ARC TALKS
WEBINAR SERIES

ATTR Clinical Trial Updates

July 31 | 12pm - 1pm ET

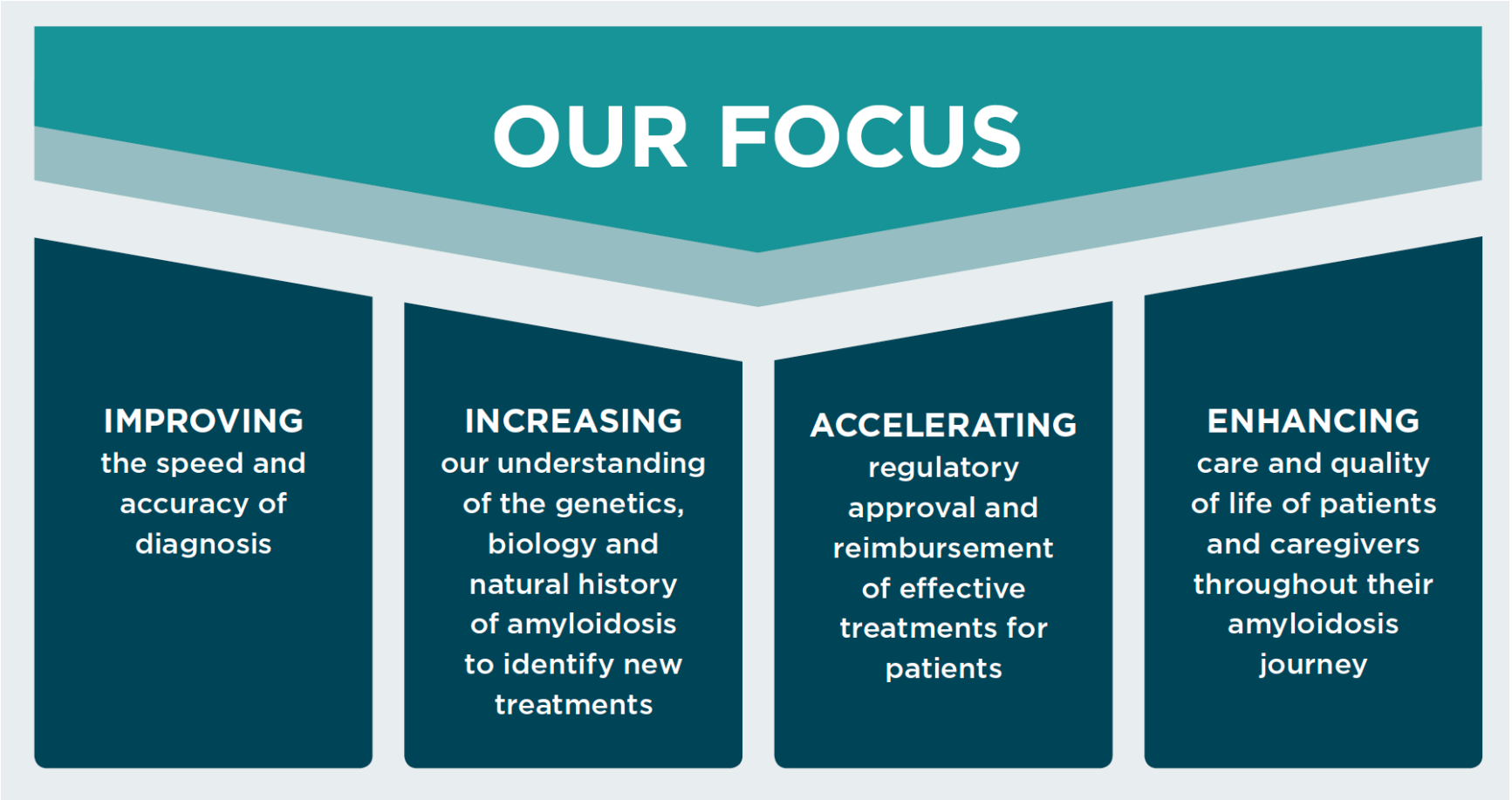
Kristen Hsu

Executive Director of Research
Amyloidosis Research Consortium

About ARC

Amyloidosis Research Consortium

ARC's mission is to improve and extend the lives of those with amyloidosis



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Before We Begin

Amyloidosis Research Consortium

This webinar is recorded. We will post the webinar on our website so you can view it again later.

Submit your questions anytime via the Q&A box. We will try to answer them at the end.

If you are having trouble with the audio using your computer, you can dial in (check your email for info).

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Amyloidosis Research Consortium

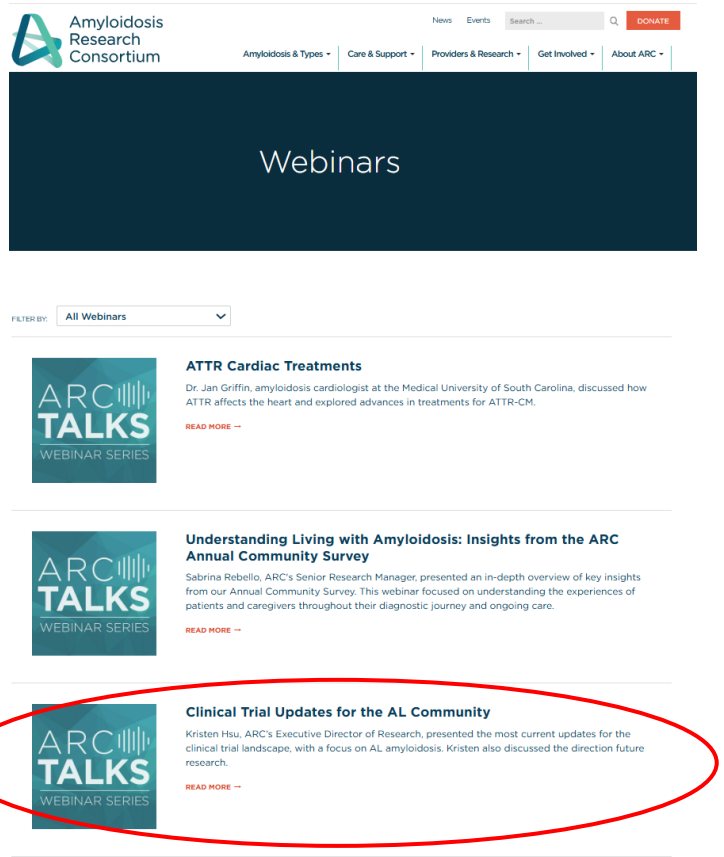
Clinical Trial Updates for the ATTR Community

