ARC TALKS
WEBINAR SERIES

Clinical Trial Updates for the AL Community

Kristen Hsu

Executive Director of Research
Amyloidosis Research Consortium

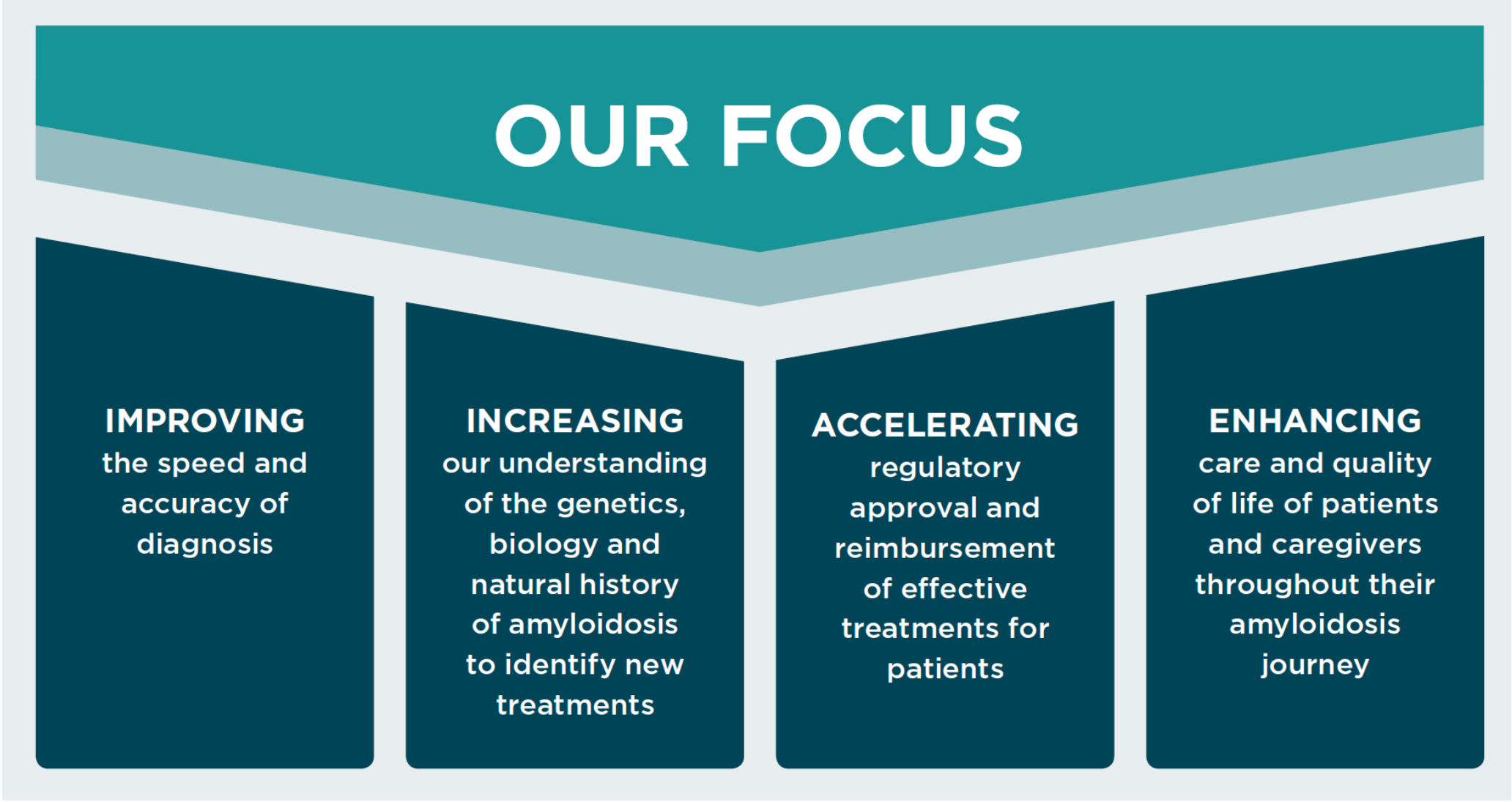
September 12 | 12pm - 1pm ET

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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Amyloidosis Research Consortium

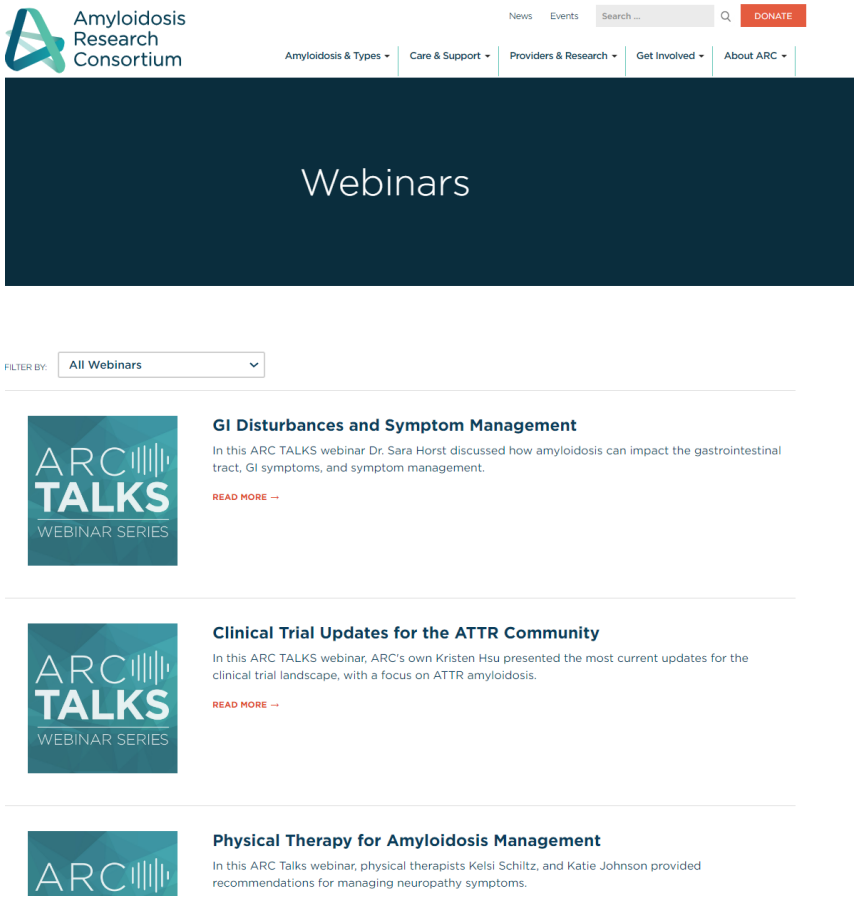
Clinical Trial Updates for the AL Amyloidosis Community

