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Advancing Transthyretin Amyloidosis Drug Development in an Evolving Treatment Landscape: Amyloidosis Forum Meeting Proceedings

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Abstract

Introduction: Hereditary transthyretin amyloidosis (ATTRv, also referred to as hATTR; ORPHA 271861) and wild-type ATTR amyloidosis (ATTRwt; ORPHA 330001) are rare, progressive,

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systemic protein misfolding disorders with heterogeneous clinical presentations. ATTRv and ATTRwt amyloidosis are characterized by the deposition of amyloid fibrils in multiple organs including the heart, nerves, eyes, and soft tissues. The management of ATTR amyloidosis is complex because of its multisystemic nature and progression despite available treatment options. Morbidity is high and there are many unmet medical needs for patients. While contemporary ATTR amyloidosis cohorts are diagnosed earlier, have lower risk disease and lower mortality compared with the previous era, these advances coupled with the emergence of effective disease-modifying therapies have confounded the design of future prospective clinical trials and interpretation of historical control data.

Main Body: The Amyloidosis Forum is a public–private partnership between the US Food and Drug Administration Center for Drug Evaluation and Research and the nonprofit Amyloidosis Research Consortium (www.arci.org). This article summarizes proceedings from the 21 June 2023 Amyloidosis Forum on advancing drug development in ATTR amyloidosis in an evolving treatment landscape. The Forum focused on elements of clinical trial design to address these challenges and discussed their strengths and weaknesses from multiple stakeholder perspectives (i.e., patient, sponsor, statistician, clinician, and regulatory authorities).

Conclusion: Given rapid evolution of natural history in ATTR amyloidosis, the utility of historical control data is limited. Leveraging contemporary real-world data is essential for clinical trial design. Evidence generation from clinical trials should address clinically relevant questions. Key factors in successful trial design must be informed by up-to-date data on natural history, prognostic factors, clinically meaningful thresholds, and sharing available clinical trial data. The Amyloidosis Forum includes the community of patients with ATTR amyloidosis, the physicians who treat them, and the sponsors and regulators who collectively stand ready to support further studies in order to develop novel effective therapies.

Keywords

Clinical trial design; Drug development; Rare diseases; Transthyretin amyloidosis

INTRODUCTION

Hereditary and Wild-type Transthyretin Amyloidosis: Features and Natural History

Systemic amyloidosis is characterized by extracellular deposition of misfolded fibrillar protein in tissues identified by green birefringence on Congo red staining (ORPHA 69); these amyloid deposits in turn disrupt tissue architecture and organ function. The different types of systemic amyloidosis all currently meet the US Food and Drug Administration (FDA) definition of a rare disease with fewer than 200,000 persons diagnosed in the USA.

Hereditary transthyretin amyloidosis (ATTRv, also referred to as hATTR; ORPHA 271861) is a rare, progressive form of systemic amyloidosis caused by inherited variants in the transthyretin (*TTR*) gene, which presents with heterogenous disease patterns including peripheral and autonomic neuropathy, intravitreal eye deposits, heart failure (HF) and atrial fibrillation, and several orthopedic manifestations including a history of carpal tunnel syndrome, spinal stenosis, or joint replacements [1, 2]. Wild-type ATTR amyloidosis (ATTRwt; ORPHA 330001) is predominately seen in older adults (> 60 years of age) and

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primarily impacts the heart. Carpal tunnel syndrome, spinal stenosis, biceps tendon rupture, and rotator cuff tear often precede diagnosis. ATTRwt amyloidosis is typically diagnosed in older men and is more common than ATTRv amyloidosis [1]. Mortality associated with ATTRv and ATTRwt amyloidosis is usually dependent on the stage of the disease, which is largely determined by the degree of cardiac dysfunction.

ATTR amyloidosis is now most commonly diagnosed without a biopsy using a combination of testing for monoclonal proteins and radionuclide scintigraphy with diphosphono-1,2-propanodicarboxylic acid, pyrophosphate (DPD), technetium pyrophosphate (PYP), or hydroxymethylene diphosphonate (HMDP) [3–6]. Widespread use of non-invasive diagnosis techniques and greater disease awareness have led to an increase in new diagnoses of ATTR amyloidosis at an earlier stage of disease (Fig. 1) [7, 8].

The natural history of ATTR amyloidosis is characterized by progressive functional decline [7]. The disease is fatal in the absence of disease-modifying therapy. Even with disease-modifying therapy, patients may continue to progress and die. Imaging studies in patients with amyloidosis demonstrate that prognosis is associated with the degree of systemic amyloid burden [9, 10]. Until 2011, liver transplantation was the only approach to treat ATTRv disease. While liver transplantation reduced variant TTR serum concentration by 95% and improved survival in patients with ATTRv polyneuropathy (ATTR-PN), such a therapeutic approach does not address wild-type disease or patients with ATTRv cardiomyopathy (ATTR-CM) and is not feasible for most patients given the shortage of organs, surgical risk, and advanced age of many affected patients.

Available Therapy and Unmet Medical Need

Two classes of drugs, silencers and stabilizers, form the basis of current disease-modifying therapy for ATTR amyloidosis. Diagnostic and therapeutic advances have led to a larger patient population with early-stage disease and lower mortality over time. Early intervention is recommended (Fig. 2) [11], as current approved drugs do not remove amyloid and are most effective before significant organ dysfunction has ensued. Approved silencer therapies (e.g., patisiran, inotersen, and vutrisiran) reduce the supply of amyloid precursor protein (TTR) and have demonstrated benefit in the treatment of ATTR-PN [12–14]. Other therapies stabilize amyloid-forming proteins [15] and have been approved for treatment of ATTR-CM (e.g., tafamidis) or have recently been reported to provide clinical benefit (e.g., acoramidis) in pivotal clinical trials [16].

Despite available treatment options, morbidity remains high and there are many unmet medical needs for patients with ATTR amyloidosis. The management of ATTR amyloidosis remains complex because of disease heterogeneity, progressive and debilitating multisystemic symptoms, limited expertise in evaluation and management of patients outside of established centers of excellence, and cost of therapies [17].