Kristen Hsu, Executive Director of Research

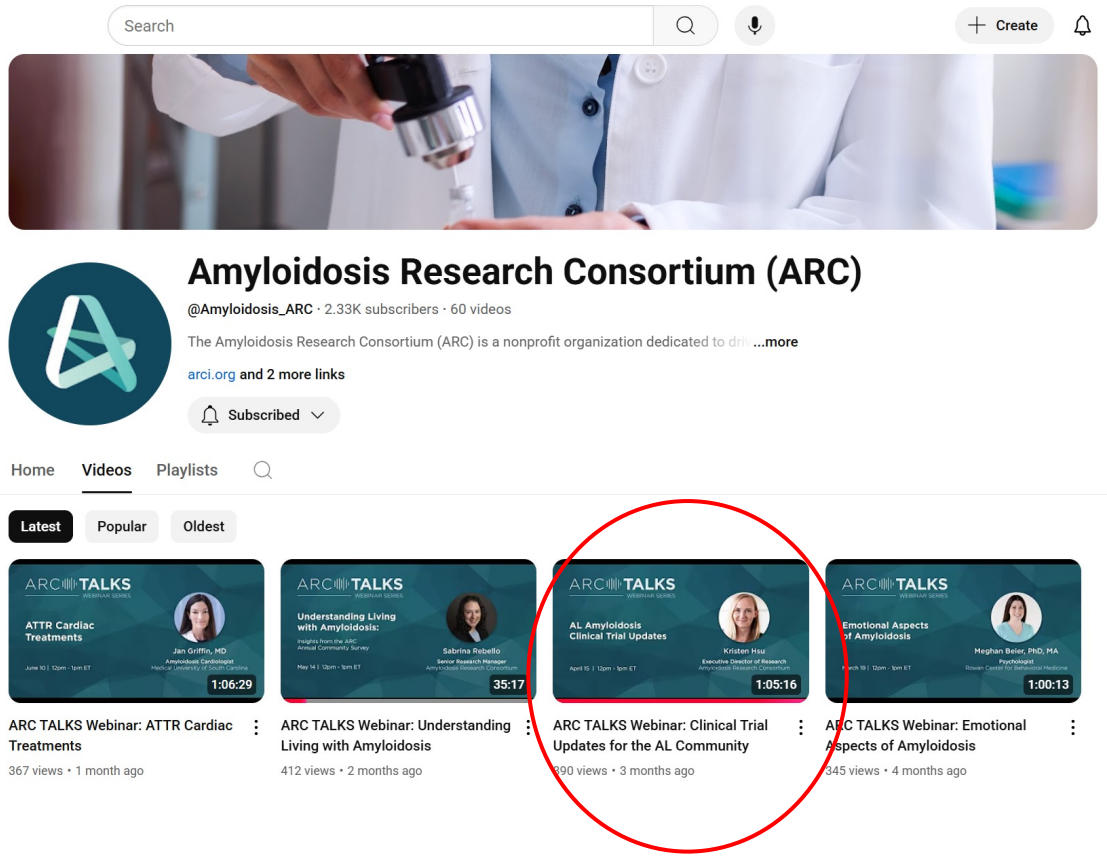
If you are here to learn about AL clinical trials…

…check out our April webinar focusing on AL amyloidosis clinical trials on our website or YouTube channel.
Our next AL amyloidosis clinical trials webinar is planned for Fall 2025

https://arci.org/resources-category/webinars/



https://www.youtube.com/@Amyloidosis_ARC



What is a Clinical Trial?

- A clinical study is research study involving human volunteers (also called participants) that is intended to add to medical knowledge.
- There are two types of clinical studies: interventional studies (also called **clinical trials**) and observational studies.

Interventional

A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.

Observational

A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to a specific interventions/treatment.

Clinicaltrials.gov/study-basics/glossary

Clinical Trial Phases

- Trials are divided into different stages, called phases.
- Each trial phase has a specific purpose and is designed to answer certain questions:

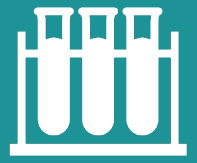
Phase 1	Phase 2	Phase 3	Phase 4
Determines a safe dose of the treatment under study (study drug) and monitors how the new treatment affects the human body (i.e. how the drug is broken down and excreted by the body).	Gather preliminary data on whether the new treatment works in people wohave a certain condition/disease and continues to evaluate safety.	Confirms how well a treatment works, monitors side effects, and compares the new treatment with the current standard treatment or a control arm in a randomized controlled study.	Post regulatory approval, gathers more information on a drug or treatment after it has been marketed to see its effect in various populations and any side effects associated with long-term use.

- The pathway develop a new drug is not always linear. This is especially true in rare disease!

What's involved?

- Most studies are interventional studies.
- These will require administration of the study drug or treatment and a sequence of monitoring visits.
- Monitoring usually takes place under clinical conditions (in a clinic), and on rare occasions may require overnight stays.

Clinical Examinations



Blood and Urine Lab Tests

Questionnaires

Functional Tests

Imaging Tests

What makes a study a good fit for me? How do I know it's safe?

- Participating in a trial or study has many potential benefits and also some possible risks.

Potential Benefits

- Treatment with investigational drugs that may not be available anywhere else
- Care from a research team
- Opportunity to learn more about your disease and how to manage it.
- Helping scientists better understand your disease and to advance treatments and ways to prevent it in the future

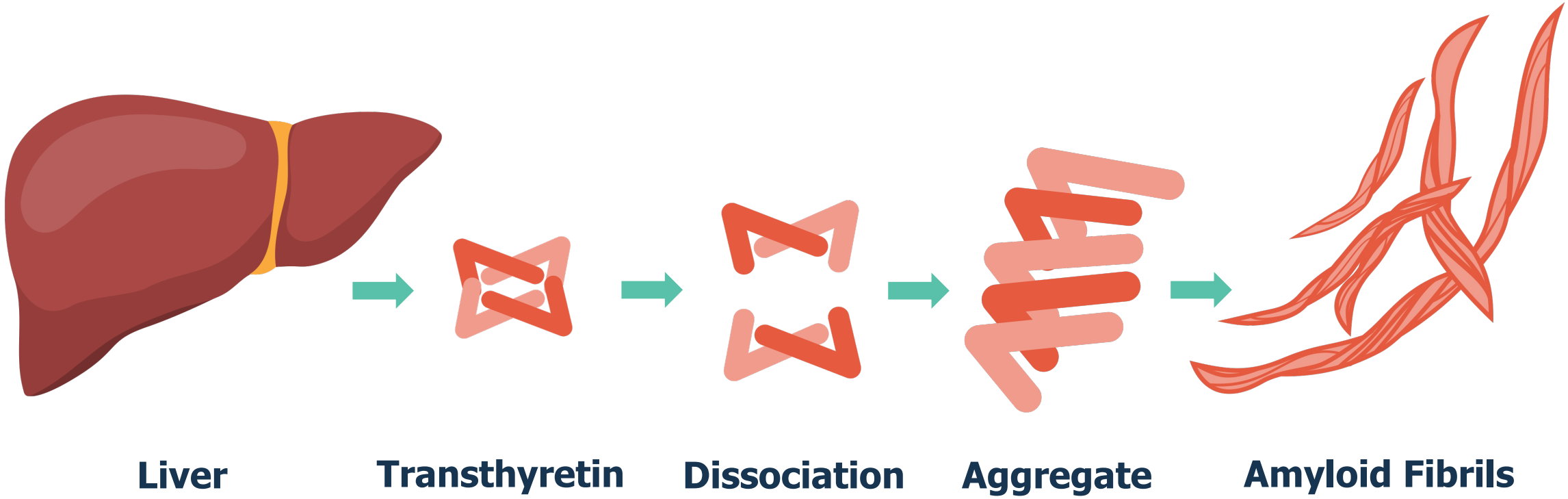
Potential Risks

- Clinical trials may involve a large time commitment and be inconvenient
- Study tests may pose a risk
- Study drug may pose risks, known and unknown
- The experimental treatment might not work
- Participants may be randomly assigned to receive a standard treatment or a placebo

