TITLE PAGE

Protocol Title: A Phase 3, Prospective, Multicenter, Open Label, 2-Part Study of the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of ALXN2060 in Japanese Participants with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTR-CM).

Protocol Number: ALXN2060-TAC-302

Amendment Number: 5.0

Compound: ALXN2060

Study Phase: 3

Short Title: A Phase 3 Study of ALXN2060 in Japanese Participants with Symptomatic ATTR-CM

Sponsor Name: Alexion Pharmaceuticals, GK

Legal Registered Address: Tamachi Station Tower N 3-1-1, Shibaura, Minato-ku, Tokyo 108-0023, Japan

Regulatory Agency Identifier Number(s): NA

Approval Date: 11 Sep 2023

Sponsor Signatory:

[redacted]

14-Sep-2023

Date

Contact Personnel for this Protocol is based in Japan

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 5.0 (11-September-2023)

Overall Rationale for the Amendment:

The main purpose of this amendment is to incorporate the administrative changes from Administrative Letter 1.0 (13 Jul 2023) and clarify the definitions of terms.

Other changes implemented through this Amendment constitute minor editorial corrections, fixing inconsistencies, and clarification.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design	Deleted text ~~stricken~~ and additional text underlined: Following the completion of Month 30 assessments in Part B, participants will be offered the opportunity to continue into the Extension Period ~~which will last until ALXN2060 is approved or~~ for up to 30~~24~~ additional months or until ALXN2060 can be provided via an Alexion post-study access program (as allowed by local laws and regulations), whichever occurs first.	To ensure treatment continuity for patients.
1.1 Synopsis	Approximately 32 months from Screening to Month 30 visit, and up to approximately 60~~56~~ months for participants who will continue treatment with ALXN2060 in the Extension Period.	To align with the updated definition of the Extension Period.
1.3 Schedule of Activities	Table header and footnote d: Extended the duration from Month 24 to Month 30.	To align with the updated definition of the Extension Period.
6.7 Intervention After the End of the Study	Eligible Participants will be offered the opportunity to continue receiving ALXN2060 800 mg bid. in the Extension Period ~~which will last until ALXN2060 is approved in Japan or~~ for up to 30~~24~~ additional months or until ALXN2060 can be provided via an Alexion post-study access program (as allowed by local laws and regulations), whichever occurs first.	To ensure treatment continuity for patients.
8.2.2 Mortality and Cardiovascular-Related Hospitalization	Hospitalizations that are submitted for adjudication and are deemed as not CV-related by the CEC will be considered SAEs. Adverse events of special interest (AESIs, Section 8.4.5) are also considered as part of the efficacy endpoint of CV-related hospitalizations.	To reflect Administrative Letter 1.0. To clarify the description in the CEC Charter as shown in Section 9.6

Section # and Name	Description of Change	Brief Rationale
8.6 Pharmacokinetics, 8.7 Pharmacodynamics	• Month 1 and every 6~~3~~ months during the ~~post~~ Extension Period: Predose	Correction. To align with Schedule of Activities.
Throughout the document	Minor editorial corrections and clarifications.	For correction and/or clarification.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Prospective, Multicenter, Open Label, 2-Part Study of the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of ALXN2060 in Japanese Participants with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTR-CM).

Short Title: A Phase 3 Study of ALXN2060 in Japanese Participants with Symptomatic ATTR-CM

Rationale: This prospective study is designed to evaluate the efficacy, safety, and tolerability, as well as to establish the pharmacokinetic (PK) and pharmacodynamic (PD) profile of ALXN2060 (previously AG10) in Japanese participants with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM), administered on a background of stable heart failure therapy. A multicenter, open label, 2-part design is considered to be the most appropriate study design for meeting this objective. Based on information gained from previous clinical experience with ALXN2060, a twice daily (bid) dose of 800 mg has been selected for this study to represent the optimal combination of potential efficacy, safety, and tolerability.

Objectives and Endpoints

Objective	Endpoints
Primary	
Part A: To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by the 6MWT	**Part A**: Change from Baseline to Month 12 of treatment in distance walked during the 6MWT
Part B: To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by all-cause mortality and cardiovascular-related hospitalization	**Part B:** All-cause mortality and cardiovascular-related hospitalization over a 30-month period
Secondary	
Part A: • To evaluate the effects of ALXN2060 800 mg bid on the 6MWT • To evaluate the effects of ALXN2060 800 mg bid on health-related quality of life as measured by KCCQ-OS in adult Japanese participants with symptomatic ATTR-CM • To assess the safety and tolerability of ALXN2060 800 mg bid in adult Japanese participants with symptomatic ATTR-CM • To assess the PD effects of ALXN2060 by circulating serum TTR concentration as an in vivo biomarker of stabilization and using established ex vivo assays of TTR	**Part A:** • Change from Baseline to Months 6 and 9 of treatment in distance walked during the 6MWT • Change from Baseline to Months 6, 9, and 12 of treatment in KCCQ-OS • Safety parameters to be assessed: treatment-emergent SAEs and AEs, adverse events leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical

Objective	Endpoints
stabilization (FPE); in addition, assess the correlation between TTR concentration/FPE and ALXN2060 concentration	safety laboratory parameters of potential clinical concern • Change from Baseline in serum TTR concentration (an in vivo measure of TTR stabilization) and established ex vivo assays of TTR stabilization (FPE) at Days 14 and 28 and subsequent visits
Part B: • To evaluate the effects of ALXN2060 800 mg bid on the 6MWT • To evaluate the effects of ALXN2060 800 mg bid on health-related quality of life as measured by KCCQ-OS in adult Japanese participants with symptomatic ATTR-CM • To assess the safety and tolerability of ALXN2060 800 mg bid administered for 30 months to adult Japanese participants with symptomatic ATTR CM • To assess the PD effects of ALXN2060 as assessed by circulating serum TTR concentration as an in vivo biomarker of stabilization and established ex vivo assays of TTR stabilization (FPE) and correlation between TTR concentration/FPE and ALXN2060 concentration	**Part B:** • Change from Baseline to Months 18, 24, and 30 of treatment in distance walked during the 6MWT. • Change from Baseline to Months 18, 24, and 30 of treatment in KCCQ-OS • Safety parameters: treatment emergent SAEs and AEs, adverse events leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern • Change from Baseline in serum TTR concentration and established ex vivo assays of TTR stabilization (FPE)
Exploratory	
• To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR CM as assessed by all-cause mortality and cardiovascular-related hospitalization (only Part A) • To explore the population PK of ALXN2060 and its metabolites under the 800 mg orally administered bid dosing regimen • To evaluate the effects of ALXN2060 800 mg bid on circulating biomarkers of myocardial wall stress and microvascular ischemia in Japanese participants with symptomatic ATTR-CM • To evaluate the effects of ALXN2060 800 mg bid on EQ-5D-5L in Japanese participants with symptomatic ATTR-CM • To evaluate the effects of ALXN2060 800 mg bid on cardiac MRI-derived measures of cardiac structure, function and tissue	• All-cause mortality and cardiovascular-related hospitalization over a 12-month period (only Part A) • Exploration of PK over 30 months for ALXN2060 and its metabolite • Changes from Baseline over Month 30 in NT-proBNP and TnI • Change from Baseline in EQ-5D-5L over Month 30 • Change from Baseline to Month 12, 24, and 30 in cardiac MRI parameters (only at selected sites and consenting patients) **Extension Period** • Safety parameters same as the Intervention Period (Part A and Part B) are assessed in the Extension Period

Objective	Endpoints
characterization, in Japanese participants with symptomatic ATTR-CM (only at selected sites and consenting patients) **Extension Period** • To assess the safety of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period • To evaluate the long-term efficacy of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period • To assess the PD effects of ALXN2060 during the Extension Period • To characterize PK of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period	• Efficacy endpoints same as the Intervention Period excluding cardiac MRI parameters are evaluated during the Extension Period • PD parameters (serum TTR concentration and TTR stabilization (FPE)) same as the Intervention Period are assessed in the Extension Period • Exploration of PK in the Extension Period for ALXN2060 and its metabolite

Abbreviations: 6MWT = six-minute walk test; AE = adverse event; ATTR-CM = transthyretin amyloid cardiomyopathy; ECG = electrocardiography; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level questionnaire; FPE = fluorescent probe exclusion; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; MRI = magnetic resonance imaging; NT-proBNP = *N*-terminal pro-brain-type natriuretic peptide; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TnI = troponin I; TTR = transthyretin.

Overall Design

This Phase 3, prospective, multicenter, open label, 2-part study will evaluate the efficacy, safety, tolerability, PK, and PD of ALXN2060 800 mg bid administered orally in Japanese participants with symptomatic ATTR-CM.

Eligible Japanese participants with symptomatic ATTR-CM (either mutant or wild type) will be enrolled based on inclusion/exclusion criteria. In order to assess the efficacy of ALXN2060 800 mg bid as monotherapy, patients with ATTR-CM will be eligible to be enrolled as long as they were untreated with tafamidis for at least 14 days prior to the first dose of ALXN2060. In case new ATTR-CM therapies will become available during the course of the study, Alexion's Medical Monitor in consultation and agreement with the Investigator will determine the pre-enrollment period needed to establish a proper TTR baseline. At the moment, the best assumptions would be a requirement of last dose administration of 90 days for patisiran and 180 days for inotersen prior to the first day of ALXN2060 dosing.