Contemporary ATTR amyloidosis cohorts are diagnosed with early stage disease and lower mortality compared with previous era [8, 11] limiting the use of historical controls and resulting in larger or longer trial duration if hard endpoints such as mortality and cardiovascular (CV) hospitalizations are components of the primary endpoint. Additionally,

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subgrouping of patients into distinct treatment populations (ATTR-CM and ATTR-PN) limits enrollment of patients into clinical trials of what is already a rare disease. Finally, the administration of disease-modifying therapies as standard of care confounds the design of future prospective clinical trials and renders enrollment and completion of placebo-controlled trials (without add-on therapy) difficult to conduct. Thus, this evolving treatment landscape poses challenges for the development of new therapies to address unmet medical needs.

The Amyloidosis Forum

The Amyloidosis Forum is a public–private partnership formed in 2019 between the US FDA Center for Drug Evaluation and Research and the nonprofit Amyloidosis Research Consortium (ARC; www.arci.org). The Amyloidosis Forum seeks to advance the understanding of the systemic amyloidoses and bridge gaps in drug discovery and drug development for these rare diseases [18].

All Amyloidosis Forum meetings are publicly available at https://amyloidosisforum.org/. Prior meetings and subsequent working groups focused on identification of clinical trial endpoints and analysis strategies for immunoglobulin light chain (AL) amyloidosis [18–21]. A recent meeting to understand potential pathways for development of imaging endpoints for clinical trials in AL and ATTR amyloidosis (Dorbala et al. in preparation) led to this effort to further understand the current state of drug development for the treatment of ATTR amyloidosis and implications for the design of clinical trials in an evolving treatment landscape.

On 21 June 2023 Amyloidosis Forum held a public meeting on the FDA campus with a hybrid virtual format. The meeting was attended by more than 400 individuals representing 19 countries. Specific goals of the meeting were to (1) review current standard of care and assess the current unmet medical needs for patients and clinicians, ensuring access to care and diversity in research, and (2) identify challenges facing drug development for ATTR amyloidosis in a changing treatment landscape. The objective of this manuscript is to summarize the Amyloidosis Forum proceedings and highlight the implications of treatment advances in ATTR amyloidosis on future drug development. Specifically, the focus is on elements of clinical trial design to address these challenges in ATTR amyloidosis and discuss their strengths and weaknesses from multiple stakeholder perspectives (i.e., patient, sponsor, statistician, clinician, and regulatory authorities).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Permission was received by the Amyloidosis Forum to publish this review article.

IMPLICATIONS OF TREATMENT ADVANCES ON DRUG DEVELOPMENT

Therapeutic advances have provided meaningful improvements in the severity and progression of ATTR amyloidosis. The Forum reviewed challenges in ATTR-CM in the context of recent pivotal trials (Table 1) and reviewed evolving unmet medical needs for patients with “non-cardiac” ATTR amyloidosis (including ATTR-PN). The need for

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clinicians and drug developers to take a multidisciplinary approach to treatment and reduce focus on individual characteristics of ATTR amyloidosis, where possible, was also discussed.

ATTR-Cardiomyopathy

ATTR-CM is a restrictive cardiomyopathy that results in HF, arrhythmias, and conduction disease and is associated with an increased risk for hospitalization and premature death. Despite improvements in care for patients with ATTR-CM, there is still significant residual morbidity and mortality to address (Table 2).

The National Amyloidosis Centre (NAC) prognostic staging system for ATTR-CM is based on renal function (estimated glomerular filtration rate, eGFR) and circulating levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) [22]. While the NAC staging system is objective, prognosis is also dependent on New York Heart Association (NYHA) class, daily dose of loop diuretics, health-related quality of life (HRQoL) and functional capacity, among other factors [15, 23–25]. NAC staging has been useful both as a prognostic indicator and its components, in particular natriuretic peptides, as an important baseline characteristic for investigational clinical trials to enrich the study population foremost at risk of more rapid progression.

Patients with early-stage HF exhibit low event rates, especially if they are not taking diuretics (NAC stage Ia, Fig. 1b) [26]. Efforts to develop new therapeutics are hampered in these patients as a result of lower incidence of subsequent morbid events (mortality and worsening HF); correspondingly an extended trial duration would therefore be required to obtain sufficient numbers of morbid events. Conversely, if clinical trials exclude patients with early stage ATTR-CM, those drugs may ultimately not be available to those patients who benefit the most from early intervention because of product access or reimbursement.

The shift to an earlier stage study population is evidenced by the shift in baseline characteristics (e.g., NYHA class, Kansas City Cardiomyopathy Questionnaire [KCCQ], NT-proBNP) of study populations from recent trials (e.g., APOLLO-B, ATTRibute-CM) compared to those enrolled previously (ATTR-ACT) (Table 2) as well as real-world data [8]. Recent ATTR-CM study populations appear to substantially outperform historical control data and previously published baseline characteristics (e.g., ATTR-ACT) and placebo arm data as a result of the shift to diagnosing patients at an earlier stage of their disease.

Earlier diagnosis combined with the availability of background disease-modifying therapy, a slower disease trajectory, and less severe baseline characteristics suggests that previously employed clinical trial endpoints may take longer to meet, given lower event rates. Therefore, in the context of available therapeutic options and earlier diagnosis, investigational drug development will require more effective drugs or larger study populations and longer duration to demonstrate changes in overall survival or hospitalization frequency. The Forum also discussed potential methods to address these emerging issues, such as using imaging and/or biomarkers to identify patients at enhanced risk of cardiac events or broadening clinical outcomes and using additional meaningful endpoints as part of composites in clinical trial design.

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Non-cardiac ATTR

ATTRv amyloidosis is a heterogenous, multisystemic disease that also involves vitreous opacities and glaucoma, and peripheral neuropathy. For patients with extended survival afforded by available therapies, focal neurologic episodes and cerebral vascular bleeding due to TTR secretion into the cerebrospinal fluid have been reported [27]. In patients with ATTRv amyloidosis, the incidence of vitreous opacities is dependent on mutation type with an estimated incidence of 5–34% and is characterized by vitreous floaters and progressive decrease in visual acuity [28]. Historically, patients with ATTRv amyloidosis died before central nervous system (CNS) pathology presented [29]. As survival improves with disease-modifying therapy targeting hepatic transthyretin, production by the retinal epithelium and choroid plexus remains unaddressed because of the lack of penetration of the blood–brain barrier by currently available therapies, leading to increases in the incidence of focal neurologic episodes and ophthalmic manifestations [28]. Cognitive dysfunction due to CNS amyloid is therefore considered an emerging phenotype [30].

