National Institute for Health and Care Excellence

Single Technology Appraisal

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy [ID6327]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	NHS England	This is an appropriate evaluation and evaluation route	Thank you for your comment.
	ABN Neuromuscular Advisory Group	Agree, appropriate.	Thank you for your comment.
	Genetic Alliance UK	ATTR-CM is a rare condition that can have a significant impact on quality of life. As this technology has been routed through an STA rather than HST pathway, its evaluation may be disadvantaged by the evidence constraints of smaller population numbers therefore this would be a good case for the committee to exercise flexibility in their decision making.	Thank you for your comment. The committee will consider evidence uncertainty during the evaluation of this technology.
	Royal College of Pathologists	This is appropriate and very important consultation	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
	Pfizer	No further comments. We believe it is appropriate to refer this topic to NICE for evaluation under the Single Technology Appraisal (STA) programme.	Thank you for your comment.
Wording	NHS England	The wording is appropriate	Thank you for your comment.
	ABN Neuromuscular Advisory Group	Agree, appropriate.	Thank you for your comment.
	UK ATTR Amyloidosis Patients' Association (UKATPA)	Background, paragraph 4 states "Current treatment options for ATTR-CM are limited and mainly focus on symptom management and supportive care such as diuretics". We believe this wording to be inappropriate as there is no treatment available in the UK that influences the disease process. Suggested wording: *There is no treatment available for ATTR-CM in the UK at present. All available therapies, such as diuretics, are for symptom management and supportive care only and do not impact the progression of the disease.*	Thank you for your comment. The scope has been updated.
	Pfizer	We agree that the wording in the draft remit appropriately reflects the issues NICE should consider.	Thank you for your comment.
Additional comments on draft remit	UK ATTR Amyloidosis Patients' Association (UKATPA)	Since the last review of this medication by NICE, we believe that there has been an improvement in healthcare professional education regarding ATTR-CM, better availability of diagnostic testing, and improved referral pathways. This means that the condition is more likely to be identified and patients referred to specialist care.	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NHS England	This is accurate	Thank you for your comment.
	ABN Neuromuscular Advisory Group	Agree, appropriate.	Thank you for your comment.
	Royal College of Pathologists	OK	Thank you for your comment.
	UK ATTR Amyloidosis Patients' Association (UKATPA)	The information that the v122i gene occurs almost exclusively in individuals of identifiable African descent is missing, from an equality perspective we feel this is a significant omission. This population is acknowledged in the draft scope to have a shorter survival time following diagnosis than other comparable groups. The significant impact of the disease on the friends and family of ATTR-CM patients is also missing from the background. Patients develop difficulties doing physical activities and as the disease progresses, they become more and more disabled and dependent on relatives or carers. Patients become unable to work and carry out activities of daily living. This puts a large burden on relatives and carers.	Thank you for your comment. The background section of the scope has been updated to reflect that the Val122Ile variant is most common in people with African or Caribbean family backgrounds. The increasing reliance on carers has also been added to the background section of the scope.
	Pfizer	We believe that the background information is accurate and complete. In this section NICE states: *"The number of new diagnoses made each year, in particular for wildtype ATTR-CM, is increasing rapidly, in part due to the wider availability of non-invasive diagnostic tests".* We agree with this statement and ask if NICE could kindly provide a supporting reference.	Thank you for your comment. This statement was included in the scope for TA696 based on clinical expert opinion heard at the scoping workshop. The scope has been updated to

Section	Consultee/ Commentator	Comments [sic]	Action
			reflect that this is the view of some clinical experts.
Population *Is the population defined appropriately?*	NHS England	The population is defined appropriately, the number of patients diagnosed with ATTR-CM amyloidosis is thought to be higher than that estimated. The service at the Royal Free will be able to provide a more accurate figure.	Thank you for your comment. The prevalence reported in the scope is an estimate. Further prevalence data may be presented in submissions during the evaluation. No changes to the scope needed.
	ABN Neuromuscular Advisory Group	Yes. The scope currently states, "The most prevalent TTR variants in the UK are Vall112Ile and T60A4. The Val122Ile variant is mostly associated with isolated cardiomyopathy without neuropathy. Reported median survival is 2.1 years following diagnosis for people with the Val122Ile variant and 3.4 years for people with the T60A variant." We feel it is worth elaborating further that Val122Ile is prevalent in the Afro-Caribbean population. It is the fourth most common cause of heart failure in Afro-Caribbeans in the UK (11.4%), and this is likely to be an underestimate as not all patients with heart failure are tested for amyloidosis.	Thank you for your comment. The background section of the scope has been updated to reflect that the Val122Ile variant is most common in people with African or Caribbean family backgrounds.
	Royal College of Pathologists	Yes	Thank you for your comment.
	Pfizer	We agree that the population defined is appropriate.	Thank you for your comment.

