ARC TALKS
WEBINAR SERIES

ATTR Amyloidosis Clinical Trial Updates

Kristen Hsu

Executive Director of Research
Amyloidosis Research Consortium

January 22 | 12pm - 1pm ET

Amyloidosis Research Consortium

The Amyloidosis Research Consortium (ARC) was founded in 2015. ARC is dedicated to accelerating the pace of development for new and innovative treatments to improve quality of life for amyloidosis patients. ARC is a patient-founded, patient-centric non-profit organization. Despite significant steps forward in recent years, the unmet needs of patients remain high and too few treatment options exist.

Our vision is to make a significant impact on the curability of amyloidosis

Amyloidosis Research Consortium

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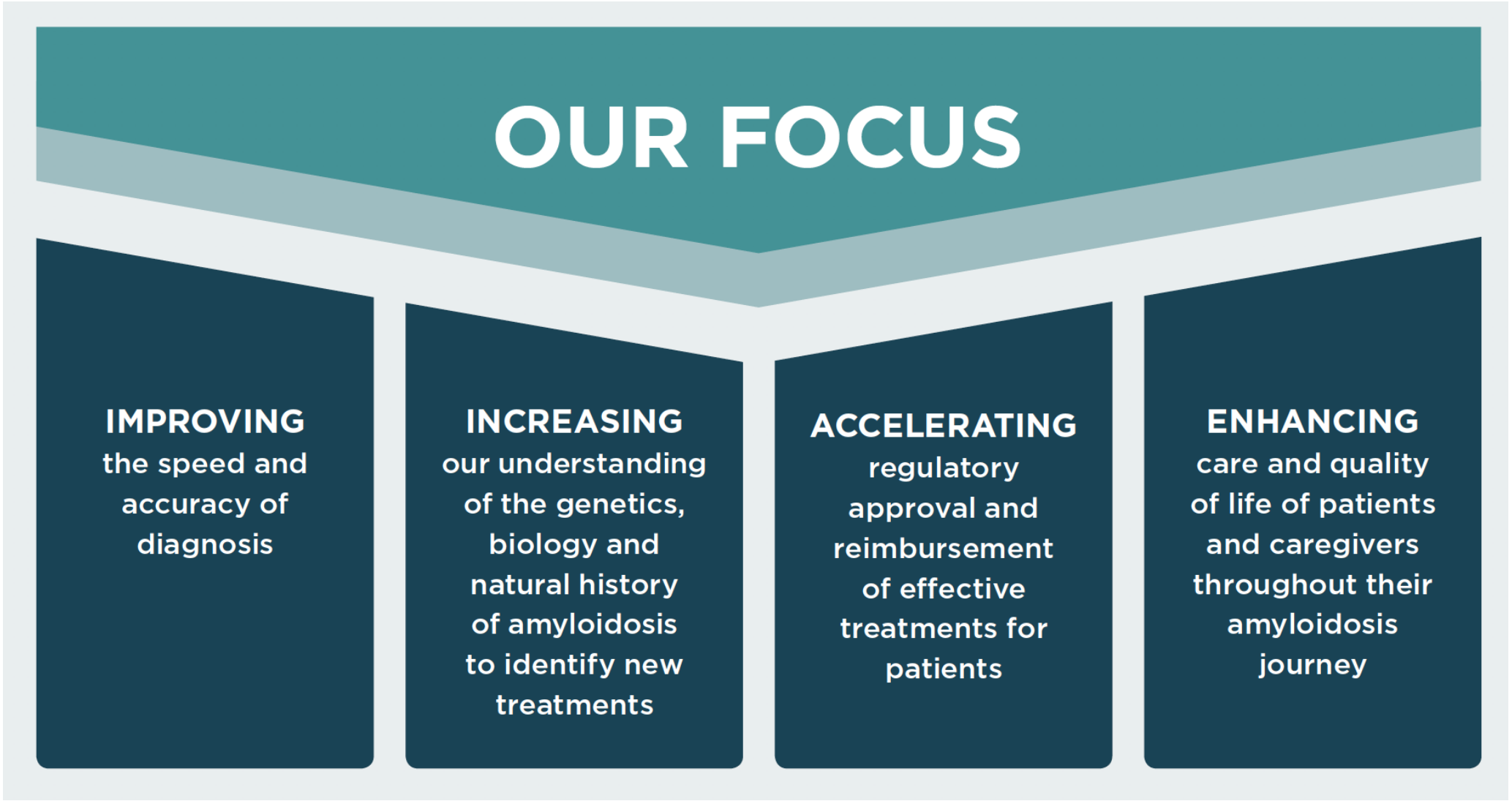

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Clinical Trial Updates for the ATTR Community

Kristen Hsu, Executive Director of Research

What is a Clinical Trial?

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- Medical research studies involving people are called clinical trials, or sometimes clinical studies.
- Clinical trials explore whether a medical strategy, drug, treatment, or device is safe and effective for patients.
- Studies can also look at other aspects of care, such as improving quality of life for patients.
- Two main types:

Interventional

Studies in which a treatment or other intervention is being given, and their outcomes are measured by the investigators

Observational

Studies in which patients are observed and their outcomes are measured by the investigators.

Clinical Trial Phases

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- 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.	Determines if the new treatment is seemingly effective and monitors any side effects.	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?

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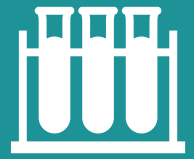
- Most studies are interventional studies.
- These will require administration of the study drug or treatment and a sequence of monitoring visits.
- Monitoring usually takes place under clinical conditions (in a clinic), and on rare occasions may require overnight stays.

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?

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- 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..!