How well available therapies cross the cerebrospinal fluid–blood and eye–blood barriers is only beginning to be understood, and whether concentrations of therapies are sufficient to address emerging CNS and ocular phenotypes requires additional study [31]. Therefore, non-cardiac presentations and especially CNS manifestations represent a phenotypic complexity in the management of ATTR amyloidosis and present an increasingly unmet medical need as patient survival improves. Multiple patient testimonials at the Forum meeting stressed the impact of impaired eyesight, orthopedic manifestations, and other non-cardiac ATTR amyloidosis sequelae as most impactful on HRQoL. For patients with non-cardiac ATTR amyloidosis, clear diagnostic criteria are required since “focal deficits” are very broad and cognitive loss or CNS bleeds may be attributable to causes other than ATTR amyloidosis.

CLINICAL OUTCOME MEASURES IN ATTR TRIALS

Overall Survival and Worsening Heart Failure

Overall survival is viewed as the “gold standard” objective primary endpoint in clinical trials. In the pivotal ATTR-ACT trial, tafamidis use resulted in a relative reduction in mortality of approximately 30% compared with placebo (HR 0.70; 95% CI 0.51–0.96) which was in part attributable to the severity of the population enrolled [15]. However, compared with 57.1% of patients in the ATTR-ACT placebo arm who were alive at month 30, data from the ATTRibute-CM and APOLLO-B trials (where background tafamidis therapy was allowed) demonstrated a trend toward improved overall survival with 74.3% of patients in the placebo arm alive at month 30 and 94.4% of patients in the placebo arm alive at month 12, respectively [15, 22, 32, 33] (Table 2).

As a result of earlier diagnosis, therapeutic interventions, and improved survival over time for patients with ATTR-CM, the natural history of the disease and clinical trial landscape have changed. The proportion of patients enrolled into ATTR amyloidosis clinical trials and prescribed disease-modifying therapy has significantly increased over time. When censoring for the start date of clinical trials and disease-modifying therapy, year of diagnosis remained

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a significant predictor of mortality in the overall population [8]. Because of these factors, trials with overall survival as the dominant component of the primary endpoint now require more patients, a longer duration, enrichment with higher-risk patients, or a combination of these approaches, to be sufficiently powered for detecting meaningful drug effects; alternatively, pre-specified analysis methodology will need to rely less on overall survival.

The Forum panel discussed the assumption that all-cause mortality/overall survival is an important clinical outcome but may no longer be feasible as the driving component of primary outcomes in pivotal interventional trials because of the size and duration of trials required to achieve statistical significance. Extrapolation of trial design elements from HF trials was also discussed as a model for potential primary composite endpoint construction, allowing outcomes other than overall survival to be drivers of the effect size [34, 35]. More reliance on composite outcomes with events focused more broadly on worsening HF (either resulting in a hospitalization, unplanned or urgent care) and healthcare utilization should be anticipated. In addition, diuretic use among patients with ATTR-CM is accepted as a prognostic indicator in clinical practice and has been used in the context of a worsening HF event as a central treatment strategy when administered urgently by an intravenous route. Worsening HF events characterized by both intravenous and oral intensification of diuretics have been shown to be particularly useful as clinical outcome measures in HF trials [36] and should be adapted for use in ATTR-CM trials moving forward.

Functional and Patient-Reported Outcomes

For patients with ATTR amyloidosis and multiple stakeholders including healthcare providers, regulatory agencies, and payers, improvements in functioning and HRQoL are considered meaningful. A series of patient-focused drug development guidance documents have been developed to provide a stepwise process to collect and submit data reflecting patient/caregiver experience to facilitate product development and regulatory decision-making (https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical).

In general, functional and patient-reported outcomes are designed to reflect the impact of an intervention on how a patient feels or functions, and are particularly relevant for heterogeneous, multisystem, progressive diseases such as ATTR amyloidosis. To date, multiple metrics beyond survival and CV events have been informative, often as secondary endpoints, in clinical trials; notably these include functional outcomes (e.g., 6 Minute Walk Distance, 6MWD), patient-reported outcomes (e.g., KCCQ), and clinician assessments (e.g., modified Neuropathy Impairment Score + 7) [37] (Table 1). However, no single metric addresses all key domains of disease impact. Forum panelists agreed the clinically meaningful differences and timings of assessments for non-ATTR-specific metrics need to be better understood particularly in light of evolving natural history [7].

In patients with ATTR-CM, functional capacity data (i.e., 6MWD) from recent clinical trials suggest the placebo control arm substantially outperformed historical controls and approached reference data for heathy adults when assessed over a 12-month period [7, 15, 38] (BridgeBio data on file; Fig. 3). Whereas patients from the NAC natural history study

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and the placebo arm of ATTR-ACT were similar (− 45 m and − 56 m declines after 12 months, respectively), trial analysis from the placebo arm of ATTRibute-CM showed an approximate annual decline in 6MWD of − 7 m at 12 months, equivalent to healthy adult control data, and a separation from active treatment only occurred after month 24 [16]. Furthermore, while a statistically significant difference between patisiran and placebo in 6MWD was achieved at month 12 in the APPOLO-B trial, the change from baseline at month 12 was small (Hodges-Lehmann estimate of median difference [patisiran – placebo] 14.7 m [95% CI 0.7, 28.7]) and a major factor in the FDA decision to issue a complete response letter [33]. These recent trials demonstrate multiple complexities in trial design, including not only the timing of functional outcome assessment but also what accounts for changes in functional outcomes (e.g., cardiac or neurologic improvement), and selection of a population likely to respond.

In patients with ATTRv-PN, CNS and ophthalmic manifestations represent an increasingly unmet medical need. For clinical trials of investigational products likely to cross the eye–blood barrier, clinical endpoints such as best corrected visual acuity (BCVA) and ophthalmic computed tomography are measurable and considered appropriate to assess in patients with ophthalmic involvement in other conditions. However, Forum expert panelists noted the importance of standardized methods to avoid participant bias and enable the sensitivity to detect treatment differences in BCVA [39], thereby necessitating the need for masked trials with adequate control arms when ophthalmic outcomes are specified as key endpoints.