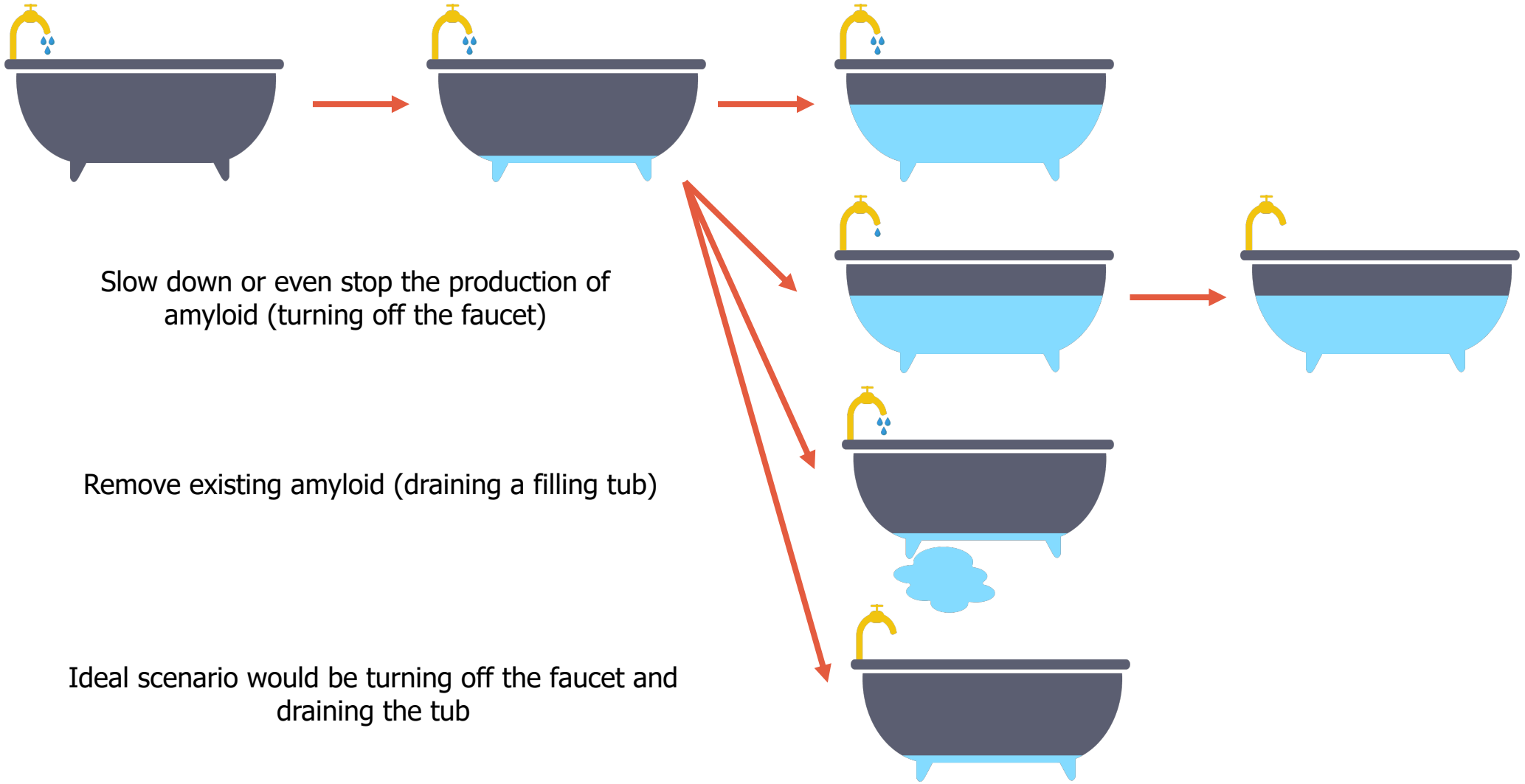
- Potential benefits and risks should be discussed carefully with study doctors and their teams.

Investigative Approaches to Treat ATTR Amyloidosis

Investigative approaches to treating ATTR Amyloidosis...



…are like treating a filling bathtub



Slow down or even stop the production of amyloid (turning off the faucet)

Remove existing amyloid (draining a filling tub)

Ideal scenario would be turning off the faucet and draining the tub

Investigative Approaches to Treat ATTR Amyloidosis

Amyloidosis Research Consortium

Knockdown of TTR

- Patisiran (Onpattro) for hATTR-PN
- Inotersen (Tegsedi) for hATTR-PN (discontinued)
- Vutrisiran (Amvuttra) for hATTR-PN and ATTR-CM
- Eplontersen (Wainua)* for hATTR-PN
- Nexiguran ziclumeran (nex-z, NTLA-2001)
- Nucresiran

*Investigational for ATTR-CM

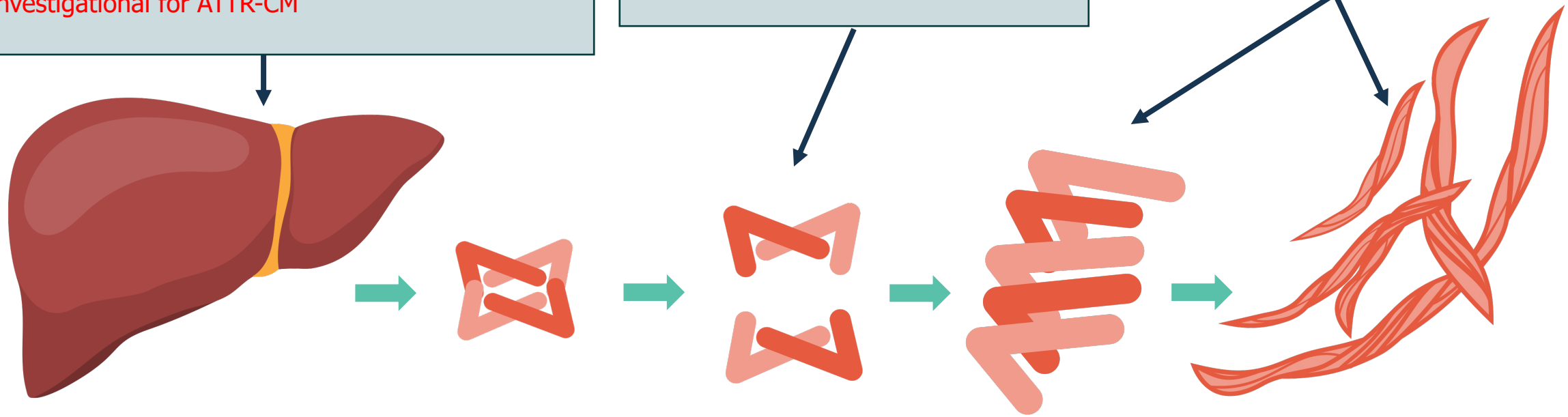
TTR Stabilizers

- Tafamidis (Vyndamax) for ATTR-CM
- Acoramidis (Attruby)* for ATTR-CM
- Diflunisal
- Tolcopone

*Investigational for ATTR gene (ATTRv) carriers

Anti-fibril agents

- Coramitug (NNC6019-0001)
- ALXN2220



Liver **Transthyretin** **Dissociation** **Aggregate** **Amyloid Fibrils**

ATTR Amyloidosis Clinical trials

Changes in Novel ATTR Therapies since Jan 2025

				Pre-clinical	Phase I	Phase II	Phase III	Commercial
TTR Stabilizers	Pfizer	Tafamidis (Vyndaqel) CM	Approved					
	BridgeBio	Acoramidis (Attruby) CM	Approved					
		Acoramidis ATTRv Carriers	P3 Recruiting					
	Corino	Tolcapone	P1 Complete					
Knockdown TTR	Alnylam	Patisiran (Onpattro) PN	Approved					
		Vutrisiran (Amvuttra) PN	Approved					
		Vutrisiran CM	**FDA Approved**					
		Nucresiran CM	**P3 Initiated**					
		Nucresiran PN	**P3 Planned 2025**					
	~~Ionis~~	~~Inotersen (Tegsedi) PN~~	~~Approved~~					
	Ionis / AZ	Eplontersen (Wainua) PN	Approved					
		Eplontersen-CM	Results 2026					
	Intellia	Nex-z (NTLA-2001) CM	P3 Recruiting					
		Nex-z (NTLA-2001) PN	P3 Recruiting					
Anti-fibril agents	Novo Nordisk	Coramitug CM (NNC6019-0001)	P2 Results 2025					
	Alexion/ AZ	**ALXN2220 (NI006) CM**	**P3 recruitment closed**					
	Attralus	~~**AT-02 CM**~~	~~**ATTR development stopped**~~					