Kristen Hsu, Executive Director of Research

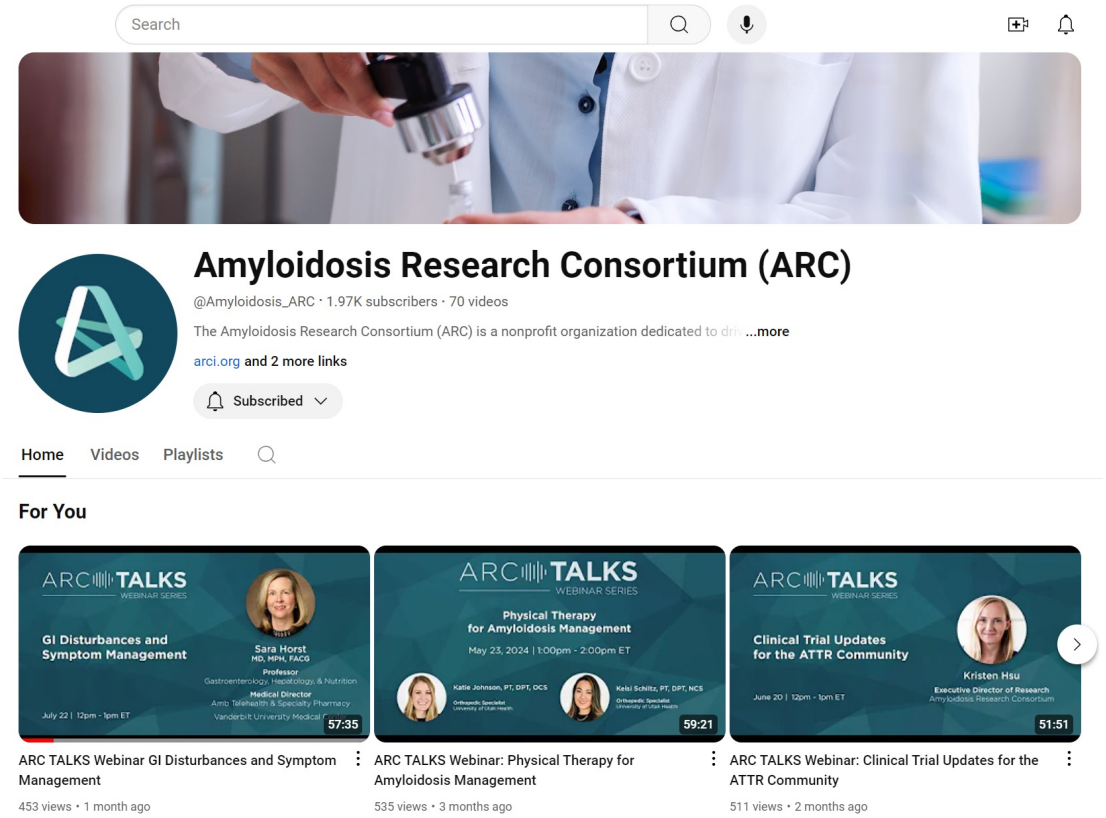
If you are here to learn about ATTR clinical trials…

…check out our June webinar focusing on ATTR amyloidosis clinical trials on our website or YouTube channel

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



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



What is a Clinical Trial?

- 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

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

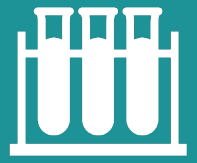
Phase 1	Phase 2	Phase 3	Phase 4
Determines a safe dose of the treatment under study (study drug) and monitors how the new treatment affects the human body.	Determines if the new treatment is seemingly effective and monitors any side effects.	Confirms how well a treatment works, monitors side effects, 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?

- 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

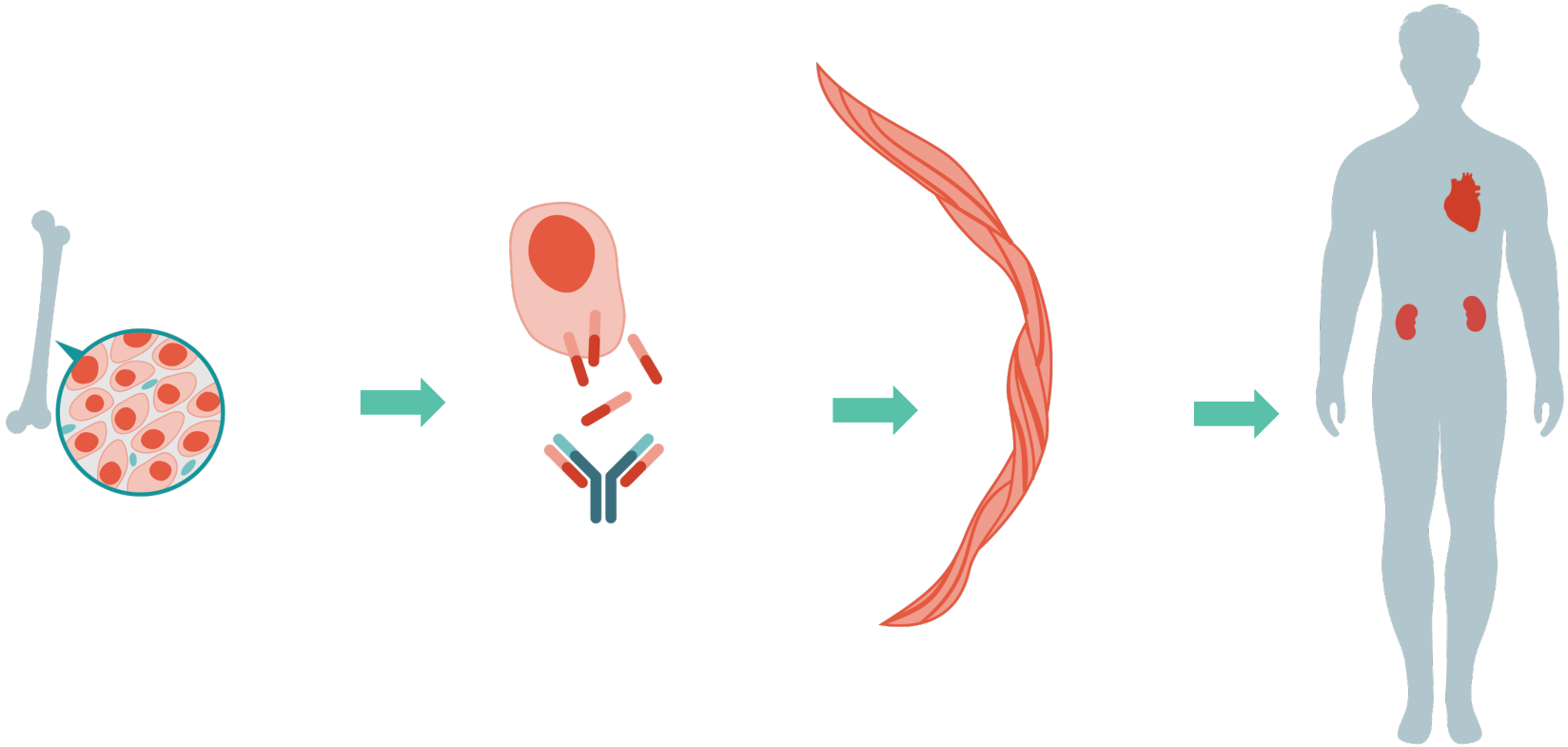
- Potential benefits and risks should be discussed carefully with study doctors and their teams.