Imaging

Non-invasive imaging modalities play a critical role in diagnosis and monitoring disease burden. Echocardiography is commonly used for initial detection of characteristic cardiac features associated with cardiac amyloidosis and to follow changes in cardiac structure and function. Cardiac magnetic resonance (CMR) imaging provides quantitative information on tissue composition, including extracellular volume fraction mapping and the ability to distinguish amyloid-related left ventricular thickening. Single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) use molecular tracers to detect amyloid deposition in the heart and other organs impacted by ATTR amyloidosis.

Development of emerging therapies to target amyloid deposition (i.e., anti-amyloid therapies) places renewed emphasis on the utility of imaging in ATTR amyloidosis clinical trials (Dorbala et al. manuscript in review). The Forum discussed the recent observations emerging from clinical trials regarding improvements in scintigraphy with therapy that do not appear to be associated with significant changes in cardiac structure and function confounding the clinical relevance and suggested caution in using serial scintigraphy. While recent reports indicating rare spontaneous reversal of the ATTR amyloidosis phenotype with accompanying structural and functional improvements in the setting of anti-TTR amyloid antibodies is encouraging [40], the potential impact of this observation in the context of differentiating treatment-induced vs spontaneous changes requires additional study.

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APPROACHES TO ADDRESS CHALLENGES IN DRUG DEVELOPMENT

In general, for regulatory approval, clinical trials need to show benefits in how a patient feels, functions, or survives that outweigh any risks, in comparison to a suitable control arm. For decision-making by clinicians and payers, and to support possible fast track or breakthrough designations, clinical development programs also need to address multiple clinically relevant questions: Does this therapy address an unmet need? Is it better than currently available therapies? Can it be combined in a cost-effective manner to improve outcomes?

Amid the many questions to be answered and decisions to be made, successful trial design for ATTR-CM is complicated by trends toward a less severe patient population owing to advances in earlier diagnosis and available effective therapies. Trials are trending toward study populations with earlier stage disease and require larger sample sizes and/or trial durations to demonstrate treatment effect (Tables 1, 2). The ongoing pivotal clinical trial, CARDIO-TTRansform (NCT04136171) initiated enrollment in FEB-2020 and subsequently expanded enrollment from 750 to 1000 and ultimately to 1400 subjects in 2022 in order to be adequately powered to detect a clinically meaningful effect on a composite assessment of mortality/CV event data. Consequently, CARDIO-TTRansform has become the largest prospective interventional trial conducted to date in patients with ATTR-CM.

Moving forward, even more attention is required for successful clinical trial design with clinically meaningful outcomes. Multiple decisions are required to define the study population, select the appropriate comparator arm, incorporate functional and patient-reported endpoints, and define appropriate analysis methods into clinical trials (Fig. 4). These design decisions need to be made holistically and informed by evidence whenever possible. The required duration of a trial will depend on the sensitivity of the selected endpoints to effects of the new drug versus the selected comparator arm in the enrolled population.

Clinical trial endpoints must be measurable, meaningful to patients (and clinicians and payors), reproducible, valid, and accepted by regulators. Surrogate endpoints—defined as a marker that is not itself a direct measurement of clinical benefit and is known to predict or reasonably likely to predict clinical benefit—may be considered as the basis of traditional or accelerated regulatory approval. A table of surrogate endpoints that were the basis of drug approval or licensure by the US FDA is available at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure for consideration. Evidence of surrogate validity may also be required in order to reduce uncertainty for economic models for reimbursement per National Institute for Health and Care Excellence (NICE) in the UK and other European regulatory authorities.

Outcomes: Clinical Measures, Possible Surrogates and Composites

Given precedent for composite outcomes in ATTR trials (e.g., ATTR-ACT), the Forum reviewed the potential applicability of composite outcomes from HF trials (e.g., VICTORIA, DELIVER, PARAGON trials) to ATTR amyloidosis trials. Options for potential composite outcome components included hospitalization or death, recurrent hospitalization events,

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days alive and out of hospital/urgent care, or progression to next level of care (January 14, 2022: Searching for a Unicorn: Understanding Stakeholder Perspectives When Selecting Outcomes for Outpatient Trials (Christopher Lindsell, PhD)—Rethinking Clinical Trials). Statistical methods for analysis of recurrent events composite outcomes include Andersen-Gill [41], Lin-Wei-Yang-Ying (LWYY) [42], and Wei-Lin-Weissfeld (WLW) [43] methodologies. The inclusion of recurrent events, rather than simply the time to first event, was discussed as a way to increase sensitivity to treatment effects, with use of appropriate statistical approaches such as joint frailty modeling for recurrent times and CV death, win ratio, and negative binomial for event numbers.

For example, in the PARAGON-HF trial (NCT01920711) that investigated sacubitril/valsartan in patients with HFpEF, the primary endpoint was a composite of total (first and recurrent) HF hospitalization and CV death [44]. As a way to quantify clinically meaningful treatment effects, post hoc analyses were conducted to illustrate an alternative, robust, and model-free approach. In a post hoc analysis of PARAGON-HF, the estimated mean cumulative count of events over time was summarized for each treatment group by the area under the curve, which can be interpreted as the mean total event-free time lost from multiple undesirable outcomes [45]. Other endpoints from multiple outcomes included analysis of days alive out of hospital (DAOH) and percent DAOH to adjust for differences in duration of follow-up [46]. Possible limitations of composite events include the need to determine and justify the subjective relative weighting of different outcome components, challenges to interpretability, and regional variability in hospitalization rates that can also be confounded by external factors (e.g., coronavirus outbreaks).

At the same time, it was observed that physicians routinely assess and review multiple biomarkers such as NT-proBNP and extracellular volume via CMR to implement care for patients with ATTR amyloidosis, which may be suitable as components of composite outcomes. The Forum further discussed whether worsening HF, defined by a persistent oral intensification of loop diuretics, as is commonly observed in ATTR-CM clinical practice could be included as part of the definition of a worsening HF event. While establishing the interpretability of composite outcomes for use in clinical trials can take special care, such outcomes could be more aligned with clinical practice, and overall meaningfulness to patients, than focusing on a single event. The Forum has also previously reviewed key attributes of composite endpoints as a potential path forward for AL amyloidosis clinical trials [47].