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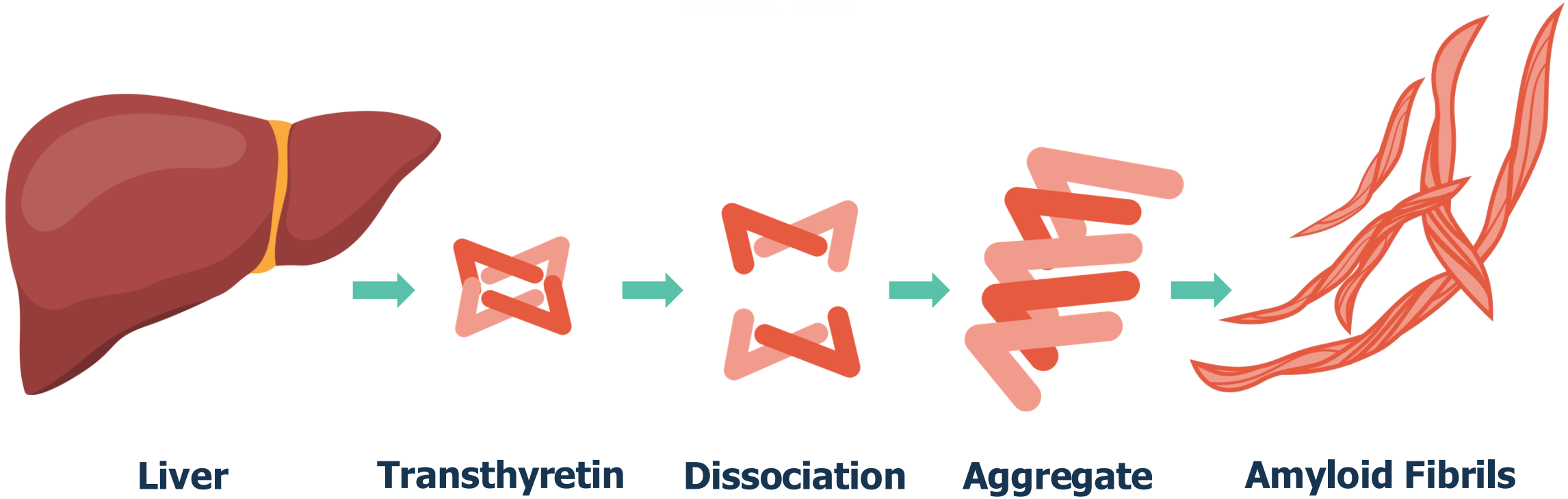

...are like treating a filling bathtub

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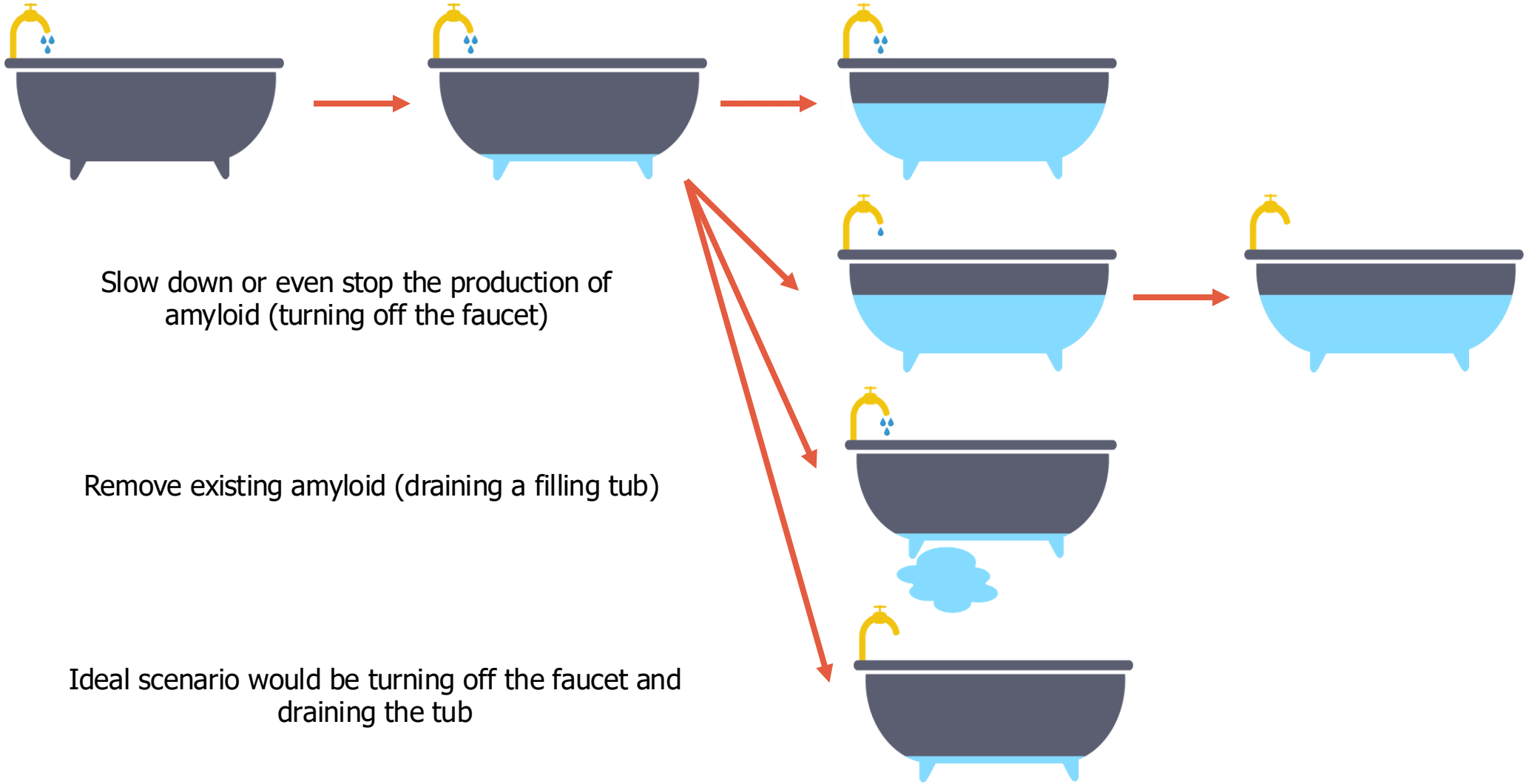

Slow down or even stop the production of amyloid (turning off the faucet)