A Screening Period of up to 35 days will confirm the participants' diagnosis of ATTR-CM and suitability for a long-term investigation. This period will also cover the requirement of last dose of tafamidis administered at least 14 days prior to the first ALXN2060 dose.

Following enrollment and screening, participants will receive ALXN2060 800 mg bid for 12 months (Part A). Following the last visit (Month 12) of Part A, participants will continue the study in Part B, which will last for 18 months (30 months from Day 1). All participants will continue to receive oral treatment with ALXN2060 800 mg bid.

Following the completion of Month 30 assessments in Part B, participants will be offered the opportunity to continue into the Extension Period for up to 30 additional months or until ALXN2060 can be provided via an Alexion post-study access program (as allowed by local

laws and regulations), whichever occurs first. Participants will continue to receive oral treatment with ALXN2060 800 mg bid.

The Study schema is presented in Section 1.2.

Disclosure Statement: This is single-arm, open-label study with ALXN2060 800 mg bid.

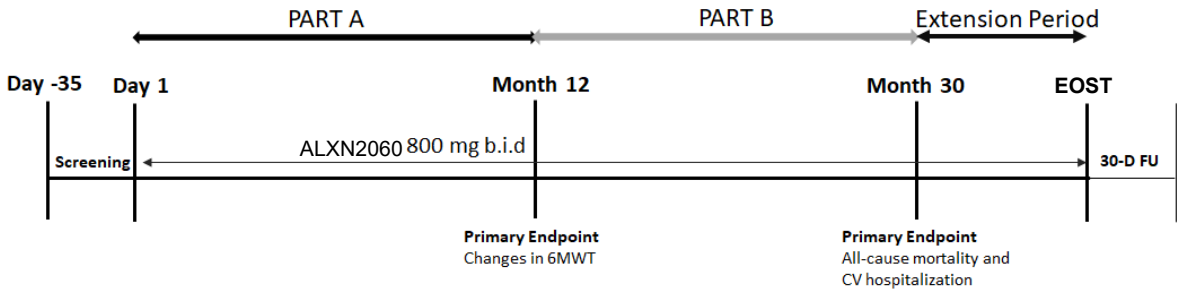
Number of Participants: Approximately 22 Japanese participants will be enrolled in this study.

Intervention Groups and Duration: Approximately 32 months from Screening to Month 30 visit, and up to approximately 60 months for participants who will continue treatment with ALXN2060 in the Extension Period.

Data Monitoring Committee: No

1.2. Schema

Figure 1: Study Design



Abbreviations: 6MWT = six-minute walk test; 30-D FU = 30-day follow up; CV = cardiovascular; EOST = end of study treatment.

1.3. Schedule of Activities (SoA)

Procedure	Screening (Up to 35 Days Before Day 1)	Intervention Period Day (D) and Month (M)							Extension Period			ED[a]/ EOST	Follow-up (30 Days After Last Dose) (± 7 Days)	Notes
		D1	D14 (± 3 Days)	D28 (± 3 Days)	Monthly Phone Contact (± 7 Days)	M3-27 (Every 3 Months) (± 7 Days)	M12 (± 7 Days)	M30[b] (± 7 Days)	M1 (± 7 Days)	Quarterly Phone Contact[c] (± 7 days)	M6-30 (Every 6 Months)[d] (± 7 Days)			
Informed consent	X													
Inclusion and exclusion criteria review[e]	X	X												see Section 5.1 and 5.2
Patient registration (to IWRS)	X	X												
Medical/surgical history	X													
NYHA class assessment	X	X		X		X	X	X	X		X	X	X	see Section 8.3.1
Echocardiogram[f]	X													see Section 8.1
Physical examination[g]	X	X	X	X		X	X	X	X		X	X	X	See Section 8.3.2
Vital signs	X	X	X	X		X	X	X	X		X	X	X	see Section 8.3.3
Electrocardiograms	X	X	X	X		X	X	X	X		X	X	X	see Section 8.3.4
Laboratory assessments	X	X	X	X		X	X	X	X		X	X	X	see Section 8.3.5
PD blood sampling[h]		X	X	X		X	X	X	X		X	X		see Section 8.7
PK blood sampling[i]		X	X	X		X	X	X	X		X	X		see Section 8.6
6MWT[j]	X					X	X	X			X	X		see Section 8.2.1
KCCQ[k]		X				X	X	X	X		X	X		see Section 8.2.3
EQ-5D-5L[k]		X				X	X	X	X		X	X		see Section 8.2.4
Cardiac MRI[l]		X				X	X	X						see Section 8.2.6
Pregnancy test[m]	X	X	X	X		X	X	X	X		X	X	X	see Section 8.3.6
Dispense/collect study drug[n]		X	X	X		X	X	X	X		X	X		

Procedure	Screening (Up to 35 Days Before Day 1)	Intervention Period Day (D) and Month (M)							Extension Period			ED[a]/ EOST	Follow-up (30 Days After Last Dose) (± 7 Days)	Notes
		D1	D14 (± 3 Days)	D28 (± 3 Days)	Monthly Phone Contact (± 7 Days)	M3-27 (Every 3 Months) (± 7 Days)	M12 (± 7 Days)	M30[b] (± 7 Days)	M1 (± 7 Days)	Quarterly Phone Contact[c] (± 7 days)	M6-30 (Every 6 Months)[d] (± 7 Days)			
Study drug compliance assessment			X	X	X	X	X	X	X	X	X	X		see Section 6.4
Exploratory Biomarkers	X											X		See Section 8.8
Prior/concomitant drug/therapy		Monitored continuously												see Section 8.3.7
Adverse events[o]/Vital status[p]		Monitored continuously												see Section 8.4

[a] Participants who discontinue treatment with study drug before the end of scheduled treatment will be followed for 30 days post last dose
[b] Day 1 visit of the Extension Period will occur on the same date as the Month 30 visit of the Intervention Period.
[c] Telephone contact will occur quarterly during months without scheduled in-clinic visits (e.g., Months 3, 9, 15, 21)
[d] In-clinic visits will occur at Month 1, Month 6, and every 6 months until Month 30.
[e] Recheck clinical status before first dose of the study drug.
[f] Resting transthoracic echocardiogram will be performed at Screening and read locally, if LV wall (interventricular septum or LV posterior wall) thickness is not documented in medical history based on echocardiogram or CMR.
[g] Full physical examination with body weight measurement is performed at all visits. Height will be measured only at screening.
[h] PD markers include TTR stabilization by FPE and serum TTR level (predose). PD samples will be collected at predose and 1-hour postdose at Day 28; predose at all other visits. Definition of the window of sample collection pre and 1 hour postdose (± x min): Predose = within 30 minutes; 1 hour postdose = ± 15 minutes. (Note that the exact time of sample collection will have to be recorded). PD backup samples may be used to measure exploratory biomarkers.
[i] PK samples will be collected at predose and 1-hour postdose at Day 28; predose at all other visits. Definition of the window of sample collection pre and 1 hour postdose (± x min): Predose = within 30 minutes; 1 hour postdose = ± 15 minutes. (Note that the exact time of sample collection will have to be recorded). PK backup samples may be used to measure exploratory biomarkers.
[j] Two baseline 6MWTs will be conducted > 24 hours to ≤ 3 weeks apart and prior to Day 1. 6MWT will be obtained on M6, M9, M12, M18, M24, and M30, and every 6 months during the Extension Period.
[k] KCCQ and EQ-5D-5L will be obtained on Day 1, M6, M9, M12, M18, M24, M30, and Month 1 and every 6 months during the Extension Period
[l] Cardiac MRI will be performed on Day 1, M12, M24 and M30. However, cardiac MRI will be conducted only at selected sites and consenting patients.
[m] A pregnancy test (urinalysis β-HCG) must be performed on all women of child bearing potential at the specified time points and verified to have a negative result. A pregnancy test may also be performed at any visit at the Investigator's discretion.
[n] Study drug is not administered at the EOS if transitioning to commercially available drug. Day 1 is for dispense only and ED/EOST is for collection only.
[o] If an AE occurs, the event will be followed up until it has stabilized or the participant has returned to the state they were in before administration of the study drug or the laboratory results return to baseline or normalize. All AEs must be managed and SAEs must be reported according to Section 8.4.
[p] For a subject who discontinues IMP and study assessments, follow the subject for up to Month 30 by completing monthly contact for vital status (dead, alive, heart transplant and receiving CMAD) or until withdrawal of consent.

Abbreviations: 6MWT = six-minute walk test; AE = adverse event; β-HCG = beta human chorionic gonadotropin; CMAD = Cardiac mechanical assist device; CMR = cardiac magnetic resonance; D = day; ED = early discontinuation; EOST = end of study treatment; EQ-5D-5L = EuroQol Health Outcomes Assessment tool; FPE = fluorescent probe

exclusion; IWRS = Interactive Web Response System; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; M = month; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse events; TTR = transthyretin.

2. INTRODUCTION

AG10 is a potent and selective stabilizer of transthyretin (TTR) that is being developed by Eidos Therapeutics, Inc (a subsidiary of BridgeBio Pharma Inc) for the treatment of TTR amyloidosis (ATTR), a progressive, fatal disease in which deposition of amyloid derived from either mutant or wild-type TTR causes severe organ damage and dysfunction (Rapezzi, 2010). Alexion received an exclusive license to develop and investigate AG10 (hereafter referred to as ALXN2060) in Japan from Eidos.