Innovative Trial Designs: Enrichment and Other Strategies

With respect to measuring disease burden in the context of clinical trials, the Forum discussed the pros and cons of study population enrichment. With the evolving natural history of ATTR-CM, amid earlier diagnosis and effective therapies, there is a need to identify patients with higher risk of events and/or faster progression of declines in function or worsening symptoms. The benefits of new therapies could be more detectable in such populations, with shorter trial durations and fewer patients allocated to placebo.

An enrichment strategy for drug development, i.e., to enroll patients with a greater chance of benefitting from treatment in clinical trials, will require suitable inclusion/exclusion

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criteria that optimally manage the tension between enhancing the population for events and generalizability of the results. Factors predicting rapid progression include disease type (ATTRv vs ATTRwt) and stage of disease (NAC classification), higher NYHA class, and daily dose of loop diuretics. Multiparametric biomarker profiles and/or proteomics/metabolomics are also possible approaches to define this cohort. However, to implement successful enrichment strategies, knowledge of predictive and prognostic factors needs to be quantitative, up-to-date, and relevant to current ATTR-CM populations. For example, while risk factors for HF events are well understood, their precise quantitative relationship with event rates in a modern treated population is less well understood. Likewise, predictive and prognostic factors for rates of decline in functional or HRQoL endpoints, such as 6MWD or KCCQ, have been less well studied.

Clinical trial design is ultimately a quantitative exercise, as the sample size and trial design need to ensure adequate power to detect meaningful drug effects, and this requires an accurate quantitative understanding of outcomes expected in the control arm. If the control arm does not perform as predicted, e.g., as a result of insufficient, out-of-date, or imprecise understanding of prognostic factors and natural history used to define enrollment, then a trial can become underpowered and fail to definitively confirm or rule out the efficacy of a new treatment—the worst possible outcome for all involved.

The Forum encouraged sponsors to share clinical trial data to predict which patients may respond to a given therapy and potentially allow for enrichment of the study population to ensure a realistic event rate in a reasonable time frame. Contemporaneous natural history data from clinical centers of excellence on outcomes of interest is essential to enable future trials to be adequately powered.

While enrichment can enable smaller trials with shorter durations of follow-up, the stringency of the enrichment strategy could lengthen the time it takes to recruit patients. Treatment effects might also not generalize to broader populations. If broader populations are hypothesized to benefit, albeit over a longer time frame, then additional longer-term evidence development would be needed to establish that effect.

Furthermore, considering the mechanism of action for the investigational therapy may allow for selection and enrichment of a study population likely to respond. In the future, the Forum will assess eligibility criteria across prior trials to evaluate the extent to which it may be possible to streamline entry criteria to both increase the probability of success, while also including the broadest patient population possible. Regulatory guidance early and often is always recommended. Similarly, identification of non-responders, identified as having advanced, unmodifiable disease trajectories, is equally important to exclude where possible to avoid exposure of participants to futile therapy.

As a complement to enrichment strategies, which aim to enroll and treat the patients expected to benefit most, “deprescribing” trials can also be considered as a way to test hypotheses about which patients might benefit least or not at all from treatment. Such questions become increasingly important amid an increasing array of therapies, the potential

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for combination therapies, and economic considerations from the patient (out of pocket) and health system perspectives looming unavoidably over real-world treatment decisions.

Beyond Randomized Controlled Trials: External Controls, Hybrid Trial Designs, Real-World Comparative Effectiveness

Overall, the Forum participants agreed that placebo-controlled trials (i.e., with no active control arm or in the absence of standard of care therapy) conducted in disease states with effective available therapies may not be operationally feasible. However, this provides a potential opportunity to obtain evidence to guide selection of therapy and address the role of combination therapy. The FDA noted development of multiple guidance documents for the use of real-world evidence to support a new indication of an approved drug or provide post-marketing information. Specifically, guidance for key regulatory considerations for external controls in clinical trials is available (https://www.fda.gov/media/164960/download) to demonstrate effectiveness. The Forum discussed the potential for use of real-world data to establish control data for clinical trials, to augment randomized controls through a hybrid design, or for use in assessing real-world comparative effectiveness. However, amid the rapidly changing landscape for diagnostics and therapeutic standards of care in ATTR amyloidosis, reliance on historical controls and/or real-world data would present a heightened risk of bias in drug development; use of data from parallel time periods would be necessary. One would also need to consider possible differences in background standards of care that might impact outcomes, such as differences in thresholds of hospitalization for HF across health systems or use of HF therapeutics such as mineralocorticoid antagonists or sodium-glucose co-transporter 2 inhibitors. Methods for identifying, assessing, and mitigating risks of bias would be needed to pursue this approach, and the expected treatment effect sizes would need to be large enough to overcome such risks of bias.

While comparing real-world data to clinical trial data is challenging in ATTR amyloidosis, with an increasing array of treatments available, real-world comparative effectiveness studies may be the only way to compare treatments and treatment combinations. Recent FDA guidance has presented considerations for the use of real-world data for the support of regulatory decision-making (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug), such evidence is also utilized by payers and other decision-makers, and is of tremendous value to clinicians. Real-world data can also help establish the prognostic importance or surrogacy of biomarkers and may be applied to inform when therapy might be futile in advanced disease (an important societal consideration in the context of expensive, long-term therapies). Opportunities exist to leverage data from amyloid centers of excellence, registry studies, and large heathcare systems databases (e.g., US Veterans Administration) towards these ends.

Given the systemic, multiorgan, heterogeneous nature of ATTR amyloidosis, the Amyloidosis Forum is working toward identifying appropriate endpoints and analytical methodologies for use in clinical trials investigating novel therapies in an evolving therapeutic landscape. Such endpoints would be meaningful to patients, caregivers, payors,

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and regulators. Establishing meaningful differences (and the time to achieve a meaningful difference) is important and is heavily dependent on an individual patient, disease stage, or drug mechanism of action.

CONCLUSIONS AND FUTURE DIRECTIONS

While the past two decades have been transformative for patients with ATTR amyloidosis in terms of earlier diagnosis and available therapies, the Amyloidosis Forum focused on approaches to clinical development of new therapies to address unmet medical needs in the context of an evolving treatment landscape. The importance of the community coming together to discuss trial design was identified as a key factor to benefits both patients and other stakeholders. While the goal is to expedite drug development and approval processes where possible, it is essential to establish clinical benefits that outweigh the risk and ensure the evidence is clear to support a claim, particularly for a long-term maintenance therapy.