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

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Knockdown of TTR

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

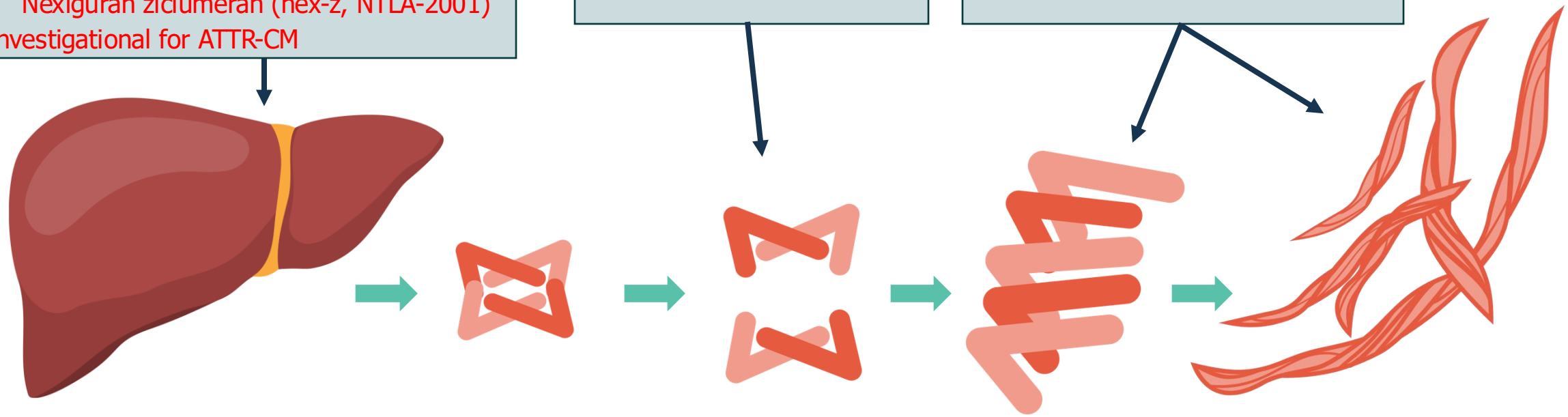
*Investigational for ATTR-CM

TTR Stabilizers

- Tafamidis (Vyndamax)
- Acoramidis (Attruby)
- Diflunisal
- Tolcopone

Anti-fibril agents

- Coramitug (NNC6019-0001)
- ALXN2220
- AT-02



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

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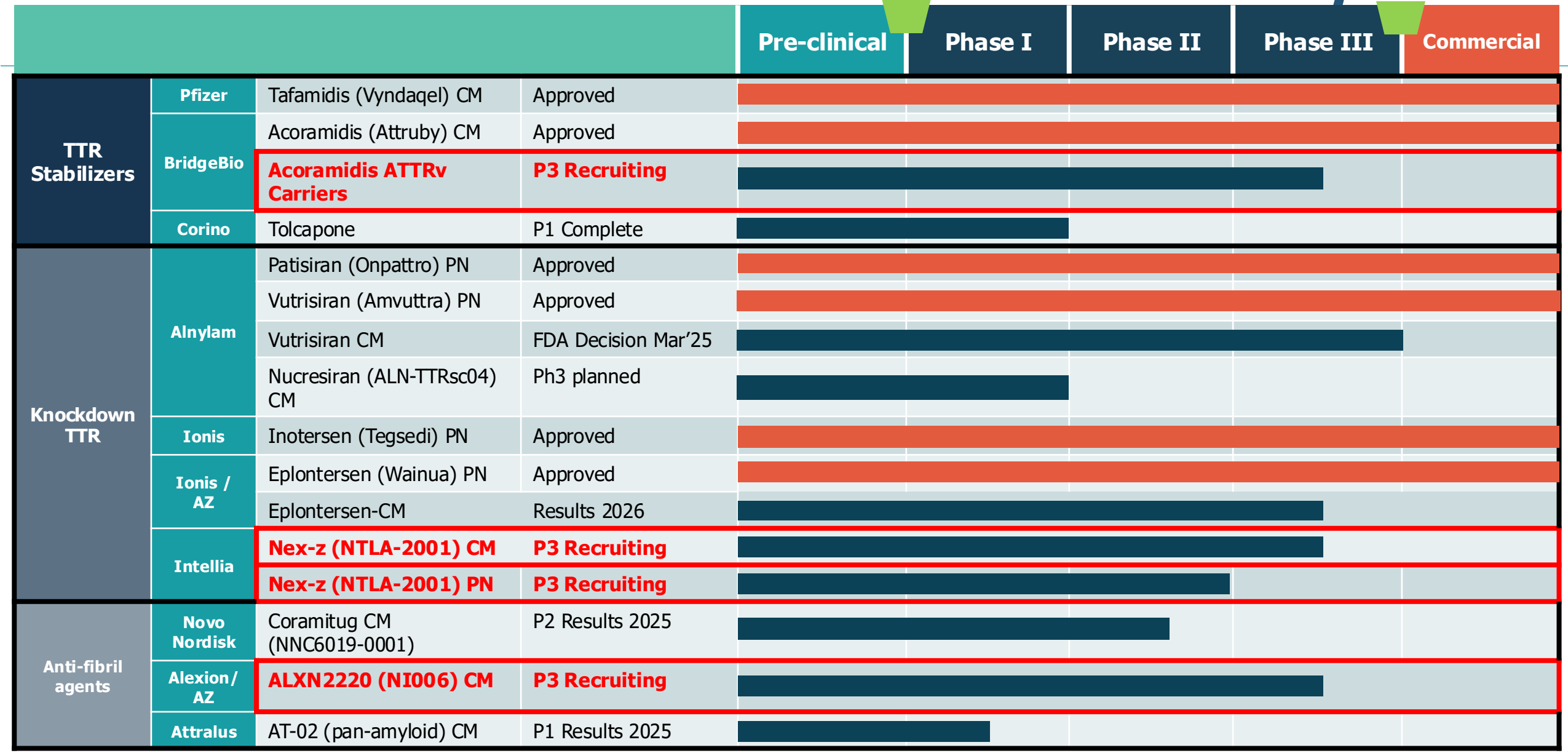
Health Care Without Harm

ATTR Amyloidosis Clinical trials

Recruiting Trials for Novel ATTR Therapies in 2025

Amyloidosis Research



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 Decision Mar'25
		Nucresiran (ALN-TTRsc04) CM	Ph3 planned
	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 Recruiting**
	Attralus	AT-02 (pan-amyloid) CM	P1 Results 2025

ACT-EARLY (acoramidis; TTR stabilizer)

Asymptomatic carriers of TTR mutations

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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

Recruiting Global ACT-Early Countries (as of 1/15/25)

