2e CONGRÈS FRANCOPHONE MULTIDISCIPLINAIRE DE L'AMYLOSE
Regards croisés et innovations !
Mardi 20 juin 2023
Espace Saint-Martin ■ PARIS
www.congres-amylose.com

Immunothérapie anti-AL

Traitements non dirigés contre le clone B

Pr Arnaud Jaccard – CHU Limoges

Centre national de référence
Amylose AL
& autres maladies par dépôts d'immunoglobulines monoclonales

CHU Centre hospitalier universitaire Limoges
CHU de Poitiers

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

Liens d'intérêt

- Honoraires : Janssen, Celgene, Takeda, Amgen
- Financement de la recherche: Celgene, Janssen, Sanofi

Traitement de l'amylose AL

- Vise à renverser l'équilibre entre
  - la formation des dépôts d'amylose qui dépend du niveau des chaînes légères libres d'immunoglobulines monoclonales
  - et leur élimination lente par l'organisme

1) En faisant baisser le taux de chaînes légères en détruisant les cellules productrices (plasmocytes dans 90% des cas)

2) En accélérant l'élimination des dépôts

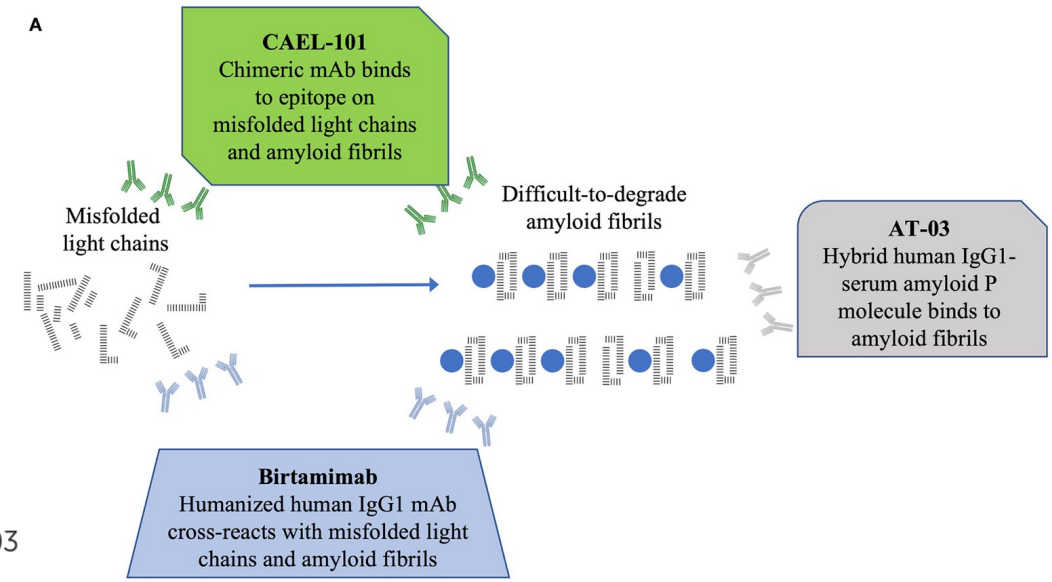
- La chimiothérapie ne joue pas sur les dépôts eux-mêmes

Traitements visants à éliminer les dépôts

- Anti-corps anti-SAP (dezamizumab) et CPHPC (miridesap)
- Anticorps conformationnels
  - NEOD 001 (Birtamimab)
  - CAEL-101
- Protéines chimériques
  - AT-O1
  - AT-03

Changing paradigm in the treatment of amyloidosis: From disease-modifying drugs to anti-fibril therapy

C. Cristina Quarta[1]*, Marianna Fontana[2], Thibaud Damy[3], Julia Catini[1], Damien Simoneau[1], Michele Mercuri[1], Pablo Garcia-Pavia[4,5], Mathew S. Maurer[6] and Giovanni Palladini[7]



TYPE Mini Review
PUBLISHED 20 December 2022
DOI 10.3389/fcvm.2022.1073503

The NEW ENGLAND JOURNAL of MEDICINE

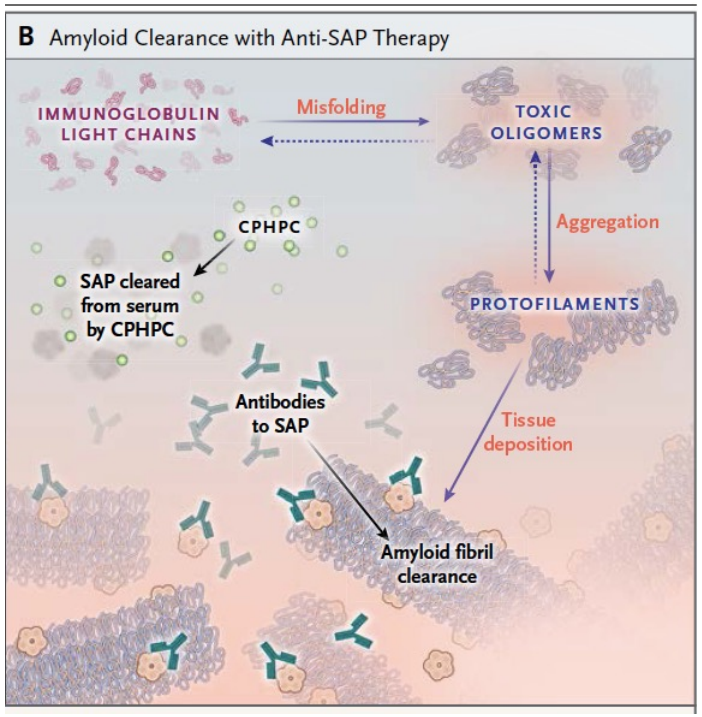
ORIGINAL ARTICLE

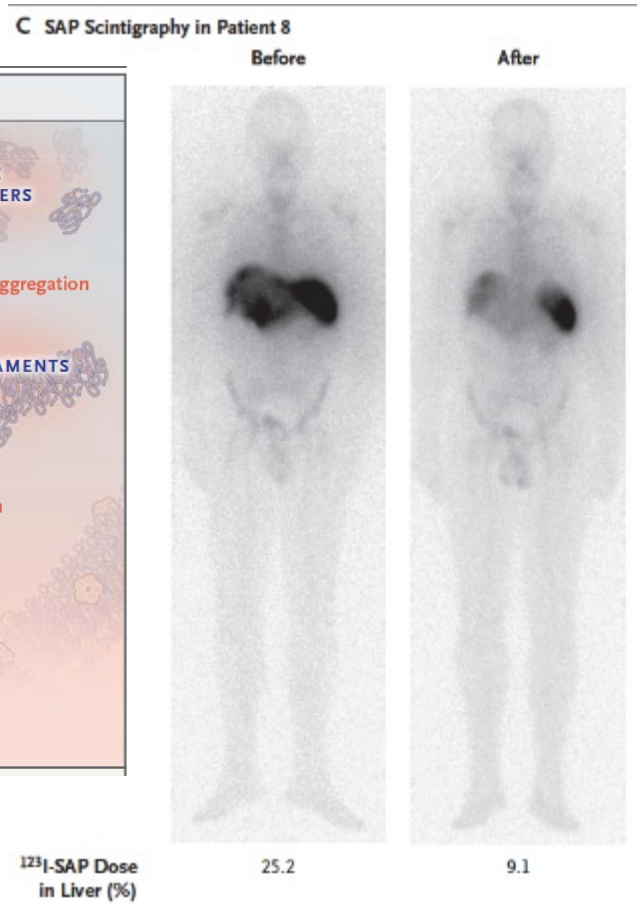
Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