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Subgroups *Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?*	NHS England	We are not aware of any subgroups, the clinicians may be best placed to answer.	Thank you for your comment.
	Royal College of Pathologists	No	Thank you for your comment.
	UK ATTR Amyloidosis Patients' Association (UKATPA)	There are no subgroups in the scope. We feel that it would be appropriate for both v122i population and Wildtype patients should be considered as subgroups. In both these subgroups ATTR-CM is present without neuropathy. The v122i population is almost exclusively individuals of identifiable African descent and survival times in this group is 1.3 years less than for the T60A variant. Therefore, the potential benefits to the v122i group are greater than for the general ATTR-CM population. The lack of treatment currently available to both these subgroups means that they will potentially benefit more than other ATTR-CM patients, both physically and psychologically from having access to tafamidis.	Thank you for your comment. The scope cannot capture all possible subgroups. The committee may consider these subgroups during the evaluation if it is presented with relevant evidence.
	Pfizer	We agree with the definition of the population and believe there are no groups within the defined population that should be considered separately.	Thank you for your comment.
Comparators	NHS England	The listed comparators are the licensed treatments used to treat patients presenting with transthyretin familial amyloid polyneuropathy. Tafamidis is being appraised for patients with ATTR-CM; there may be some patients who present with a mixed phenotype, but a significant proportion of patients will not have polyneuropathy in whom standard clinical management is currently more likely to be focused on symptom relief and supportive care. The National amyloidosis centre at the Royal Free NHS FT also use an unlicensed treatment, difunisal for patients in the latter stages of the disease.	Thank you for your comment. The scope has been updated.

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	ABN Neuromuscular Advisory Group	Agree with comparators listed including best supportive care for wild-type ATTR-CM and genetic therapies for hereditary ATTR-CM with neuropathy. Agree liver transplant is not relevant as a comparator as not usually used if any cardiac problems. Should other TTR stabilisers e.g. diflunisal also be considered as a comparator?	Thank you for your comment. The scope has been updated.
	Royal College of Pathologists	There are no comparators as there is no other currently licenced therapy or available therapy for this population. It is very significant and crucial unmet medical need.	Thank you for your comment. The appropriateness of the comparators listed in the scope will be considered by the committee during the evaluation.
	Pfizer	We agree that the relevant comparator(s) have been identified.	Thank you for your comment.
Outcomes *Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits*	NHS England	The outcomes are appropriate	Thank you for your comment.
	ABN Neuromuscular Advisory Group	Yes. We would like to add that ATTR-CM causes significant progressive heart failure and death, with impact not just on the affected patient, but their families and carers also. Improving functional capacity and cardiovascular-related hospitalizations for these patients would have a wider societal impact beyond these patient centred outcomes also.	Thank you for your comment. The outcomes list has been updated to include health-related quality of life of patients and carers.

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(and harms) of the technology?	Royal College of Pathologists	Yes	Thank you for your comment.
	UK ATTR Amyloidosis Patients' Association (UKATPA)	For patients 'fewer hospital visits' and 'improved mental/psychological health' are both important outcomes that are not currently listed in scope. We welcome having 'Overall survival' listed as an outcome as this captures the idea of 'living longer' which is also very important to patients.	Thank you for your comment. The outcomes list is not intended to be exhaustive. Cardiovascular-related hospitalisation is already included in the outcomes. Mental and psychological health will be measured as part of health-related quality of life measures. No changes to the scope are needed.
	Pfizer	We agree that the listed outcomes are appropriate and should capture the most important health related benefits (and harms) of the technology.	Thank you for your comment.
Equality	NHS England	Black patients are much more likely to present with ATTR-CM amyloidosis but without polyneuropathy. Currently they are not eligible for the other commissioned therapies and receive only best supportive care. They may be eligible for tafamidis. The scope does not prejudice the care of any patient with other protected characteristics.	Thank you for your comment. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.