Clinically, ATTR presents as either a cardiomyopathy (transthyretin amyloid cardiomyopathy [ATTR-CM]), an infiltrative, restrictive cardiomyopathy characterized by progressive left and right heart failure, or as a peripheral polyneuropathy (ATTR-PN), a length-dependent neurodegenerative disease affecting sensorimotor and autonomic functions (Rapezzi, 2010).

Familial ATTR-CM (ATTRm-CM), or FAC, and familial ATTR-PN or FAP, are driven by pathogenic point mutations in the TTR gene; over 140 such mutations have been described (Rowczenio, 2019). In addition, older individuals may develop ATTR derived from wild-type TTR (ATTRwt, formerly called senile systemic amyloidosis or SSA). In ATTRwt, the major organ involved is the heart, although carpal tunnel syndrome and tendon involvement is also common (Ruberg, 2019).

Destabilization, misfolding, and aggregation of TTR lead to deposition of TTR amyloid and tissue damage (Rapezzi, 2010).

Previous studies reported that both in Japan and in the US, 12% to 25% of autopsied hearts from octogenarians showed TTR amyloid deposits (Cornwell, 1983), (Ueda, 2011). More recent autopsy reports suggest that the prevalence of TTR amyloid deposits in the myocardium of patients with heart failure and preserved ejection fraction increases significantly above the age of 80 (Mirzoyev, 2010). However, the prevalence of the overt manifestations of the disease is much lower and the nationwide survey on ATTRwt-CM conducted in 4,629 Japanese sites from 2012 to 2014 identified only 51 patients (Sekijima, 2019). This gap may be attributed to difficulty in diagnosis, but also highlights the existence of unknown factors that contribute to the disease (Rapezzi, 2010).

The estimation of the number of ATTRm patients is about 700 based on a nationwide survey that identified 208 cases with a definite diagnosis, where the early onset variant of Val30Met (V30M) accounts for most cases (77%) and shows a predominantly neuropathic phenotype (Ando, 2016). This is consistent with the fact that Japan is among those countries in which ATTRm associated with V30M TTR variant is endemic. In line with this, the Transthyretin Amyloidosis Outcome Survey, a global, multi-center, longitudinal, observational survey of patients with both ATTRm and ATTRwt, enrolled 119 Japanese patients between 2007 and 2017, 112 of whom had ATTRm (Sekijima, 2019). Among symptomatic patients (n = 100), 90% were V30M carriers, the most common phenotype in symptomatic ATTRm subjects was neurologic (61 of 100; 61.0%), only 10% of symptomatic patients had an exclusive cardiac phenotype, and 29% showed a mixed cardiac and neurologic phenotype (Sekijima, 2019)).

Several small molecules have been shown to bind to and stabilize TTR, potentially preventing the initiation the amyloidogenesis cascade. Eidos' therapeutic hypothesis is that a highly

effective TTR stabilizer will halt or slow ATTR disease progression in ATTR-CM (both ATTRm and ATTRwt) and ATTR-PN.

2.1. Study Rationale

This prospective study is designed to evaluate the efficacy, safety and tolerability, as well as to establish the pharmacokinetic (PK) and pharmacodynamic (PD) profile of ALXN2060 in Japanese participants with symptomatic ATTR-CM, administered on a background of stable heart failure therapy. A multicenter, open label, 2-part design followed by an Extension Period is considered to be the most appropriate study design for meeting this objective. Based on information gained from previous clinical experience with ALXN2060, a twice daily (bid) dose of 800 mg has been selected for this study to represent the optimal combination of potential efficacy, safety, and tolerability.

The dose proposed in this Phase 3 study on Japanese participants is the same as that used in the Global Phase 3 study (Eidos Study AG10-301). The chosen inclusion and exclusion criteria as well as the endpoints follow Eidos AG10-301 study as closely as possible.

2.2. Background

Currently, tafamidis is the only drug approved in Japan for the treatment of ATTR-CM. Transthyretin stabilization, as achieved by tafamidis, is proven to be beneficial to participants with symptomatic ATTR-CM (Maurer, 2018). As the main pathophysiological mechanism of ATTR involves the dissociation of the homo-tetrameric protein into monomers, TTR stabilizers that act by binding to TTR at the level of its binding site for thyroxine (T4), and therefore stabilizing the tetramer, prevent its dissociation and subsequent misfolding. Preventing the protein misfolding reduces the risk associated with the deposition of amyloid into various tissues, thereby enabling organ recovery and slowing the progress and/or arresting the progressive organ dysfunction (Maurer, 2018).

ALXN2060 is a potent, highly selective, small molecule TTR stabilizer. It demonstrated ability to stabilize TTR in vivo following oral dosing to nonhuman mammals, in healthy volunteers, and in cardiomyopathy patients (Miller, 2018), (Fox, 2020), (Judge, 2019).

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

AG10 has been well-tolerated in toxicology studies at what are predicted to be supra-therapeutic exposures. Results from Phase 1 studies (AG10-001, AG10-003, AG10-004, and AG10-005) and Phase 2 (AG10-201) study to date, have shown that ALXN2060 was generally well tolerated without ALXN2060-related safety signals of potential clinical concern (Judge, 2019). The reported serious adverse events (SAEs) are consistent with those anticipated in this population.

Currently, there are no important identified or potential risks for ALXN2060. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of AG10 (hereafter referred to as ALXN2060) may be found in the Investigator's Brochure.

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in Japan at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the changes that exist as a result of the pandemic. This assessment is described in Section 10.5.

2.3.2. Benefit Assessment

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a serious, progressive, and life-threatening disease associated with either wild-type TTR or, in the familial form of the disease, with pathogenic mutations in the TTR gene. While such loss-of-function mutations may accelerate the development and progression of ATTR-CM, age-related dissociation of the destabilized, native tetrameric form of the protein is the initiating pathophysiological event (Rapezzi, 2010). The degree to which individual mutations promote destabilization of the tetramer is associated with a higher degree of penetrance, an earlier onset of symptoms, and/or a more aggressive and rapidly progressive clinical course (Rapezzi, 2010).

Dissociation of tetrameric TTR into intrinsically unstable monomeric TTR favors misfolding and aggregation into amyloidogenic precursors that are deposited in affected tissues and organs, leading to local cytotoxicity and both architectural and functional disruption. Small molecule stabilizers like ALXN2060 reduce the likelihood of tetramer dissociation and this mechanism provides the therapeutic rationale supporting their use in halting or slowing progression of the disease. The preclinical data and clinical efficacy and safety data collected to date support the continued clinical assessment of ALXN2060 in participants with symptomatic ATTR-CM.

2.3.3. Overall Benefit: Risk Conclusion

Alexion considers the benefit-risk balance to be favorable for the continuation of the development of ALXN2060 in participants with symptomatic ATTR-CM.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoints
Primary	
Part A: To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by the 6MWT	**Part A**: Change from Baseline to Month 12 of treatment in distance walked during the 6MWT
Part B: To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by all-cause mortality and cardiovascular-related hospitalization	**Part B:** All-cause mortality and cardiovascular-related hospitalization over a 30-month period
Secondary	
Part A: • To evaluate the effects of ALXN2060 800 mg bid on the 6MWT • To evaluate the effects of ALXN2060 800 mg bid on health-related quality of life as measured by KCCQ-OS in adult Japanese participants with symptomatic ATTR-CM • To assess the safety and tolerability of ALXN2060 800 mg bid in adult Japanese participants with symptomatic ATTR-CM • To assess the PD effects of ALXN2060 by circulating serum TTR concentration as an in vivo biomarker of stabilization and using established ex vivo assays of TTR stabilization (FPE); in addition, assess the correlation between TTR concentration/FPE and ALXN2060 concentration	**Part A:** • Change from Baseline to Months 6 and 9 of treatment in distance walked during the 6MWT • Change from Baseline to Months 6, 9, and 12 of treatment in KCCQ-OS • Safety parameters to be assessed: treatment-emergent SAEs and AEs, adverse events leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern • Change from Baseline in serum TTR concentration (an in vivo measure of TTR stabilization) and established ex vivo assays of TTR stabilization (FPE) at Days 14 and 28 and subsequent visits

