- 1294 participants (87.7%) in the Cohort B tafamidis group.

A total of 131 participants left the study because of medical problems including 22 participants (12.9%) in the Cohort A tafamidis/tafamidis group, 12 participants (14.6%) in the Cohort A placebo/tafamidis group, and 97 participants (6.6%) in the Cohort B group.

There were no participants in the Cohort A tafamidis/tafamidis group or the Cohort A placebo/tafamidis group who left the study because of medical problems that the researchers thought were related to the study drug. There were 9 participants (0.6%) in the Cohort B tafamidis group who left the study because of medical problems that the researchers thought were related to the study drug.

The most common medical problems – those reported by more than 10% of participants in any of the treatment groups – are described below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by more than 10% of participants in any of the treatment groups are listed.
- The **2nd** column tells how many of the 170 participants in the Cohort A tafamidis/tafamidis group reported each medical problem. Next to this number is the percentage of the 170 participants who reported the medical problem.
- The **3rd** column tells how many of the 82 participants in the Cohort A placebo/tafamidis group reported each medical problem. Next to this number is the percentage of the 82 participants who reported the medical problem.
- The **4th** column tells how many of the 1476 participants in the Cohort B tafamidis group reported each medical problem. Next to this number is the percentage of the 1476 participants who reported the medical problem.
- Using these instructions, you can see that 41 out of the

170 participants (24.1%) in the Cohort A tafamidis/tafamidis group and 34 out of the 82 participants (41.5%) in Cohort A placebo/tafamidis group reported fall. A total of 146 out of the 1476 participants (9.9%) in the Cohort B tafamidis group reported fall.

Table 1. Commonly reported medical problems by study participants

Medical Problem	Cohort A Tafamidis/ Tafamidis (170 Participants)	Cohort A Placebo/ Tafamidis (82 Participants)	Cohort B Tafamidis (1476 Participants)
Fall	41 out of 170 participants (24.1%)	34 out of 82 participants (41.5%)	146 out of 1476 participants (9.9%)
Fluid on the lungs	23 out of 170 participants (13.5%)	24 out of 82 participants (29.3%)	58 out of 1476 participants (3.9%)
Low blood pressure	14 out of 170 participants (8.2%)	20 out of 82 participants (24.4%)	70 out of 1476 participants (4.7%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Cohort A Tafamidis/ Tafamidis (170 Participants)**	**Cohort A Placebo/ Tafamidis (82 Participants)**	**Cohort B Tafamidis (1476 Participants)**
Shortness of breath	31 out of 170 participants (18.2%)	18 out of 82 participants (22.0%)	110 out of 1476 participants (7.5%)
Cough	29 out of 170 participants (17.1%)	18 out of 82 participants (22.0%)	81 out of 1476 participants (5.5%)
Limb swelling	26 out of 170 participants (15.3%)	18 out of 82 participants (22.0%)	100 out of 1476 participants (6.8%)
Irregular heartbeat	32 out of 170 participants (18.8%)	17 out of 82 participants (20.7%)	150 out of 1476 participants (10.2%)
Low blood potassium	23 out of 170 participants (13.5%)	17 out of 82 participants (20.7%)	61 out of 1476 participants (4.1%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Cohort A Tafamidis/ Tafamidis (170 Participants)**	**Cohort A Placebo/ Tafamidis (82 Participants)**	**Cohort B Tafamidis (1476 Participants)**
Infection of the kidneys, bladder, or urethra	18 out of 170 participants (10.6%)	16 out of 82 participants (19.5%)	75 out of 1476 participants (5.1%)
Feeling tired	19 out of 170 participants (11.2%)	15 out of 82 participants (18.3%)	78 out of 1476 participants (5.3%)
Hard or dry stool	18 out of 170 participants (10.6%)	15 out of 82 participants (18.3%)	117 out of 1476 participants (7.9%)
Sudden (“acute”) kidney injury	15 out of 170 participants (8.8%)	15 out of 82 participants (18.3%)	54 out of 1476 participants (3.7%)
Joint pain	29 out of 170 participants (17.1%)	12 out of 82 participants (14.6%)	78 out of 1476 participants (5.3%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Cohort A Tafamidis/ Tafamidis (170 Participants)**	**Cohort A Placebo/ Tafamidis (82 Participants)**	**Cohort B Tafamidis (1476 Participants)**
Difficulty falling asleep	13 out of 170 participants (7.6%)	13 out of 82 participants (15.9%)	57 out of 1476 participants (3.9%)
Skin wound	12 out of 170 participants (7.1%)	13 out of 82 participants (15.9%)	46 out of 1476 participants (3.1%)
Low blood sodium	11 out of 170 participants (6.5%)	13 out of 82 participants (15.9%)	35 out of 1476 participants (2.4%)
Long-term (“chronic”) kidney disease	10 out of 170 participants (5.9%)	13 out of 82 participants (15.9%)	20 out of 1476 participants (1.4%)
Back pain	18 out of 170 participants (10.6%)	12 out of 82 participants (14.6%)	65 out of 1476 participants (4.4%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Cohort A Tafamidis/ Tafamidis (170 Participants)**	**Cohort A Placebo/ Tafamidis (82 Participants)**	**Cohort B Tafamidis (1476 Participants)**
Low red blood cell count	14 out of 170 participants (8.2%)	12 out of 82 participants (14.6%)	78 out of 1476 participants (5.3%)
Loss of strength or energy	13 out of 170 participants (7.6%)	12 out of 82 participants (14.6%)	54 out of 1476 participants (3.7%)
Infection of the lung	10 out of 170 participants (5.9%)	12 out of 82 participants (14.6%)	38 out of 1476 participants (2.6%)
Dizziness	24 out of 170 participants (14.1%)	11 out of 82 participants (13.4%)	97 out of 1476 participants (6.6%)
Arm or leg pain	24 out of 170 participants (14.1%)	9 out of 82 participants (11.0%)	55 out of 1476 participants (3.7%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Cohort A Tafamidis/ Tafamidis (170 Participants)**	**Cohort A Placebo/ Tafamidis (82 Participants)**	**Cohort B Tafamidis (1476 Participants)**
High level of fluid in body	10 out of 170 participants (5.9%)	11 out of 82 participants (13.4%)	76 out of 1476 participants (5.1%)
Presence of blood in the urine	7 out of 170 participants (4.1%)	11 out of 82 participants (13.4%)	47 out of 1476 participants (3.2%)
Heart failure	22 out of 170 participants (12.9%)	9 out of 82 participants (11.0%)	167 out of 1476 participants (11.3%)
Pain and swelling in joints caused by uric acid crystals (“gout”)	18 out of 170 participants (10.6%)	10 out of 82 participants (12.2%)	113 out of 1476 participants (7.7%)

