Le point sur les avancées thérapeutiques dans la maladie d'Alzheimer et les grands essais en cours

Pierre-Jean OUSSET

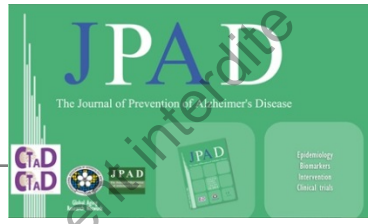
Toulouse GÉRONTOPÔLE

Une recherche difficile

The Journal of Prevention of Alzheimer's Disease - JPAD©
Volume 1, Number 1, 2014

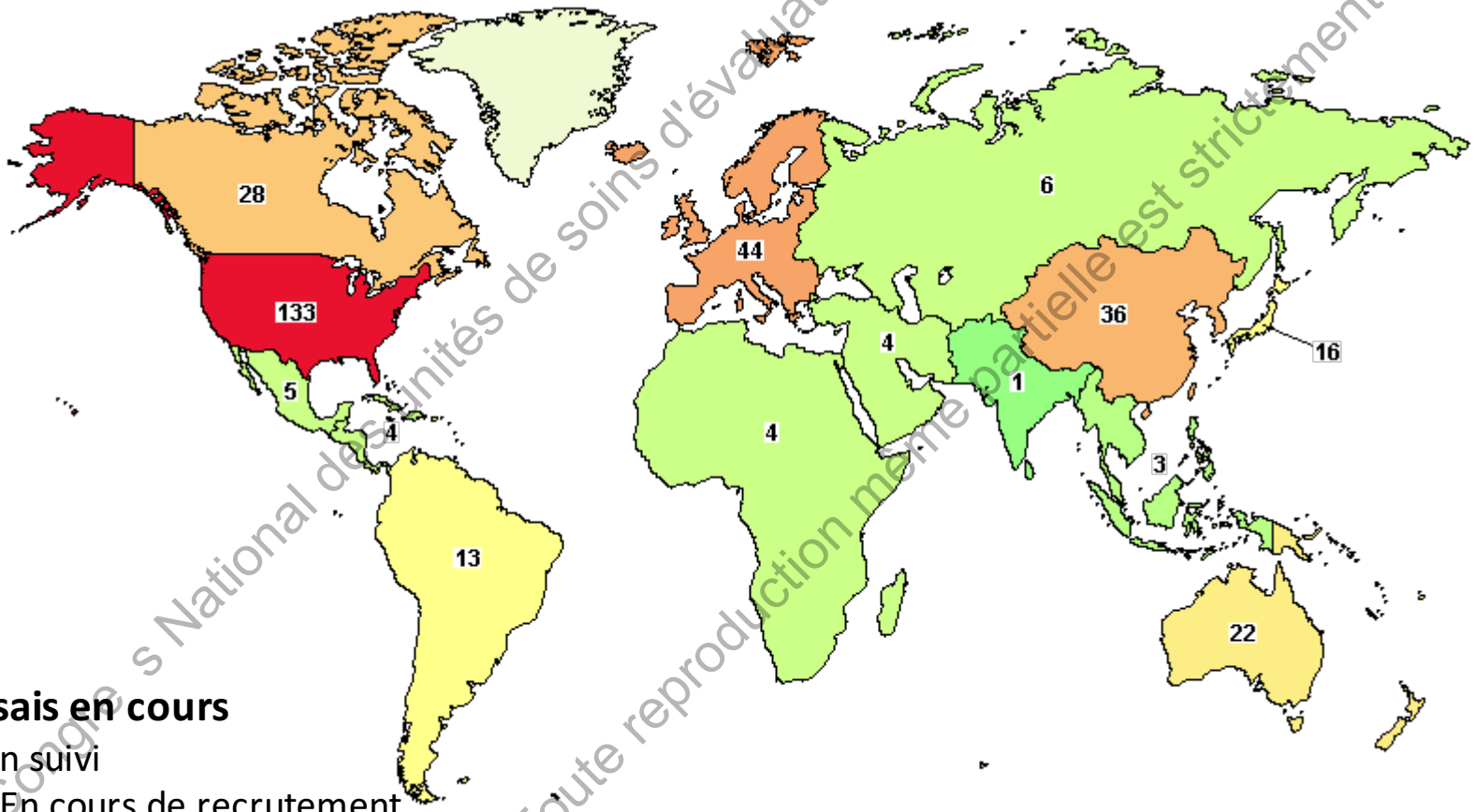
Is Alzheimer's Disease Drug Development Broken? What Must Be Improved