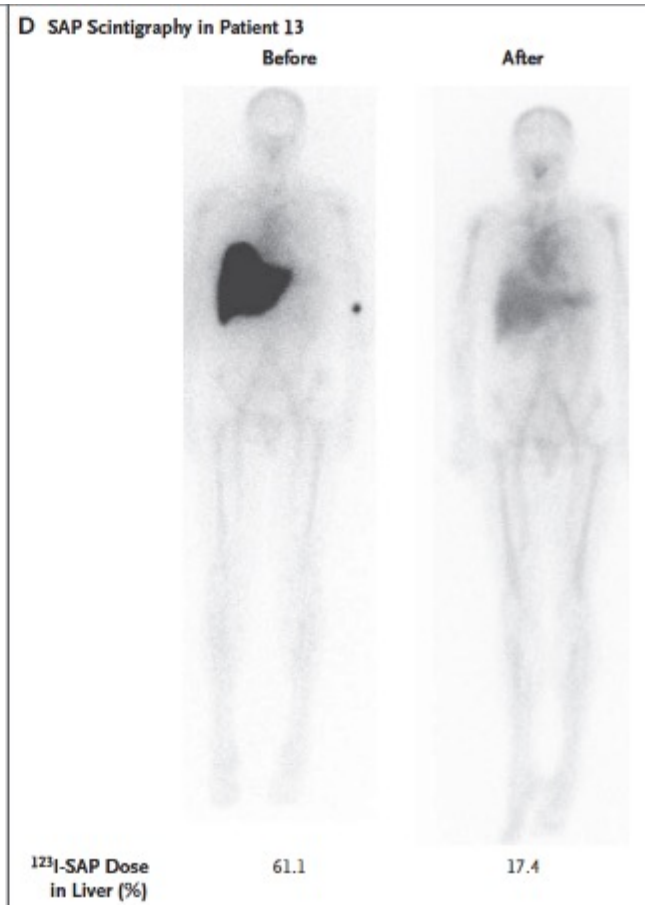
Duncan B. Richards, D.M., Louise M. Cookson, B.Sc., Alienor C. Berges, Pharm.D., Sharon V. Barton, M.Sc., Thirusha Lane, R.N., M.Sc., James M. Ritter, D.Phil., F.Med.Sci., Marianna Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D., Julian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci., and Mark B. Pepys, Ph.D., F.R.S.

July 15, 2015

15 patients
Elimination très rapide des dépôts hépatiques:
Coeur et rein ?







Janvier 2018

SYSTEMIC AMYLOIDOSIS

Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis

Duncan B. Richards,[1] Louise M. Cookson,[1] Sharon V. Barton,[1] Lia Liefaard,[1] Thirusha Lane,[2] David F. Hutt,[2] James M. Ritter,[3] Marianna Fontana,[2] James C. Moon,[4] Julian D. Gillmore,[2] Ashutosh Wechalekar,[2] Philip N. Hawkins,[2] Mark B. Pepys[2,5]*

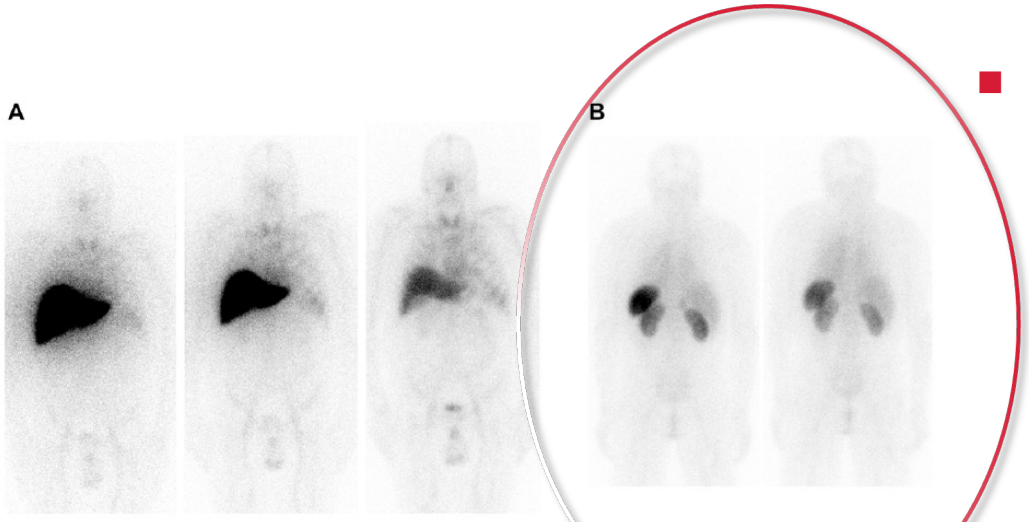


Fig. 2. Effect on amyloid load of miridesap followed by dezamizumab. (**A**) Anterior views of radiolabelled serum amyloid P component (SAP) scintigraphy scans for amyloid in subject 014 with systemic immunoglobulin light chain (AL) amyloidosis. Images shown are for before treatment (left), 42 days after first dezamizumab dose (center), and 42 days after second dezamizumab dose (right). (**B**) Posterior views of radiolabelled SAP scintigraphy scans for amyloid in subject 017 with hereditary systemic fibrinogen A α-chain (AFib) amyloidosis. Images shown are before treatment (left) and 42 days after dezamizumab treatment (right).