Objective	Endpoints
Part B: • To evaluate the effects of ALXN2060 800 mg bid on the 6MWT • To evaluate the effects of ALXN2060 800 mg bid on health-related quality of life as measured by KCCQ-OS in adult Japanese participants with symptomatic ATTR-CM • To assess the safety and tolerability of ALXN2060 800 mg bid administered for 30 months to adult Japanese participants with symptomatic ATTR-CM • To assess the PD effects of ALXN2060 as assessed by circulating serum TTR concentration as an in vivo biomarker of stabilization and established ex vivo assays of TTR stabilization (FPE) and correlation between TTR concentration/FPE and ALXN2060 concentration	**Part B:** • Change from Baseline to Months 18, 24, and 30 of treatment in distance walked during the 6MWT. • Change from Baseline to Months 18, 24, and 30 of treatment in KCCQ-OS • Safety parameters: treatment emergent SAEs and AEs, adverse events leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern • Change from Baseline in serum TTR concentration and established ex vivo assays of TTR stabilization (FPE)
Exploratory	
• To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR CM as assessed by all-cause mortality and cardiovascular-related hospitalization (only Part A) • To explore the population PK of ALXN2060 and its metabolites under the 800 mg orally administered bid dosing regimen • To evaluate the effects of ALXN2060 800 mg bid on circulating biomarkers of myocardial wall stress and microvascular ischemia in Japanese participants with symptomatic ATTR-CM • To evaluate the effects of ALXN2060 800 mg bid on EQ-5D-5L in Japanese participants with symptomatic ATTR-CM • To evaluate the effects of ALXN2060 800 mg bid on cardiac MRI-derived measures of cardiac structure, function and tissue characterization, in Japanese participants with symptomatic ATTR-CM (only at selected sites and consenting patients) **Extension Period**	• All-cause mortality and cardiovascular-related hospitalization over a 12-month period (only Part A) • Exploration of PK over 30 months for ALXN2060 and its metabolite • Changes from Baseline over Month 30 in NT-proBNP and TnI • Change from Baseline in EQ-5D-5L over Month 30 • Change from Baseline to Month 12, 24, and 30 in cardiac MRI parameters (only at selected sites and consenting patients) **Extension Period** • Safety parameters same as the Intervention Period (Part A and Part B) are assessed in the Extension Period • Efficacy endpoints same as the Intervention Period excluding cardiac MRI parameters are evaluated during the Extension Period • PD parameters (serum TTR concentration and TTR stabilization (FPE)) same as the Intervention Period are assessed in the Extension Period • Exploration of PK in the Extension Period for ALXN2060 and its metabolite

Objective	Endpoints
• To assess the safety of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period • To evaluate the long-term efficacy of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period • To assess the PD effects of ALXN2060 during the Extension Period • To characterize PK of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period	

Abbreviations: 6MWT = six-minute walk test; AE = adverse event; ATTR-CM = transthyretin amyloid cardiomyopathy; ECG = electrocardiography; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level questionnaire; FPE = fluorescent probe exclusion; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; MRI = magnetic resonance imaging; NT-proBNP = *N*-terminal pro-brain-type natriuretic peptide; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TnI = troponin I; TTR = transthyretin.

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, prospective, multicenter, open label, 2-part study will evaluate the efficacy, safety, tolerability, PK, and PD of ALXN2060 800 mg bid administered orally in Japanese participants with symptomatic ATTR-CM. The Study schema is presented in Section 1.2.

Eligible Japanese participants with symptomatic ATTR-CM (either mutant or wild type) will be enrolled based on inclusion/exclusion criteria. In order to assess the efficacy of ALXN2060 800 mg bid as monotherapy, patients with ATTR-CM will be eligible to be enrolled as long as they were untreated with tafamidis for at least 14 days prior to first dose of ALXN2060. In case new ATTR-CM therapies will become available during the course of the study, Alexion's Medical Monitor in consultation and agreement with the Investigator will determine the pre-enrollment period needed to establish a proper TTR baseline. At the moment, the best assumptions would be a requirement of last dose administration of 90 days for patisiran and 180 days for inotersen prior to first day of ALXN2060 dosing.

A Screening Period of up to 28 ± 7 days will confirm the participants' diagnosis of ATTR-CM and suitability for a long-term investigation. This period will also cover the requirement of last dose of tafamidis administered at least 14 days prior to the first ALXN2060 dose.

Following enrollment and screening, participants will receive ALXN2060 800 mg bid for 12 months (Part A). Following the last visit (Month 12) of Part A, participants will continue the study in Part B, which will last for 18 months (30 months from Day 1). All participants will continue to receive oral treatment with ALXN2060 800 mg bid.

Following the completion of Month 30 assessments in Part B, participants will be offered the opportunity to continue into the Extension Period for up to 30 additional months or until ALXN2060 can be provided via an Alexion post-study access program (as allowed by local laws and regulations), whichever occurs first. Participants will continue to receive oral treatment with ALXN2060 800 mg bid.

4.2. Scientific Rationale for Study Design

A multicenter, open label, 2-part design is considered to be the most appropriate study design for meeting the study objectives. Based on information gained from previous clinical experience with ALXN2060 (see Section 2), a dose of 800 mg bid has been selected for this study to represent the optimal combination of potential efficacy, safety, and tolerability.

4.2.1. Participant Input Into Design

There were no inputs from participants into the study design.

4.3. Justification for Dose

The dose selected for this study (ALXN2060 800 mg bid) is based on the results of 2 Phase 1 studies in healthy participants: a single and multiple ascending dose Phase 1 study (Study AG10-001) and a Phase 1 bridging study assessing comparability of exposure in Japanese and non-Japanese healthy volunteers (Study AG10-004), and a Phase 2 study in patients with

symptomatic ATTR-CM (Study AG10-201). In addition, the dose selected for this study is the same dose and regimen as in the ongoing global Phase 3 study in participants with symptomatic ATTR-CM (Study AG10-301).

The first-in-human study (Study AG10-001) was conducted in healthy volunteers and evaluated 4 single oral doses of AG10 (50, 150, 300, and 800 mg) in a sequential manner and 3 multiple oral doses of AG10 (100, 300, and 800 mg every 12 hours for a total of 12 days). In this study AG10 was well tolerated, with no SAEs or AEs, or any safety signals of potential clinical concern considered related to the administration of AG10.

In the Phase 1 PK bridging study (Study AG10-004), Japanese and non-Japanese healthy volunteers were administered 400 or 800 mg of AG10 and showed similar exposure and PK parameters.

In the Phase 2 study (Study AG10-201), 49 adults with symptomatic ATTR-CM were randomized to oral doses of placebo (n = 17), AG10 400 mg (n = 16), or 800 mg (n = 16) bid. The study showed that AG10 was well tolerated and there were no AG10-related safety signals of potential clinical concern.

Transthyretin stabilization as measured by fluorescent probe exclusion (FPE) demonstrated complete stabilization at peak and > 90% stabilization at trough at the higher dose with low inter-subject variability. Average change from Baseline in serum TTR concentrations, a direct in vivo reflection of TTR stabilization, showed a clear dose response: after 28 days of treatment, serum TTR concentrations increased on average by 36% in the 400 mg bid group and by 51% in the 800 mg bid group; serum TTR decreased on average by 7% in patients administered with placebo.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed both Part A and Part B of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of study for each participant is defined as his/her last visit in the study. The end of the study is defined as the last participant's last visit in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Male or female participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Male or females ≥ 20 and ≤ 90 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have an established diagnosis of ATTR-CM with either wild-type TTR or a variant TTR genotype (confirmed by genotyping) based on either (a) endomyocardial biopsy with confirmatory TTR amyloid typing by either immunohistochemistry, mass spectrometry, or immunoelectron microscopy, or (b) positive technetium-99m (^{99m}Tc)-pyrophosphate or bisphosphonate (DPD or HMPD) scan, combined with accepted laboratory criteria excluding a diagnosis of light-chain (AL) amyloidosis (based on both immunofixation electrophoresis [IFE] of serum and urine, and serum free light chain [sFLC] analysis) and extracardiac biopsy (eg, abdominal fat aspiration) documenting TTR amyloid deposits; participants with concurrent monoclonal gammopathy of undetermined significance (MGUS) may require confirmation of the diagnosis of ATTR-CM by tissue biopsy with confirmatory TTR amyloid typing by either immunohistochemistry, mass spectrometry, or immunoelectron microscopy.
3. Have (a) a history of heart failure evidenced by at least one prior hospitalization for heart failure or (b) clinical evidence of heart failure without prior heart failure hospitalization manifested by signs or symptoms of volume overload or elevated pressures (eg, elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, or peripheral edema), or (c) heart failure symptoms that required or requires ongoing treatment with a diuretics.
4. Have New York Heart Association (NYHA) Class I-III symptoms due to ATTR-CM.
5. Participants taking cardiovascular (CV) medical therapy, with the exception of diuretic drugs, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to Screening.
6. Have completed ≥ 150 m on the six-minute walk test (6MWT) on at least 2 tests > 24 hours to ≤ 3 weeks apart and prior to Day 1. The distance walked must be within 15% on 2 tests. If one of the first 2 tests is not ≥ 150 m or the first 2 tests are not within 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. The patient will be ineligible if the third test is still not ≥ 150 m or within 15% of one of the first 2 tests.
7. Have left ventricular (LV) wall (interventricular septum or LV posterior wall) thickness ≥ 12 mm as measured by transthoracic echocardiogram (ECHO) or cardiac magnetic

resonance (CMR) documented in medical history within 10 years of Screening or at Screening ECHO or CMR.

8. Have biomarkers of myocardial wall stress: *N*-terminal pro-brain-type natriuretic peptide (NT-proBNP) level ≥ 300 pg/mL at Screening

Sex

9. Women of childbearing potential (WOCBP) who engage in heterosexual intercourse must agree to use highly effective methods of contraception beginning with Screening and continuing for 30 days after the last dose of the study drug as detailed in Section 10.4 . A man who is sexually active with WOCBP and has not had a vasectomy must agree to use highly effective methods of contraception from Day 1 to at least 90 days after the last dose of the study drug as detailed in Section 10.4.