Despite advances in the diagnosis and management of ATTR amyloidosis, unmet needs remain, especially in patients with advanced disease. Multisystem manifestations, specifically ophthalmic and neurologic complications, are inadequately addressed by current therapies and healthcare systems. Given the rapid evolution of natural history, the utility of historical control data is limited. Leveraging real-world data will inform clinical trial design. Evidence generation from clinical trials should address clinically relevant questions. The multisystemic nature of ATTR amyloidosis and the evolving treatment landscape warrants consideration of innovative approaches to trial design and analyses of clinical outcome data. The development of endpoints to address CNS and ocular effects is critical to address unmet medical need in patients with ATTR amyloidosis. Furthermore, for ATTR-CM, there is still currently only one FDA approved therapy, a TTR stabilizer (tafamidis), that has been shown to slow down progression of the disease.

Overall, approaches to future clinical trial design will need to incorporate elements of combination therapy, population enrichment based on drug mechanism of action, and be adequate and well controlled. Successful trial design requires multiple decisions to define the study population, to incorporate functional and patient-reported endpoints, and define the trial duration, targeted effect size, and pre-specified analysis methodology (Fig. 4); these design decisions need to be made holistically and informed by evidence. Successful trial design must be informed by contemporaneous natural history, prognostic factors, clinically meaningful thresholds, validated endpoints, and pre-specified analysis. Ideally, evidence is specific to ATTR amyloidosis, contemporaneous, quantitative, and can be measured in a reasonable time frame for the benefit of patients and all other stakeholders. The Amyloidosis Forum includes the community of patients with ATTR amyloidosis, the physicians who treat them, and the sponsors and regulators who collectively stand ready to support further studies in order to develop novel effective therapies.

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Data Availability.

All Amyloidosis Forum meetings are publicly available (https://amyloidosisforum.org/). Recordings from the 21 June 2023 meeting, Advancing Drug Development in ATTR Amyloidosis in an Evolving Treatment Landscape, are available at https://amyloidosisforum.org.

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Key Summary Points

Despite available treatment options, the management of transthyretin amyloidosis (ATTR amyloidosis) remains complex because of disease heterogeneity, progressive and debilitating multisystemic symptoms, limited expertise in evaluation and management, critical knowledge gaps, and cost of therapies.

Fortunately, there is a trend toward identification of a less severely affected patient population owing to advances in diagnosis and available effective therapies; this trend, however, is proving challenging for successful trial design in the development of novel treatments for ATTR amyloidosis.

Given the rapid evolution of natural history in ATTR amyloidosis, the utility of historical control data is limited, and use of contemporary real-world data is essential to inform innovative clinical trial designs that must account for healthier patients and the availability of approved disease-modifying therapies.

The Amyloidosis Forum is a public–private partnership that includes the community of patients with ATTR amyloidosis, the physicians who treat them, and the sponsors and regulators who collectively stand ready to support further studies in order to develop novel effective therapies.

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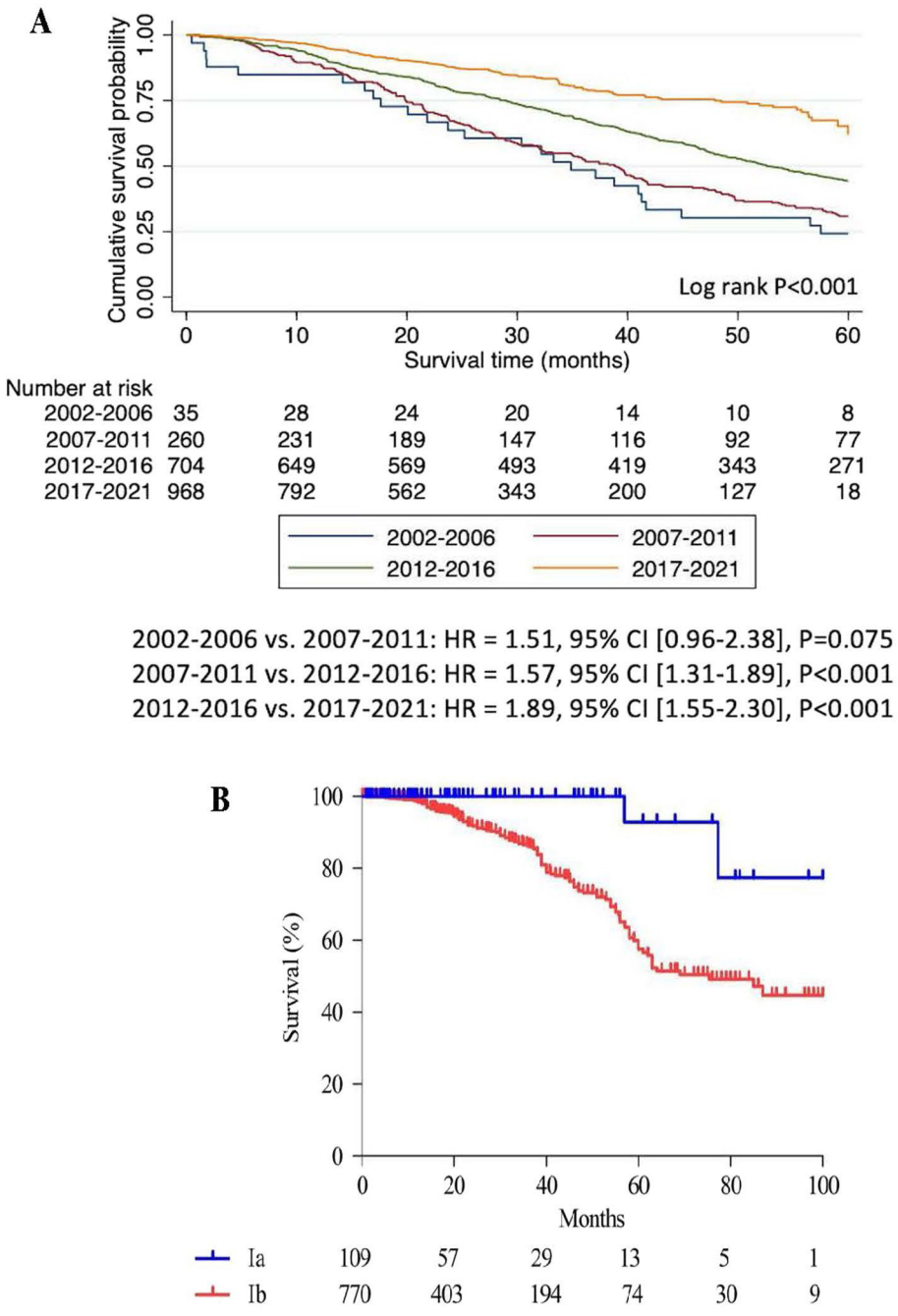

Fig. 1.