Table 1. Commonly reported medical problems by study participants			
Medical Problem	**Cohort A Tafamidis/ Tafamidis (170 Participants)**	**Cohort A Placebo/ Tafamidis (82 Participants)**	**Cohort B Tafamidis (1476 Participants)**
Nausea	17 out of 170 participants (10.0%)	10 out of 82 participants (12.2%)	48 out of 1476 participants (3.3%)
Abnormal heart rhythm	10 out of 170 participants (5.9%)	9 out of 82 participants (11.0%)	20 out of 1476 participants (1.4%)
Joint disease (osteoarthritis)	12 out of 170 participants (7.1%)	9 out of 82 participants (11.0%)	20 out of 1476 participants (1.4%)

Did study participants have any serious medical problems?

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.

A total of 591 out of 1728 participants (34.2%) (94 participants in the Cohort A tafamidis/tafamidis group, 57 participants in the Cohort A placebo/tafamidis group, and 440 participants in the Cohort B tafamidis group) had at least 1 serious medical problem during the B3461045 study.

The most common serious medical problem was heart failure.

- 30 out of 170 participants (17.6%) reported heart failure in the Cohort A tafamidis/tafamidis group
- 17 out of 82 participants (20.7%) reported heart failure in the Cohort A placebo/tafamidis group
- 169 out of 1476 participants (11.4%) reported heart failure in the Cohort B tafamidis group.

A total of 11 out of 1728 participants (0.6%) had serious medical problems related to the study medication.

- 1 out of 170 participants (0.6%) in the Cohort A tafamidis/tafamidis group had their heart stop beating
- 1 out of 82 participants (1.2%) in the Cohort A placebo/tafamidis group had hard or dry stool
- 9 out of 1476 participants (0.6%) in the Cohort B tafamidis group had serious medical problems related to treatment, which were all reported for single participants except for feeling tired (reported in 2 participants [0.1%]).

A total of 247 participants (14.3%) died during the B3461045 study period. Researchers do not believe any of the deaths were related to tafamidis.

During the B3461045 study period:

- In the Cohort A tafamidis/tafamidis group, 38 out of 170 participants (22.4%) died during the B3461045 study period. Most deaths (34 participants) were considered due to ATTR-CM.
- In the Cohort A placebo/tafamidis group, 25 out of 82 participants (30.5%) died during the B3461045 study period. Most deaths (32 participants) were considered due to ATTR-CM.
- In the Cohort B tafamidis group, 184 out of 1476 participants (12.5%) died during the B3461045 study period. Most deaths (147 participants) were considered due to ATTR-CM.

After the study period (defined as up to 60 months after entering the study):

- In the Cohort A tafamidis/tafamidis group, 27 out of 170 participants (15.9%) died
- In the Cohort A placebo/tafamidis group, 23 out of 82 participants (28.0%) died
- In the Cohort B tafamidis group, 154 out of 1476 participants (10.4%) died

Overall, there were 451 participants (26.1%) who died from when the study started until after the study period had ended (defined as up to 60 months after entering the study).

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number B3461045

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT02791230**
www.clinicaltrialsregister.eu	Use the study identifier 2016-000868-42

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!