Informed Consent

10. Able to understand and sign a written Informed Consent Form (ICF), which must be obtained prior to initiation of study procedures. Participants must be capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Had an acute myocardial infarction, acute coronary syndrome, or coronary revascularization within 90 days prior to Screening.
2. Experienced stroke or transient ischemic attack (TIA) within 90 days prior to Screening.
3. Have CV hemodynamic instability at Screening that, in the judgment of the Investigator, would pose too great a risk for participation in the study.
4. Are likely to undergo heart transplantation within a year of screening.
5. Have known hypersensitivity to ALXN2060, its metabolites, or formulation excipients.
6. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before study drug is administered. A negative urine pregnancy test at Screening and at Day 1 are required for WOCBP.
7. In the judgment of the Investigator or Medical Monitor, have any clinically important ongoing medical condition or laboratory abnormality or condition that might jeopardize the patient's safety, increase their risk from participation, or interfere with the study.

Prior/Concomitant Therapy

8. Are receiving treatment for ATTR-CM with tafamidis, with marketed drug products lacking a labeled indication for ATTR-CM (eg, diflunisal, doxycycline); or with natural products or derivatives used as unproven therapies for ATTR-CM (eg, the green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol) within 14 days prior to dosing; treatment with patisiran, inotersen, or any other gene silencing agent: within 90 days for

patisiran and 180 days for inotersen, and 5 half-lives for any other gene silencing agent, prior to dosing.

9. Requires treatment with calcium channel blockers with conduction system effects (eg, verapamil, diltiazem). The use of dihydropyridine calcium channel blockers is allowed. The use of digitalis will only be allowed if required for management of atrial fibrillation with rapid ventricular response.

Prior/Concurrent Clinical Study Experience

10. Are participating in another investigational drug or investigational device study, within 30 days prior to the first day of ALXN2060 dosing, with potential residual effects that might confound the results of this study.

Diagnostic Assessments

11. Have confirmed a diagnosis of AL amyloidosis.
12. Have abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) or total bilirubin > 3 × ULN.
13. Have NT-ProBNP ≥ 8,500 pg/mL at Screening.
14. Have an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 as calculated by Modification of Diet in Renal Disease (MDRD) formula at Screening.

Other Exclusions

15. Have any condition that, in the opinion of the Investigator or Medical Monitor would preclude compliance with the study protocol such as a history of substance abuse, alcoholism or a psychiatric condition.

5.3. Lifestyle Considerations

No specific restrictions are applicable for this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but did not meet eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any SAEs and any concomitant medication, during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The study intervention is ALXN2060 800 mg bid administered orally (Table 1).

Table 1: Study Intervention, Dosage, and Mode of Administration

Study Drug Name	ALXN2060
Type	Drug
Dose Formulation	Film-coated Tablet
Unit Dose Strength(s)	400 mg ALXN2060
Dosage Level(s)	800 mg bid
Route of Administration	Oral
Use	Experimental
Sourcing	Provided centrally by Alexion
Packaging and Labeling	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to productcomplaints@alexion.com within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical trial material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.

4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

There is no randomization or blinding in this single-arm, open-label study of approximately 22 participants.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Record of the doses dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for planned and unplanned intervention delays and/or dose reductions will also be recorded in the eCRF.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

As stated in Section 5.1, participants taking CV medical therapy, with the exception of diuretic drugs, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to Screening.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Allowed Medicine and Therapy

Participants may continue medications required to treat existing medical conditions as long as they are not anticipated to interfere with the conduct or outcome of the study. Participants should avoid starting or stopping medications and all potential medication changes for CV medical therapy should be reviewed by the Investigator and consulted with the Medical Monitor to ensure changes are not expected to interfere with the outcome of the study.

6.5.2. Disallowed Medicine and Therapy

The following is prohibited as listed in Section 5.2:

- Use of patisiran, inotersen, tafamidis or any other approved or investigational agent for the treatment of ATTR-CM is prohibited during the study.
- Use of marketed drug products lacking a labeled indication for ATTR-CM (e.g., diflunisal, doxycycline) or of natural products or derivatives used as unproven therapies for ATTR-CM (e.g., green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol) is prohibited.

- Use of calcium channel blockers with conduction system effects (eg, verapamil, diltiazem) is prohibited. Use of dihydropyridine calcium channel blockers is allowed. The use of digitalis will only be allowed if required for management of atrial fibrillation with rapid ventricular response.

6.6. Dose Modification

Dose modification is not applicable to this study.

6.7. Intervention After the End of the Study

Eligible Participants will be offered the opportunity to continue receiving ALXN2060 800 mg bid. in the Extension Period for up to 30 additional months or until ALXN2060 can be provided via an Alexion post-study access program (as allowed by local laws and regulations), whichever occurs first.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants should be considered for discontinuation from intervention if any of the following occur during the study:

1. Serious hypersensitivity reaction;
2. Use of disallowed medication as defined in Section 6.5
3. Received heart or liver transplant or received Cardiac mechanical assist device (CMAD) at any time during the trial
4. Pregnancy or planned pregnancy (Section 10.4.3); or
5. Alexion or the Investigator deems it is necessary for the participant.

7.1.1. Temporary Discontinuation

If considered necessary, as per Investigator's discretion, IMP may be interrupted (e.g., in case of AE, hospitalization or procedure), however IMP should be resumed as soon as practically possible, unless there are safety concerns. Investigators are encouraged to discuss such cases with a Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF
- A participant may withdraw from the study with or without agreement for follow-up at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

  Note: If a subject discontinues IMP and study assessments, all efforts must be made to continue to follow the subject for up to Month 30 by completing monthly contact for vital status (dead, alive, heart transplant and receiving CMAD) or until withdrawal of consent.
- At the time of discontinuing from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA (Section 1.3) for data to be collected

at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent. Alexion will obtain final vital status for such patients.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. General Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the patient qualifies for study participation.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Resting transthoracic ECHO will be performed at Screening and read locally, if LV wall (interventricular septum or LV posterior wall) thickness not documented in medical history within 10 years of Screening based on transthoracic ECHO or CMR
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.2. Efficacy Assessments

8.2.1. Six-Minute Walk Test (6MWT)

Prior to Day 1, at least two 6MWTs will be conducted > 24 hours to ≤ 3 weeks apart. The walking distances must be ≥ 150 meters and the distance walked must be within 15% on two tests on different days. If one of the first 2 tests is not ≥ 150 m or the first 2 test results are not within the 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. If the third test is still not ≥ 150 m or within 15% of one of the first two tests, the subject will not be eligible for participation.

If the subject has a need for a walking aid (eg, cane) or supplemental oxygen at Baseline, it must be consistently used at each subsequent 6MWT throughout the study.

The 6MWT should be conducted after completion of the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ) and European Quality of Life Health 5-item questionnaire dimensions 5 level questionnaire (EQ-5D-5L) at the visits where required.

The 6MWT with Borg Scale will be conducted based on the guidelines of the American Thoracic Society with appropriate modifications for the patient population. Complete details on the

procedures for the 6MWT are provided in the Study Procedures Manual. The 6MWT will be obtained on M6, M9, M12, M18, M24, and M30, and every 6 months during the Extension Period.

8.2.2. Mortality and Cardiovascular-Related Hospitalization

Mortality (including CMAD and heart transplant) and CV-related hospitalizations are endpoints for the trial but the events that lead to death or hospitalization will be reported as AEs to the Sponsor throughout the trial. These events will be reviewed and adjudicated by an independent Clinical Events Committee (CEC) and determined whether reason for hospitalization and cause of death meet the definition of protocol-specified efficacy endpoints (Section 9.6). Hospitalizations that are submitted for adjudication and are deemed as not CV-related by the CEC will be considered SAEs. Adverse events of special interest (AESIs, Section 8.4.5) are also considered as part of the efficacy endpoint of CV-related hospitalizations.

The Investigator is responsible for ensuring potential study endpoints, including dates of admissions and discharge, are collected and documented; for providing Investigator assessment whether the hospitalization is CV-related; and for submitting Adverse Event notification for all AEs that result in deaths or hospitalizations.

8.2.3. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item questionnaire developed to measure health status and health-related quality of life in participants with heart failure. Items include heart failure symptoms, impact on physical and social functions, and how their heart failure impacts their quality of life. The KCCQ questionnaire is completed during Part A and Part B (Day 1, M6, M9, M12, M18, M24, and M30) and during the Extension Period (every 6 months) (Section 1.3). Complete details are provided in the Study Procedures Manual.

8.2.4. EuroQoL-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a brief, self-administered generic health status instrument that takes about 5 minutes to complete and should be conducted after completion of the KCCQ. The instrument includes two parts. In the first part, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having five levels of function (1-no problem, 2-slight problem, 3-moderate problem, 4-severe problem, and 5-extreme problem). The second part is a respondents self-rating of current health status on a Visual Analog Scale (EQ VAS) with endpoints labeled “best imaginable health state” (score of 100) and “worst imaginable health state” (score of 0). The scores from the 5 dimensions may be used to calculate a single index value, also known as a utility score. Complete details of administration and scoring are provided in the Study Procedures Manual.

Scores for EQ-5D-5L will be obtained on during Part A and Part B (Day 1, M6, M9, M12, M18, M24, and M30) and during the Extension Period (every 6 months) (Section 1.3).