AL Amyloidosis Clinical trials

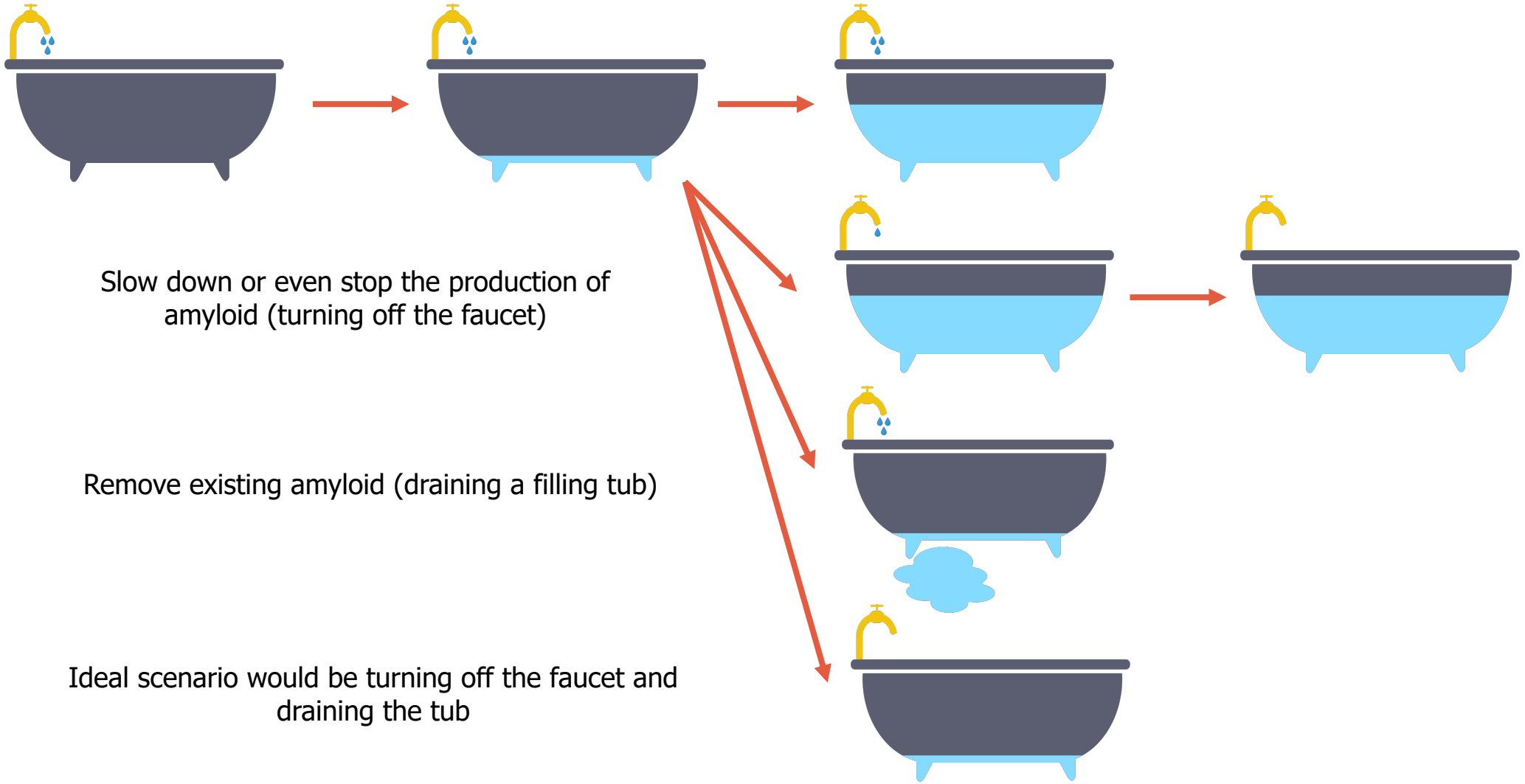
Definitions

- **Disease staging system:** Helps doctors assess how much AL amyloidosis is affecting the heart and estimate how aggressive the disease might be; assigned to patients at the time of their diagnosis
- **Newly diagnosed/treatment naïve:** Patients who have recently been diagnosed and have never received targeted treatment for AL amyloidosis
- **Relapsed:** AL amyloidosis that responded to a previous treatment but shows signs of returning
- **Refractory:** AL amyloidosis that has failed to respond to previous treatment
- **Front line therapy:** first line of treatment given to patients when they are newly diagnosed
- **Maintenance therapy:** treatment that is given to help keep the disease in control and prevent if from coming back after it has disappeared following initial therapy
- **CyBorD (aka VCD):** Common treatment regimen of cyclophosphamide (Cytoxan®), bortezomib (Velcade®), and dexamethasone

Investigative approaches to treating AL Amyloidosis....



…are like treating a filling bathtub



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

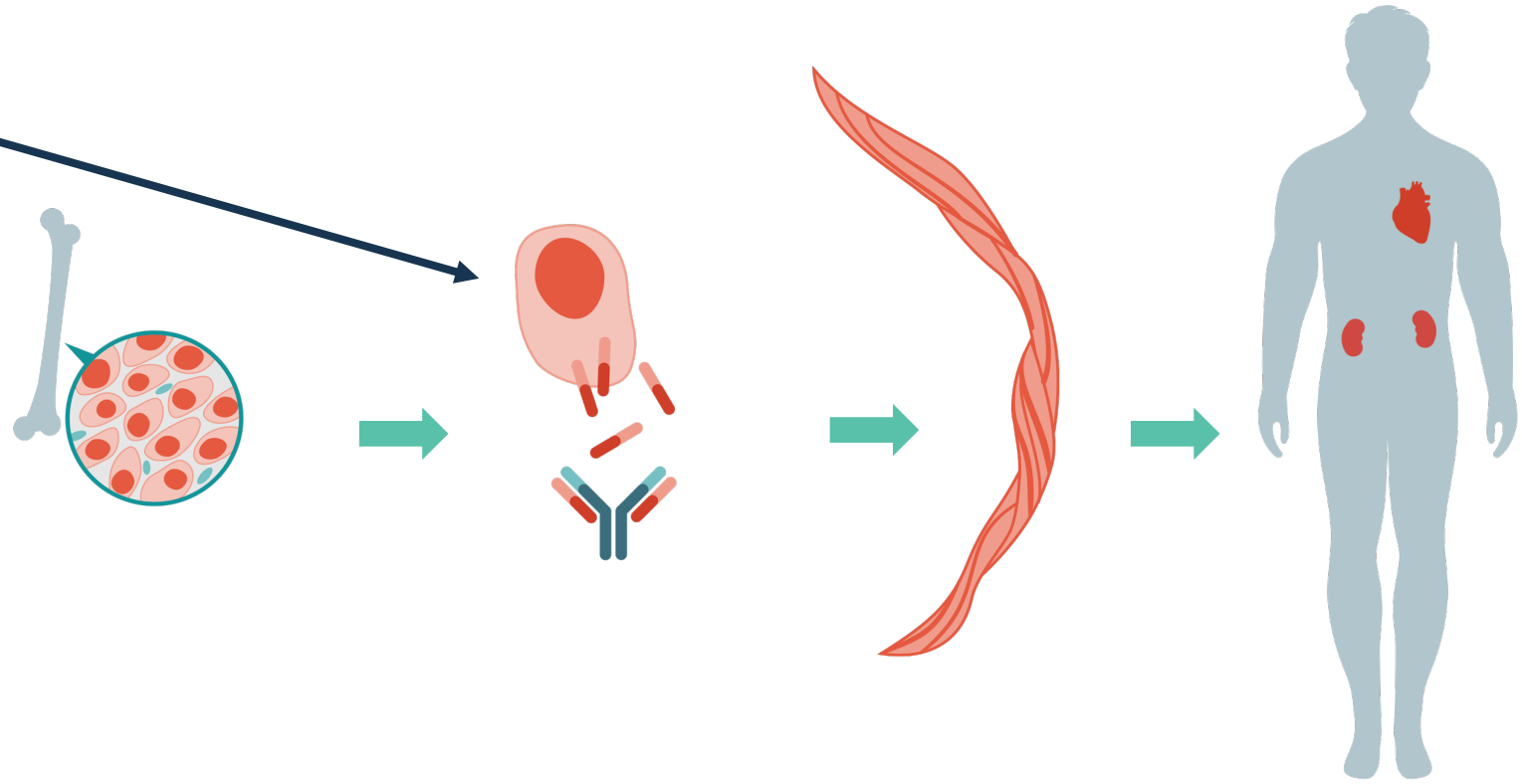
Remove existing amyloid (draining a filling tub)