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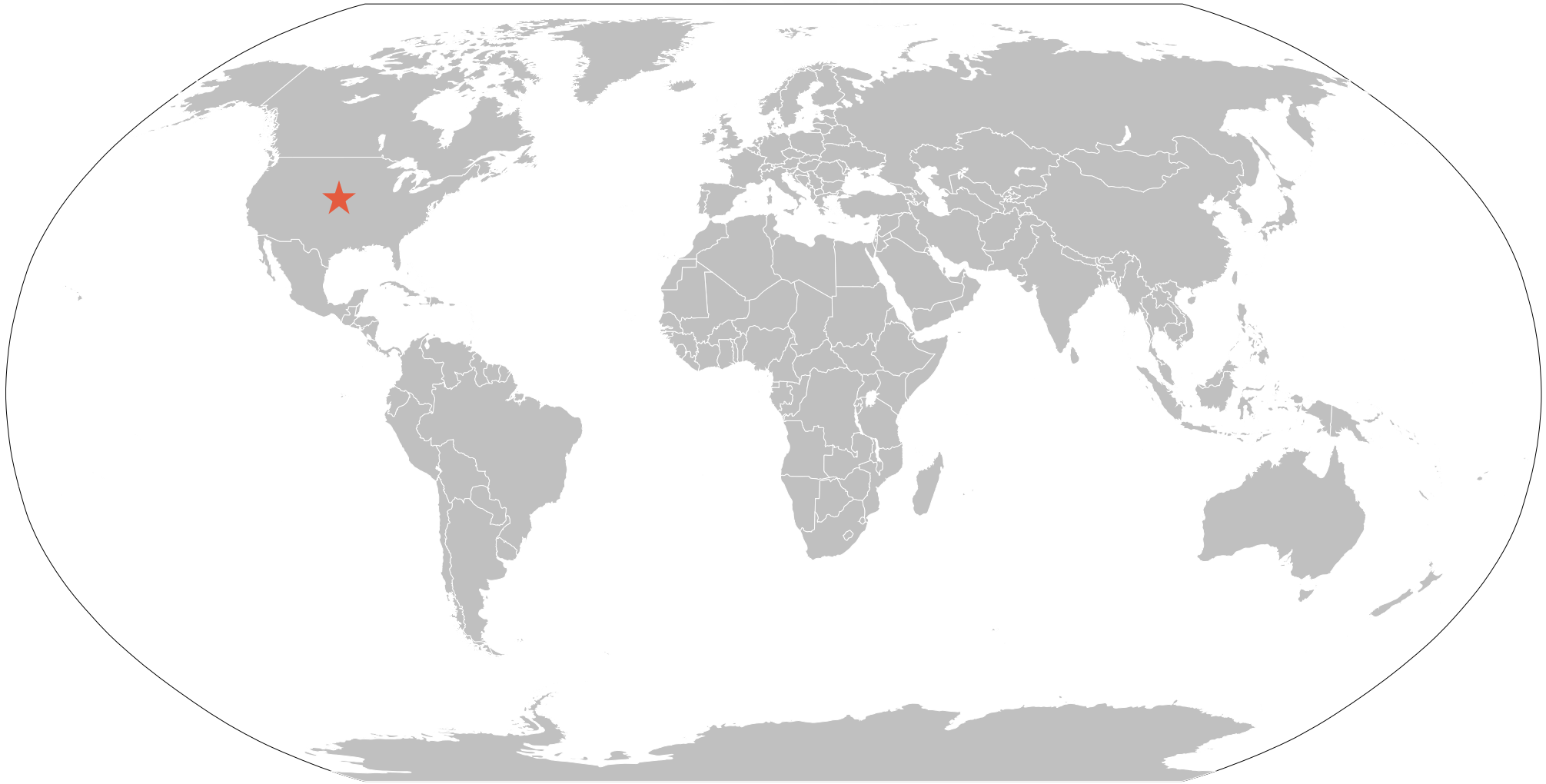

Recruiting ACT-Early US Centers (as of 1/15/25)

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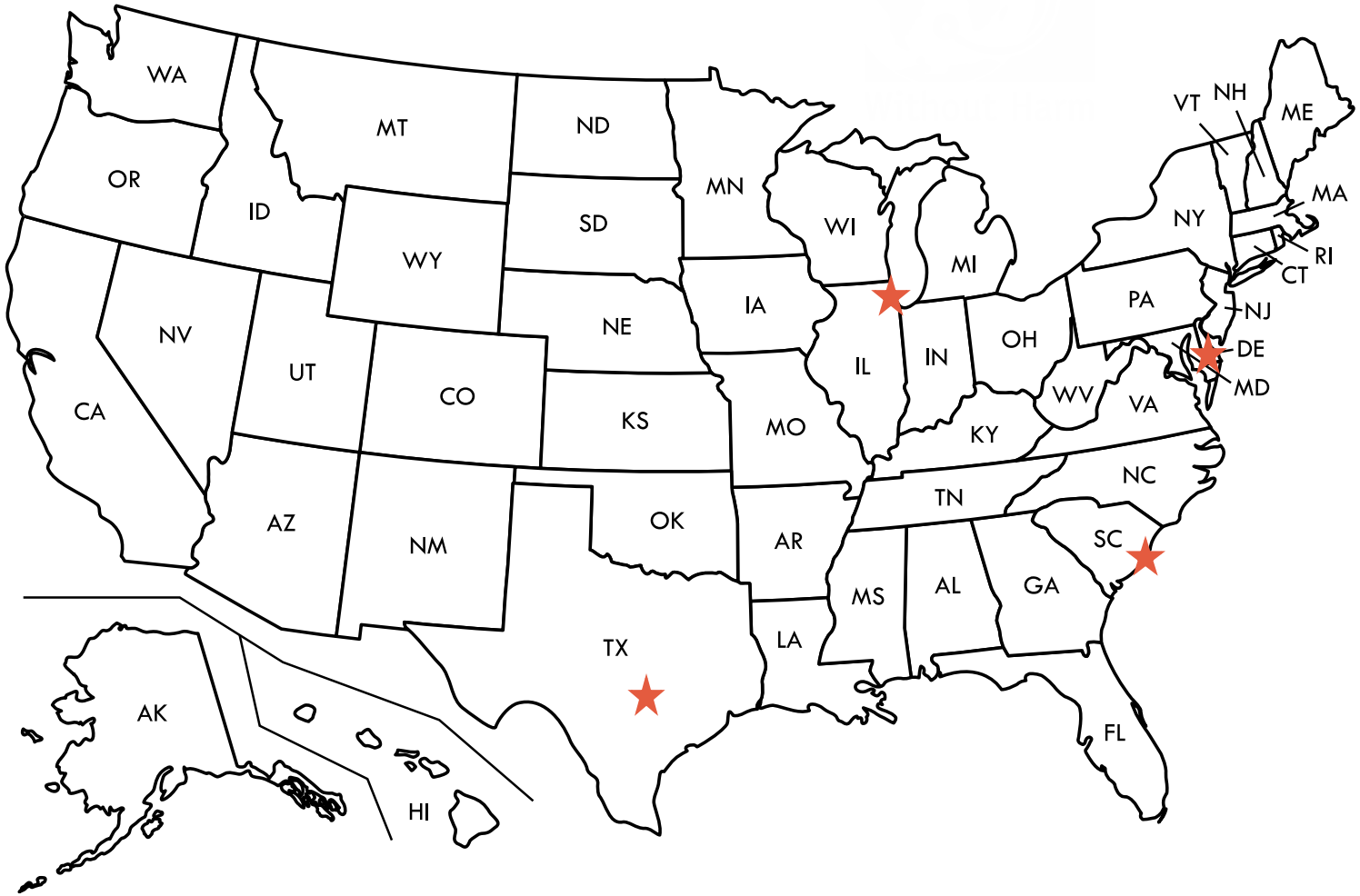

Recruiting Centers:

- **District of Columbia-** Washington
- **Illinois-** Chicago
- **South Carolina-** Charleston
- **Texas-** Austin

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

ATTR-CM (wildtype or hereditary)

Amyloidosis Research Consortium

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 >1000 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 1/15/25)

