National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: June 2018

Tafamidis for transthyretin amyloid cardiomyopathy

NIHRIO (HSRIC) ID: 5124 NICE ID: 9509

Transthyretin amyloidosis (ATTR) is a rare, life-threatening disease resulting from aggregation and deposition of a defective type of protein called ('amyloids') in various tissues. These deposits damage the structure and function of the tissues and cause serious disease which is usually fatal if it affects major organs. Transthyretin amyloidosis cardiomyopathy (ATTR-CM) primarily affects the heart, causing thickening and stiffening of the heart tissues. Symptoms usually start after age 60 years and include shortness of breath, sometimes after only mild exertion; palpitations and abnormal heart rhythms, most frequently atrial fibrillation or atrial flutter; ankle swelling (oedema); fatigue; fainting, and angina (chest pain). ATTR-CM is progressive and ultimately leads to death. Current treatment focuses mainly on managing the symptoms although heart transplantation may be appropriate for some patients.

Tafamidis is an oral (taken by mouth) drug that has the potential to slow the formation of the amyloid deposits that can produce heart problems in people with ATTR-CM. Tafamidis works by specifically interfering with the disease process that leads to the formation and deposition of the amyloids within the heart tissues. If approved, tafamidis will become the first medicinal treatment option specifically indicated for treating ATTR-CM, in patients that currently have very limited options available and that mostly focus on symptom management.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Transthyretin amyloid cardiomyopathy (adult; symptomatic) – first line.

TECHNOLOGY

DESCRIPTION

Tafamidis meglumine (PF-06291826-83) is the meglumine salt form of tafamidis, the only active ingredient contained in tafamidis meglumine soft gelatin capsules. Tafamidis is a novel specific stabilizer of the native tetrameric form of both wild-type and amyloidogenic variants of transthyretin (TTR). TTR ordinarily assumes a tetramer configuration that primarily serves to transport retinol-binding protein-vitamin A complex and thyroxine (to a small degree) in the blood. In TTR-related disorders, tetramer dissociation is accelerated and results in unregulated amyloidogenesis and amyloid fibril formation. The unwanted deposition of such formations in various tissues eventually contributes to a spectrum of disease characterised by neurological and/ or cardiac dysfunction.[1]

Tafamidis binds to TTR at the thyroxine binding site and inhibits TTR tetramer dissociation, the rate limiting step in the amyloidogenic process. By stabilising the tetrameric native state of TTR, tafamidis increases the activation barrier associated with tetramer dissociation and therefore mimics the tetrameric stabilisation effect observed with naturally occurring protective trans-suppressor variants. By interfering with the essential step in the disease process, tafamidis has the potential to slow the progression of amyloid disease.[2]

Tafamidis is intended for use in adults with symptomatic transthyretin cardiomyopathy. In the recently completed, randomized, double-blinded, placebo-controlled, clinical trial (NCT01994889); participants were given an oral daily dose of 20 mg or 80 mg tafamidis meglumine capsules or placebo; treatment lasted for the entire follow-up period (30 months).[3]

In the UK, tafamidis capsules (20mg per day) are indicated for the treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in patients with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment.[4] The most common side effects with tafamidis meglumine (Vyndaqel) (seen in more than 1 patient in 10) are urinary tract infection (infection of the structures that carry urine), vaginal infection, upper abdominal pain (stomach ache) and diarrhoea.[5, 6]

INNOVATION and/or ADVANTAGES

The dissociation of the transthyretin tetramer to monomers is the rate limiting step in the pathogenesis of TTR amyloidogenic process. Tafamidis has a unique mechanism of action to slow the disease progression. If licensed, tafamidis will be the first treatment option for adult patients with ATTR-CM. In the UK, there are no alternative medicinal products licensed for this indication.

DEVELOPER

Pfizer Ltd.

PATIENT GROUP

BACKGROUND

Transthyretin amyloidosis (ATTR) is a rare, life-threatening disease resulting from aggregation and deposition of transthyretin amyloid fibrils in various tissues. There are two predominant phenotypic presentations of the disease: hereditary ATTR with polyneuropathy (ATTR-PN), which primarily affects the peripheral nerves, and ATTR cardiomyopathy (ATTR-CM), which primarily affects the heart and includes both wild-type and hereditary forms.[2]

ATTR-CM is an underdiagnosed, life-threatening disease characterized by the accumulation of amyloid fibrils composed of misfolded transthyretin protein in the heart.[7] Misfolded monomers or oligomers of transthyretin deposit in the myocardium leading to cardiomyopathy and symptoms of heart failure (HF) including dyspnoea, fatigue, effort intolerance, orthostatic hypotension and syncope.[8] Additionally, infiltration of the conduction system can lead to bundle branch block, atrioventricular block, sinoatrial disease, and atrial fibrillation.[8]