8.2.5. NT-proBNP and Troponin I

Exploratory assessments of NT-proBNP and Tn I evaluation effects of ALXN2060 on circulating biomarkers of myocardial wall stress and microvascular ischemia will be performed by standardized methods at time points for laboratory tests specified in Section 1.3**,**

8.2.6. Cardiac MRI

The cardiac MRI parameters will include structural measures, functional measures, and tissue characterization. The cardiac MRI will be performed on Day 1, M12, M24, and M30 (only at selected sites and consenting patients). Complete details are provided in the Study Procedures Manual.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. NewYork Health Assessment

The NYHA classification is employed to classify patient's heart failure according to the severity of their symptoms. Physicians will assess and place participants in one of four categories based on their limitation during physical activity according to Table 2 below. Planned time points for NYHA assessments are provided in the SoA (Section 1.3).

Table 2: NYHA Class Assessment

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

8.3.2. Physical Examinations

- Physical examination with body weight measurement is performed at all visits. Height will be measured only at screening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at each study visit.

- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.

8.3.3. Vital Signs

- Pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed predose after a 5-minute rest.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.4. Electrocardiograms

- A standard 12-lead ECG will be conducted at timings specified in the SoA (see Section 1.3).
- Electrocardiograms will be performed in the supine position after a 5-minute rest at predose. The 1-hour postdose ECG will be conducted on Day 28.
- The Investigator or Sub-Investigator will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded in the source documents (ECG results will be confirmed centrally).

8.3.5. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant

management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3.6. Pregnancy

- Pregnancy data from WOCBP and female spouses/partners of male participants will be collected from the signing of the ICF until the Follow-up Visit (see Section 1.3). Additional pregnancy tests may be performed at any visit at the Investigator's discretion
- Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention. The Investigator must immediately inform Alexion within 24 hours awareness of the pregnancy and follow the procedures outlined in Section 10.4
- For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues study intervention or withdraws from the study. The corresponding infant must be followed for 3 months postpartum.
- Pregnancy is not considered an AE (Section 10.4.3) unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 8.4). Elective abortions without complications should not be reported as AEs.

8.3.7. Prior and Concomitant Medications

Medications taken as discussed in the exclusion criteria (Section 5.2) before the start of the first dose of study drug, will be recorded in the eCRF.

Concomitant medications (defined in Section 6.5) are those received on or after the first dose of the study drug (Day 1), including those started before Day 1 and continued after Day 1. At each study visit, participants should be questioned about any new medication or non-drug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications and non-drug therapies should be recorded in the source documents and the patient's eCRF.

Concomitant medications must be recorded in the patient's source document/medical chart and eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up until resolution or until AE is deemed stable, or the laboratory results return to baseline or normalize. AEs that are serious, considered related to the study intervention or study procedures, or that have caused the participant to discontinue the study (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3 (Appendix 3).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the Follow-up Visit specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 Appendix 3. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to Alexion of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Suspected unexpected serious adverse reactions (SUSAR) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Adverse Events of Special Interest

Adverse events of special interest are defined as medical visits (eg, emergency department/ward, urgent care clinic, day clinic, etc) of less than 24 hours where diagnosis and interventions indicate that the purpose of the visit was for intravenous diuretic therapy for management of decompensated heart failure.

8.5. Treatment of Overdose

For this study, any dose of ALXN2060 greater than that specified in the protocol will be considered an overdose.

Alexion does not recommend specific treatment for an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately
2. Closely monitor the participant for any AE/SAE
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

In a subgroup of participants, PK samples will be collected at the following times to determine ALXN2060 plasma concentrations:

- Day 1, Day 14 and at every 3 months study visits during Part A and B: Predose
- Day 28: Predose and at 1-hour postdose
- Month 1 and every 6 months during the Extension Period: Predose

- Early Discontinuation

PK backup samples may be used to measure exploratory biomarkers.

8.7. Pharmacodynamics

In a subgroup of participants, PD properties of ALXN2060 will be assessed by established assays of TTR stabilization, including FPE assay. Sampling will be done at the following times to perform these PD assays:

- Day 1, Day 14, and at every 3 months study visits during Part A and B: Predose
- Day 28: Predose and at 1-hour postdose
- Month 1 and every 6 months during the Extension Period: Predose
- Early Discontinuation

PD backup samples may be used to measure exploratory biomarkers.

8.8. Exploratory Biomarkers

Blood samples will be collected for assessing exploratory biomarkers for potential evaluation of TTR stabilization effects and analysis of TTR variants evaluation effects at screening and EOST or ED (Section 1.3).

8.9. Immunogenicity Assessments

Immunogenicity assessments are not performed in this study.

8.10. Health Economics Data and Medical Resource Utilization

These assessments are not performed in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of this study is to assess the efficacy of ALXN2060 for the parameters listed in section 3. No formal statistical hypothesis is defined for this study. The success criteria based on both Part A and Part B of the study are defined in section 9.4. The sample size is set to detect the change in 6MWT at 12 months with certain precision (Section 9.2) as part of the success criteria in Part A.

9.2. Sample Size Determination

A total of 22 Japanese participants are planned for enrollment in this study. The primary endpoint in Part A is the change from Baseline to Month 12 in the distance achieved in the 6MWT, which is an important indicator to investigate functional improvement.

Assuming similarity with the tafamidis ATTR-ACT study (Maurer, 2018), where the mean change in 6MWT distance from Baseline to Month 12 in placebo group was estimated as -60 m, which could be considered as the minimum threshold for the changes to be clinically relevant for this study; and also assuming the mean change (standard deviation [SD]) from Baseline to Month 12 in ALXN2060 group was -25 (50) m, an estimated sample size of 19 will provide over 80% power for the lower limit of a 95% confidence interval (CI) of change from Baseline to Month 12 in 6MWT to be over -60 m.
The primary endpoints in Part B are all-cause mortality and CV-related hospitalizations over a 30-month period. A sample size of 19 will have over 80% probability to show consistency between this study and AG10-301 study with respect to the two primary endpoints in Part B, respectively, based on simulations.

Considering a missing rate of 10% to 15% for 6MWT at Month 12, the target sample size of 22 is set for Study ALXN2060-TAC-302.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled Set	All consented participants meeting eligibility criteria.
Safety Set (SS)	All participants who have received at least 1 dose of ALXN2060.
Full Analysis Set (FAS)	All participants who have received at least 1 dose of ALXN2060.
Per-Protocol Set (PPS)	All FAS participants without major protocol deviations that may affect the primary efficacy endpoint.
Pharmacokinetic Analysis Set (PKAS)	All participants who have received at least 1 dose of ALXN2060 and who have at least one evaluable ALXN2060 concentration.
Pharmacodynamic Analysis Set (PDAS)	All participants who have received at least 1 dose of ALXN2060 and who have evaluable pharmacodynamics (PD) data.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP).

All analyses will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc, Cary, NC, USA) or other validated statistical software.

Continuous variables will be summarized using descriptive statistics, including number of observations and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of participants.

All data and all outcomes derived from the data will be presented in detailed data listings or summary tabulations. Graphical displays may also be provided when appropriate.

9.4.1. Efficacy Analyses

9.4.1.1. Analyses of Primary Efficacy Endpoint

The primary endpoints are the change from Baseline to Month 12 of treatment in distance walked during the 6MWT (Part A) and all-cause mortality and CV-related hospitalizations over a 30-months' period (Part B). Descriptive statistics will be presented for all the endpoints. The mean and its 95% CI will be presented for the change in 6MWT from Baseline to Month 12. In addition, summary statistics from the Kaplan-Meier analysis of all-cause mortality at Month 12 and Month 30 will be provided as point estimates along with 95% CIs. The Kaplan-Meier curve will also be plotted. Cumulative frequency of CV-related hospitalization will be estimated using negative binomial regression analysis with no covariates but an offset term equal to log of each subject's study duration included in the model. The CV-related hospitalization per person per year at Month 30 will be presented with 95% CI.

Success criterion for Part A is defined as the lower bound of the 95% CI of the change in 6MWT from Baseline to Month 12 is greater than -60 m.

Success criterion for Part B is defined as the estimated survival probability at Month 30 is greater than that for placebo patients in Study AG10-301. The success criterion for Part B is based on all-cause mortality only, because it is considered more clinically important than CV-related hospitalizations.

9.4.1.2. Analyses of Secondary Efficacy Endpoint(s)

Changes from Baseline in 6MWT and KCCQ-OS will be analyzed using mixed model repeated measures (MMRM) model adjusting for baseline measures and visits.

9.4.1.3. Pharmacokinetic/Pharmacodynamic Analysis

Descriptive statistics will be provided, PK/PD correlation and population PK analyses will be explored on ALXN2060 and its metabolite.

9.4.1.4. Analyses of Exploratory Endpoint(s)

Statistical analysis of the endpoints will depend on the nature of the endpoint and will be described in the Statistical Analysis Plan. All-cause mortality at Month 12 will be analyzed using

Kaplan-Meier method. Summary statistics will be provided as point estimates with 95% CIs. The Kaplan-Meier curve will also be plotted. The CV-related hospitalization over 12 months will be estimated using negative binomial regression analysis with no covariates. Changes from Baseline in NT-proBNP, TnI, cardiac MRI parameters and EQ-5D-5L will be analyzed by MMRM model adjusting for baseline measures and visits.