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	ABN Neuromuscular Advisory Group	As mentioned earlier, the scope currently states, "The most prevalent TTR variants in the UK are Vall112Ile and T60A4. The Val122Ile variant is mostly associated with isolated cardiomyopathy without neuropathy. Reported median survival is 2.1 years following diagnosis for people with the Val122Ile variant and 3.4 years for people with the T60A variant." We feel it is worth elaborating further that Val122Ile is prevalent in the Afro-Caribbean population. It is at least the fourth most common cause of heart failure in Afro-Caribbeans in the UK (11.4%), and this is likely to be an underestimate as not all patients with heart failure are tested for amyloidosis. Patients from ethnic minorities often face difficulties accessing appropriate healthcare investigations and can have delays in receiving both diagnosis and treatment. Currently, the Val122Ile patient that typically has isolated cardiomyopathy without neuropathy would only be offered best supportive treatment even after this diagnosis is made.	Thank you for your comment. The background section of the scope has been updated to reflect that the Val122Ile variant is most common in people with African or Caribbean family backgrounds. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
	Royal College of Pathologists	There is significant ethnic minority cohort who are disadvantaged with delayed diagnosis with poorer outcomes.	Thank you for your comment. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.

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	UK ATTR Amyloidosis Patients' Association (UKATPA)	We feel that this scope does not acknowledge the needs of the V122I population. This population is almost exclusively found in individuals of identifiable African descent. It is known that this population is diagnosed later and has worse outcomes than other ATTR-CM patients. The v122I population develops cardiomyopathy without neuropathy so at present they have no treatments available in the UK. *Patients with V122I-hATTR-CM were more impaired functionally (P<0.001) and had worse measures of cardiac disease (P<0.001) at the time of diagnosis, a greater decline in quality of life, and poorer survival (P<0.001) in comparison with the other subgroups* Lane, T. et al (2019). Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. *Circulation*, 140(1), pp.16–26. doi:https://doi.org/10.1161/circulationaha.118.038169.	Thank you for your comment. The background section of the scope has been updated to reflect that the Val122Ile variant is most common in people with African or Caribbean family backgrounds. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
	Pfizer	The proposed scope is within the equality legislation, as both wild-type and hereditary ATTR-CM patients are included.	Thank you for your comment.
Other considerations	Royal College of Pathologists	All patients with ATTR cardiac amyloidosis	Thank you for your comment.
	Pfizer	No other considerations.	Thank you for your comment.
Questions for consultation	Alnylam Pharmaceuticals	**Where do you consider tafamidis will fit into the existing care pathway for transthyretin amyloid cardiomyopathy?** Based on our discussions with key UK experts in transthyretin amyloidosis, we believe that:	Thank you for your comment. The comparators in the scope are intended to be inclusive and the appropriateness of each comparator will be considered by the

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		• Vutrisiran will continue to be the first line therapy for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy I.e., patients presenting with 'pure' neuropathy and for hATTR amyloidosis patients with neuropathy and cardiomyopathy (mixed symptomology). Noting that almost all UK hATTR amyloidosis patients presenting with neuropathy or with neuropathy and cardiomyopathy who are initiated on-treatment today receive vutrisiran. Furthermore, most of these patients who, prior to the launch of vutrisiran received patisiran, have since switched to vutrisiran. • Tafamidis will be the first line therapy for wtATTR patients and for hATTR amyloidosis patients with 'pure' cardiomyopathy Tafamidis is not currently used in the NHS for hATTR amyloidosis patients with polyneuropathy or for hATTR amyloidosis patients with neuropathy and cardiomyopathy (mixed symptomology) because it received a negative reimbursement decision from AGNSS in 2013. This negative decision appears to have been due to 'the lack of a significant difference between tafamidis and placebo in the primary analysis' of the pivotal FX-005 trial and a lack of trial evidence in patients with mutations other than V30M (Tafamidis for TTR FAP Evidence Review Group assessment of manufacturer submission, 2013). To our knowledge, there are no reasons for NICE or the NHS to reverse this reimbursement decision and so we assume that tafamidis will continue to not be used to treat the neurological impairment of patients with hATTR amyloidosis. Given this we not do believe that vutrisiran, patisiran or inotersen should be comparators.	committee during the evaluation. No changes to the scope needed.