Transthyretin amyloid cardiomyopathy may occur due to wild-type ATTR-CM (wtATTR-CM) (also known as senile systemic amyloidosis or SSA or senile cardiac amyloidosis or SCA) and hereditary ATTR-CM (hATTR-CM) (also known as Familial Amyloid Cardiomyopathy or FAC).[9] Wild-type ATTR cardiomyopathy is almost exclusively a disease that affects older individuals (most patients are more than 60 years of age) with a 10-fold male predominance.[8] Hereditary ATTR cardiomyopathy is usually associated with a single amino acid substitution caused by a point mutation in the TTR gene.[8] Amyloidogenic TTR variants are thought to be less stable than their wild-type counterpart, underlying their increased propensity to form amyloid fibrils.[8] To date, at least 120 point mutations of the TTR gene have been identified, most of which are associated with amyloidosis. However, just a few of these variants, including Val30Met, Thr60Ala, Ser77Tyr and Val122Ile, are responsible for the majority of cases of hereditary ATTR amyloidosis worldwide.[8] The most prevalent TTR variants in the UK population are Val122Ile and Thr60Ala; Val30Met is the most common TTR amyloidosis type worldwide.[9]

ATTR-CM patients may present with restrictive cardiomyopathy, with varying degrees of chronic heart failure and possible brady/tachyarrhythmias.[10] ATTR-CM is often difficult to diagnose. The clinical progression of ATTR-CM depends upon fibril type (wild-type vs. variant), specific mutation, age of onset, and potentially, fragmented versus full-length fibrils.[8] Untreated, ATTR-CM progresses to intractable heart failure and death due to systolic heart failure or dysrhythmia. Survival in wild type TTR disease appears more favourable than in the hereditary type. The reported median survival is 2.1 years following diagnosis for Val122Ile and 3.6 years for ATTRwt.[11, 12]

CLINICAL NEED and BURDEN OF DISEASE

Data from the National Amyloidosis Centre in the UK reports that about 600 new cases of amyloidosis (including all different types) are diagnosed each year.[13] The latest Hospital Episode Statistics (HES) data for 2016/2017 recorded a total of 1,473 finished consultant episodes (FCEs), 1,077 admissions and 612 day cases for organ-limited amyloidosis of any type (ICD-10 code E85.4).[14]

The largest UK series of ATTR-CM patients seen at the National Amyloidosis Centre reported on 553 patients with wild-type ATTR-CM and 316 patients with hereditary ATTR-CM seen prior to May 2017.[15] This study did not report the years of data collection, therefore it is not possible to derive a point prevalence.

The prevalence of ATTR-CM in the UK remains unknown and is difficult to reliably estimate due to both under-diagnosis and under-reporting of the condition. Evidence from autopsy series and imaging studies using nuclear scintigraphy suggest that it may be more common than is currently recognised.[9, 16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

There is currently no published NICE guidance on treatment of transthyretin cardiomyopathy. Related guidance is listed below:

- NICE Highly Specialised Technology. Inotersen for treating hereditary transthyretin-related amyloidosis (GID-HST10013). Expected publication date to be confirmed.
- NICE Highly Specialised Technology. Patisiran for treating hereditary transthyretin-related amyloidosis (GID-HST10014). Expected publication date to be confirmed.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for cardiology: Inherited cardiac conditions (All ages). A09/S/c
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Amyloidosis (All Ages). E13/S(HSS)/c

OTHER GUIDANCE

- A new staging system for cardiac transthyretin amyloidosis. European Heart Journal.[15]
- Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet Journal of Rare Diseases.[17]
- 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. ESC.[18]

CURRENT TREATMENT OPTIONS

Current treatment of ATTR-CM is typically focused on symptom management,[2] however the use of conventional heart failure therapies may cause harm and several are contraindicated.[7] Liver transplantation is not indicated for wild type ATTR-CM, and in the case of hereditary ATTR-CM is generally reserved for patients with early stage disease associated with the Val30Met mutation that is rarely found in the UK. [19, 20]

There are currently no approved drugs for the treatment of ATTR-CM.

EFFICACY and SAFETY

Trial	**ATTR-ACT, NCT01994889, EudraCT Number 2012-002465-35; Study B3461028; adults aged 18 to 90 years; tafamidis meglumine vs placebo; phase III**
Sponsor	Pfizer
Status	Completed
Source of Information	Trial registry;[3] Publication[2]
Location	EU (inc UK), USA, Brazil, Canada, Japan
Design	Randomised, placebo-controlled
Participants	N=(441); adults with medical history of HF; evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm; presence of amyloid deposits in biopsy tissue and presence of a variant TTR genotype and/or TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry
Schedule	Randomised to one of three blinded treatment arms: • Arm 1: tafamidis meglumine 20 mg in soft gel capsules administered once a day for 30 months; • Arm 2: tafamidis meglumine 80 mg in soft gel capsules administered once a day for 30 months; • Arm 3: placebo in soft gel capsules administered once a day for 30 months
Follow-up	Active treatment and follow-up for 30 months
Primary Outcomes	A hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalization applying the analysis method of Finkelstein-Schoenfeld.
Secondary Outcomes	• 6-Minute Walk Test (6MWT). Change from Baseline to Month 30 in the total distance walked in 6 minutes. • Kansas City Cardiomyopathy Questionnaire (KCCQ). Change from Baseline to Month 30 in the KCCQ Overall Score. • Cardiovascular-related mortality [Time Frame: From Baseline to Month 30]. The total number of deaths adjudicated as being related to cardiovascular causes. • Frequency of cardiovascular-related hospitalization [Time Frame: From Baseline to Month 30]. The number of times that a subject is hospitalized for cardiovascular-related causes. • All-cause mortality [Time Frame: From Baseline to Month 30]. The total number of deaths in the study. • TTR stabilization at Month 1. Tafamidis stabilizes the transthyretin (TTR) tetramer by binding with very high affinity to the two thyroxine binding sites, preventing the tetramer from dissociating along the weak dimer-dimer interface. TTR stabilization is a measure of the degree of stabilization afforded the TTR molecule by tafamidis, expressed as a percentage change from baseline.
Key Results	-
Adverse effects (AEs)	-