Last Update July 30, 2025

Recruiting Trials for Novel ATTR Therapies in 2025

Amyloidosis Research

				Pre-clinical	Phase I	Phase II	Phase III	Commercial
TTR Stabilizers	Pfizer	Tafamidis (Vyndaqel) CM	Approved					
	BridgeBio	Acoramidis (Attruby) CM	Approved					
		Acoramidis ATTRv Carriers	**P3 Recruiting**					
	Corino	Tolcapone	P1 Complete					
Knockdown TTR	Alnylam	Patisiran (Onpattro) PN	Approved					
		Vutrisiran (Amvuttra) PN	Approved					
		Vutrisiran CM	Approved					
		Nucresiran CM	**P3 Recruiting**					
		Nucresiran PN	P3 planned 2025					
	Ionis	~~Inotersen (Tegsedi) PN~~	~~Approved~~					
	Ionis / AZ	Eplontersen (Wainua) PN	Approved					
		Eplontersen-CM	Results 2026					
	Intellia	**Nex-z (NTLA-2001) CM**	**P3 Recruiting**					
		Nex-z (NTLA-2001) PN	**P3 Recruiting**					
Anti-fibril agents	Novo Nordisk	Coramitug CM (NNC6019-0001)	P2 Results 2025					
	Alexion/ AZ	ALXN2220 (NI006) CM	P3 Results 2027					

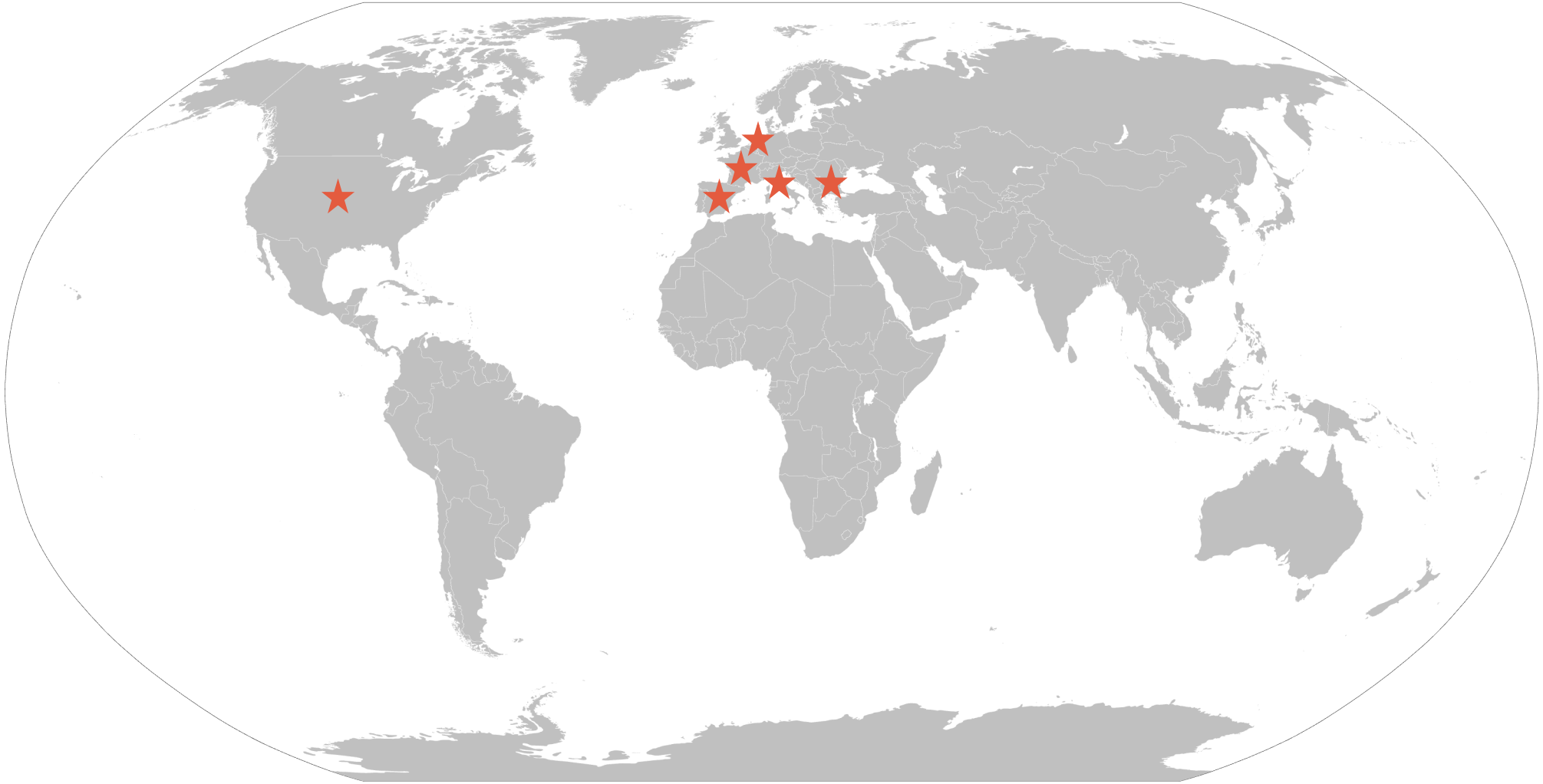
ACT-EARLY (acoramidis; TTR stabilizer)

Asymptomatic carriers of TTR mutations

Amyloidosis Research Consortium

Study Phase	Phase 3
Purpose of the study	Determine whether treatment with acoramidis in participants with ATTRv who have not yet developed any symptoms of disease can prevent or delay the development of disease
Primary endpoint	Assess whether treatment with acoramidis delays time to development of ATTR-CM (through biopsy or imaging-based diagnosis) or ATTR-PN (through onset of new signs or symptoms and biopsy-based diagnosis
Key eligibility criteria	- Asymptomatic carriers of a known pathogenic TTR gene variant - 18 to 75 years old - Age is within 10 years of predicted age of disease onset or older based either on family history or published literature (if family history is insufficient or unknown)
Number of patients	582
Study Drug	Daily tablets, twice a day
Chance of receiving study drug?	1/2 (50% chance) will receive acoramidis
How long?	Up to 7 years
Website	https://clinical-trials.bridgebio.com/

Recruiting Global ACT-Early Countries (as of 7/30/25)



Recruiting ACT-Early US Centers (as of 7/30/25)

Recruiting Centers:

- **California-** Stanford
- **Connecticut-** New Haven
- **District of Columbia-** Washington
- **Florida-** Jacksonville
- **Georgia-** Atlanta
- **Illinois-** Chicago
- **Maryland-** Baltimore (x2)
- **Massachusetts-** Boston
- **Minnesota-** Rochester
- **Missouri-** Kansas City
- **New Jersy-** New Brunswick
- **New York-** New York
- **South Carolina-** Charleston, Greenville
- **Texas-** Austin