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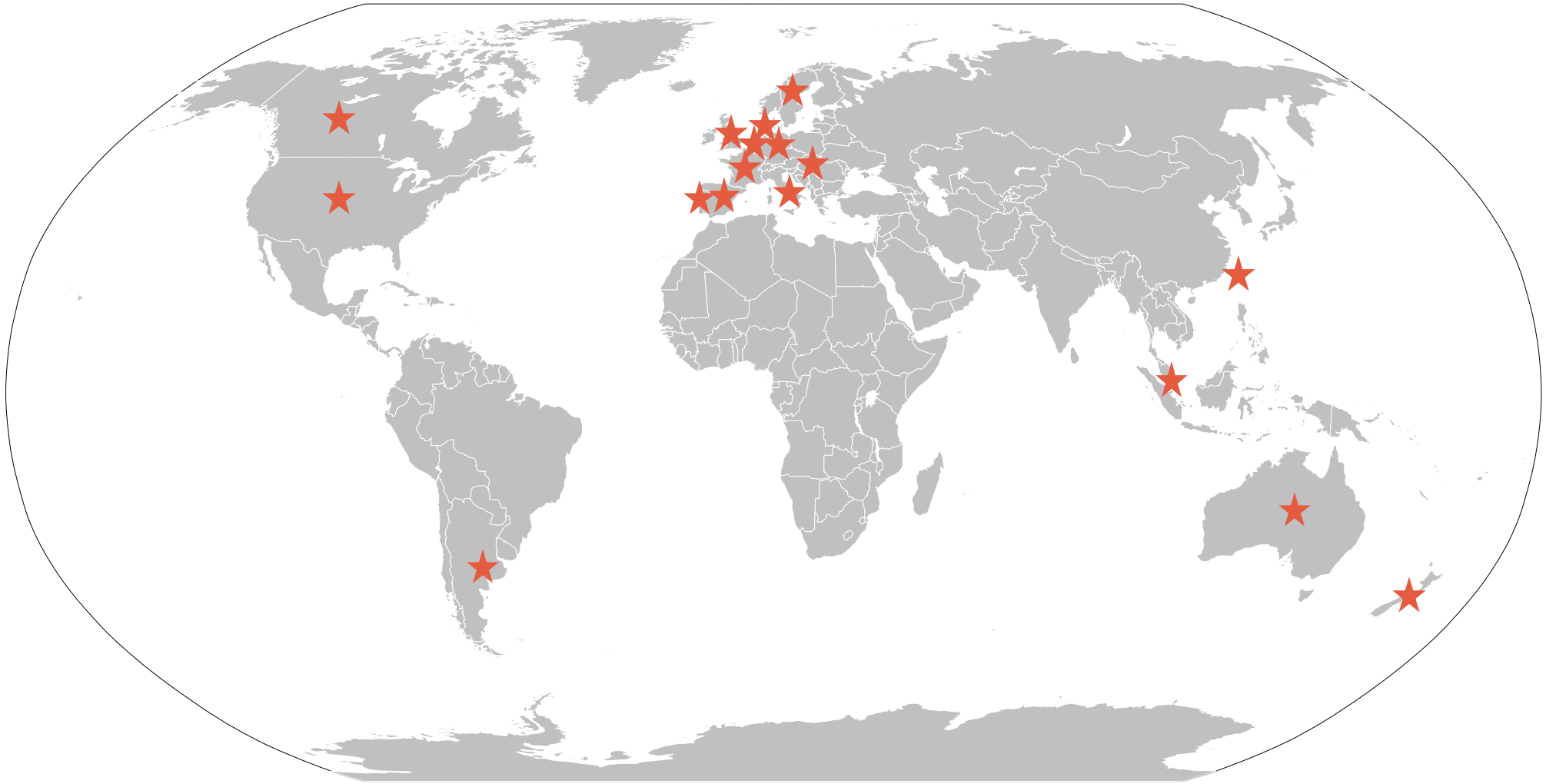

Recruiting MAGNITUDE-CM US Centers (as of 1/15/25)

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Recruiting Centers:

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

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

ATTR-PN (hereditary only)

Amyloidosis Research Consortium

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 1/15/25)

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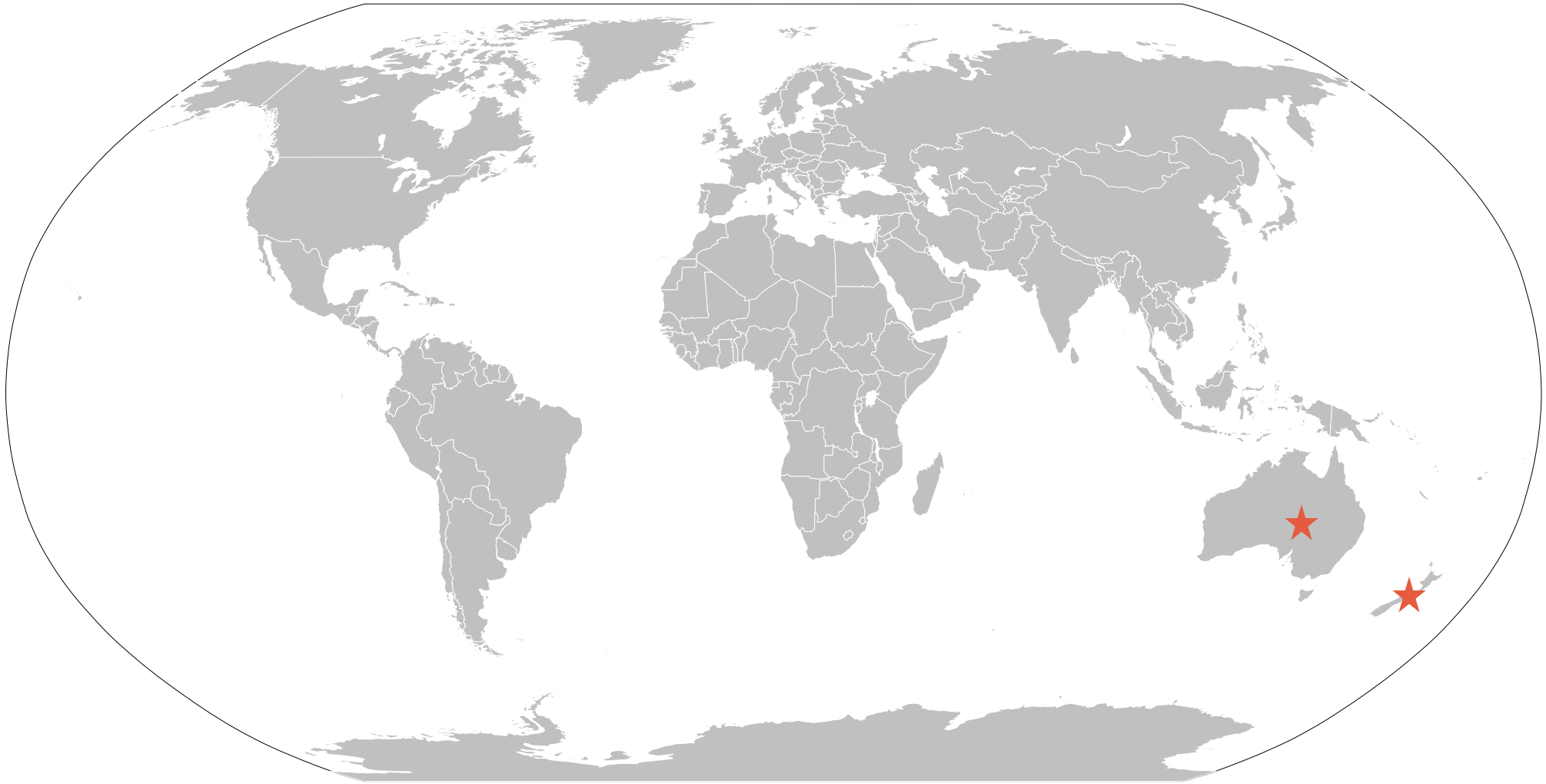