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

Investigative Approaches to Treat AL Amyloidosis

Amyloidosis Research Consortium

Anti-plasma cell therapies



Investigative Approaches to Treat AL Amyloidosis

Anti-plasma cell therapies

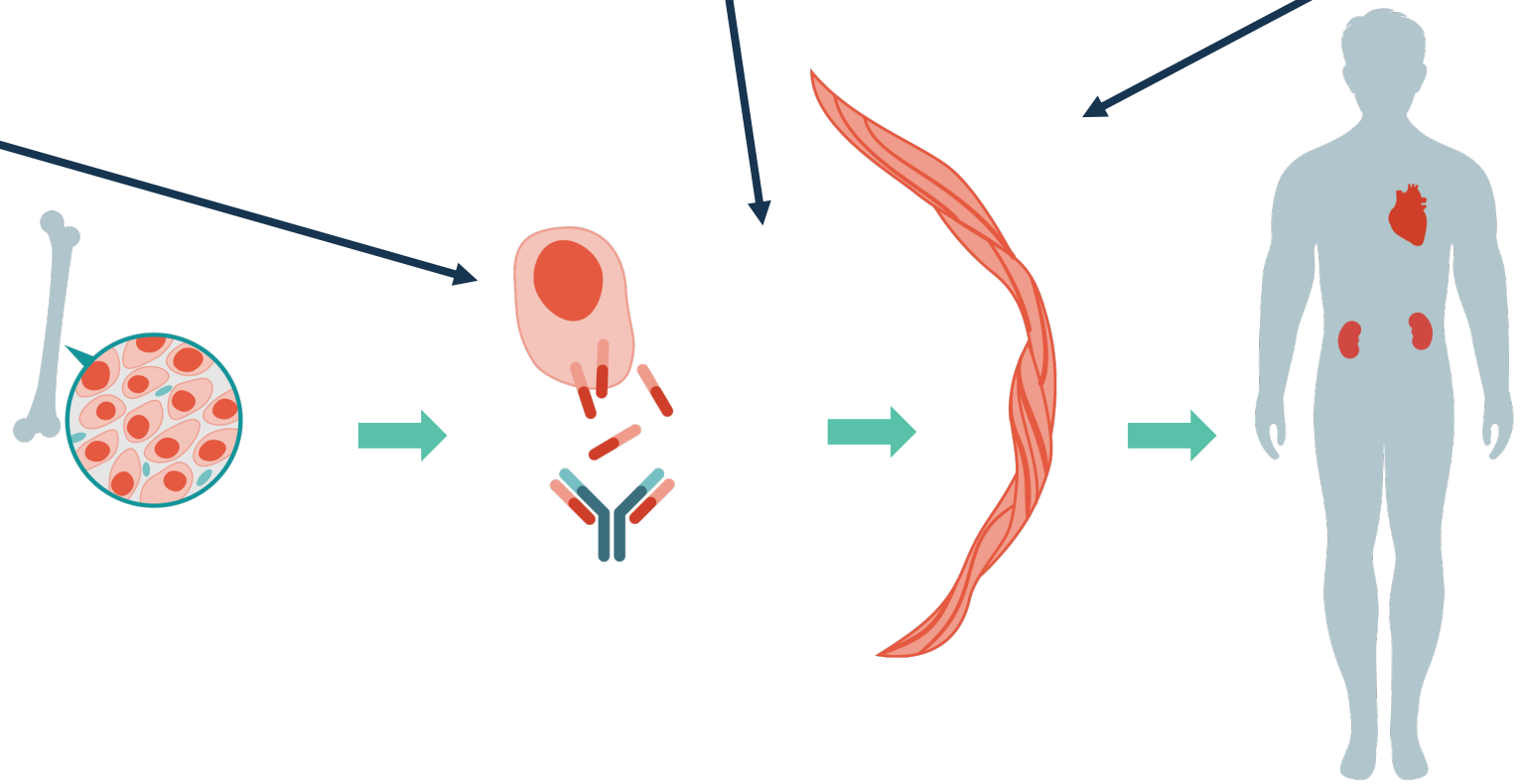
- Monoclonal antibodies
  - Daratumumab (Darzalex)
  - Isatuximab (Sarclisa)
  - Elotuzumab (Empliciti)
  - Belantamab mafodotin (Blenrep)
- BCL-2 Inhibitors
  - Venetoclax (Venclexta)
- Bispecific Antibodies and Cellular Therapies
  - Teclistimab (Tecvayli)
  - Linvoseltamab
  - ABBV-383
  - CAR-T cells

Light chain Stabilizers

- Name TBD

Anti-Fibril Agents

- Anselamimab (CAEL-101)
- Birtamimab (NEOD001)
- AT-02



Treatment types

- **Monoclonal antibodies:** attach themselves to specific surface proteins on abnormal plasma cell clones, directly kill them, and/or allow the immune system to identify and destroy them
- **BCL-2 Inhibitors:** May stop the growth of cancer cells by blocking Bcl-2, a protein needed for cancer cell survival
- **Bispecific T-cell engager (BiTE) antibodies:** composed of two fragments, binding to two different types of cell at the same time: (1) attaches to the plasma cells responsible for making faulty light chains, which may help stop or slow down the production of light chains, and (2) binds to the immune system's fighter cells (T cells), signaling them to attack and destroy the harmful plasma cells that make the faulty light chains.
- **CAR-T, or chimeric antigen receptor (CAR)-T cellular therapies:** a type of cellular therapy in which a patient's T cells are changed in the laboratory so they will attack cancer cells. Doctors first collect T cells from a patients blood, then modify the cells by giving them a "GPS" that helps them find and attack cancer cells, then grow these T cells in large numbers and put them back in the patient’s body
- **Light chain stabilizers:** a new treatment approach in AL amyloidosis designed to prevent the abnormal folding of light chains, helping them keep their correct shape so they don’t misfold into toxic forms, preventing them from clumping together and forming amyloid deposits
- **Anti-fibril agents:** attach to amyloid fibrils that have formed in organs (heart, kidneys, etc) and then either break the fibrils apart directly or mark them for removal by the immune system