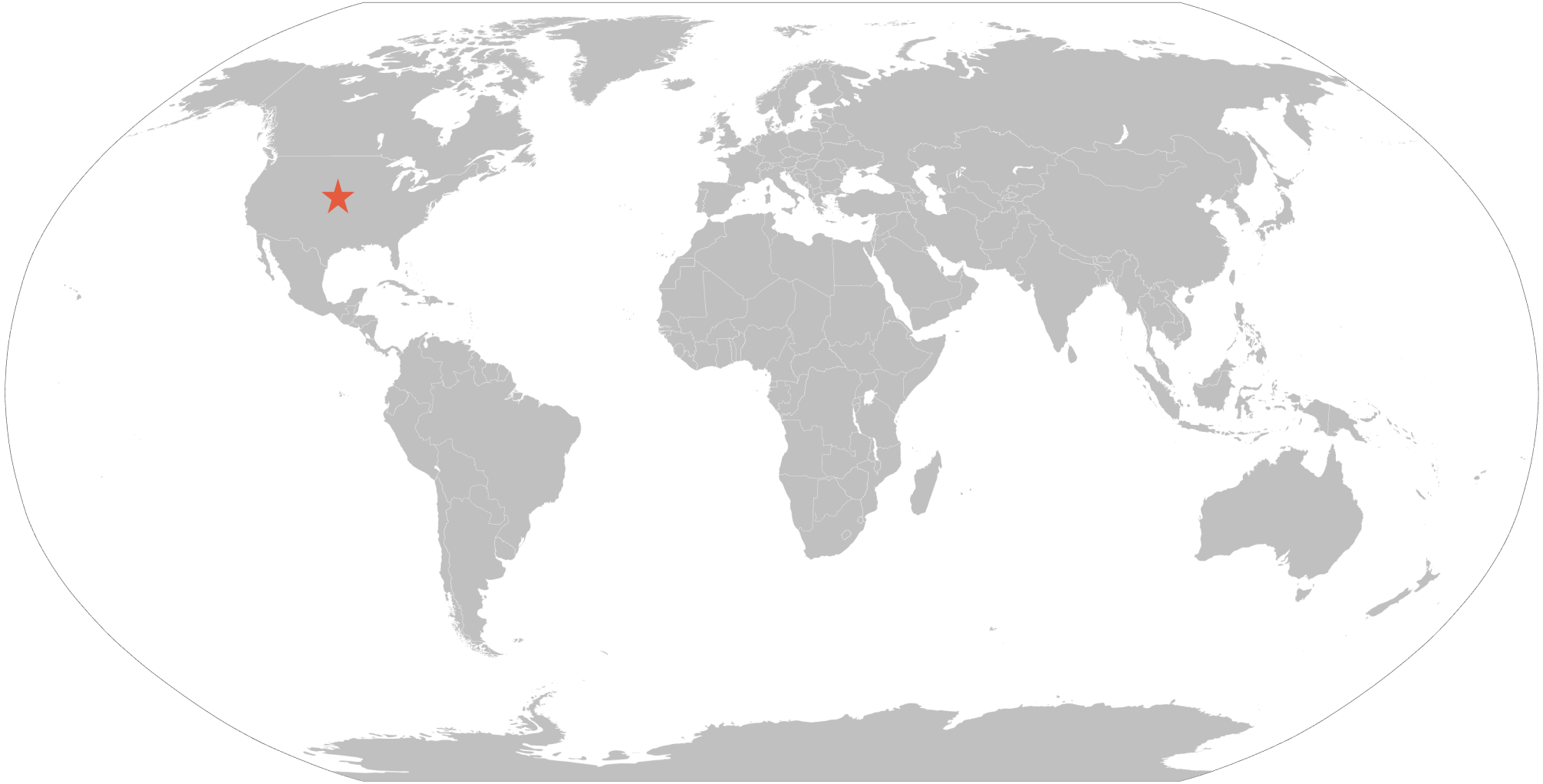
TRITON-CM (nucresiran; gene silencer)

ATTR-CM (wildtype or hereditary)

Amyloidosis Research Consortium

Study Phase	Phase 3
Purpose of the study	Evaluate the efficacy of nucresiran compared to placebo on reducing all-cause mortality and cardiovascular events, on additional assessments of cardiovascular events and/or death, and on patient-reported health status and health-related quality of life
Primary endpoint	Assess whether treatment with nucresiran reduces the risk of death and recurrent cardiovascular events (cardiovascular hospitalizations and urgent heart failure visits)
Key eligibility criteria	- Medical history of heart failure, NT-proBNP >300 ng/L and < 8,500 ng/L. - If afib, screening NT-proBNP >600 ng/L and <8500 ng/L. - No prior or current TTR-lowering therapy - Stabilizer use is allowed
Number of patients	1250
Study Drug	Subcutaneous (under the skin) injection every 6 months
Chance of receiving study drug?	2/3 (66.7% chance) will receive nucresiran
How long?	Up to 5 years
Website	https://alnylam-sponsor-trials.xogene.com/trials/7052903

Recruiting TRITON-CM Countries (as of 7/30/25)



Recruiting TRITON-CM US Centers (as of 7/30/25)

Recruiting Centers:

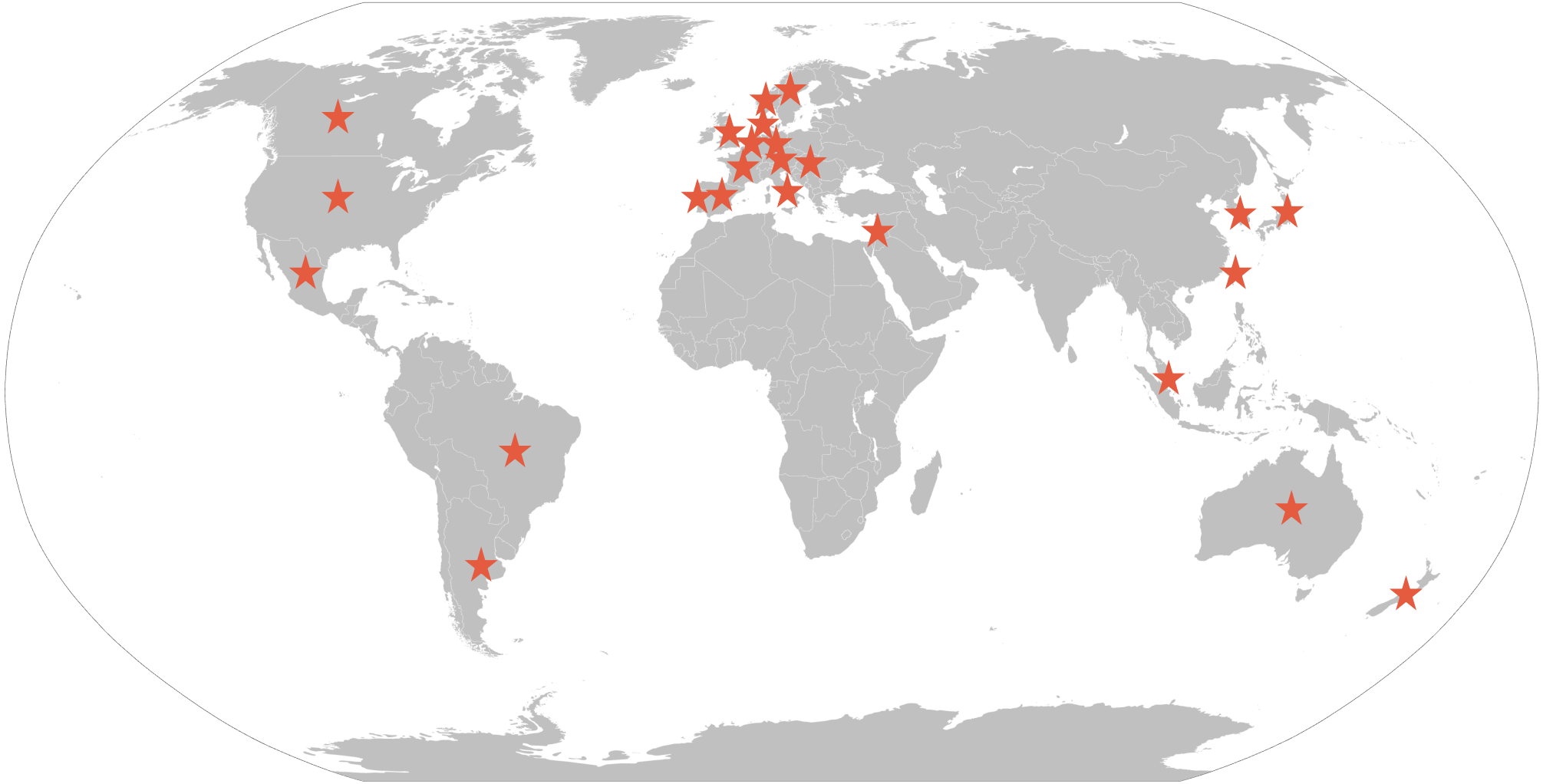
- **Georgia-** Cumming
- **Massachusetts-** Boston (pending)