- 23 patients, 15 de la précédente série
- Jusqu'à 3 injections (10 pts)
  - AL: 12 pts
  - Afib: 5 pts
  - ATTR: 3 pts
  - AA: 2 pts
  - AApoA1: 1 pt
- Demie vie courte
- Elimination amylose hépatique ++

Wechalekar *et al.*
BMC Cardiovascular Disorders (2022) 22:49
https://doi.org/10.1186/s12872-021-02407-6

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Pharmacodynamic evaluation and safety assessment of treatment with antibodies to serum amyloid P component in patients with cardiac amyloidosis: an open-label Phase 2 study and an adjunctive immuno-PET imaging study

Ashutosh Wechalekar[1*], Gunnar Antoni[2], Wasfi Al Azzam[3,9], Mats Bergström[4], Swethajit Biswas[4,10], Chao Chen[4], Joseph Cheriyan[5], Matthew Cleveland[4], Louise Cookson[6], Paul Galette[3], Robert L. Janiczek[4], Raymond Y. Kwong[7], Mary Ann Lukas[3], Helen Millns[4], Duncan Richards[4,10], Ian Schneider[6,11], Scott D. Solomon[7], Jens Sörensen[2], James Storey[4], Douglas Thompson[4], Guus van Dongen[8], Danielle J. Vugts[8], Anders Wall[2], Gerhard Wikström[2] and Rodney H. Falk[7]

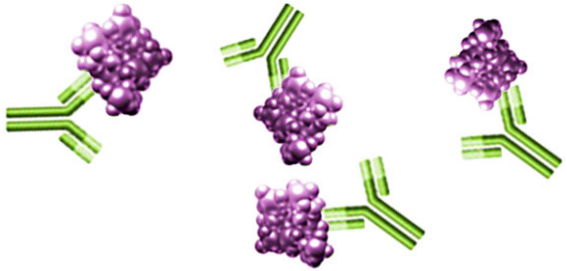
Conclusions: Unlike previous observations of visceral amyloid reduction, there was no appreciable evidence of amyloid removal in patients with cardiac amyloidosis in this Phase 2 trial, potentially related to limited cardiac uptake of dezamizumab as demonstrated in the immuno-PET study. The benefit-risk assessment f or dezamizumab in cardiac amyloidosis was considered unfavourable after the incidence of large-vessel vasculitis and development for this indication was terminated.

Potential NEOD001 MOA: Neutralizes Soluble Toxic Aggregates and Clears AL Amyloid Deposits

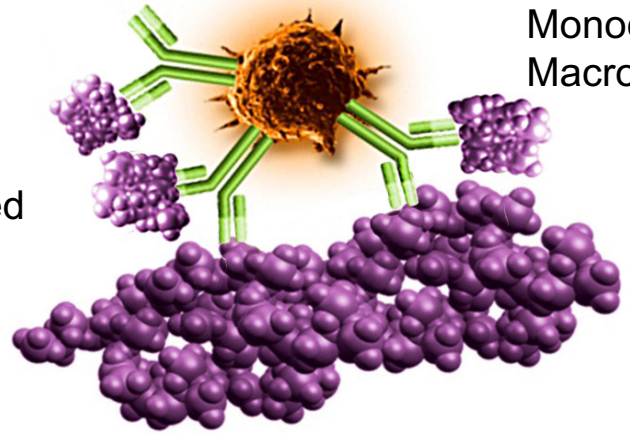
Potential Mechanism of Action for NEOD001

Neutralize or facilitate clearance of amyloid protein

Neutralization



Soluble Aggregates of Amyloid Protein



Monocyte/ Macrophage

Deposited Amyloid

Clearance

NEOD001 Demonstrates Organ Biomarker Responses in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction: Final Results From a Phase 1/2 Study

Morie A. Gertz,[1] Raymond L. Comenzo,[2] Heather Landau,[3] Vaishali Sanchorawala,[4] Brendan Weiss,[5] Jeffrey Zonder,[6] Jackie Walling,[7] Gene G. Kinney,[8] Martin Koller,[8] Dale B. Schenk,[8] Spencer D. Guthrie,[8] Enchi Liu,[8] Michaela Liedtke[9]

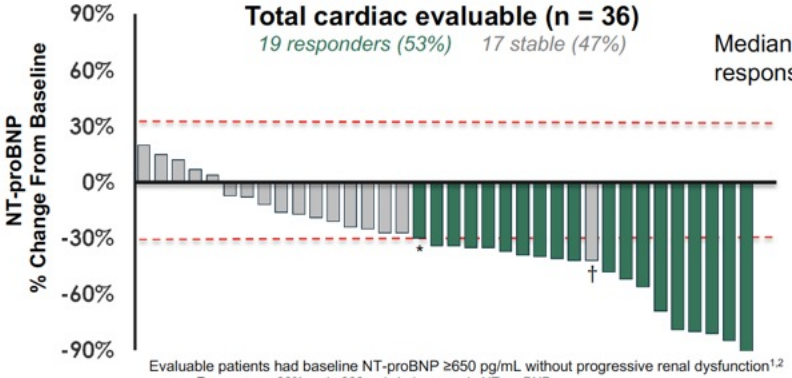
Organ Biomarker Responses in Patients With Light Chain Amyloidosis Treated With NEOD001 Are Independent of Previous Hematologic Responses

Michaela Liedtke,[1] Raymond L. Comenzo,[2] Heather Landau,[3] Vaishali Sanchorawala,[4] Brendan Weiss,[5] Jeffrey Zonder,[6] Jackie Walling,[7] Gene G. Kinney,[8] Martin Koller,[8] Dale B. Schenk,[8] Spencer D. Guthrie,[8] Enchi Liu,[8] Morie A. Gertz[9]

ASH 2016

NEOD001: Cardiac Biomarker Response

Best Response Analysis



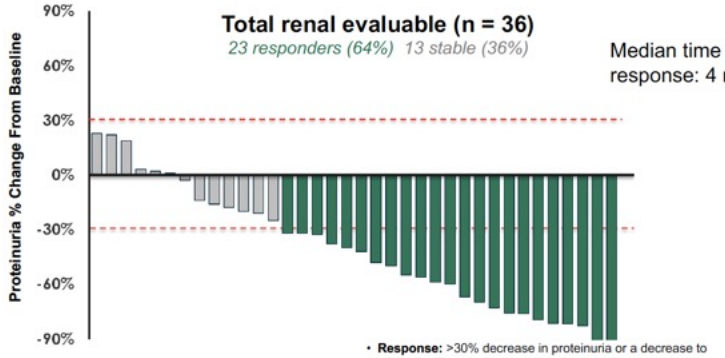
Evaluable patients had baseline NT-proBNP ≥650 pg/mL without progressive renal dysfunction[1,2]

- **Response:** >30% and >300 pg/mL decrease in NT-proBNP
- **Progression:** >30% and >300 pg/mL increase in NT-proBNP
- **Stable disease:** Neither response nor progression