Recruiting Trials for Novel AL Therapies in 2024

Amyloidosis Research Consortium

Monoclonal Antibodies	Janssen	Daratumumab (Darzalex)	Approved (accelerated); PMS underway
	Sanofi	Isatuximab	Phase 1 and 2 ISTs recruiting
	BMS	Elotuzumab	Phase 2 IST ongoing
	GSK	Belantamab mafodotin	Phase 1/2 and 2 ISTs recruiting
Bispecific Antibodies and Cellular Therapies	Janssen	Teclistimab	ISTs planned
	Regeneron	Linvoseltamab	Phase 1 recruiting
	AbbVie	ABBV-383	Phase 1 recruiting
	Nexcella	NXC-201	Phase 1 recruiting
BCL2 Inhibitors	AbbVie	Venetoclax	Phase 1/2 ISTs recruiting
LC Stabilizer	Protego	TBD	Preclinical
Anti-Fibril Agents	Prothena	Birtamimab	Phase 3 recruiting
	Alexion/AZ	Anselamimab (CAEL-101)	Phase 3 ongoing
	Attralus	AT-02 (pan-amyloid)	Phase 1 ongoing

Last Update September 10, 2024

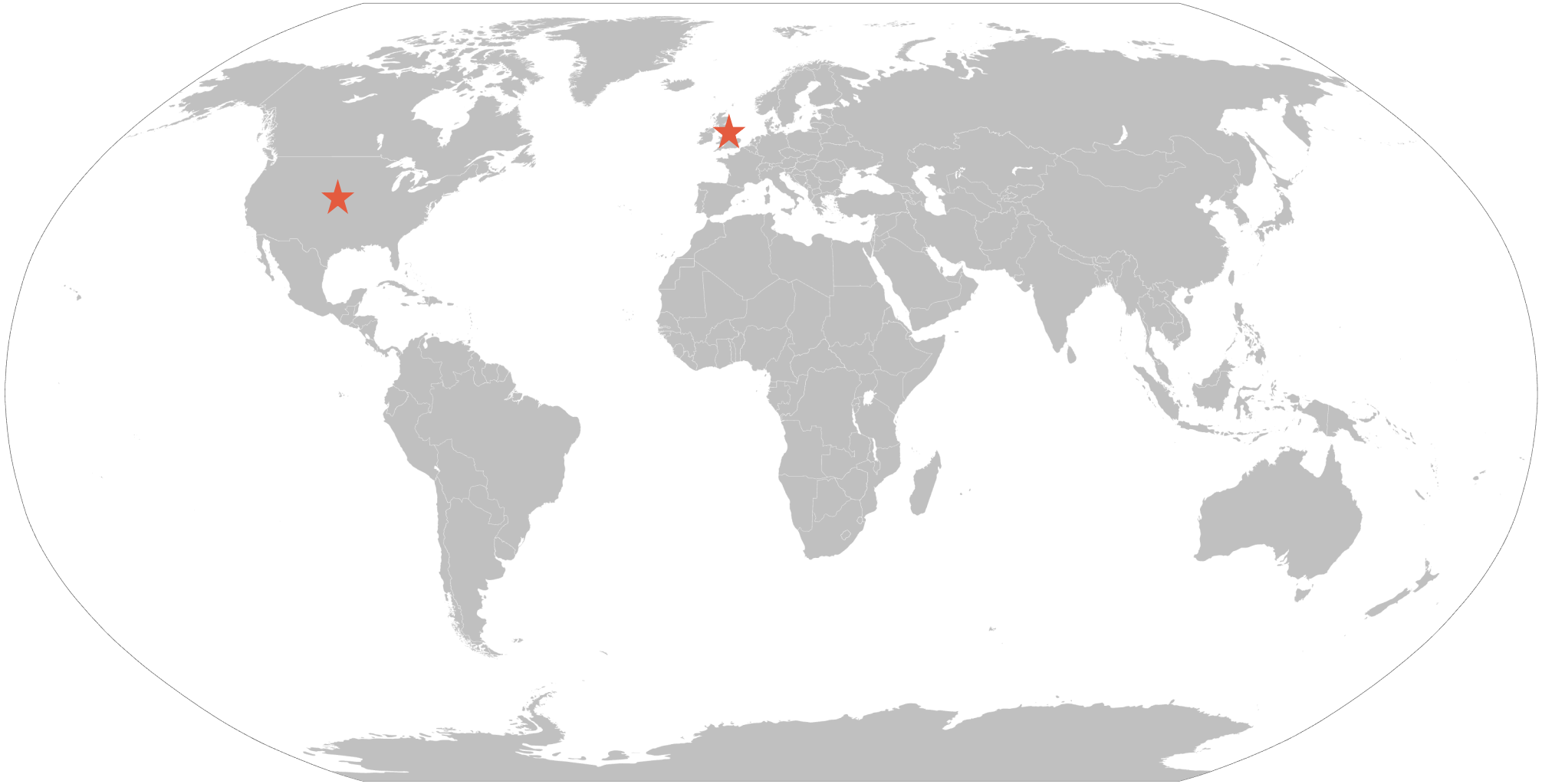
AQUARIUS (daratumumab; anti-CD38 monoclonal antibody)

Newly diagnosed AL amyloidosis

Amyloidosis Research Consortium

Study Phase	Phase 2
Purpose of the study	- Cohort 1: Understand the cardiac safety of Daratumumab, Cyclophosphamide, Bortezomib, and Dexamethasone (D-VCd) treatment regimens in patients with cardiac involvement. - Cohort 2: Understand how the bodies of patients of various racial and ethnic backgrounds interact with daratumumab injections in, when treated with D-VCd.
Primary endpoint	- Cohort 1: number of patients with cardiac events - Cohort 2: concentration of daratumumab reached immediately before next dose
Key eligibility criteria	- Cohort 1: Cardiac involvement (Mayo Cardiac Stage II and Stage IIIa) - Cohort 2: ≥1 organs impacted by AL amyloidosis; self-identified racial and ethnic minorities, including Asian, Hispanic or Latino American, Black, African American, Pacific Islander, Native Hawaiian, or American Indian
Number of patients	150 total (30 in Cohort 2)
Study Drug	Subcutaneous injections of daratumumab weekly > 2 weeks > 4 weeks
Chance of receiving study drug?	All patients will receive D-VCd
How long?	1 - 2 years (up to 24 cycles of 28 days)

Recruiting Global AQUARIUS Countries (as of 9/10/24)



Recruiting AQUARIUS Centers (as of 9/10/24)

Recruiting Centers:

- **California-** Duarte
- **Connecticut-** New Haven
- **Florida-** Tampa
- **Georgia-** Atlanta
- **Massachusetts-** Boston (2 centers)
- **Michigan-** Detroit
- **New York-** New York
- **North Carolina-** Charlotte
- **Ohio-** Cleveland, Columbus
- **Texas-** Dallas
- **Virginia-** Richmond
- **Washington-** Seattle