For the extension period, endpoints will be analyzed from the baseline of the Intervention Period to the end of the extension period to assess long term efficacy.

9.4.2. Safety Analyse(s)

All safety analyses will be made on the Safety Set. The safety and tolerability of ALXN2060 in participants with ATTR-CM will be assessed based on AEs, ECG abnormalities, clinical laboratory data, physical examinations, and vital sign measurements, and will be presented using descriptive statistics. No formal hypothesis testing will be performed for the safety parameters.

9.5. Interim Analyses

No formal interim analyses are planned for decision making on the continuity of the study. Month 12 (Part A) data will be analyzed together at the time of Part B analysis as described in Section 9.4.

9.6. Clinical Events Committee

An independent CEC will review and adjudicate Investigator-reported events of death and CV-related hospitalizations to determine whether reason for hospitalization and cause of death meet the definition of protocol-specified efficacy endpoints for Part B. Investigators will follow the SAE notification process (Section 8.4.4). Additional details regarding the responsibilities of the CEC are available in the CEC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, Pharmaceutical and Medical Devices (PMD) Act, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) informed consent from all study participants prior to any study-related procedures including screening assessments.

- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations and ICH guidelines requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

The charter for 1 committee (CEC, see Section 9.6) included in this study is available.

10.1.6. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, Clinicaltrials.gov. and Japic CTI), as appropriate, and in accordance with national, regional, and local regulations.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 8 to 10 years after the last marketing application approval, or if not approved, 3 years following the discontinuance of the study intervention, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the first participant is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the end of study or early discontinuation visit, all data has been collected, entered and cleaned in EDC, all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12-18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. Alexion will ask Eidos, the licensor of ALXN2060 (Code number at Eidos: AG10), for the review of it based on the licensing agreement between them. This allows Alexion and Eidos to protect proprietary information and to provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.

- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy Testing: WOCBP should only be enrolled after a negative urine pregnancy test result at screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3).]

Table 3: Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, complete blood count (CBC), and differential
Chemistry	Sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, prealbumin, retinol-binding protein (RBP), free thyroxine (FT4), alkaline phosphatase, calcium, phosphorus, total and fractionated (indirect or direct) bilirubin, uric acid, thyroid-stimulating hormone (TSH), troponin I (Tn I), creatine kinase (CK), CK-MB, and *N*-terminal pro-brain-type natriuretic peptide (NT-proBNP)
Urinalysis	Complete urinalysis (specific gravity, pH, glucose, protein, hemoglobin, leukocyte esterase, and nitrite. Additionally, albumin to creatinine ratio and a microscopic urinalysis will be performed on every specimen and will specifically look for casts, bacteria, WBCs, epithelial cells, and red blood cells
Others	Follicle-stimulating hormone (FSH) only to confirm post-menopausal status at Screening in female subjects who do not have menses for at least 12 months and are not using hormonal contraception or hormone replacement therapy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause
Pregnancy test	Highly sensitive urine test at all visits as outlined in the Schedule of Assessments (female subjects of childbearing potential only)

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.

Events NOT Meeting the AE Definition
• Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations:

A SAE is defined as any untoward medical occurrence that, at any dose:
• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017: • Grade 1: Mild (awareness of sign or symptom, but easily tolerated) • Grade 2: Moderate (discomfort sufficient to cause interference with normal activities) • Grade 3: Severe (incapacitating, with inability to perform normal activities) • Grade 4: Life-threatening • Grade 5: Fatal

Assessment of Causality
• The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows: – **Not related:** There is no reasonable possibility the study intervention caused the adverse event.

Assessment of Causality

  - The adverse event has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
  - The event does not follow a reasonable temporal relationship to administration of the study intervention.
- **Related**: There is a reasonable possibility the study intervention caused the adverse event.
  - The adverse event has a temporal relationship to the administration of the study intervention.
  - The event does not have a likely alternative etiology.
  - The event corresponds with the known pharmaceutical profile of the study intervention.
  - There is improvement on discontinuation and/or reappearance on rechallenge.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness,
- The primary mechanism for reporting an SAE to Alexion will be the electronic data collection tool.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure.
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- The site will enter the SAE data into the electronic data capture (EDC) system as soon as it becomes available.
- When further information becomes available, the EDC system should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion global drug safety (GDS) via the RAVE Safety Gateway.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to Alexion GDS by telephone.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     – A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

10.4.2.1. Guidance for Female Participants

Female participants of non-child bearing potential are exempt from contraception requirements. Non-child bearing potential for female participants is defined as any of the following:

1. Prior to first menses
2. Postmenopausal, as documented by amenorrhea for at least 1 year prior to the Day 1 visit and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status
3. Permanent sterilization at least 6 weeks prior to the Day 1 visit:
4. Hysteroscopic sterilization
5. Bilateral tubal ligation or bilateral salpingectomy
6. Hysterectomy
7. Bilateral oophorectomy

Female participants of child-bearing potential must use a highly effective method of contraception, including at least one of the following:

1. Intrauterine device (without copper) in place for at least 6 weeks
2. Progestogen-only oral hormonal contraception for at least 6 weeks
3. Intrauterine progestogen releasing system for at least 6 weeks
4. Bilateral tubal occlusion for at least 6 weeks
5. Combined (estrogen and progestogen containing) hormonal oral contraception for at least 6 weeks. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the Day 1 visit. Estrogen-containing hormonal contraception may not be initiated during the study period;
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within the prior 6 months)
7. Sexual abstinence for female participants
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants who wish to initiate a highly effective method of contraception during the study must refrain from heterosexual intercourse.
    b. Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) is not considered a highly effective method of contraception for female participants.

Other methods of contraception that are not considered highly effective for female participants:

1. Barrier methods, such as male or female condoms, diaphragm, or cervical cap, used alone or in combination, are not acceptable.
2. Spermicides or spermicidal sponges, used alone or in combination with barrier methods, are not acceptable.

Withdrawal (coitus interruptus) is not acceptable.

Lactational amenorrhea is not acceptable.

Female participants must not donate ova from the Day 1 up to 30 days after the last dose of the study drug.

10.4.2.2. Guidance for Male Participants

Contraception is the responsibility of the heterosexually active male participants, regardless of his female partner's method of contraception.

Male participants who have not had a vasectomy must agree to use a barrier method of birth control.

10.4.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participants' s preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods for a female partner) is not considered a highly effective method of contraception for male participants.

Male participants must not donate sperm from the Day 1 to at least 90 days after the last dose of study drug.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency Failure rate of < 1% per year when used consistently and correctly.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• **Highly Effective Methods [b] That Are User Dependent** Failure rate of < 1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral
• Progestogen-only hormone contraception associated with inhibition of ovulation • Oral
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
• a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

- b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected from Day 1 through 30 days after the last dose of study drug for all female participants and female spouses/partners of male participants. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. If a female participant or a male participant's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the Pregnancy/Breastfeeding Reporting and Outcome Form) and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention.

10.4.3.1. Male Participants with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive ALXN2060.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate Pregnancy/Breastfeeding Reporting and Outcome Form and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.3.2. Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial Information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will be 3 months following the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: COVID-19 Risk Assessment

ATTR-CM can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. In this particular case, the fact that the study is open-label and every participant is treated with the study intervention also contributes to the potential benefit a participant may derive from partaking in the study. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 4.

Table 4: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules, and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or participant study

Table 4: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		discontinuations due to COVID-19).

Abbreviation: COVID-19 = coronavirus disease 2019.

10.6. Appendix 6: Abbreviations

Abbreviation	Definition
6MWT	six-minute walk test
AE	adverse event
AL amyloidosis	light-chain amyloidosis
ATTR	TTR amyloidosis
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTRm	mutated ATTR
ATTR-PN	ATTR peripheral polyneuropathy
ATTRwt	wild-type ATTR
CEC	Clinical Events Committee
CI	confidence interval
CMR	cardiac magnetic resonance
COVID-19	coronavirus disease 2019
ECHO	echocardiogram
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life Health 5-item questionnaire dimensions 5 level
FPE	fluorescent probe exclusion
HRT	hormonal replacement therapy
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Score
LV	left ventricular
MRI	magnetic resonance imaging
NT-proBNP	*N*-terminal pro-brain-type natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	serious adverse event
TIA	transient ischemic attack
TTR	transthyretin
WOCBP	women of childbearing potential

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 4.0 (12-January-2023)

Overall Rationale for the Amendment:

The main purpose of this amendment was to align the terminology definitions with Study AG10-301 Protocol Amendment 6.0 and to align the timing of study visits in the Extension Period with Study AG10-304.

Other changes implemented through this Amendment constituted minor editorial corrections, fixing inconsistencies, and clarification.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3 Objectives and Endpoints	Clarified the Extension Period objectives and endpoints in the table.	For clarification.
1.3 Schedule of Activities	Added quarterly phone contacts to the Extension Period. Changed the visit timing in the Extension Period from every 3 months to every 6 months. Added KCCQ and EQ-5D-5L assessments to Month 1.	To align with Study AG10-304.
1.3 Schedule of Activities	Added a footnote for vital status to be collected during follow-up.	To align with Study AG10-301.
6.5.2 Disallowed Medicine and Therapy	Updated text to prohibit the use of tafamidis and other drugs for the treatment of ATTR-CM during the study.	For clarification.
7.1.1 Temporary Discontinuation	Added a section for IMP interruption.	To align with Study AG10-301.
7.2 Participant Discontinuation/Withdrawal from the Study	Added text that vital status to be collected include dead, alive, heart transplant, receiving CMAD.	To align with Study AG10-301.
8.2.2 Mortality and Cardiovascular-Related Hospitalization	Added text to indicate mortality includes CMAD and heart transplant.	To align with Study AG10-301.
9.4.1.1 Analyses of Primary Efficacy Endpoint	Added the following text for analysis plan clarification: Cumulative frequency of CV-related hospitalization will be estimated using negative binomial regression analysis with no covariates but an offset term equal to log of each subject's study duration included in the model. The CV-	For clarification.