10

NEOD001: Renal Biomarker Response

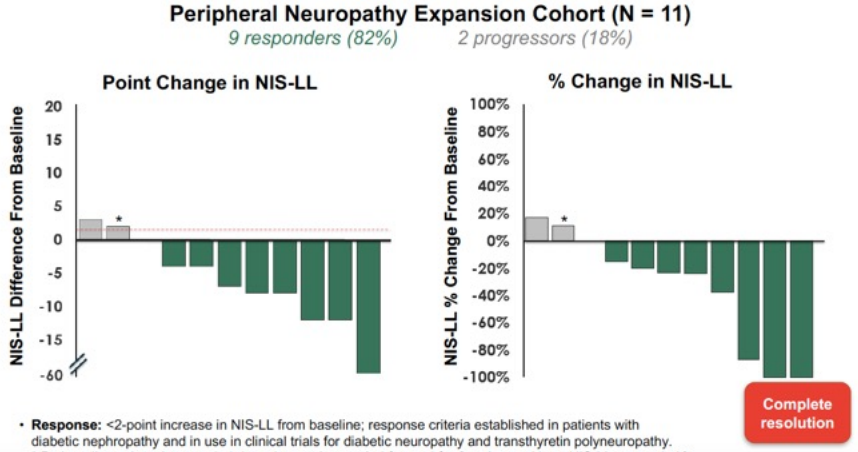
Best Response Analysis



- **Response:** >30% decrease in proteinuria or a decrease to <0.5 g/24 hours in the absence of renal progression
- **Progression:** >25% worsening in eGFR
- **Stable disease:** Neither response nor progression

13 eGFR, estimated glomerular filtration rate.
Evaluable patients had baseline proteinuria >0.5 g/24 hours
Palladini G et al. *Blood*. 2014;124:2325-2332.

NEOD001: Neuropathy Response at Month 10 (NIS-LL)



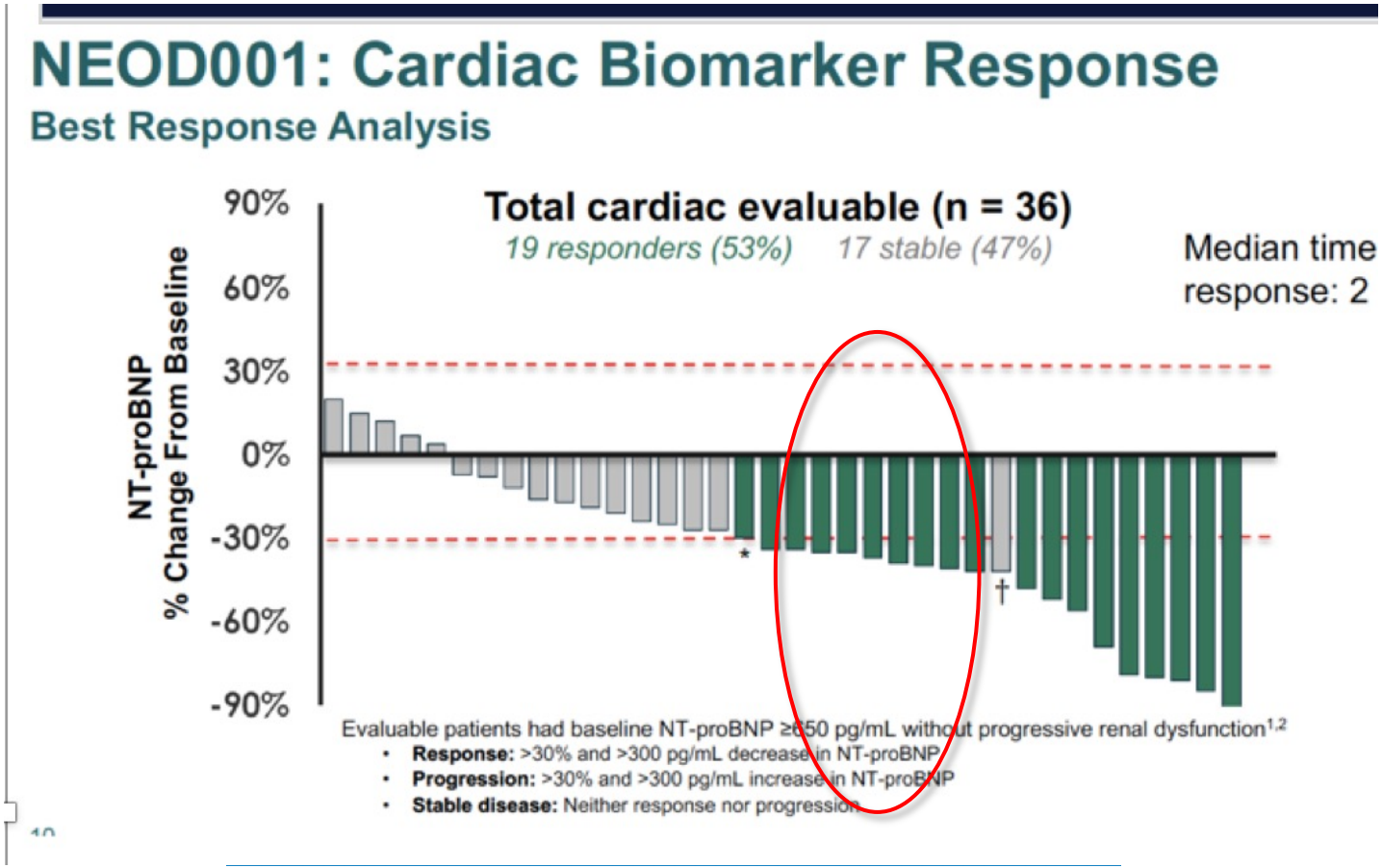
- **Response:** <2-point increase in NIS-LL from baseline; response criteria established in patients with diabetic nephropathy and in use in clinical trials for diabetic neuropathy and transthyretin polyneuropathy.

* Patient discontinued at month 4; last observation carried forward for 2 patients without NIS-LL at month 10.

16

ANDROMEDA: Réponse cardiaque à 6 et 18 mois

- **Cardiac responses :**
  - in patients with NT-proBNP ≥ 650 ng/l or NYHA III or IV (D-VCd, n = 118 ; VCd, n = 117)
  - ≥ 30 % drop in NT-proBNP serum level (> 300 ng/l) or NYHA, (drop > 2 classes in patients NYHA III or IV)



Phase 2b:

THE

Pas de différence avec placebo

116 pts / 100 prévus

Phase 3:

THE

Etude de futilité négative

236 pts / 236

prothena

Prothena Reports Results from the Phase 3 VITAL Amyloidosis Study of NEOD001 (birtamimab) in AL Amyloidosis

April 18, 2019

- **Results from final analysis of the composite primary endpoint were consistent with the futility analysis reported in April 2018**
- **Results from post hoc analyses revealed a potential survival benefit with NEOD001 in the category of patients at the highest risk for early mortality (Mayo Stage IV)**