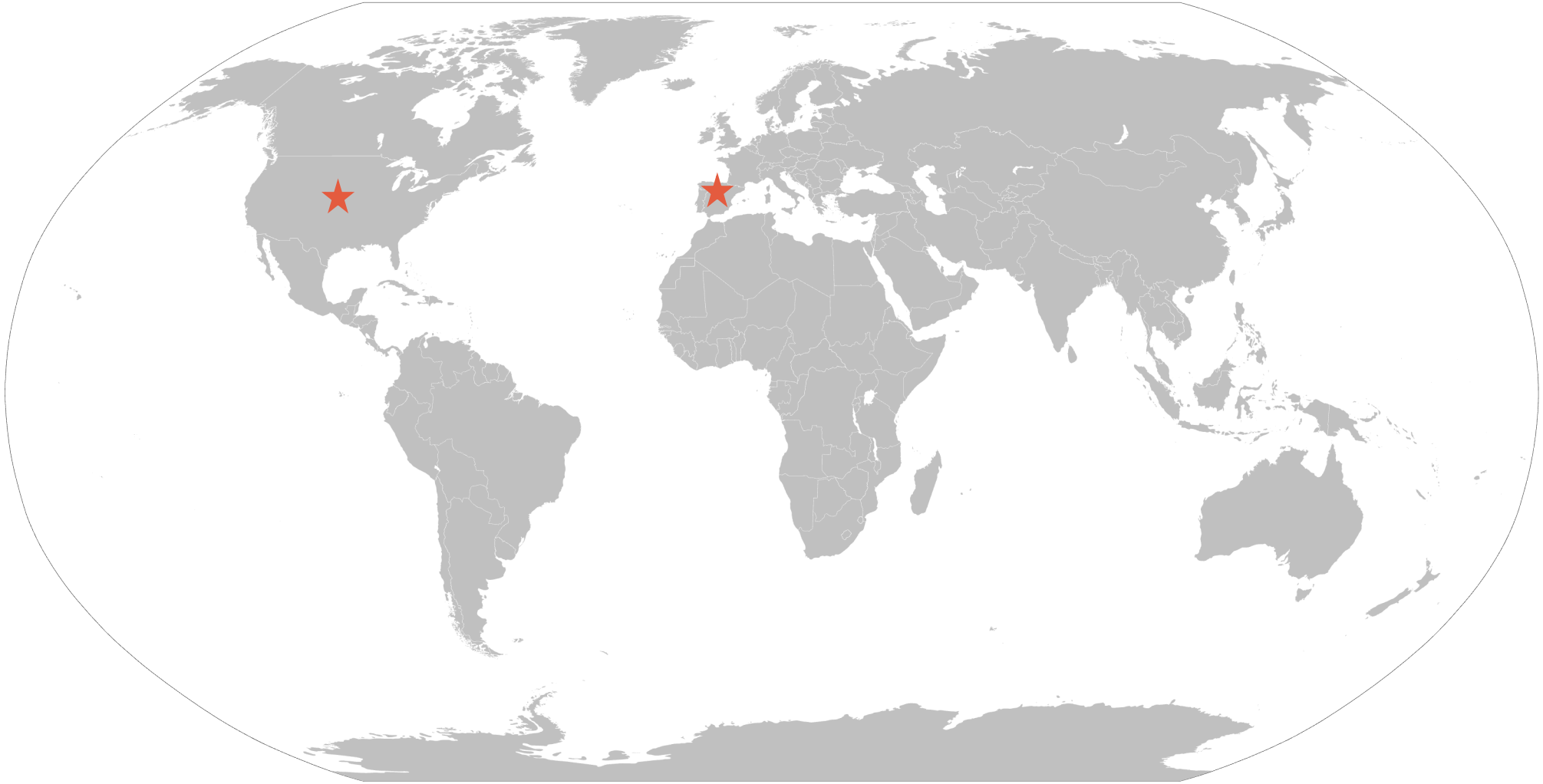
LINKER-AL2 (linvoseltamab; BCMA-CD3 bispecific antibody)

Relapsed/refractory AL amyloidosis

Amyloidosis Research Consortium

Study Phase	Phase 1/2
Purpose of the study	- Phase 1: Evaluate the safety of linvoseltamab and determine recommended Phase 2 dose - Phase 2: Evaluate the safety and efficacy of linvoseltamab
Primary endpoint	- Phase 1: Evaluate the safety of linvoseltamab and determine recommended Phase 2 dose - Phase 2: Evaluate the safety and efficacy of linvoseltamab
Key eligibility criteria	Patients with at least 1 but ≤ 4 prior lines of therapy and still requires further treatment
Number of patients	220
Study Drug	linvoseltamab
Chance of receiving study drug?	All patients will receive study drug
How long?	~3 years

Recruiting LINKER-AL2 Countries (as of 9/10/24)



Recruiting LINKER-AL2 Centers (as of 9/10/24)

Recruiting Centers:

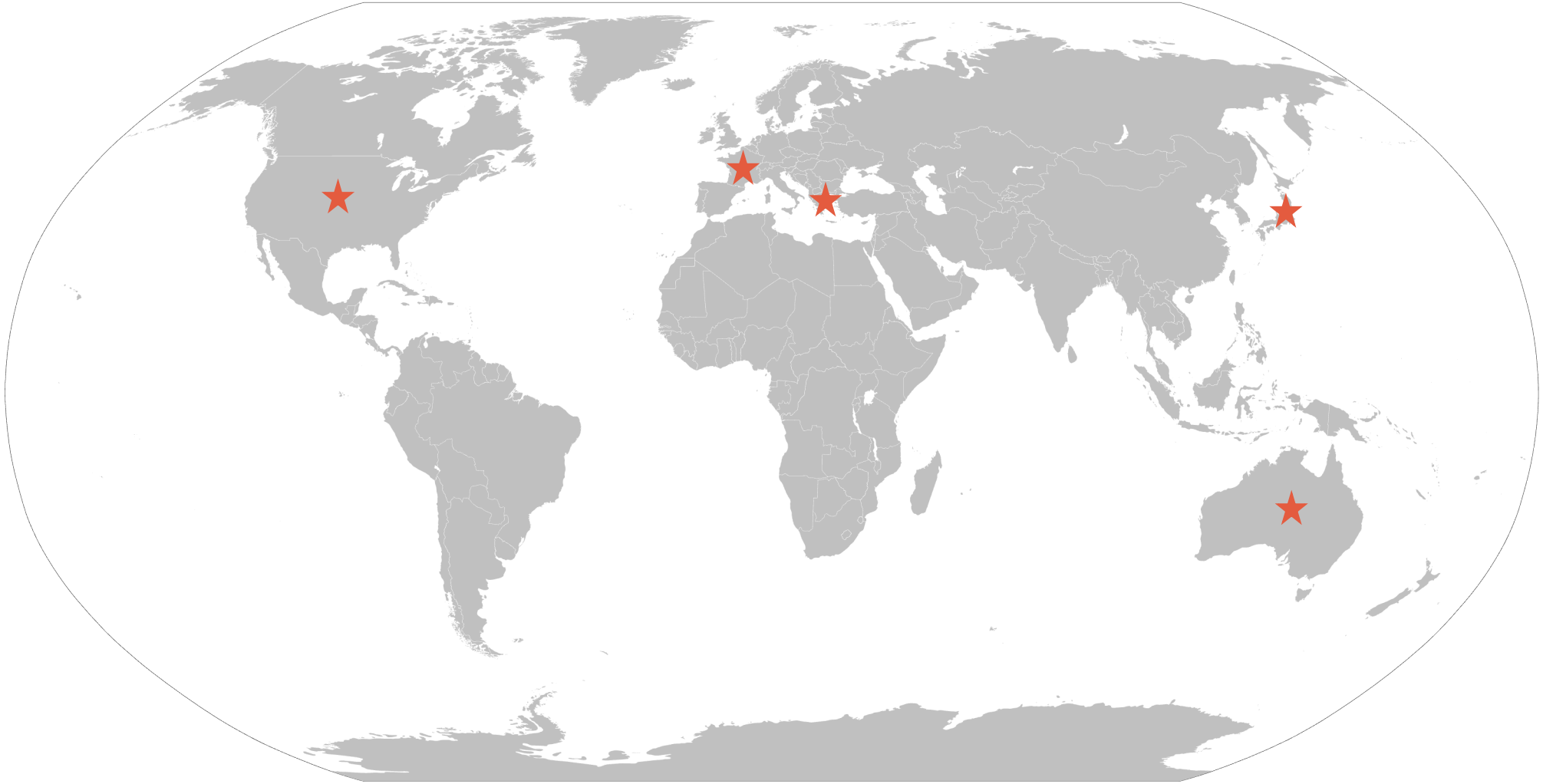
- **California-** Duarte

ABBV-383 study (BCMA-CD3 bispecific antibody)