MAGNITUDE [nexiguran ziclumeran (nex-z, NTLA-2001); CRISPR gene editing]

ATTR-CM (wildtype or hereditary)

Study Phase	Phase 3
Purpose of the study	Evaluate the efficacy and safety of nex-z in patients with ATTR-CM
Primary endpoint	Assess whether treatment with nex-z reduces the risk of cardiovascular related events (death, urgent heart failure visits, and cardiovascular hospitalizations)
Key eligibility criteria	- Medical history of heart failure, NT-proBNP >600 pg/mL and < 10,000 pg/mL - No treatment with patisiran (Onpattro), inotersen (Tegsedi), or eplontersen (Wainua) w/in 12 months prior to enrollment - No prior experience with vutrisiran (Amvuttra)
Number of patients	765
Study Drug	1 time infusion
Chance of receiving study drug?	2/3 (67% chance) will receive nex-z 1/3 (33% chance) will receive placebo
How long?	18 months to ~4 years
Website	https://www.magnitudestudy.com/

Recruiting Global MAGNITUDE Countries (as of 7/30/25)



Recruiting MAGNITUDE-CM US Centers (as of 7/30/25)

Recruiting Centers:

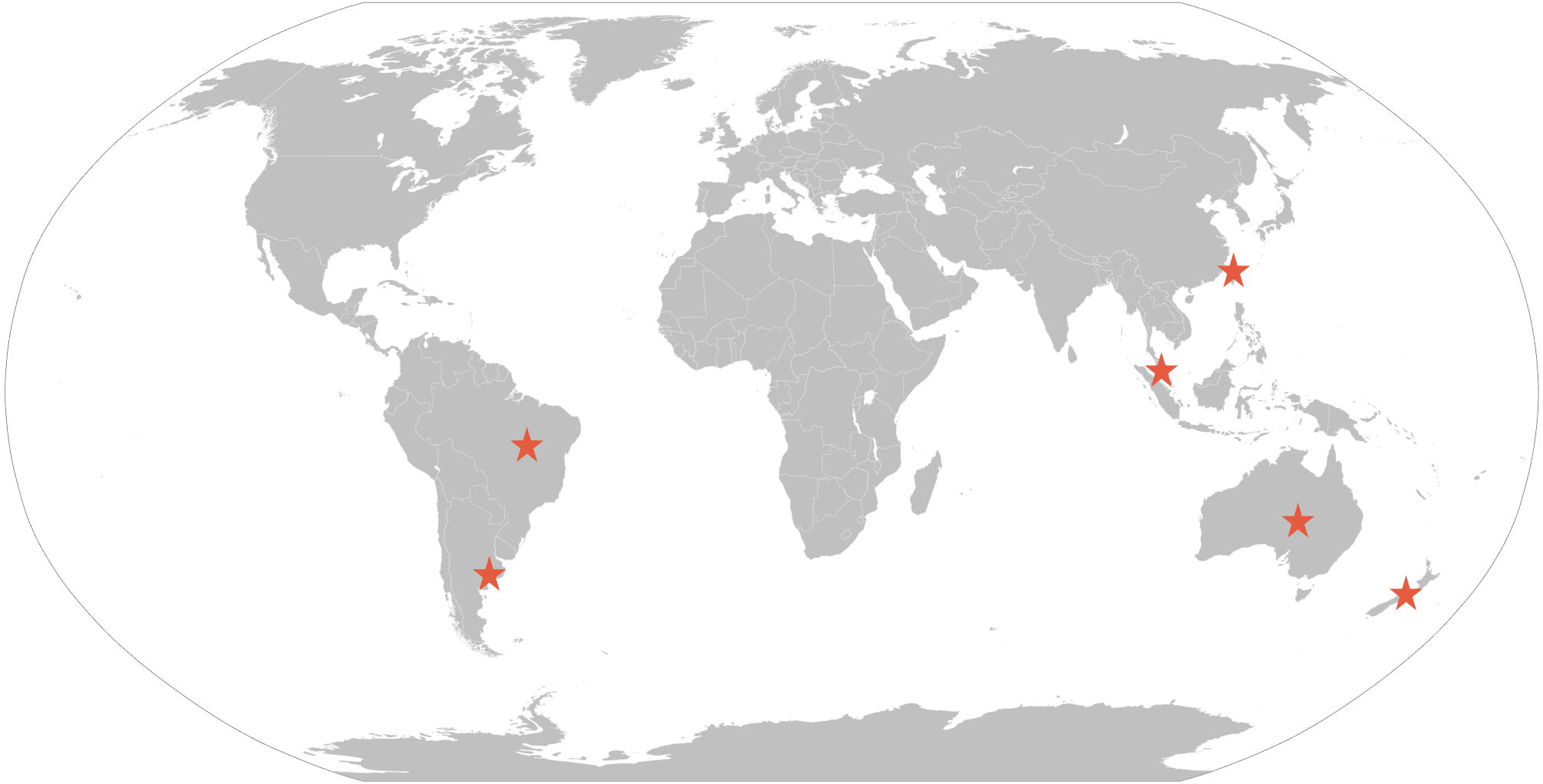
- **Arizona-** Tucson
- **California-** Los Angeles (x2), Palo Alto
- **Colorado-** Denver
- **Connecticut-** New Haven
- **District of Columbia-** Washington DC
- **Florida-** Jacksonville, Weston
- **Georgia-** Atlanta
- **Illinois-** Chicago
- **Indiana-** Indianapolis
- **Kentucky-** Lexington
- **Maryland-** Baltimore
- **Massachusetts-** Boston (2 centers)
- **Michigan-** Ann Arbor, Detroit
- **Minnesota-** Rochester
- **Missouri-** Kansas City
- **New York-** New York (2 centers)
- **Ohio-** Cleveland, Columbus
- **Oregon-** Portland
- **Pennsylvania-** Philadelphia, Pittsburgh (x2)
- **South Carolina-** Charleston
- **Texas-** Dallas, Houston (2 centers), Plano
- **Virginia-** Falls Church, Richmond

MAGNITUDE-2 [nexiguran ziclumeran (nex-z, NTLA-2001); CRISPR gene editing]

ATTR-PN (hereditary only)

Study Phase	Phase 3
Purpose of the study	Evaluate the efficacy and safety of nex-z in patients with ATTR-PN
Primary endpoint	Assess the impact of a single dose of nex-z on neuropathy. measured by the Modified Neuropathy Impairment Score +7 (mNIS+7)
Key eligibility criteria	- Diagnosis of ATTRv-PN, without advanced heart failure - Able to care for themselves, though may require occasional assistance - No prior treatment with patisiran (Onpattro), vutrisiran (Amvuttra), inotersen (Tegsedi), or eplontersen (Wainua)
Number of patients	50
Study Drug	1 time infusion
Chance of receiving study drug?	1/2 (50% chance) will receive nex-z, 1/2 (50% chance) will receive placebo; opportunity for crossover
How long?	18 months

Recruiting Global MAGNITUDE-2 Countries (as of 7/30/25)



Upcoming Milestones for Novel ATTR Therapies in 2025

Amyloidosis Research

				Pre-clinical	Phase I	Phase II	Phase III	Commercial
TTR Stabilizers	Pfizer	Tafamidis (Vyndaqel) CM	Approved					
	BridgeBio	Acoramidis (Attruby) CM	Approved					
		Acoramidis ATTRv Carriers	P3 Recruiting					
	Corino	Tolcapone	P1 Complete					
Knockdown TTR	Alnylam	Patisiran (Onpattro) PN	Approved					
		Vutrisiran (Amvuttra) PN	Approved					
		Vutrisiran CM	Approved					
		Nucresiran CM	P3 Recruiting					
		Nucresiran PN	**P3 Planned 2025**					
	Ionis	Inotersen (Tegsedi) PN	Approved					
	Ionis / AZ	Eplontersen (Wainua) PN	Approved					
		Eplontersen-CM	**Results 2026**					
	Intellia	Nex-z (NTLA-2001) CM	P3 Recruiting					
		Nex-z (NTLA-2001) PN	P3 Recruiting					
Anti-fibril agents	Novo Nordisk	**Coramitug CM (NNC6019-0001)**	**P2 Results 2025**					
	Alexion/ AZ	**ALXN2220 (NI006) CM**	**P3 Results 2027**					