	NEOD001 + SOC (n=130)	Placebo + SOC (n=130)	Total (N=260)
Mayo Stage N (%)			
I	11 (8%)	10 (8%)	21 (8%)
II	34 (26%)	28 (22%)	62 (24%)
III	47 (36%)	53 (41%)	100 (38%)
IV	38 (29%)	39 (30%)	77 (30%)

prothena

AFFIRM-AL STUDY

Site Initiation Visit

NEOD001-301

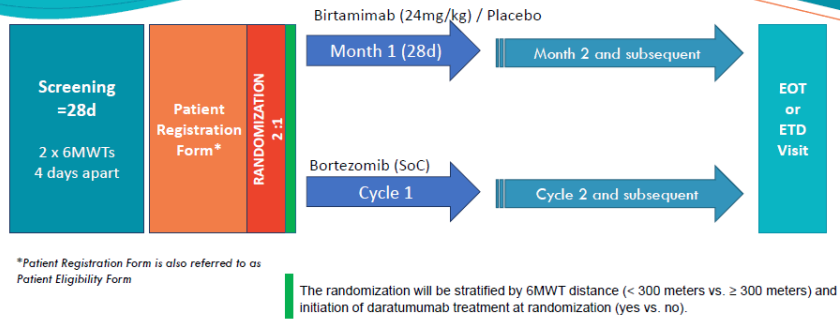
A Phase 3, Randomized Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs. Placebo Plus Standard of Care in Mayo Stage IV Subjects with Light Chain (AL) Amyloidosis

Protocol Version 2 dated 10-Jan-2022

Version date 09-Mar-2022

STUDY DESIGN

AFFIRM-AL STUDY

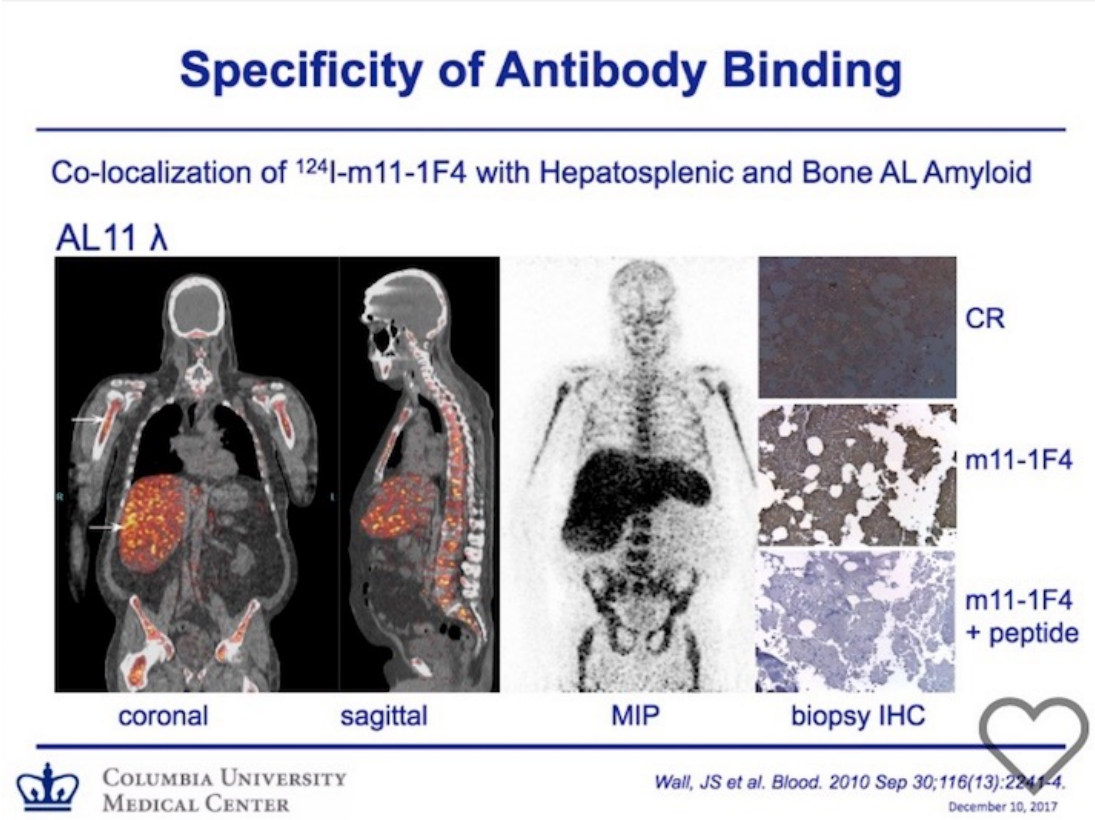


**Patient Registration Form is also referred to as Patient Eligibility Form*

The randomization will be stratified by 6MWT distance (< 300 meters vs. ≥ 300 meters) and initiation of daratumumab treatment at randomization (yes vs. no).

CAEL-101

CAEL-101 est un anticorps monoclonal IgG1k
qui se lie directement à un épitope conformationnel
présent sur les fibrilles amyloïdes, quel que soit
l'isotype (κ ou λ)



Safety and Tolerability of CAEL-101, an Anti-Amyloid Monoclonal Antibody, Combined With Anti-Plasma Cell Dyscrasia Therapy in Patients With Light-Chain Amyloidosis: 18-Month Results of a Phase 2 Study

Michaela Liedtke[1], Jason Valent[2], Jeffrey Zonder[3], María Angélica Molina[4], Chandrasekhar Udata[5], Juliana Ianus[5], John Tripptree[5], Julia Catini[5], Candida Cristina Quarta[5]

[1]Stanford University Medical Center, Palo Alto, CA, USA; [2]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [3]Karmanos Cancer Center, Detroit, MI, USA; [4]IQVIA, Durham, NC, USA; [5]Alexion, AstraZeneca Rare Disease Inc., Boston, MA, USA

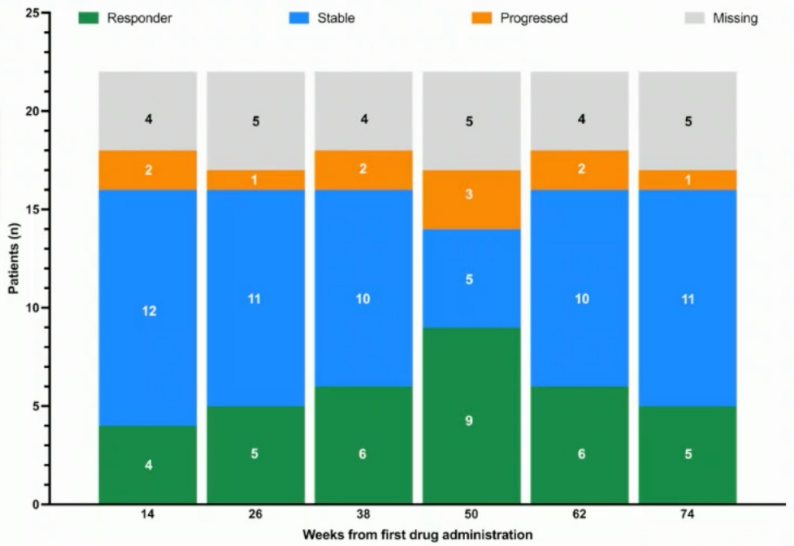
Date: June 11, 2023
Program section: MM and CLL final analyses/long term follow up of clinical trials

Cardiac Response

- The overall analysis of serum NT-proBNP levels over time shows improvement or stabilization of cardiac function
- Response was observed even after cessation of anti-PCD therapy

????