Relapsed/refractory AL amyloidosis

Study Phase	Phase 1
Purpose of the study	Safety evaluation and preliminary activity
Primary endpoint	Dose limiting toxicities and recommended dose of ABBV-383 monotherapy in AL amyloidosis (Secondary: preliminary activity of ABBV-383 monotherapy in AL amyloidosis)
Key eligibility criteria	• Patients with at least 1 prior therapy that includes prior proteosome inhibitor and anti-CD38 • At least one organ historically involved • Must not have other non-AL amyloid disease, plasma cell leukemia, multiple myeloma, Waldenstrom's macroglobulinemia
Number of patients	Approximately 76 patients
Study Drug	Infusions of ABBV-383 every 4 weeks
Chance of receiving study drug?	All patients will receive study drug
How long?	Up to 2 years

Recruiting ABBV-383 Countries (as of 9/10/24)



Recruiting ABBV-383 Centers (as of 9/10/24)

Recruiting Centers:

- **Massachusetts-** Boston
- **New York-** New York (2 centers)
- **North Carolina-** Charlotte

NEXICART-2 (NXC-201; BCMA-targeted investigational chimeric antigen receptor T (CAR-T) cell therapy)

Relapsed or refractory AL amyloidosis

Amyloidosis Research Consortium

Study Phase	Phase 1b
Purpose of the study	Measure the safety and efficacy NXC-201
Primary endpoint	- Number of patients with adverse events - Confirm the maximum tolerated dose and recommended phase 2 dose
Key eligibility criteria	- ≥1 line of therapy with a CD38 monoclonal antibody and a proteosome inhibitor and not be in VGPR or CR at the time of inclusion. - Patients who did not reach VGPR after two cycles of initial therapy or patients who did achieve VGPR or better but with a hematological relapse can be included
Number of patients	40
Study Drug	Single infusion following leukopharesis and lymphodepletion
Chance of receiving study drug?	All patients will receive NXC-201
How long?	2 years

Recruiting NEXICART-2 Centers (as of 9/10/24)

Recruiting Centers:

- **New York-** New York

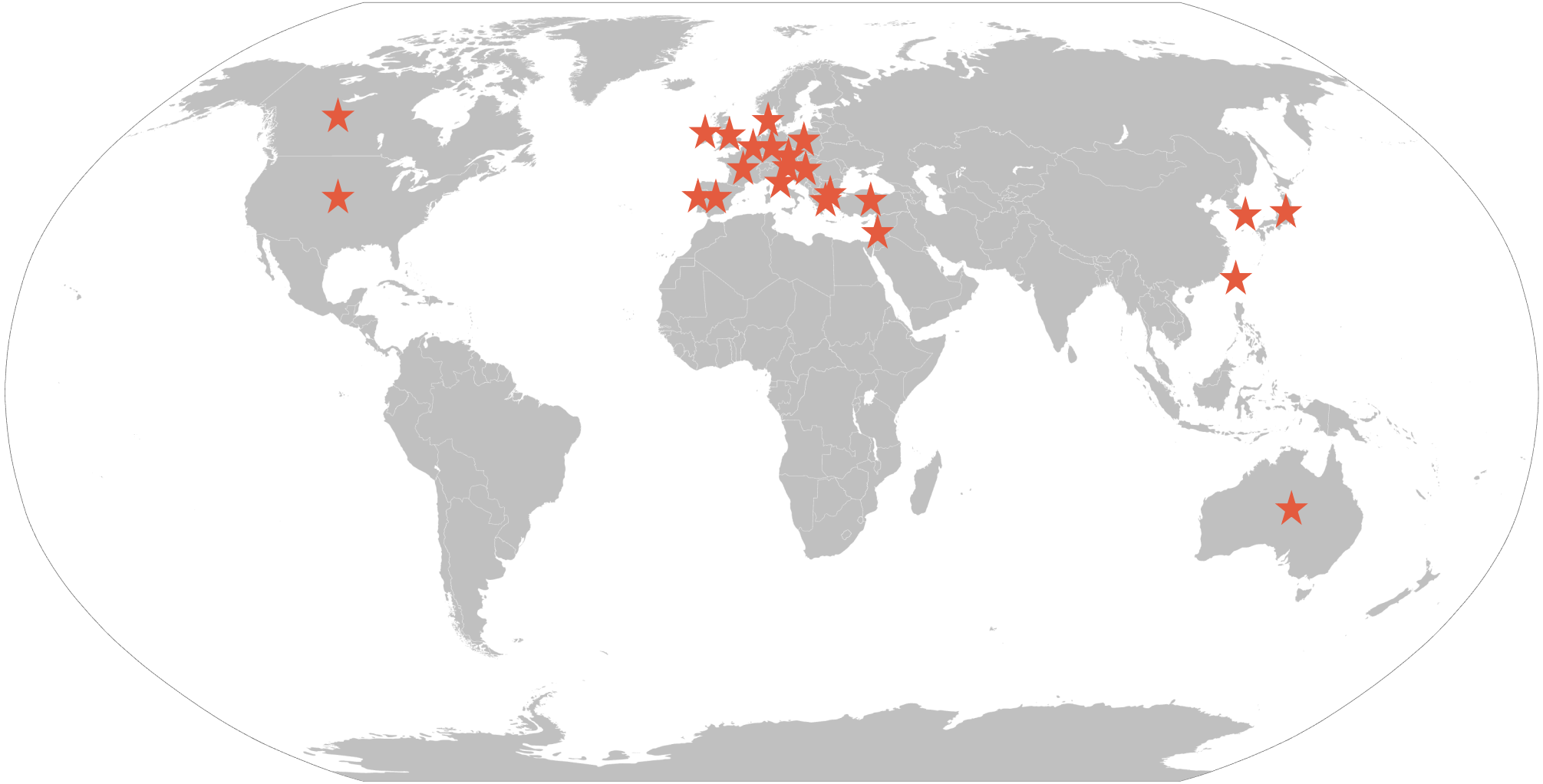
AFFIRM-AL (birtamimab; anti-amyloid antibody)

Newly diagnosed AL amyloidosis

Amyloidosis Research Consortium

Study Phase	Phase 3
Purpose of the study	Measure the efficacy and safety of birtamimab plus chemotherapy in adult patients with AL amyloidosis
Primary endpoint	Assess whether treatment with birtamimab reduces the risk of death
Key eligibility criteria	- Newly diagnosed (no prior treatment) - Mayo Stage IV
Number of patients	220
Study Drug	Infusions of birtamimab every 4 weeks
Chance of receiving study drug?	2/3 (67% chance) will receive birtamimab and standard of care 1/3 (33% chance) will receive placebo and standard of care
How long?	2.5-3 years

Recruiting AFFIRM-AL Countries (as of 9/10/24)



