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) 61mg] in Subjects Diagnosed with Transthyretin Cardiomyopathy (ATTR-CM))

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To obtain additional, long term, safety data for tafamidis in subjects with transthyretin amyloid cardiomyopathy (ATTR CM). To provide investigational product, tafamidis, to ATTR CM subjects who complete 30 months of blinded treatment on protocol...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON53130

Source
ToetsingOnline

Brief title
Tafamidis - B3461045

Condition

- Heart failures

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

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ATTR-CM, cardiomyopathy, tafamidis, transthyretin amyloid

Outcome measures

Primary outcome

Safety as measured by:

* All cause mortality.

* Incidence of treatment emergent adverse events.

Secondary outcome

Other Endpoints

* Cardiovascular related mortality.

* Frequency of all cause hospitalization.

* Frequency of cardiovascular related hospitalization (including heart failure, arrhythmia, myocardial infarction, stroke and other cardiovascular related events).

* Change from baseline at each visit in Kansas City Cardiomyopathy Questionnaire Overall Score and domain scores (Physical limitation, Symptom stability, Symptoms, Self efficacy, Social limitation, and Quality of life) and domain summary scores (Functional summary and Clinical summary).

* New York Heart Association classification at each visit.

* Change from baseline in Body Mass Index/modified Body Mass Index at each

visit.

* Assessment of physical examinations, use of concomitant medications,

electrocardiograms (ECGs), clinical laboratory testing, vital signs at each

visit.

Study description

Background summary

Pfizer is developing tafamidis, an oral small molecule, for the treatment of transthyretin amyloid diseases. Transthyretin cardiomyopathy (ATTR CM) occurs when transthyretin (ATTR) 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.
Tafamidis is a novel specific stabilizer of both wild type and amyloidogenic variants of ATTR. Tafamidis binds to ATTR at the thyroxine binding sites and inhibits ATTR tetramer dissociation, the rate limiting step in the amyloidogenic process. It is hypothesized that tafamidis would stop or slow the progression of ATTR CM and therefore represents a disease modifying therapy.

Study objective

To obtain additional, long term, safety data for tafamidis in subjects with transthyretin amyloid cardiomyopathy (ATTR CM).
To provide investigational product, tafamidis, to ATTR CM subjects who complete 30 months of blinded treatment on protocol B3461028.

Study design

This is a Phase 3, open-label long-term extension safety study designed to obtain additional safety data for tafamidis meglumine 20 mg and 80 mg tafamidis (or tafamidis 61 mg where available), and to continue to provide enrolled subjects with tafamidis for up to 60 months, or until subject has access to tafamidis for ATTR-CM via prescription, whichever occurs first. The study will also end before 60 months if the sponsor discontinues the study. Subjects withdrawn from the study due to commercial access to prescription tafamidis in their respective countries will be considered study completers. The decision to withdraw subjects for transition to commercial

tafamidis will be made by the sponsor

Patients who received 20 mg or 80 mg (or potentially 40 mg) tafamidis in Study B3461028, will continue to receive tafamidis at the dose of 61 mg.
New patients will receive 61 mg Tafemidis.

Intervention

Tafamidis is available in 61 mg soft gel capsules, and subjects will take 1 capsules per day

Study burden and risks

Very Common (reported in at least 10% of patients)
o Fall
o Heart failure
o Dyspnea
o Atrial fibrillation
o Peripheral edema
o Fatigue
o Dizziness
o Constipation

From a study in which 65 patients with ATTR-PN received tafamidis 20 mg daily for up to 18 months, the following risks are considered associated with tafamidis use in ATTR-PN patients.

Very Common (reported in at least 10% of patients)
o Diarrhea
o Urinary tract infection
o Upper abdominal pain.
o Vaginal infections in women

Risks from Study Procedures:
* Biopsy: The risks of a biopsy can include bleeding, pain, and infection.
* Blood draws: A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.
* ECG: The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches that are used to conduct the measurements.
* Questionnaires: A questionnaire may contain questions that are sensitive in nature.
* Scintigraphy: The amount of radiation received as part of this study is small. There is no significant risk from this total amount of radiation.
* Testing of DNA and/or RNA: The genetic analysis is for research purposes

only, and is not a medical test. The Sponsor and researchers will put measures in place to minimize the possibility for the results from this research being linked to the subject, but there is always the remote possibility that information from participation in the research may be disclosed.

Possible benefit:
Previous results demonstrated that tafamidis reduced all-cause mortality and cardiovascular (CV)-related hospitalisation in addition to better function and quality of life compared with placebo.

Contacts

Public
Pfizer

East 42nd Street 235
New York NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male and female subjects with TTR amyloid cardiomyopathy who have completed

30 months of study treatment on Protocol B3461028.
2. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception hroughout the study and for at least 28 days after the last dose of assigned treatment.
Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):
* Have undergone a documented hysterectomy and/or bilateral oophorectomy;
* Have medically confirmed ovarian failure; or
* Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum folliclestimulating hormone (FSH) level confirming the post-menopausal state.
All other female subjects (including females with tubal ligations) will be considered o be of childbearing potential.
Aanvullend voor cohort B:
5. Documentatie van de genetische tests voor transthyretineamyloïdose
6. Documentatie van diagnose en gebruikte criteria of congestief hartfalen en de aanwezigheid van
amyloïde afzettingen in biopsieweefsel, b.v. vetaspiratie, speekselklier, nervus medianus
bindweefselschede of cardiaal
7.Documentatie dat primaire (lichte keten) amyloïdose ziekte is geëvalueerd en uitgesloten
8. Bewijs van NYHA-classificatie I, II, III of IV

Exclusion criteria

1. Chronic use of diflunisal, TTR stabilizer, tauroursodeoxycholate, doxycycline, digitalis, patisaran, calcium channel blockers, investigational drug(s) or other experimental interventions, other than tafamidis, independently or as part of a study within 30 months prior to enrollment, or inotersen within 6 months prior to enrolment

2. Use of certain non-steroidal anti-inflammatory drugs (NSAIDs)
3. Liver and/or heart transplant, or implanted cardiac mechanical assist device.
4. Pregnant females (or planning to become pregnant during the study interval); breastfeeding females; male subjects with partners currently pregnant.
5. Require initiation of treatment with calcium channel blockers.
6. Urinary retention requiring chronic self-catheterization.

7. Breach of compliance with treatment/significant protocol violations during conduct of B3461028 for which the subject was accountable.
8. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of he study.
9. Other severe acute or chronic medical or psychiatric condition or laboratory bnormality that may increase the risk associated with study participation or investigational product administration, or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject an appropriate for entry into this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2018
Enrollment:	12
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:	01-05-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-09-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-03-2021

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-07-2022
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	EUCTR2016-000868-42-NL
CCMO	NL58803.028.17