Section # and Name	Description of Change	Brief Rationale
	related hospitalization per person per year at Month 30 will be presented with 95% CI.	
9.4.1.2 Analyses of Secondary Efficacy Endpoint(s)	Updated the following text for analysis plan clarification: Changes from Baseline in 6MWT and KCCQ-OS will be analyzed using mixed model repeated measures (MMRM) model adjusting for baseline measures and visits.	For clarification.
9.4.1.4 Analyses of Exploratory Endpoint(s)	Updated the following text for analysis plan clarification: The CV-related hospitalization over 12 months will be estimated using negative binomial regression analysis with no covariates. Changes from Baseline in NT-proBNP, TnI, cardiac MRI parameters and EQ-5D-5L will be analyzed by MMRM model adjusting for baseline measures and visits. Added the following text for clarification: For the extension period, endpoints will be analyzed from the baseline of the Intervention Period to the end of the extension period to assess long term efficacy.	For clarification.
9.5 Interim Analyses	Clarified that Part A analysis will be performed at the same time as Part B analysis.	To accurately reflect the current plan.

Amendment 3 (15-February-2021)

Overall Rationale for the Amendment:

The main purpose of this amendment was to add an exploratory endpoint (cardiac MRI) and to add text referring to COVID-19 considerations.

Other changes implemented through this Amendment constituted minor editorial corrections and fixing inconsistencies.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Changed from 28days +-7 to 35 days	To correct the text

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 3 OBJECTIVES AND ENDPOINTS 8.2.6 Cardiac MRI 9.4.1.4 Analysis of Exploratory Endpoint(s)	Added an explanation of cardiac MRI.	Measurement of cardiac MRI will be added as an exploratory endpoint to evaluate the effects of ALXN2060 on cardiac MRI- derived measures of cardiac structure, function and tissue characterization.
1.3 Schedule of Activities 8.6 Pharmacokinetics 8.7 Pharmacodynamics	Added text referring to PK/PD backup samples as exploratory biomarkers.	PK/PD backup samples may be used to measure exploratory biomarkers.
2.3.1.1 Coronavirus Disease 2019 10.5 Appendix 5: COVID-19 Risk Assessment	Added text referring to COVID-19 considerations.	To allow treatment continuity and ensure patients safety during COVID-19 pandemic
10.2 Appendix 2: Clinical Laboratory Tests	Changed from “serum” to “urine”	To correct the text
10.4.2.2 Guidance for Male Participants	Changed from “have had a vasectomy” to “have not had a vasectomy”	To correct the text

Amendment 2 (24-July-2020)

Overall Rationale for the Amendment:

The main purpose of this amendment was minor changes for consistency.

Section # and Name	Description of Change	Brief Rationale
TITLE PAGE	Removed “(previously AG10)”	Cosmetic change
1.3 Schedule of Activities (SoA)	“Dispense participant safety card” was deleted	Not to use “Dispense participant safety card” in this study
5.1 Inclusion Criteria 9.	Corrected description of period of contraception for female	To correct description

Amendment 1 (20-July-2020)

Overall Rationale for the Amendment:

The main purpose of this amendment was to respond to inquiries from PMDA on contraception guidance for male and TTR genotyping.

In addition, minor editorial changes were implemented for consistency.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	“AG10 800 mg b.i.d” was changed to “ALXN2060 800 mg b.i.d”.	To keep consistency of the study drug name

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 7.2 Participant Discontinuation/Withdrawal from the Study	Added "Note: If a subject discontinues IMP and study assessments, all efforts must be made to continue to follow the subject for up to Month 30 by completing monthly contact for vital status or until withdrawal of consent. Added "Vital status" after "Adverse event"	To align with CRF and protocol of AG10-301 study.
1.3 Schedule of Activities (SoA) 8.8 Genetics	Removed section 8.8 Genetics and "confirm genotype" in SoA.	TTR genotyping is conducted in all study sites to establish ATTR-CM diagnosis before informed consent.
1.3 Schedule of Activities (SoA)	6MWT evaluation timepoint was corrected as the approved PCS.	For consistency with the actual procedure as well as with AG-301 study
1.3 Schedule of Activities (SoA)	In the footnote, the sample collection timeframe for PD was added.	To clarify the timeframe
5.1 Inclusion Criteria	"the first dose of ALXN2060" was changed to "Day 1"	To keep consistency with SoA footnote and actual procedure
5.1 Inclusion Criteria	Corrected description of the methods of contraception for a male	To keep consistency with section 10.4
5.1 Inclusion Criteria	Added "from Day 1 to at least 90 days after the last dose of the study drug"	To clarify the guidance for Male participants in response to PMDA inquiries
8.2.3 Kansas City Cardiomyopathy Questionnaire (KCCQ)	"KCQG" was corrected to "KCCQ"	Typo
8.3.4 Electrocardiograms	Added "(ECG results will be confirmed centrally)"	To clarify and make it consistent with actual procedure
8.6 Pharmacokinetics 8.7 Pharmacodynamics	Added "Day 14"	To keep consistency with SoA footnote and actual procedure
10.1.3 Informed Consent Process	Deleted "[or assent]"	It does not apply to this study.
10.1.10 Publication Policy	"AG10" was changed to "ALXN2060 (Code number at Eidos: AG10)"	To be consistent

Section # and Name	Description of Change	Brief Rationale
10.3.1 Definition of AE	Deleted "· The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE."	To correct overlapping with the latter half of the previous bullet
10.4.2.2.1 Guidance for Female Participants	Deleted superscript "c"	No corresponding footnote
10.5 Appendix 5	"Appendix 11" was corrected to "Appendix 5".	Typo

DOCUMENT HISTORY		
Document	**Date**	**Overall Rationale for the Amendment**
Amendment 5	11-September-2023	The main purpose of this amendment is to incorporate the changes from Administrative Letter 1.0 and to clarify the terminology definitions.
Amendment 4	12-January-2023	The main purpose of this amendment was to align the terminology definitions with Study AG10-301 Protocol Amendment 6.0 and to align the timing of study visits in the Extension Period with Study AG10-304.
Amendment 3	15-February-2021	The main purpose of this amendment was to add an exploratory endpoint (cardiac MRI) and to add text referring to COVID-19 considerations.
Amendment 2	24-July-2020	The purpose of this amendment was minor changes for consistency.
Amendment 1	20-July-2020	The main purpose of this amendment was to respond to inquiries from PMDA on contraception guidance for male and TTR genotyping.
Original protocol	19-June-2020	-

11. REFERENCES

Ando Y, Ikeda S, Sekijima Y, et al. National Epidemiological Survey of Hereditary Transthyretin Amyloidosis; Report of Research Group on Amyloidosis (Report in Japanese). Health and Labor Science Research Grant. 2016. Available: https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201610022B [Accessed: 12-Jun-2020]

Cornwell GG, 3rd, Murdoch WL, Kyle RA, Westermark P, Pitkanen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. Am J Med. 1983;75(4):618-623.

Fox JC, Hellawell JL, Rao S, et al. First-in-Human Study of AG10, a Novel, Oral, Specific, Selective, and Potent Transthyretin Stabilizer for the Treatment of Transthyretin Amyloidosis: A Phase 1 Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Adult Volunteers. Clin Pharmacol Drug Dev. 2020;9(1):115-129.

Judge DP, Heitner SB, Falk RH, et al. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2019;74(3):285-295.
Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-1016.

Miller M, Pal A, Albusairi W, et al. Enthalpy-Driven Stabilization of Transthyretin by AG10 Mimics a Naturally Occurring Genetic Variant That Protects from Transthyretin Amyloidosis. J Med Chem. 2018;61(17):7862-7876.

Mirzoyev SA, Edwards WD, Mohammed SF, et al. Abstract 17926. Circulation. 2010;122.
Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol. 2010;7(7):398-408.

Rowczenio D, Quarta CC, Fontana M, et al. Analysis of the TTR gene in the investigation of amyloidosis: A 25-year single UK center experience. Hum Mutat. 2019;40(1):90-96.

Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-2891.

Sekijima Y, Mundayat R, Ishii T, Ando Y. The current status of the Transthyretin Amyloidosis Outcomes Survey (THAOS) in Japan. Amyloid. 2019;26(sup1):61-62.

Ueda M, Horibata Y, Shono M, et al. Clinicopathological features of senile systemic amyloidosis: an ante- and post-mortem study. Mod Pathol. 2011;24(12):1533-1544.

ALXN2060-TAC-302 Protocol Amendment 5.0_11Sep2023_final

Final Audit Report 2023-09-15

Created:	2023-09-15 (Japan Standard Time)
By:	[redacted]
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