Recruiting AFFIRM-AL Centers (as of 9/10/24)

Recruiting Centers:

- **Connecticut-** Hartford, North Haven, Trumbull
- **District of Columbia**
- **Florida-** Weston
- **Indiana-** Goshen
- **Maryland-** Bethesda
- **Massachusetts-** Boston (2 centers)
- **Michigan-** Ann Arbor, Detroit
- **Minnestoa-** Rochester
- **Nebraska-** Omaha
- **New Jersy-** Hackensack
- **New York-** Buffalo, New York (3 centers)
- **North Carolina-** Durham, Winston-Salem
- **Ohio-** Cleveland, Columbus
- **Tennessee-** Knoxville, Nashville
- **Texas-** Dallas
- **Washington-** Seattle
- **Wisconsin-** Milwaukee

Future Development for Novel AL Therapies

Amyloidosis Research Consortium

				Pre-clinical	Phase I	Phase II	Phase III	Commercial
Monoclonal Antibodies	Janssen	Daratumumab (Darzalex)	Approved (accelerated); PMS underway					
	Sanofi	Isatuximab	Phase 1 and 2 ISTs recruiting					
	BMS	Elotuzumab	Phase 2 IST ongoing					
	GSK	Belantamab mafodotin	Phase 1/2 and 2 ISTs recruiting					
Bispecific Antibodies and Cellular Therapies	Janssen	Teclistimab	ISTs planned					
	Regeneron	Linvoseltamab	Phase 1 recruiting					
	AbbVie	ABBV-383	Phase 1 recruiting					
	Nexcella	NXC-201	Phase 1 recruiting					
BCL2 Inhibitors	AbbVie	Venetoclax	Phase 1/2 ISTs recruiting					
LC Stabilizer	Protego	TBD	Preclinical					
Anti-Fibril Agents	Prothena	Birtamimab	Phase 3 recruiting					
	Alexion/AZ	Anselamimab (CAEL-101)	Phase 3 ongoing					
	Attralus	AT-02 (pan-amyloid)	Phase 1 ongoing					

Last Update September 10, 2024

Other Recruiting and Planned Clinical Trials

- Investigator Sponsored and Single Center Trials
  - Venetoclax trials
    - Phase 1 Trial of Venetoclax, MLN9708 (Ixazomib Citrate) and Dexamethasone for the Treatment of Relapsed or Refractory AL Amyloidosis (24 patients, 15 locations) https://clinicaltrials.gov/study/NCT04847453
    - ALTITUDE: Open-label Phase I/II Trial of Venetoclax, Daratumumab, and Dexamethasone in Patients Previously Treated for AL Amyloidosis With t(11;14) (46 patients, 1 center in CA) https://clinicaltrials.gov/study/NCT05486481
    - Open-label Phase I/II Trial of Venetoclax-Dexamethasone in Relapsed and/or Refractory t(11;14) AL Amyloidosis (53 patients, MN, NY, WI) https://clinicaltrials.gov/study/NCT05451771
  - Monoclonal Phase 3 Trial Comparing Dara-VCD Chemotherapy Plus Stem Cell Transplant to Dara-VCD Chemotherapy Alone for People Who Have Newly Diagnosed AL Amyloidosis (338 patients, 35 centers in the US) https://clinicaltrials.gov/study/NCT06022939
  - Phase 2 Trial of Daratumumab, Pomalidomide, and Dexamethasone (DPd) in Relapsed/Refractory AL Amyloidosis Patients Previously Exposed to Daratumumab (21 patients, CA, NY, MA, WI) https://clinicaltrials.gov/study/NCT04270175
  - EMILIA: Phase 2 Trial of Daratumumab Maintenance Therapy for Improving Survival in Patients With AL Amyloidosis (96 patients, MN, AZ, FL) https://clinicaltrials.gov/study/NCT05898646
  - Phase 1/2a Study of Belantamab Mafodotin in Relapsed or Refractory AL Amyloidosis (37 patients, TX, CA, MA, MN) https://clinicalrials.gov/study/NCT05145816
  - A Phase I/II, Open Label, Study of Elranatamab in Patients With Relapsed or Refractory AL Amyloidosis (49 patients, MA) https://clinicaltrials.gov/study/NCT06569147
- Imaging trials
  - CArdiag: Efficacy of [18F]Florbetaben PET for Diagnosis of Cardiac AL Amyloidosis (CArdiag) https://clinicaltrials.gov/study/NCT05184088
- Observational trials

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)

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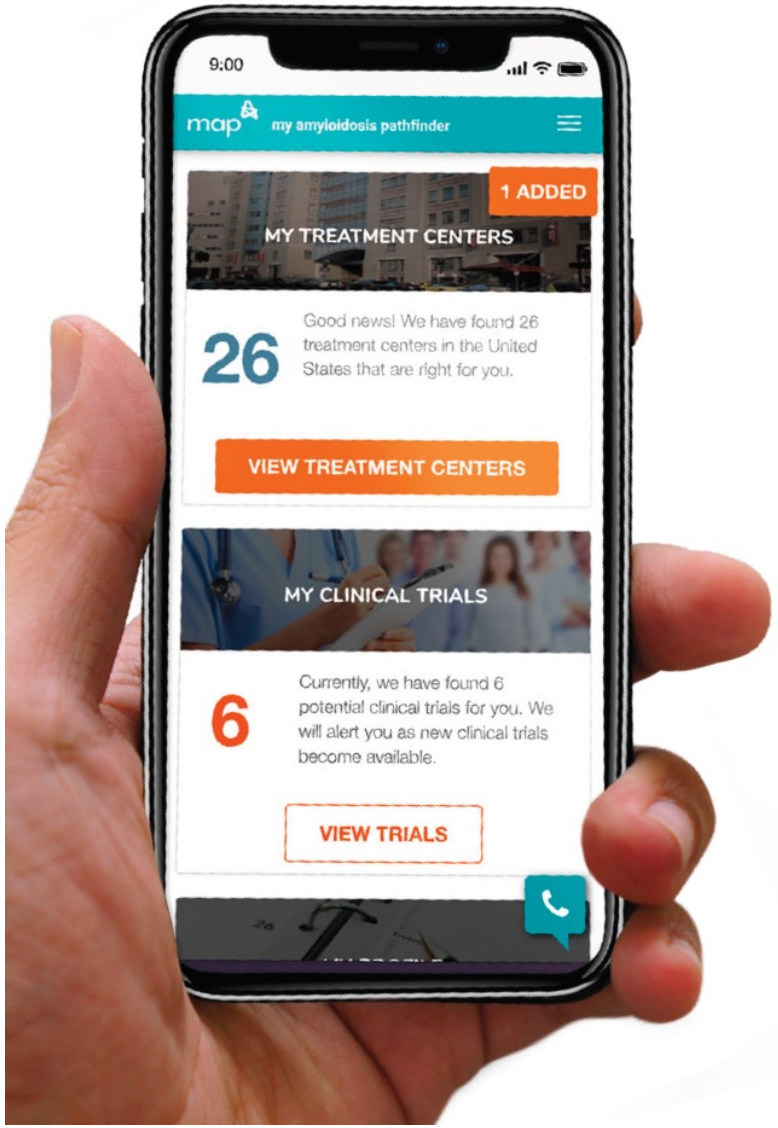

Discover Personalized Treatment Centers & Clinical Trials for Your Amyloidosis

myamyloidosispathfinder.org

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