CARDIO-TTRansform (eplontersen; gene silencer)

ATTR-CM (wildtype or hereditary)

Study Phase	Phase 3
Purpose of the study	Evaluate the efficacy of eplontersen compared to placebo in participants with ATTR-CM receiving available standard of care
Primary endpoint	Assess whether treatment with eplontersen improves outcomes of cardiovascular mortality and recurrent cardiovascular events compared to placebo
Number of patients	1438
Study Drug	Subcutaneous (under the skin) injection every 4 weeks
Chance of receiving study drug?	1:1 eplontersen to placebo
How long?	140 weeks (2.69 years)
Keep an eye out for	Results 2026

Coramitug (NNC6019-0001) Ph2 CM; anti-amyloid fibril

ATTR-CM (wildtype or hereditary)

Study Phase	Phase 2
Purpose of the study	Evaluate the efficacy and safety of NNC6019-0001 at two dose levels in participants with ATTR-CM
Primary endpoint	Change in 6 minute walk test and change in NT-proBNP at 52 weeks
Number of patients	99
Study Drug	Intravenous (into a vein) infusions every 4 weeks
Chance of receiving study drug?	2:1 coramitug to placebo
How long?	64 weeks
Keep an eye out for	Results 2025

DepleTTR-CM (ALXN2220; amyloid depleter)

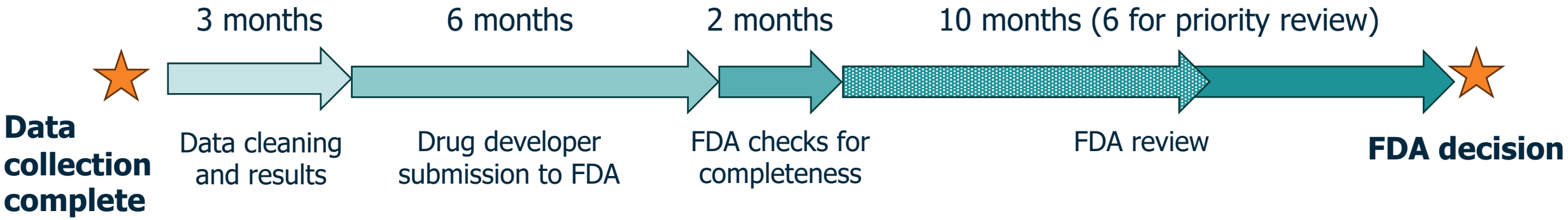
ATTR-CM (wildtype or hereditary)

Study Phase	Phase 3
Purpose of the study	Evaluate the efficacy and safety of ALXN2220 in patients with ATTR-CM
Primary endpoint	Assess whether treatment with ALXN2220 reduces the risk of all cause mortality and cardiovascular clinical events
Key eligibility criteria	-History of heart failure, NT-proBNP >2000 pg/mL -No prior treatment with an ATTR amyloid depleter, but patients may be on locally approved standard of care therapy
Number of patients	1158
Study Drug	Intravenous (into a vein) infusions every 4 weeks
Chance of receiving study drug?	2/3 (67% chance) will receive ALXN2220 1/3 (33% chance) will receive placebo
How long?	2-4 years
Website	https://deplettrcmstudy.alexionclinicaltrials.com/

Q: How long does FDA approval take after Phase 3?

Amyloidosis Research Consortium

Answer: Approval timelines can vary, many steps along the way



Factors that can influence timelines:

- FDA Advisory Committees (if needed)
- Priority Review Designation
- Breakthrough Therapy and Fast Track Designation
- Quality and Completeness of Submission
- FDA Resource Allocation and Review Capacity
- Communication and Information Requests

Other Recruiting and Planned Clinical studies

	Study Name/Description	Clinicaltrials.gov link
Imaging Trials	REVEAL: Research With I-124 Evuzamitide to Elucidate Cardiac AmyLoidosis	https://clinicaltrials.gov/study/NCT06788535
	CArdiag: Efficacy of [18F]Florbetaben PET for Diagnosis of Cardiac AL Amyloidosis	https://clinicaltrials.gov/study/NCT05184088
Single center trials	CAPACITY (Cardiac Amyloidosis and Physical ACtivITY) Study	https://clinicaltrials.gov/study/NCT06096675
	Exercise Training in Transthyretin Cardiac Amyloidosis	https://clinicaltrials.gov/study/NCT05797857
	Intracardiac Flow Assessment in Cardiac Amyloidosis	https://clinicaltrials.gov/study/NCT05379101
Observational Studies	Subclinical Transthyretin Cardiac Amyloidosis in V122I TTR Carriers	https://clinicaltrials.gov/study/NCT05489549
	Southeastern ATTR Amyloidosis Consortium: SEATTRAC Family Registry	https://clinicaltrials.gov/study/NCT05974644
	Canadian Registry for Amyloidosis Research	https://amyloidregistry.ca/home
	Cardiac Amyloidosis Registry Study (CARS)	https://clinicaltrials.gov/study/NCT05174338
Company sponsored registries and real world evidence studies	AstraZeneca: Non-interventional Study of Patients With ATTR Amyloidosis (MaesTTRo)	https://clinicaltrials.gov/study/NCT06465810
	Alnylam: A Global Observational Study of Patients With ATTR Amyloidosis (ConTTRibute)	https://clinicaltrials.gov/study/NCT04561518

REVEAL (I-124 Evuzamitide; diagnostic radiotracer)

Suspected cardiac amyloidosis: All types (AL, ATTR, ApoA4, etc.)

Amyloidosis Research Consortium

Study Phase	Phase 3
Purpose of the study	To evaluate the effectiveness of I-124 Evuzamitide to diagnose cardiac amyloidosis
Primary endpoint	Sensitivity and specificity of I-124 Evuzamitide to detect cardiac amyloidosis
Key eligibility criteria	Inclusion: Patients with suspected cardiac amyloidosis, including those with positive amyloid from carpal tunnel surgery or spinal laminectomy as long as no other organs have been identified Exclusion: Previously diagnosed with systemic amyloidosis; EGFR <15
Number of patients	Up to 200
Study Drug	Single intravenous (into a vein) infusion
Chance of receiving study drug?	100%; All participants will receive I-124 Evuzamitide
How long?	60 days, 3 in-person visits required

REVEAL Centers (as of 7/30/2025)

Planned Centers:

- Arizona- Scottsdale
- California- Duarte, San Francisco
- **Connecticut- New Haven**
- Florida- Weston
- Illinois- Chicago (x2)
- **Massachusetts- Boston**
- Michigan- Ann Arbor
- Minnesota- Rochester
- **Missouri- Kansas City, St. Louis**
- New Jersy- New Brunswick
- **New York- New York**
- North Carolina- Durham, Greensboro
- Ohio- Cleveland
- **Oregon- Portland**
- Pennsylvania- Pittsburgh
- South Carolina- Charleston
- Texas- Houston
- **Wisconsin- Milwaukee**

