A multicentre, international, phase 3, double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of daily oral dosing of tafamidis meglumine (PF-06291826) 20 mg or 80 mg in comparison to placebo in subjects diagnosed with transthyretin cardiomyopathy (TTR-CM).

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The objective of this study is to determine the efficacy, safety, and tolerability of tafamidis in subjects with transthyretin cardiomyopathy.The primary objective is to assess the efficacy, safety, and tolerability of an oral dose of 20 mg or 80 mg...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON41905

Source
ToetsingOnline

Brief title
B3461028-Tafamidis- TTR-CM

Condition

- Myocardial disorders

Synonym
chronic heart failure, transthyretin amyloid cardiomyopathy (TTR-CM)

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: Tafamidis, Transthyretin cardiomyopathy (TTR-CM)

Outcome measures

Primary outcome

The primary analysis uses a hierarchical combination applying the method of Finkelstein-Schoenfeld (Finkelstein 1999) to all-cause mortality and frequency of cardiovascular-related hospitalizations, which is defined as the number of times a subject is hospitalized (i.e., admitted to a hospital) for cardiovascular-related morbidity.

Secondary outcome

Secondary Endpoints:

1. Change from Baseline to Month 30 on the distance walked during the 6-Minute Walk Test (6MWT),

2. Change from Baseline to Month 30 on the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS).

3. Cardiovascular-related mortality,

4. Frequency of cardiovascular-related hospitalization,

5. All-cause mortality,

6. TTR Stabilization at Month 1.

Study description

Background summary

Transthyretin amyloid disease is a rare and fatal condition characterized by the deposition of amyloid derived from transthyretin (a plasma protein) in various organs and tissues. Deposition of TTR amyloid is associated with two distinct clinical presentations: transthyretin familial amyloid polyneuropathy (TTR FAP) when the peripheral nerves are primarily affected and transthyretin amyloid cardiomyopathy (TTR-CM) when the heart is primarily affected. Both TTR-FAP and TTR CM are associated with genetic variants of transthyretin but TTR CM may also occur in the absence of any genetic mutation and may be due to wild-type TTR amyloid deposition. At this time, with the exception of the approval of tafamidis for TTR-FAP in the European Union (EU) and Japan, there are no approved pharmacotherapies for these conditions.
TTR-CM occurs when TTR amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death.
Pfizer is developing tafamidis, an oral small molecule, for the treatment of transthyretin amyloid diseases. It has been demonstrated to bind selectively to TTR in human blood and slow fibril formation in vitro (Razavi 2003). It binds to the 2 thyroxine binding sites with negative cooperativity, exhibiting dissociation constants of 2 nM [Kd1] and 154 nM [Kd2] (DeVit 2006) and kinetically stabilizing the TTR tetramer when bound (Sekijima 2009).
TTR stabilization has been hypothesized to lead to slowing or halting of disease progression. This hypothesis was confirmed in a double-blind, placebo-controlled, 18-month study in subjects with TTR FAP, in which those subjects receiving tafamidis had better neurologic outcomes compared with those receiving placebo. In order to improve the understanding of the natural history of TTR CM, a longitudinal, observational clinical study of 29 subjects with either the V122I genetic variant (11 subjects) or wild type (18 subjects) associated TTR CM (Transthyretin Amyloid Cardiac Study; TRACS) was undertaken.
A follow-up Phase 2 open label interventional study (Study Fx1B-201) demonstrated TTR stabilization in subjects with V122I and wild-type TTR CM and an acceptable safety profile following 12 months of tafamidis 20 mg given once

daily.
Study B3461031 was designed to evaluate the effect of tafamidis on the corrected QT (QTc) interval in healthy volunteers. The primary objective was to characterize the effect of a supra-therapeutic tafamidis concentration (~20 *g/mL) on the QTc interval relative to placebo in healthy volunteers. A supra-therapeutic, single, 400 mg oral-dose of tafamidis solution in healthy volunteers demonstrated a lack of an effect on QTc interval prolongation. Single doses of moxifloxacin 400 mg established that the study had adequate sensitivity to detect increases in the QTc interval.

Study objective

The objective of this study is to determine the efficacy, safety, and tolerability of tafamidis in subjects with transthyretin cardiomyopathy.
The primary objective is to assess the efficacy, safety, and tolerability of an oral dose of 20 mg or 80 mg tafamidis meglumine soft gel capsules in comparison to placebo and given once daily, in addition to standard of care, for 30 months in subjects diagnosed with either a TTR variant or wild-type TTR-CM. The study is designed to assess the potential for benefit from treatment with tafamidis relative to placebo based on all-cause mortality and frequency of cardiovascular-related hospitalizations (including heart failure, arrhythmia, myocardial infarction, and stroke as well as other cardiovascular-related events).

Study design

This is a Phase 3, multicenter, international, three-arm, parallel design, placebo-controlled, randomized study with a 30-month double-blind treatment phase, to determine efficacy, safety and tolerability of tafamidis on clinical outcomes in subjects with either transthyretin
genetic variants or wild-type transthyretin resulting in amyloid cardiomyopathy (TTR-CM).

Intervention

1 group receives 20 mg tafamidis meglumine, 1 group receives 80 mg tafamidis meglumine and 1 group receives placebo

Study burden and risks

For a list of the associated risks and side effects, please refer to section E9 of this form and the Subject Information Sheet and Informed Consent Form.
It is possible that the condition of participants stabilizes due to participation in this study. However, there is no guarantee that the subject will benefit in any way. Information from this study may help other people in

the future.