Response	Criteria
Responder	>30% decrease from baseline AND a decrease of NT-proBNP >300 ng/L in patients with a baseline NT-proBNP of ≥650 ng/L
Stable disease	Neither responder nor progression
Disease progression	>30% increase from baseline and ≥300 ng/L NT-proBNP, in the absence of decline in estimated glomerular filtration rate (eGFR) ≥25% from baseline



NT-proBNP, N-terminal pro-brain natriuretic peptide; PCD, plasma cell dyscrasia.

Caelum CARES Phase 3 Program Initiated

Caelum CARES

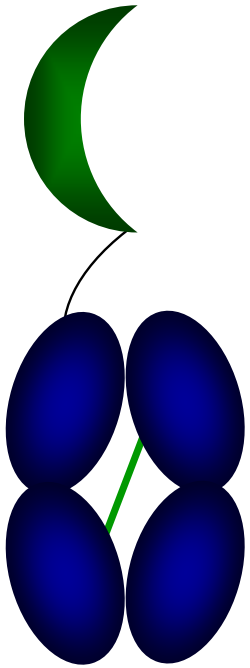
Mayo Stage IIIb Newly Diagnosed Treatment Naive	
CAEL-101 + CyBorD 74 Patient	Placebo + CyBorD 37 Patients
4 weekly doses followed by a maintenance dose every 2 – 4 weeks	
Primary endpoint: Overall Survival Secondary endpoints: 6MWT, QoL, NT-proBNP, GLS, Cardiac MRI, Proteinuria	

Mayo Stage IIIa Newly Diagnosed Treatment Naive	
CAEL-101 + CyBorD 178 Patient	Placebo + CyBorD 89 Patients
4 weekly doses followed by a maintenance dose every 2 – 4 weeks	
Primary endpoint: Overall Survival Secondary endpoints: 6MWT, QoL, NT-proBNP, GLS, Cardiac MRI, Proteinuria	