DepleTTR-CM (ALXN2220; amyloid depleter)

ATTR-CM (wildtype or hereditary)

Amyloidosis Research Consortium

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	1000
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/

Recruiting Global DepleTTR-CM Countries (as of 1/15/2025)

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Recruiting DepleTTR-CM US Centers (as of 1/15/2025)

Amyloidosis Research Consortium

Recruiting Centers:

- **California-** Irvine, La Jolla, Palo Alto, San Francisco
- **Colorado-** Aurora
- **District of Columbia-** Washington DC
- **Florida-** Jacksonville, Weston
- **Georgia-** Atlanta (x2)
- **Indiana-** Indianapolis
- **Kansas-** Kansas City
- **Massachusetts-** Boston (x2)
- **Missouri-** Kansas City, St. Louis
- **New York-** New York (x2), Stony Brook
- **North Carolina-** Chapel Hill, Durham
- **Ohio-** Cleveland, Columbus
- **Oregon-** Portland
- **Pennsylvania-** Danville, Philadelphia
- **South Carolina-** Charleston, Greenville
- **Tennessee-** Nashville
- **Texas-** Fort Worth, Houston
- **Virginia-** Falls Church, Richmond
- **Washington-** Seattle
- **Wisconsin-** Madison

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	**FDA Decision Mar25**					
		Nucresiran (ALN-TTRsc04) CM	Ph3 planned					
	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 Recruiting					
	Attralus	**AT-02 (pan-amyloid) CM**	**P1 Results 2025**					

HELIOS-B (vutrisiran; gene silencer)

ATTR-CM (wildtype or hereditary)

Amyloidosis Research Consortium

Study Phase	Phase 3
Purpose of the study	Evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM
Primary endpoint	Assess whether treatment with vutrisiran impacts outcomes of all cause mortality and recurrent cardiovascular events (CV hospitalizations and urgent HF visits) compared to placebo, in overall population and in monotherapy population
Number of patients	655
Study Drug	Subcutaneous (under the skin) injection every 3 months
Chance of receiving study drug?	1:1 vutrisiran to placebo
How long?	30-36 months (2.5-3 years)
Results	Vutrisiran reduced the risk of death and cardiovascular complications in patients with ATTR-CM, while also helping to maintain physical function and quality of life
Keep an eye out for	FDA Decision expected by 23 March 2025

CARDIO-TTRansform (eplontersen; gene silencer)

ATTR-CM (wildtype or hereditary)

Amyloidosis Research Consortium

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)

Amyloidosis Research Consortium

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

AT-02; pan-amyloid anti-fibril

Cardiac AL and ATTR amyloidosis

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Study Phase	Phase 1 (3 parts)
Purpose of the study	Part 3: Evaluate the safety and tolerability of multiple doses of AT-02 in patients with cardiac AL and ATTR amyloidosis, and to assess clinical activity
Primary endpoint	Safety (treatment-emergent adverse events, dose limiting toxicities, abnormal lab values, and treatment emergent anti-drug antibodies)
Number of patients	Up to 100
Study Drug	2 intravenous (into a vein) infusions 4 weeks apart
Chance of receiving study drug?	All participants received AT-02 in Part 3
How long?	8 weeks, with additional 2 year open label treatment
Keep an eye out for	Results 2025

Future Trials for Novel ATTR Therapies in 2025

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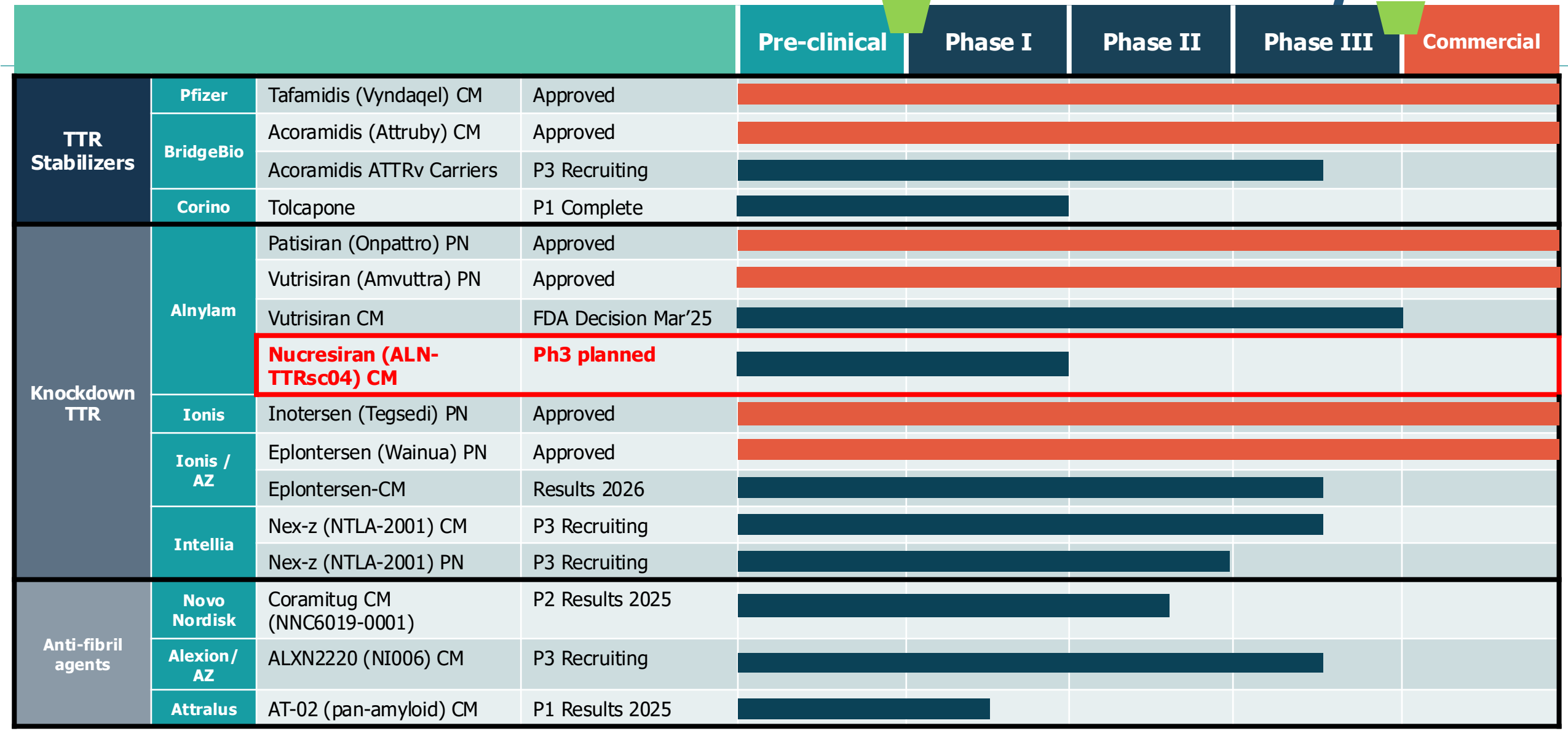