A Kaplan–Meier analysis demonstrates the prognostic effect of the year of ATTR-CM diagnosis between 2002 and 2021, followed by multivariable Cox proportional hazards regression analysis, adjusted for age, comparing the risk of death in each 5-year interval between 2002 and 2021 (in the absence of disease-modifying therapies). Reproduced per open access article from Ioannou et al. [8]. **B** Kaplan–Meier survival curves stratified by National Amyloidosis Centre transthyretin amyloid stage for the whole ATTR-CM cohort. Median estimated survival among patients with stage Ia was not met at 100 months and was 75 months (95% CI 57–93) in patients with stage Ib ($P = 0.0002$). Adapted per open

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access article from Law et al. [26]. *ATTR-CM* transthyretin amyloid cardiomyopathy, *CI* confidence interval, *HR* hazard ratio

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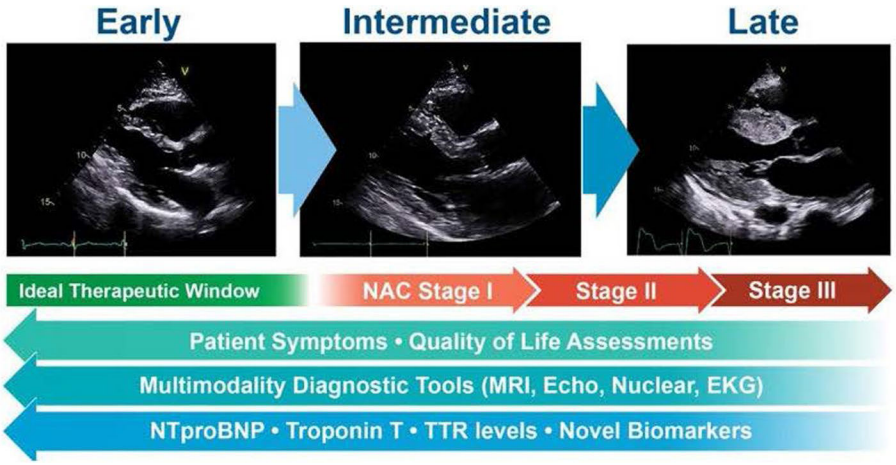

Fig. 2.

Representation of echocardiographic images (parasternal long-axis view) at different levels of wall thickness in transthyretin amyloid cardiomyopathy. Identification of patients at the earliest stage possible with minimal cardiac dysfunction at a time before more rapid declines in health-related quality of life, elevations in cardiac biomarkers, and overt cardiac manifestations of disease ensue is an important goal. Reproduced per open access article from Martyn et al. [11]. *NAC* National Amyloidosis Centre, *MRI* magnetic resonance imaging, *EKG* electrocardiogram, *NTproBNP* N-terminal pro-brain natriuretic peptide, *TTR* transthyretin, *Echo* echocardiography

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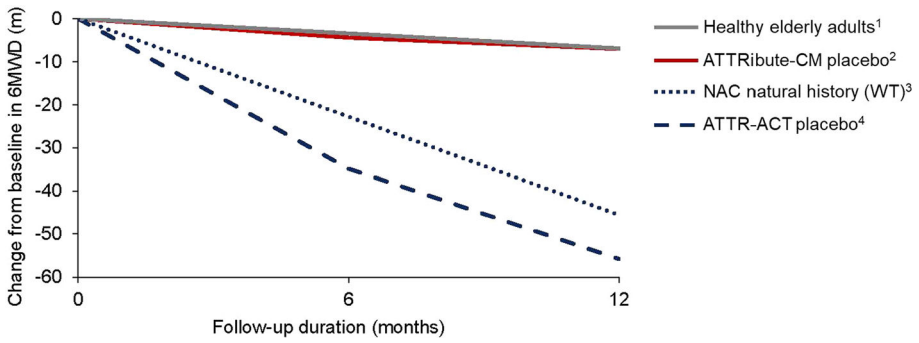

Fig. 3.

ATTRibute-CM placebo group substantially outperformed historical controls regarding changes in 6MWT distance at 1 year. 1. Adapted with permission from Enright PL, Sherril DL. Am J Respir Crit Care Med. 1998;158(5 Pt1):1384–7. *N* = 117 healthy elderly adults. 2. BridgeBio, data on file. Observed ATTRibute-CM drah results, *N* = 160 at month 12. 3. Adapted with permission from Lane T, et al. Circulation. 2019;140(1):16–26. *N* = 289 ATTRwt-CM at month 12. 4. Adapted with permission from Maurer MS, et al. N Engl J Med. 2018;379(11):1007–16. *N* = 136 at month 12. *NAC* National Amyloidosis Centre, *ATTR-ACT* Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *6MWD* 6 Minute Walk Distance