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	Royal College of Pathologists	This should be prescribed by all physicians who have confirmed diagnosis of ATTR amyloidosis and prescription or assessment must NOT be restricted to the National amyloidosis centre. There are elderly frail patients where travel and even video contact is a serious challenge and may deny them treatment.	Thank you for your comment. The implementation of tafamidis is outside the remit of this evaluation.
	UK ATTR Amyloidosis Patients' Association (UKATPA)	**Where do you consider tafamidis will fit into the existing care pathway for transthyretin amyloid cardiomyopathy?** There is currently no treatment available for ATTR-CM while the rate of diagnosis is increasing, Tafamadis would therefore fill a significant, missing part of the current care pathway. Tafamadis is orally administered, well tolerated, and has few side effects. It has been widely used in other countries so it will be straightforward for care providers to integrate tafamadis into the existing care pathways. **Would tafamadis be a candidate for managed access?** Yes. We recognise that there are questions about the effectiveness of tafamadis and that there are other, potentially more effective treatments currently under development. The fact that there is no treatment currently available in the UK coupled with the fact that tafamadis is widely available in other countries has a hugely detrimental effect on the psychological well-being of patients, their friends, and families. A managed access arrangement would allow patients to access tafamadis while the question of efficacy is addressed and alternative tretments developed. That said, Tafamidis is not a new drug. There is real-world use data available and published demonstrating its safety end effectiveness. **Do you consider that the use of tafamidis can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**	Thank you for your comment.

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		Some of the effects of amyloidosis are not measured and considered in studies, even when they are important to the patients, like autonomic neuropathy and neuropathic pain. These are likely to be improved by the administration of tafamidids. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** • Takashio, S., Morioka, M., Ishii, M., Morikawa, K., Hirakawa, K., Hanatani, S., Oike, F., Usuku, H., Kidoh, M., Oda, S., Yamamoto, E., Matsushita, K., Ueda, M. and Tsujita, K. (2023). Clinical characteristics, outcome, and therapeutic effect of tafamidis in wild-type transthyretin amyloid cardiomyopathy. *ESC heart failure*, [online] 10(4), pp.2319–2329. doi:https://doi.org/10.1002/ehf2.14380. • Morbach, C., Papagianni, A., Ihne-Schubert, S., Cejka, V., Steinhardt, M., Fette, G., Held, • M., Geier, A., Einsele, H., Frantz, S., Knop, S., Sommer, C. and Störk, S. (2023). Tafamidis for cardiac transthyretin amyloidosis: application in a real-world setting in Germany. Clinical Research in Cardiology: Official Journal of the German Cardiac Society. [online] doi:https://doi.org/10.1007/s00392-023-02163-x. • Miyamoto, M., Nakamura, K., Nakagawa, K., Nobuhiro Nishii, Kawada, S., Akira Ueoka, Asada, S., Watanabe, A., Morita, H. and Ito, H. (2023). Prevalence and Treatment of Arrhythmias in	

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		Patients With Transthyretin and Light-Chain Cardiac Amyloidosis. doi:https://doi.org/10.1253/circrep.cr-23-0022. • Elliott, P., Gundapaneni, B., Sultan, M.B., Ines, M. and Garcia-Pavia, P. (2023). Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. *European Journal of Heart Failure*. [online] doi:https://doi.org/10.1002/ejhf.2974. • Merkel, M., Danese, D., Chen, C., Wang, J., Wu, A., Yang, H. and Lin, H. (2023). Indirect treatment comparison (ITC) of the efficacy of vutrisiran and tafamidis for hereditary transthyretin-mediated amyloidosis with polyneuropathy. Expert Opinion on Pharmacotherapy, [online] 24(10), pp.1205–1214. doi:https://doi.org/10.1080/14656566.2023.2215925. • Tsai, C.-H., Yu, A.-L., Wu, Y.-K.A., Su, M.-Y., Cheng, M.-F., Chou, C.-H., Shun, C.-T., Hsueh, H.-W., Juang, J.J.-M., Lee, M.-J., Tseng, P.-H., Hsieh, S.-T., Chao, C.-C. and Lin, Y.-H. (2023). Efficacy of Tafamidis in Patients with Ala97Ser Hereditary Transthyretin Cardiac Amyloidosis: A Six-Month Follow-Up Study. Acta Cardiologica Sinica, [online] 39(4), pp.619–627. doi:https://doi.org/10.6515/ACS.202307_39(4).20221116A. • Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, Ebede B, Gundapaneni B, Li B, Sultan MB, Shah SJ. Long-term survival in people with transthyretin amyloid cardiomyopathy who took tafamidis: A Plain Language Summary. Future Cardiol. 2023 Jan;19(1):7-17. doi: 10.2217/fca-2022-0096. Epub 2023 Jan 30. PMID: 36715498. • Nakamura M, Imamura T, Ushijima R, Kinugawa K. Prognostic Impact of the Increase in Cardiac Troponin Levels during Tafamidis Therapy in Patients with Transthyretin Cardiac	