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		Acoramidis ATTRv Carriers	P3 Recruiting
	Corino	Tolcapone	P1 Complete
Knockdown TTR	Alnylam	Patisiran (Onpattro) PN	Approved
		Vutrisiran (Amvuttra) PN	Approved
		Vutrisiran CM	FDA Decision Mar'25
		Nucresiran (ALN-TTRsc04) CM	**Ph3 planned**
	Ionis	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 Recruiting
	Attralus	AT-02 (pan-amyloid) CM	P1 Results 2025

Other Recruiting and Planned Clinical Trials

Amyloidosis Research Consortium

- Imaging trials
  - REVEAL
  - Cardiag (https://life-mi.com/cardiag-study/)
- 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
- 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)

REVEAL (I-124 Evuzamitide; diagnostic radiotracer)

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

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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 1/16/2025)

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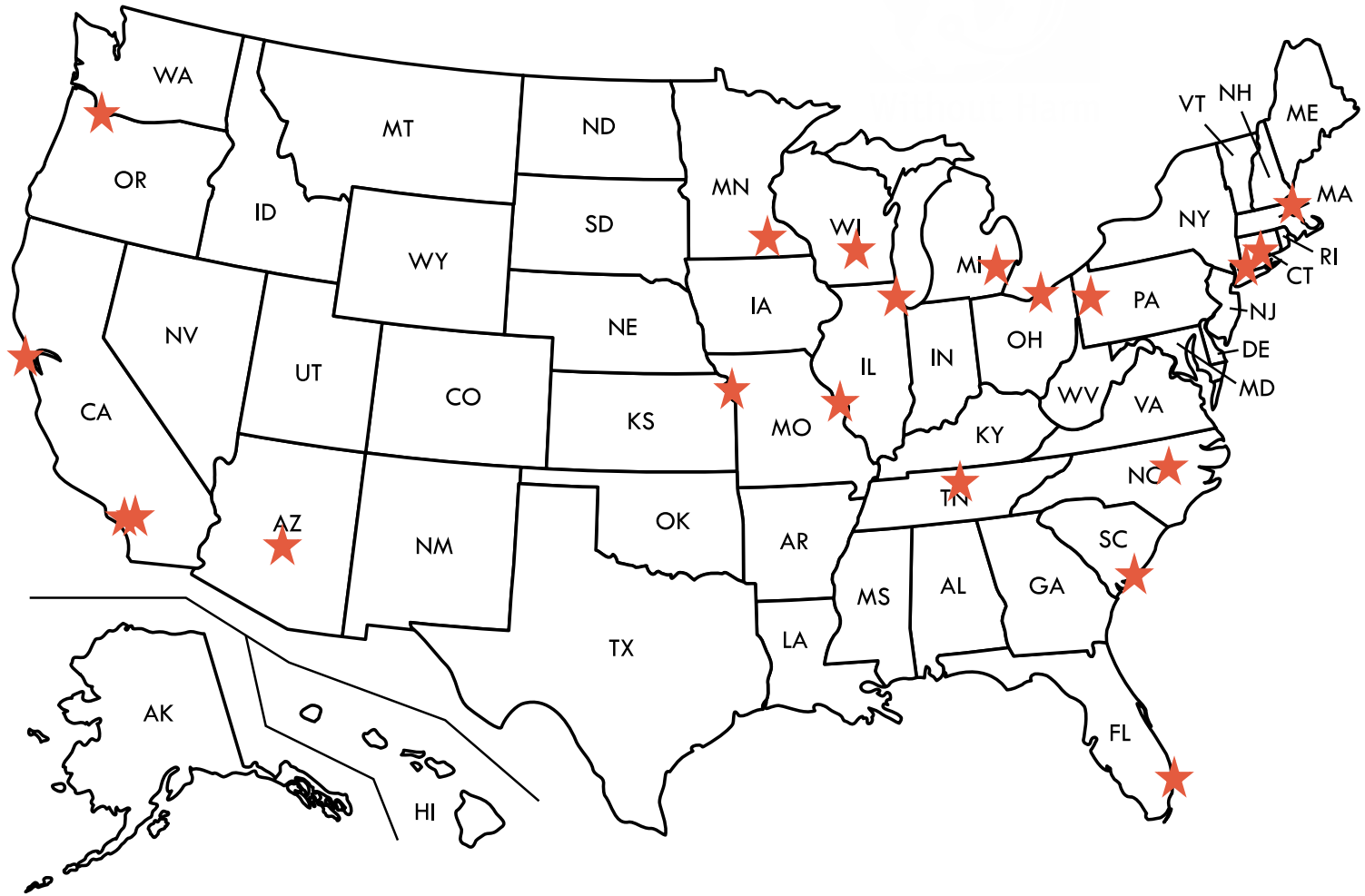

Planned Centers:

- Arizona- Phoenix
- California- Duarte, Los Angeles, San Francisco
- Connecticut- New Haven
- Florida- Weston
- Illinois- Chicago
- **Massachusetts- Boston**
- Michigan- Ann Arbor
- Minnesota- Rochester
- Missouri- Kansas City, St. Louis
- New York- New York
- Ohio- Cleveland
- Oregon- Portland
- Pennsylvania- Pittsburgh
- South Carolina- Charleston
- Tennessee- Nashville
- Wisconsin- Madison

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 1/15/25)