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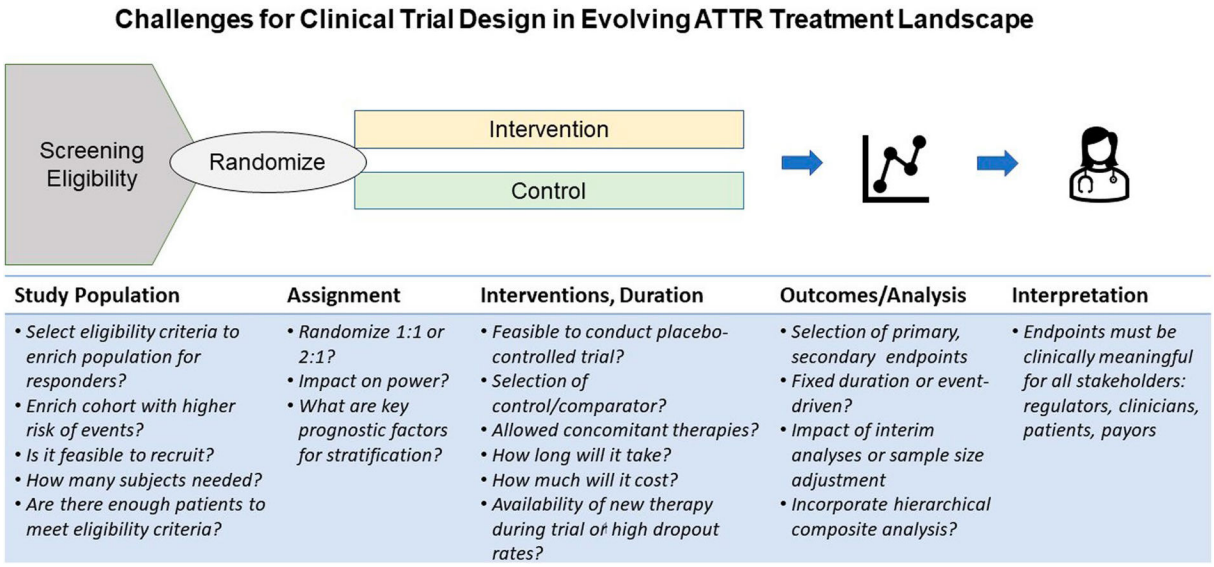

Fig. 4.

Challenges for clinical trial design in evolving ATTR treatment landscape. Successful trial design for ATTR-CM is complicated by trends toward a patient population with less severe disease owing to advances in earlier diagnosis and available effective therapies. Trial design must be based on contemporaneous data with input from key stakeholders. *ATTR* transthyretin amyloidosis, *ATTR-CM* transthyretin amyloid cardiomyopathy

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Table 1

Design of recent pivotal clinical trials in ATTR-CM

Trial (identifier)	ATTR-ACT NCT01994889	ATTRibute-CM NCT03860935	APOLLO-B NCT03997383
Trial design	*Randomized, double-blind, placebo-controlled*		
Enrollment period	December 2013–August 2015	March 2019–September 2022	September 2019–June 2021
Treatment duration	30-month DBTP (based on median OS at time of study)	30-month DBTP (tafamidis allowed after month 12)	12-month DBTP
Randomization Stratification	2:1:2 (80 mg: 20 mg: placebo) Baseline NYHA; TTR genotype	2:1 (800 mg: placebo)	1:1 (0.3 mg/kg: placebo) Baseline tafamidis use; TTR genotype, baseline NYHA, age
Intervention/comparator (*n*)	Tafamidis, 20 or 80 mg PO QD (*n* = 264)	Acoramidis, 800 mg PO BID (*n* = 421)	Patisiran, 0.3 mg/kg IV Q3W (*n* = 178)
	Placebo (*n* = 177)	Placebo (*n* = 211)	Placebo (*n* = 181)
Population Key eligibility	ATTR-CM (wild-type [WT] or variant)	ATTR-CM (wild-type [WT] or variant)	ATTR-CM (wild-type [WT] or variant)
	History of HF (≥ 1 HF hospitalization, clinical, diuretic use) 6MWD > 100 m NT-proBNP ≥ 600 pg/mL LV thickness ≥ 12 mm	History of HF (≥ 1 HF hospitalization, clinical evidence, diuretic use) 6MWD > 150 m NT-proBNP ≥ 300 pg/mL LV thickness ≥ 12 mm	History of HF (≥ 1 HF hospitalization, clinical evidence, diuretic use) Tafamidis naive or currently on (≥ 6 months) with disease progression 6MWD > 150 m NT-proBNP ≥ 300 pg/mL < 8500 pg/mL LV thickness > 12 mm
Endpoints			
Primary outcome Analysis methodology	Hierarchical analysis allcause mortality, frequency of CV-related hospitalization (per independent adjudication committee; Finkelstein-Schoenfeld method)	Change in 6MWD at month 12 (part A) Hierarchical analysis all-cause mortality, frequency of CV-related hospitalization, change in NT-proBNP, change in 6MWD (Finkelstein- Schoenfeld method) (part B)	Change in 6MWD at month 12
Functional/HRQoL outcomes	6MWD KCCQ-OS	6MWD KCCQ-OS	KCCQ-OS

DBTP double-blind treatment period, *NYHA* New York Heart Association, *TTR* transthyretin, *PO* per orum, *QD* once daily, *HF* heart failure, *LV* left ventricular, *CV* cardiovascular, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *OS* overall score, *ATTR-CM* transthyretin amyloid cardiomyopathy, *NTproBNP* N-terminal pro-brain natriuretic peptide, *6MWD* 6 Minute Walk Distance

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Table 2

ATTR-CM study populations: trend toward earlier stage baseline characteristics

Trial (identifier)	**ATTR-ACT** NCT01994889	**ATTRibute-CM** NCT03860935	**APOLLO-B** NCT03997383
Enrollment period	December 2013–August 2015	March 2019–September 2022	September 2019–June 2021
Demographics (*N*)	*N* = 441	*N* = 632	*N* = 360
Age (years)	74 ± 7	77 ± 7	76
Sex, male	90.2%	90.2%	89.4%
Race	White (81%)	White (87.8%)	White (77%)
	Black (14.3%)	Black (4.7%)	Black (8.6%)
Key baseline characteristics			
Genotype, ATTRv	24%	9.7%	19.8%
NYHA class			
I	8.3%	10.8%	7.0%
II	59.6%	72.0%	85.2%
III	31.9%	17.2%	7.8%
NT-proBNP (pg/mL)	3078	2325	~ 2300
6MWD, mean	~ 350 m	~ 350 m	~ 370 m
KCCQ-OS, mean	~ 66	71	~ 70
Baseline tafamidis use	N/A	N/A	25%
Survival at primary analysis			
Patients alive (%)	Tafamidis: 70.5%	Acoramidis: 80.7%	Patisiran: 96.7%
	Placebo: 57.1%	Placebo: 74.3%	Placebo: 94.4%
	(Month 30)	(Month 30)	(Month 12)

NYHA New York Heart Association, *TTR* transthyretin, *6MWD* 6 Minute Walk Distance, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *OS* overall score, *ATTR-CM* transthyretin amyloid cardiomyopathy, *NTproBNP* N-terminal pro-brain natriuretic peptide