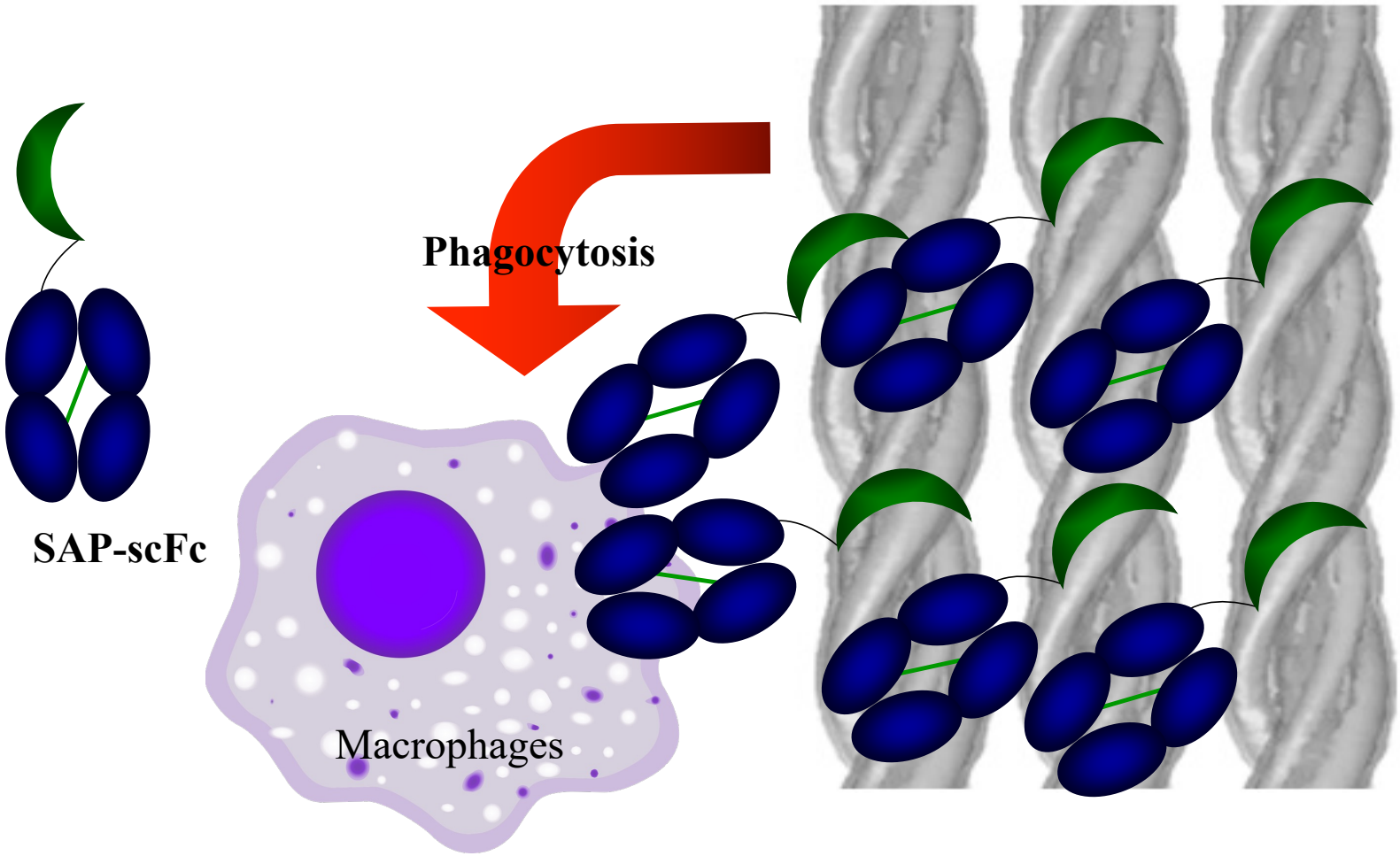
Christophe Sirac

SAP-Fc

Utilisant l'avidité de la SAP (sérum amyloid protein) pour les dépôts d'amylose



Christophe Sirac

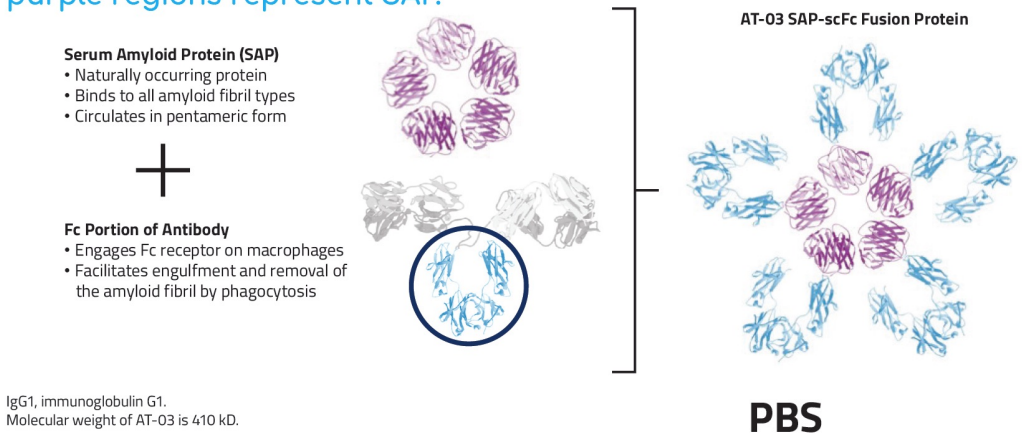


Preclinical Characterization of a Novel Fusion Protein, AT-03, With Pan-Amyloid Binding and Removal

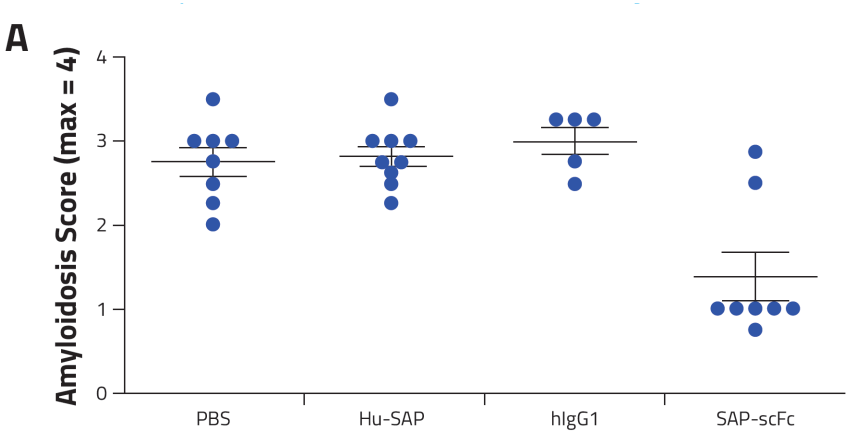
Christophe Sirac,[1] Arnaud Jaccard,[1] Roussine Codo,[1] Sébastien Bender,[1] Gemma Martinez Rivas,[1] Frank Bridoux,[2] Gregory Bell,[3] Spencer Guthrie,[3] Suganya Selvarajah,[3] Stephen J. Kennel,[4] Angela D. Williams,[4] James S. Foster,[4] Jonathan S. Wall[4]

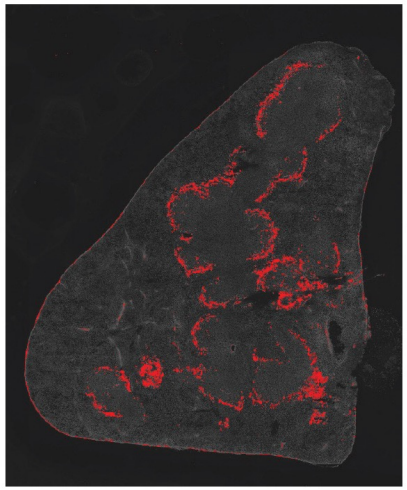
[1]CRIBL Laboratory, CNRS UMR7276, National Reference Center for AL Amyloidosis, Limoges, France; [2]CRIBL Laboratory, CNRS UMR7276, National Reference Center for AL Amyloidosis, Limoges, and CHU Poitiers, Poitiers, France; [3]Attralus, South San Francisco, CA, USA; [4]University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

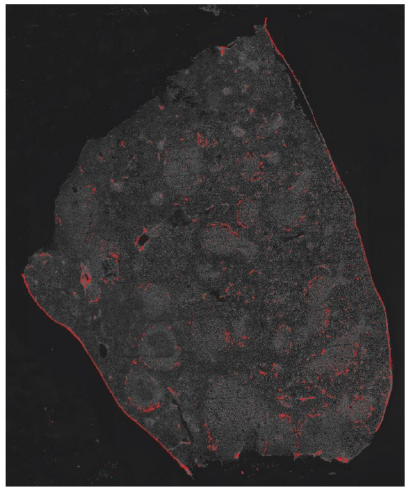
Figure 1. AT-03 SAP-scFc fusion protein designed to promote opsonization of amyloid. AT-03 pentamer consists of 5 AT-03 monomers. The peripheral blue regions represent human IgG1 Fc (CH2 and CH3), and the central purple regions represent SAP.



IgG1, immunoglobulin G1.
Molecular weight of AT-03 is 410 kD.