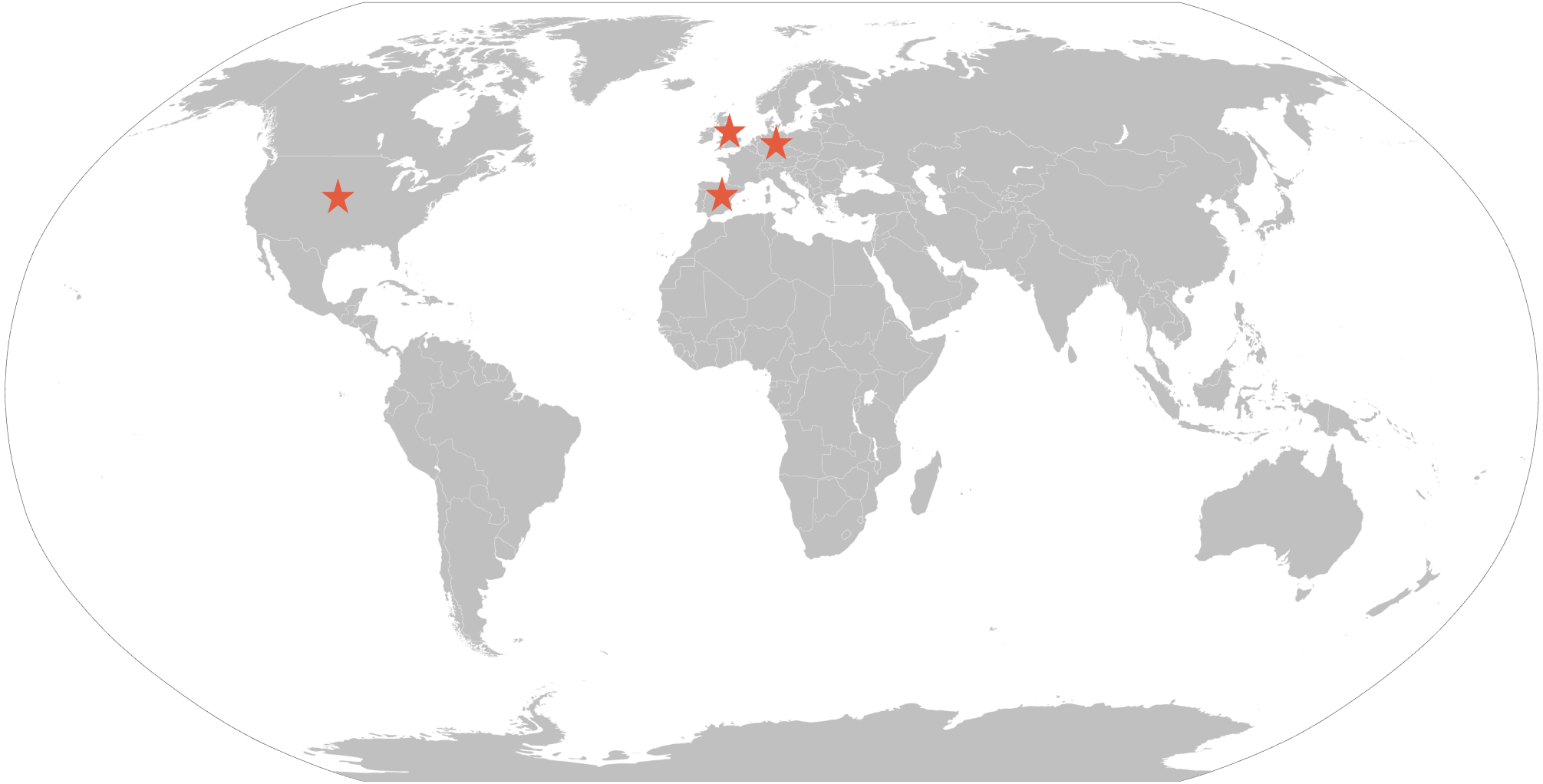
CArdiag ([18F]Florbetaben; diagnostic radiotracer)

Suspected cardiac amyloidosis: AL and ATTR amyloidosis)

Amyloidosis Research Consortium

Study Phase	Phase 3
Purpose of the study	To evaluate the efficacy and safety of [18F]Florbetaben positron emission tomography (PET) imaging to diagnose cardiac AL amyloidosis - Additional goals of the study are the differentiation between AL and ATTR cardiac disease
Primary endpoint	Sensitivity and specificity of [18F]Florbetaben to detect cardiac amyloidosis
Key eligibility criteria	Patients being considered for a possible diagnosis of cardiac amyloidosis with a planned diagnostic procedure to establish diagnosis and cardiac involvement
Number of patients	200
Study Drug	Single intravenous (into a vein) infusion
Chance of receiving study drug?	100%; All participants will receive [18F]Florbetaben
How long?	12 weeks

Recruiting Global CArdiag Countries (as of 7/30/25)



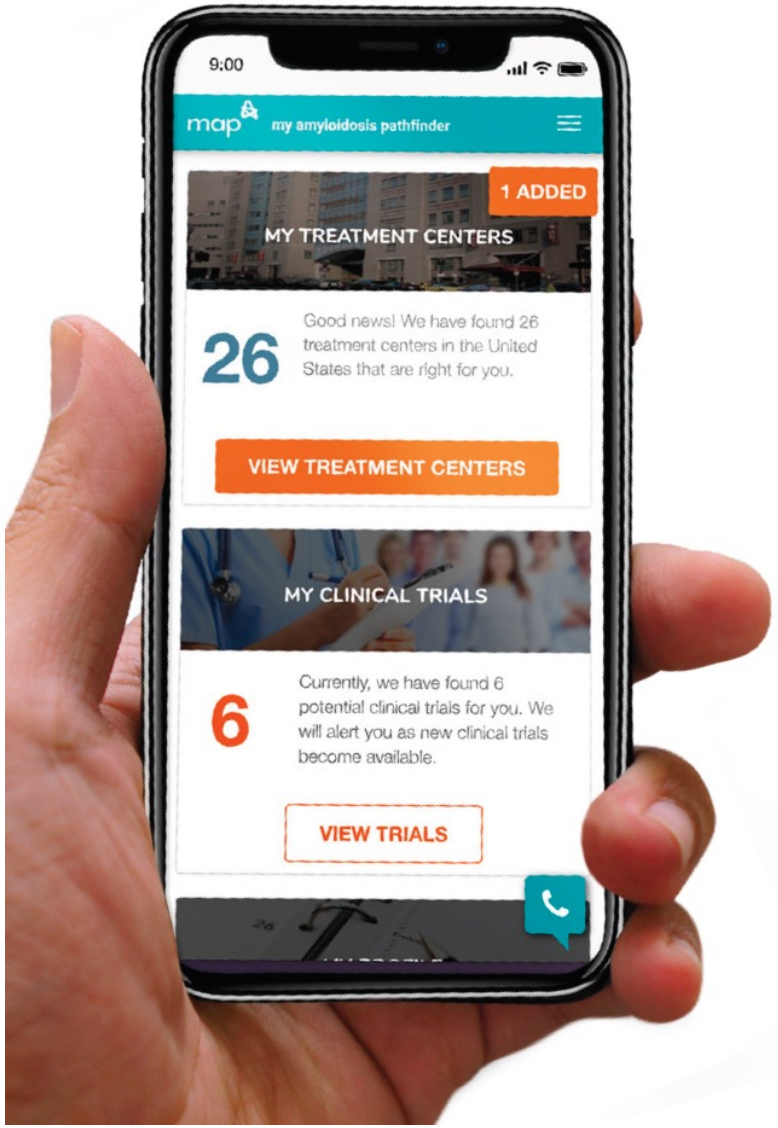
Recruiting CArdiag US Centers (as of 7/30/25)

Recruiting Centers:

- **Kansas-** Kansas City
- **Pennsylvania-** Philadelphia, Pittsburgh

How to find clinical trials

- You can find and stay informed of clinical trials a few different ways:
  - Clinicaltrials.gov
  - Talk to your healthcare provider
  - Follow patient organizations like ARC, ASG, etc.
  - Sign up for My Amyloidosis Pathfinder (MAP)



Discover Personalized Treatment Centers & Clinical Trials for Your Amyloidosis

myamyloidosispathfinder.org

map

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