Expected reporting date	Previously reported as Feb 2018.

ESTIMATED COST and IMPACT

COST

The NHS indicative price of tafamidis meglumine 20 mg (Vyndaqel 20 mg) for a 30 capsules pack is £10,685.00 for the treatment of transthyretin familial amyloid polyneuropathy to delay peripheral neurologic management, in addition to standard care.[4, 6]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services: *reduced need for CV-related hospitalisations*

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduced need for interventional procedures*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

1 Drugbank.ca. *Tafamidis*. 2018 May 2018. Available from: https://www.drugbank.ca/drugs/DB11644 [Accessed 30 May 2018]

2 Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, et al. Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). *Circ Heart Fail*. 2017 Jun;10(6). Available from: 10.1161/circheartfailure.116.003815 [Accessed 30 May 2018]

3 ClinicalTrials.gov. *Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)*: *NCT01994889*. Nov 2013. Last Updated: May 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01994889 [Accessed 30 May 2018]

4 British National Formulary (BNF). *Tafamidis*. 2018. Available from: http://dx.doi.org/10.18578/BNF.277238528 [Accessed 30 May 2018]

5 European Medicines Agency. *Vyndaqel (tafamidis)*. 2011. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002294/human_med_001498.jsp&mid=WC0b01ac058001d124 [Accessed 30 May 2018]

6 eMC. *Vyndaqel 20 mg soft capsules*. 2018. Available from: https://www.medicines.org.uk/emc/medicine/27125/SPC/Vyndaqel+20+mg+soft+capsules/ [Accessed 18 July 2018]

7 Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nature Reviews Cardiology*. 2010;7(7):398. Available from, [Accessed 19 June 2018]

8 Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. *Circulation*. 2012;126(10):1286-300. Available from: 10.1161/CIRCULATIONAHA.111.078915 [Accessed 31 May 2018]

9 Patel K, Hawkins P. Cardiac amyloidosis: where are we today? *Journal of internal medicine*. 2015;278(2):126-44. Available from: 10.1111/joim.12383 [Accessed 31 May 2018]

10 Orphanet. *ATTRV122I amyloidosis*. 2018. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=85451 [Accessed 31 May 2018]

11 Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, et al. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. *Circulation: Heart Failure*. 2015:CIRCHEARTFAILURE. 113.000890. Available from, https://doi.org/10.1161/CIRCHEARTFAILURE.113.000890 [Accessed 18 June 2018]

12 Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *Journal of the American College of Cardiology*. 2016;68(10):1014-20. Available from, [Accessed 19 June 2018]

13 University College London - Centre for Amyloidosis and acute phase proteins. *Amyloidosis Overview*. 2018. Available from: http://www.ucl.ac.uk/amyloidosis/nac/amyloidosis-overview/#amyloidosis [Accessed 5 June 2018]

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17. 2017*. Geographic coverage: England, Data collection period: Dataset downloaded: Available from: http://digital.nhs.uk/catalogue/PUB22378 [Accessed

15 Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. *European Heart Journal*. 2017:ehx589-ehx. Available from: 10.1093/eurheartj/ehx589 [Accessed 1 June 2018]

16 González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *European Heart Journal*. 2015;36(38):2585-94. Available from, [Accessed 19 June 2018]

17 Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon B-G, Ikeda S-i, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet Journal of Rare Diseases*. 2013;8(1):31. Available from, [Accessed 20 June 2018]

18 Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal*. 2014;35(39):2733-79. Available from, [Accessed 20 June 2018]

19 Dungu JN, Anderson LJ, Whelan CJ, Hawkins PN. Cardiac transthyretin amyloidosis. *Heart*. 2012:heartjnl-2012-301924. Available from, [Accessed 199 June 2018]

20 Ericzon B-G, Wilczek HE, Larsson M, Wijayatunga P, Stangou A, Pena JR, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation*. 2015;99(9):1847-54. Available from, doi: 10.1097/TP.0000000000000574 [Accessed 20 June 2018]