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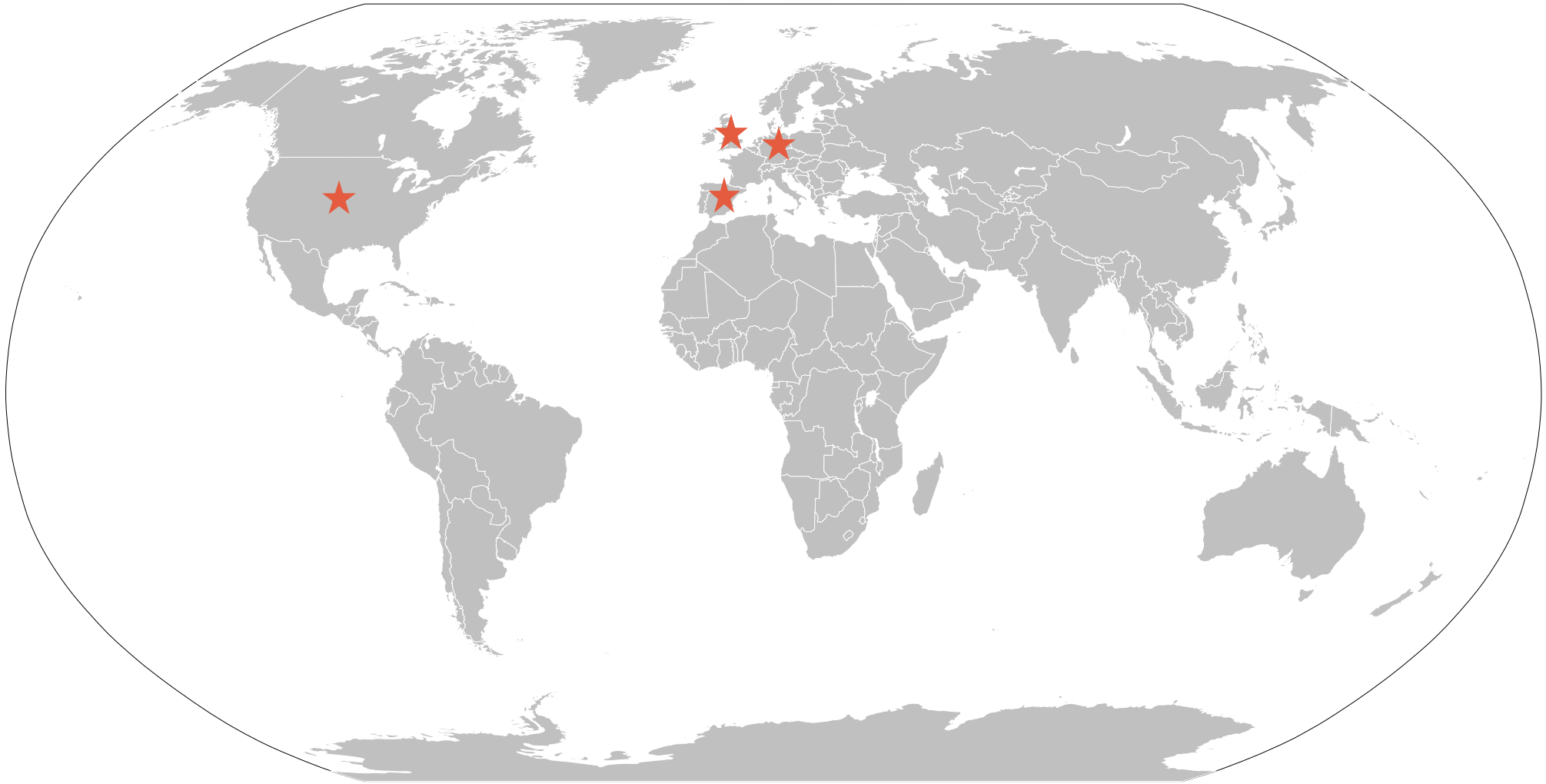


Recruiting CArdiag US Centers (as of 1/15/25)

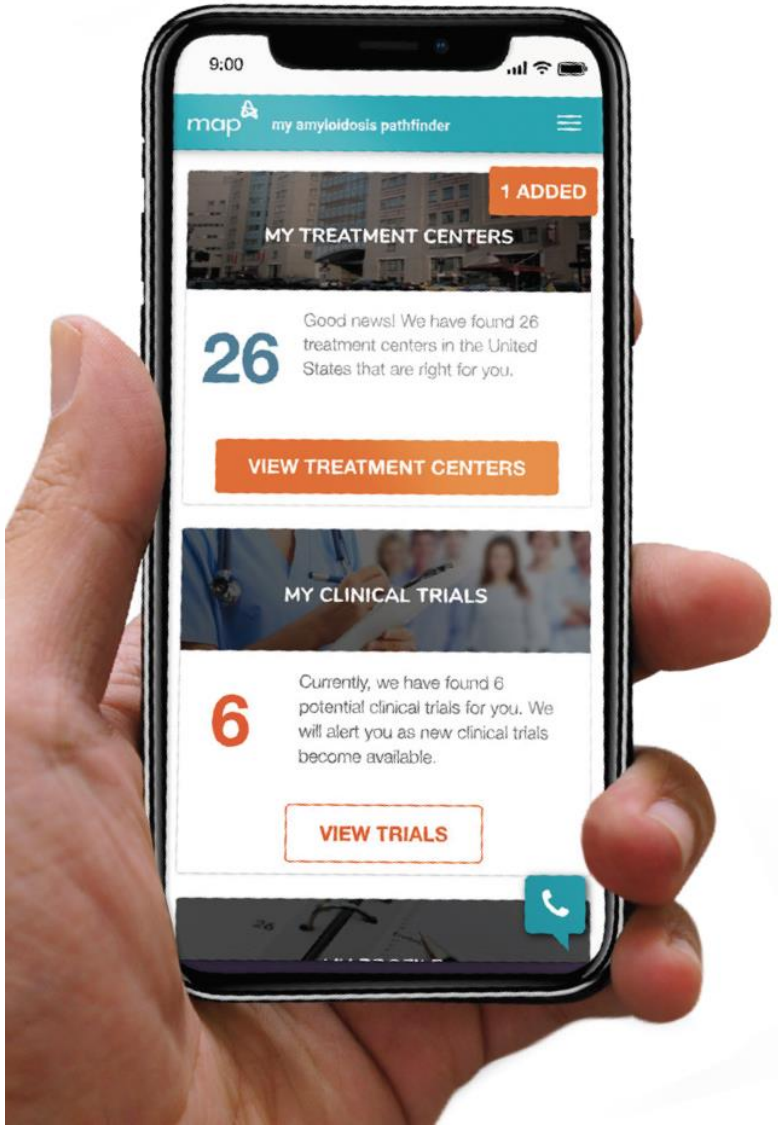
Amyloidosis Research Consortium

Recruiting Centers:

- **Kansas-** Kansas City
- **Pennsylvania-** Philadelphia

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, country specific groups, etc.
  - Sign up for My Amyloidosis Pathfinder (MAP)



Discover Personalized Treatment Centers & Clinical Trials for Your Amyloidosis

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