Contacts

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Pfizer

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Scientific
Pfizer

East 42nd Street 235
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:;1.Evidence of a personally signed and dated Informed Consent Document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study and evidence of a personally signed and dated Release of Medical Information Form regarding access to medical records as well as vital status/transplant status follow-up by the site with the subject or the subject*s caregivers 30 months after study randomization. In some cases, sites may combine these two forms into one form, as is their standard practice.;2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures,;3. Age greater than or equal to 18 and

less than or equal to 90 years old at the time of randomization,;4. Medical history of Heart Failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that required/requires treatment with a diuretic for improvement,;5. Subject has documented TTR amyloid cardiomyopathy in accordance with institutional site standard of care, which is defined as:;a. Variant TTR amyloid cardiomyopathy defined by all of the following:;i. presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype (e.g., a history of congestive heart failure),;1. TTR genotyping is required at Screening unless documentation (ie original laboratory result, or copy) of a prior determination of a TTR genotype is produced.;2. Subjects with a confirmed diagnose of mutant (variant genotype) TTR-CM with concurrent monoclonal gammopathy of undetermined significance (MGUS) based on serum or urine light chain determinations, should be tested in the same manner as in the case of equivocal immunohistochemistry for subjects with wild type TTE-CM below.;ii. evidence of cardiac involvement by echocardiography with an enddiastolic interventricular septal wall thickness > 12 mm,;iii. presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or alcian blue stain).;b. Wild-type TTR amyloid cardiomyopathy defined by all of the following:
i. absence of a variant TTR genotype,
ii. evidence of cardiac involvement by echocardiography with an enddiastolic interventricular septal wall thickness > 12 mm,
iii. presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or alcin blue stain),
iv. TTR precursor protein identification by mass spectrometry. ;1. In the case where immunohistochemistry (IHC) outcome is equivocal such as staining suggestive of lambda or kappa light chains, additional confirmatory testing is required to confirm the diagnosis of TTR cardiomyopathy. This confirmatory test may be performed using one of the following: (a) mass spectrometry (b) immunohistochemistry with electron microscopy or immunoelectron microscopy or immune-gold microscopy (c) scintigraphy with tracer e.g. 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC- PYP [Pyrophosphate] and also 99mTC-HMDP [hydroxymethylene diphosphonate];6. Biopsy used to determine the presence of amyloid and demonstration of TTR precursor protein must be done during Screening or documented as having been performed previously.;7. Subject must be able to read in native language and complete self-administered questionnaires independently,;8. Subject*s symptoms of HF are optimally managed and clinically stable with no cardiovascular-related hospitalizations within 2 weeks prior to Baseline, as assessed by the Principal Investigator,;9. Male and female subjects of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active,;10. Subject must have a Screening visit NT-proBNP concentration * 600 pg/mL, (the conversion factor from conventional pg/mL to SI units is to divide by 8.45).;11. Subjects must be able to complete > 100 m on the 6-Minute Walk Test at screening.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study:;1. Subjects with echocardiogram assessment at Screening that is not deemed interpretable by the central echocardiogram reader for the measurement of wall thickness,;2. Subjects using non-steroidal anti-inflammatory drugs (NSAIDs) that are not allowable in the protocol within 30 days prior to the Baseline visit. ;3. Subjects with an mBMI below 600,;4. Subjects with a history of drug or alcohol abuse within the past 5 years that in the opinion of the investigator would interfere with compliance with study procedures or follow-up visits,;5. Subjects taking or have previously taken tafamidis,;6. Subjects requiring treatment with calcium channel blockers (e.g. verapamil diltiazem) or digitalis,;7. Subjects with primary (light chain) amyloidosis,;8. Subjects who have prior liver or heart transplantation,or implanted cardiac mechanical assist device.;9. Subject has known or suspected hepatitis B, C, Human Immunodeficiency Virus (HIV) infection positive serology for hepatitis B (HBsAg), hepatitis C (anti-HCV), or HIV,;10. Subjects with renal failure requiring dialysis and/or have an estimated glomerular filtration rate (eGFR) of < 25mL/min/1.73m2;11. Subjects with urinary retention requiring self-catheterization,;12. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.;13. Subjects who have symptoms indicative of New York Heart Association Classification IV at the Screening or Baseline visit,;14. Subjects with liver function test abnormalities (alanine transaminase and/or aspartate transaminase) greater than 2 times the upper limit of normal that are considered to be due to reduced liver function or active liver disease,;15. Subjects with participation in studies involving investigational drug(s) (Phases 1- 4) within 30 days before the current study begins and/or during study participation. For diflunisal, tauroursodeoxycholate and doxycycline this time period will be within 30 days before the Baseline visit and/or any time during study participation,;16. Subjects with other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study,;17. Subjects who are pregnant females; breastfeeding females; male subjects with partners currently pregnant, males and females of childbearing potential who are unwilling or unable to use two (2) highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days, after last dose of investigational product;;18. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular (AV) nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker is indicated but will not be placed,;19. Subjects with heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (e.g. prior myocardial infarction with documented history of cardiac enzymes and ECG changes), or uncorrected valvular disease and not primarily due to transthyretin amyloid cardiomyopathy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2015
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vyndaqel
Generic name:	Tafamidis meglumine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-09-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-03-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002465-35-NL
ClinicalTrials.gov	NCT01994889
CCMO	NL49864.028.14