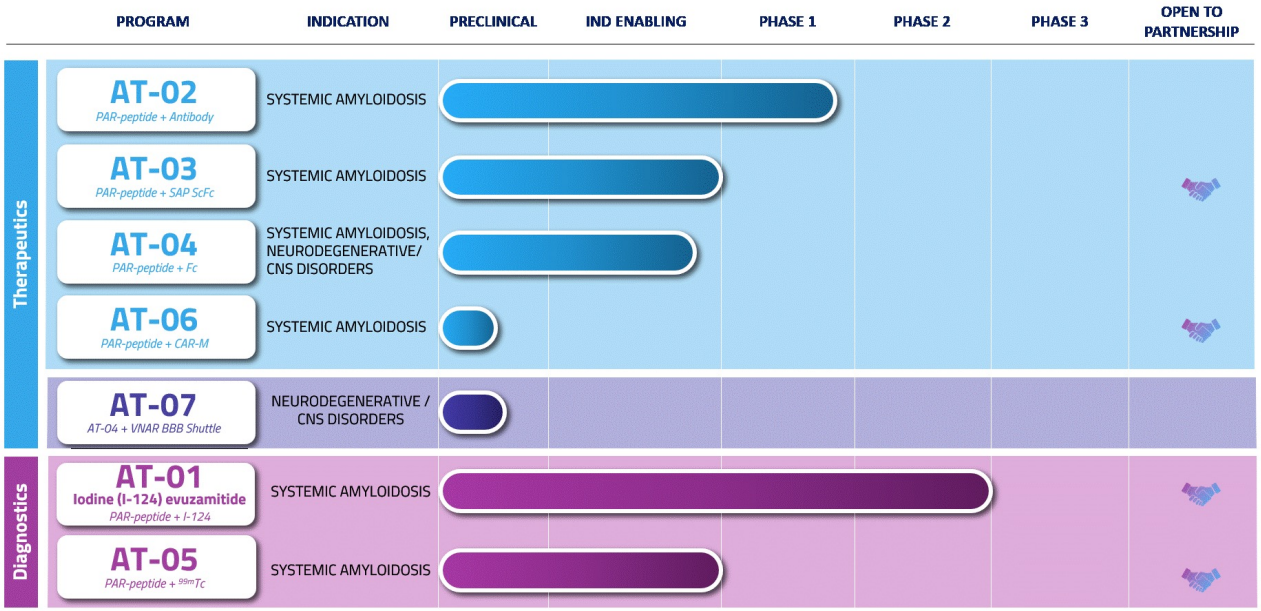


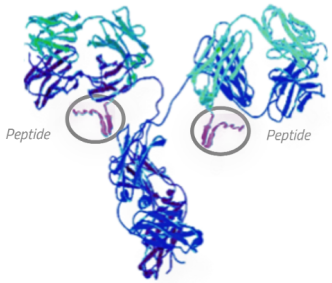




ASH dec 2021

OUR PIONEERING PAN-AMYLOID PIPELINE





AT-02

PAR-Peptide + IgG1 Antibody

AT-02 is a fusion of our PAR-peptide with an IgG1 antibody. The proprietary peptide binds to all types of amyloid and delivers the antibody to the site of disease to stimulate the immune system to remove amyloid.

XVIII. International Symposium on Amyloidosis 4th – 8th September 2022 | Heidelberg

Development of CAR-Macrophages (CAR-M) as a Potential Therapeutic to Facilitate Amyloid Clearance

Manasi Balachandran

James. S. Foster, Joseph. W. Jackson, Tina Richey, Emily Martin, Stephen Kennel, Angela Williams, Sallie Macy, Craig Wooliver and Jonathan. S. Wall

Amyloidosis and Cancer Theranostics Program

Department of Medicine, University of Tennessee Medical Center

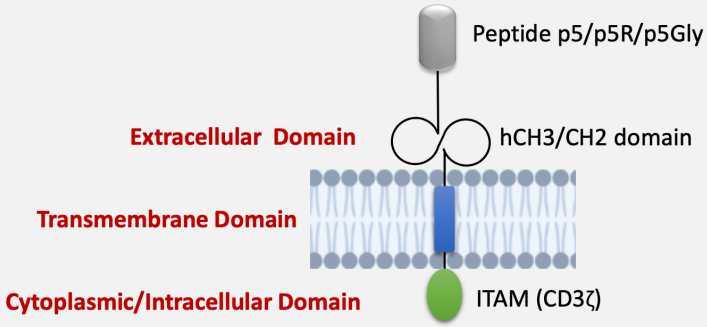
Knoxville, Tennessee, USA

THE UNIVERSITY of TENNESSEE GRADUATE SCHOOL OF MEDICINE

The Exemplary CAR Structure for Amyloid Binding

- CAR technology originally developed for cancer immunotherapy (CAR-T and CAR-M)
- The amyloid-reactive CAR incorporates the pan amyloid-reactive peptide p5 (lysine version) or p5R (arginine version). The uncharged p5Gly (glycine version) serves as a negative control

Amyloid-binding CAR



- The IgG1 heavy chain domains, hCH3 and hCH2, provide rigidity to the structure and may facilitate complement activation
- The intracellular signal activation domain CD3ζ has three ITAMs and is a phagocytosis signal enhancer

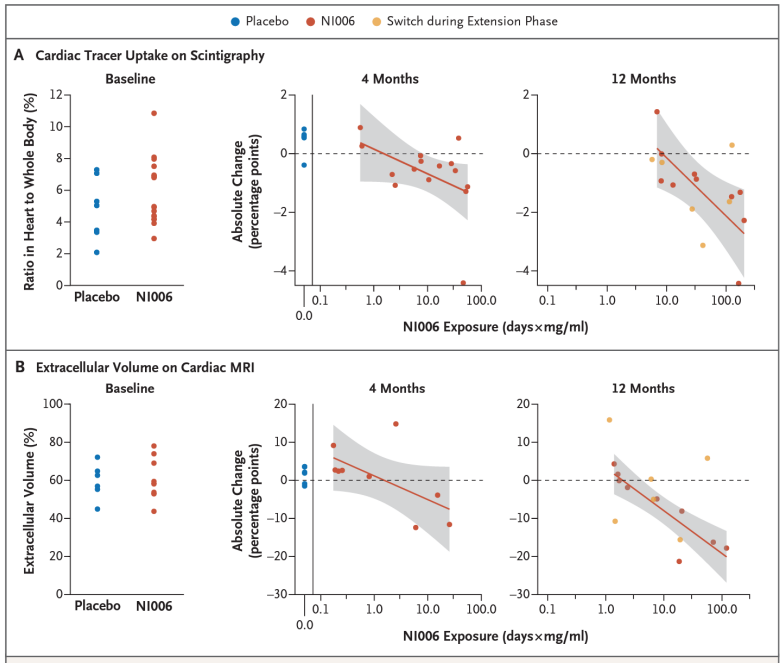
May 20, 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.



N ENGL J MED 388;23 NEJM.ORG JUNE 8, 2023

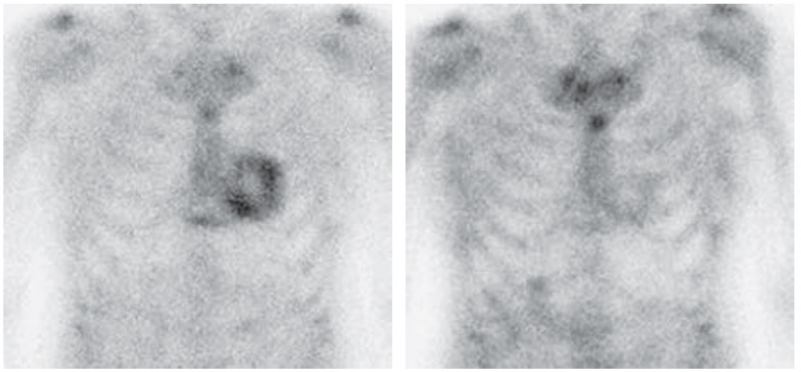
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Antibody-Associated Reversal of ATTR Amyloidosis–Related Cardiomyopathy

We investigated the possibility that the 3 patients had had an antiamyloid immune response, and we identified high-titer circulating polyclonal IgG antibodies to human ATTR amyloid in each of the patients.

The cause and clinical significance of the anti-ATTR amyloid antibodies are intriguing and presently unclear. However, the clinical recovery of these patients establishes the unanticipated potential for reversibility of ATTR-CM and raises expectations for its treatment.



DPD Scintigraphy

Remerciements

- Tous les centres participants au réseau du Centre de référence Amylose AL et autres maladies par dépôt d'IG monoclonales
- L'association Française contre l'amylose
- Equipes de recherche clinique à Limoges et Poitiers
- UMR CNRS 7276 INSERM 1262 CRIBL