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		Amyloidosis. J Clin Med. 2023 Jul 12;12(14):4631. doi: 10.3390/jcm12144631. PMID: 37510746; PMCID: PMC10380493. • Kim MM, Prasad M, Burton Y, Kolseth CM, Zhao Y, Chandrashekar P, Nazer B, Masri A. Comparative Outcomes of a Transthyretin Amyloid Cardiomyopathy Cohort Versus Patients With Heart Failure With Preserved Ejection Fraction Enrolled in the TOPCAT Trial. J Am Heart Assoc. 2023 Aug;12(15):e029705. doi: 10.1161/JAHA.123.029705. Epub 2023 Jul 31. PMID: 37522238. • Falcão de Campos C, Conceição I. Updated Evaluation of the Safety, Efficacy and Tolerability of Tafamidis in the Treatment of Hereditary Transthyretin Amyloid Polyneuropathy. Drug Healthc Patient Saf. 2023 Feb 17;15:51-62. doi: 10.2147/DHPS.S338577. PMID: 36824481; PMCID: PMC9942506.	
Additional comments on the draft scope	ABN Neuromuscular Advisory Group	Wild-type ATTR-CM is related to aging. With increasing awareness of the disease and our aging population, it is worth considering in which situations drugs for this disease will be started and when it might be appropriate to stop treatment as these would have significant financial implications.	Thank you for your comment. The implementation of stopping rules will be considered by the committee during the evaluation.
	UK ATTR Amyloidosis Patients' Association (UKATPA)	We would welcome an economic analysis that includes the cost of care provided by friends and family of ATTR-CM as this can be significant. In 2018 the American Heart Association stated that the "Costs of informal caregiving for patients with cardiovascular disease represent an additional 11% of medical and productivity costs attributable to cardiovascular disease."	Thank you for your comment. The reference case states that the economic evaluation should take an NHS and Personal Social Services perspective. The committee may also

Section	Consultee/ Commentator	Comments [sic]	Action
			consider uncaptured benefits of tafamidis.
	Pfizer	**Where do you consider tafamidis will fit into the existing care pathway for transthyretin amyloid cardiomyopathy?** We would expect tafamidis to be the first line treatment for ATTR-CM in conjunction with symptomatic management of heart failure and its complications. There are currently no approved disease-modifying pharmacological treatments for ATTR-CM in the UK. Following a diagnosis, the aims of treatment are the management of symptoms of heart failure and prevention of arrhythmogenic complications. Judicious use of diuretics forms the mainstay of treatment to relieve the symptoms of heart failure in ATTR-CM. Atrial fibrillation is common in ATTR-CM, as are other arrhythmias, increasing the risk of thromboembolic complications. There are no absolute contraindications to anticoagulation in this setting and a low threshold for initiation is recommended.[1] It is therefore expected that tafamidis (subject to ongoing NICE evaluation) would be first line and the only available treatment option for patients with wild-type or hereditary ATTR-CM. **Would tafamidis be a candidate for managed access?** No, we do not consider tafamidis a suitable candidate for managed access. We believe there are no major evidence gaps/ uncertainties which could be addressed from the collection of real-world evidence. As a result of the ATTR-ACT extension study, there is now overall survival and treatment discontinuation data with substantial additional follow up. These long-term data help address uncertainties which arose during the original NICE STA [ID1531].	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of tafamidis can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The ATTR-ACT study did not measure endpoints directly related to caregiver burden. However, observational data in patients with heart failure in general do support a reduced caregiver burden with improvements in some of the secondary endpoints assessed in ATTR-ACT. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** A longitudinal study conducted in patients with heart failure and their caregivers in Edinburgh found that severity of heart failure measured by NYHA classification was associated with poor quality of life (QoL) in carers.[2] A further observational study conducted in the Netherlands was in agreement that physical health status of HF patients is significantly associated with markers of poor caregiver QoL, specifically the disruption of daily schedule and loss of physical strength among caregivers.[3]	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

British Liver Trust