P.-J.Ousset[1,2,3], J. Cummings[4], J. Delrieu[1], V. Legrand[5], N. Prins[4], B. Winblad[6], J. Touchon[7], M.W. Weiner[8], B. Vellas[1,2]



- Février 2018 : Merck interrompt l'essai APECS **Verubecestat**
- Mai 2018 : Janssen annonce l'arrêt du programme **Atabecestat**
- Juin 2018 : Arrêt des programmes AMARANTH and DAYBREAK-ALZ du **Lanabecestat**
- Octobre 2018 : Arrêt par Lilly du **LY3202626**
- Mars 2019 : Arrêt des essais EMERGE et ENGAGE avec l'**Aducanumbab** (analyse de futilité)
- Juillet 2019 : Interruption du Programme Generation, **Umibecestat** (Novartis)
- Septembre 2019 : Interruption des essais **Elenbecestat** (Eisai)

Une recherche qui reste très active

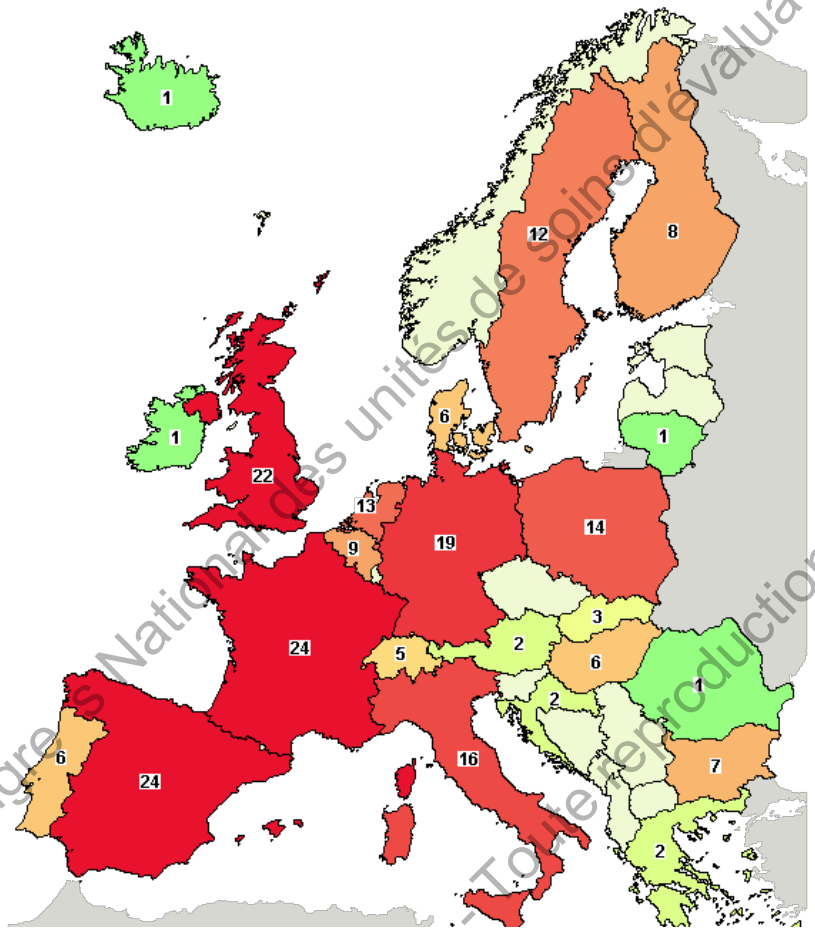


189 essais en cours

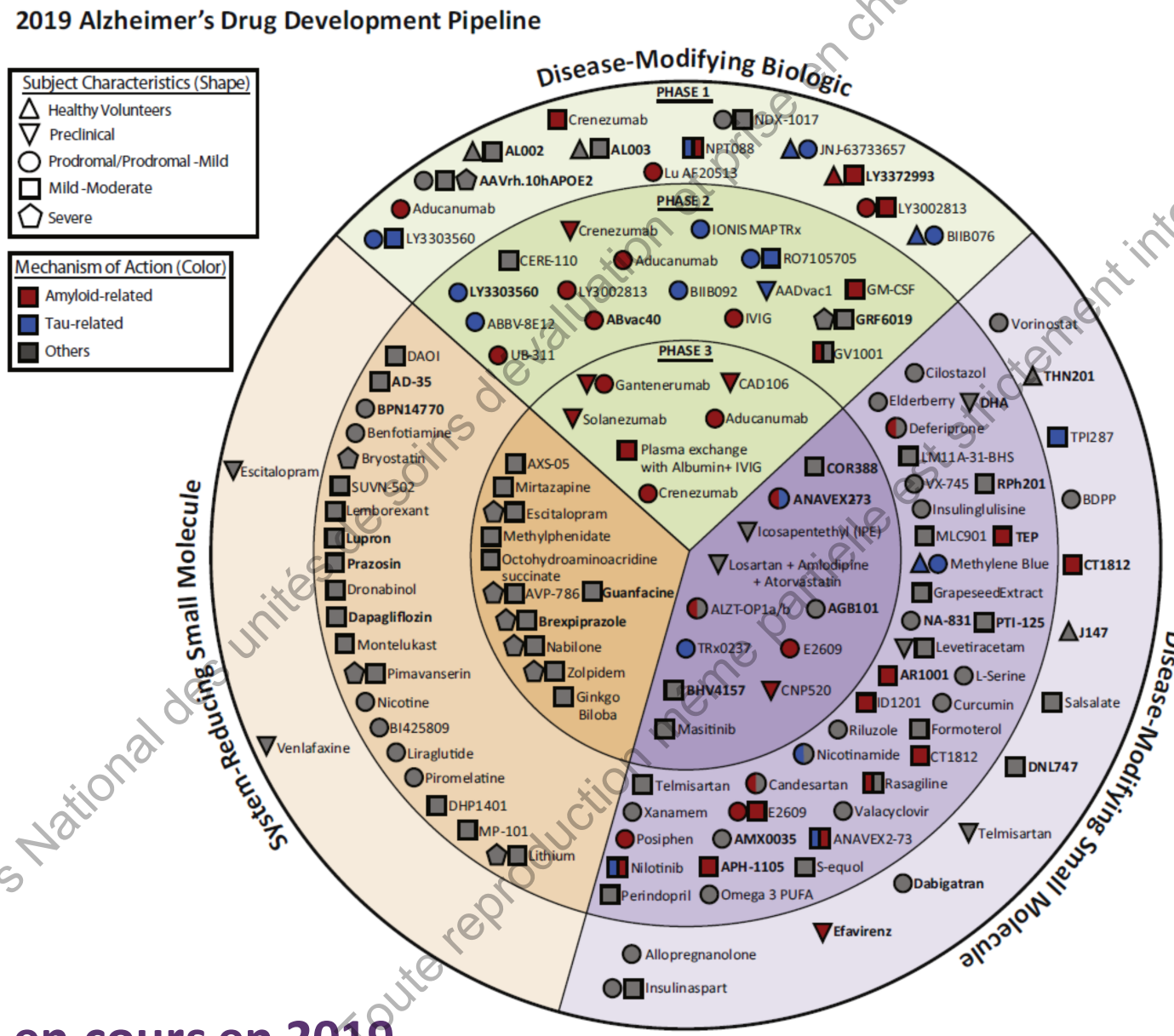
- 50 en suivi
- 139 En cours de recrutement
- phase I: 51 ; Phase II: 96 ; Phase 3: 42

ClinicalTrials.gov
DEC 2019

La France dans le peloton de tête européen



ClinicalTrials.gov
DEC 2019



Les essais en cours en 2019

Cummings J et al. Alzheimer's Dementia 2019

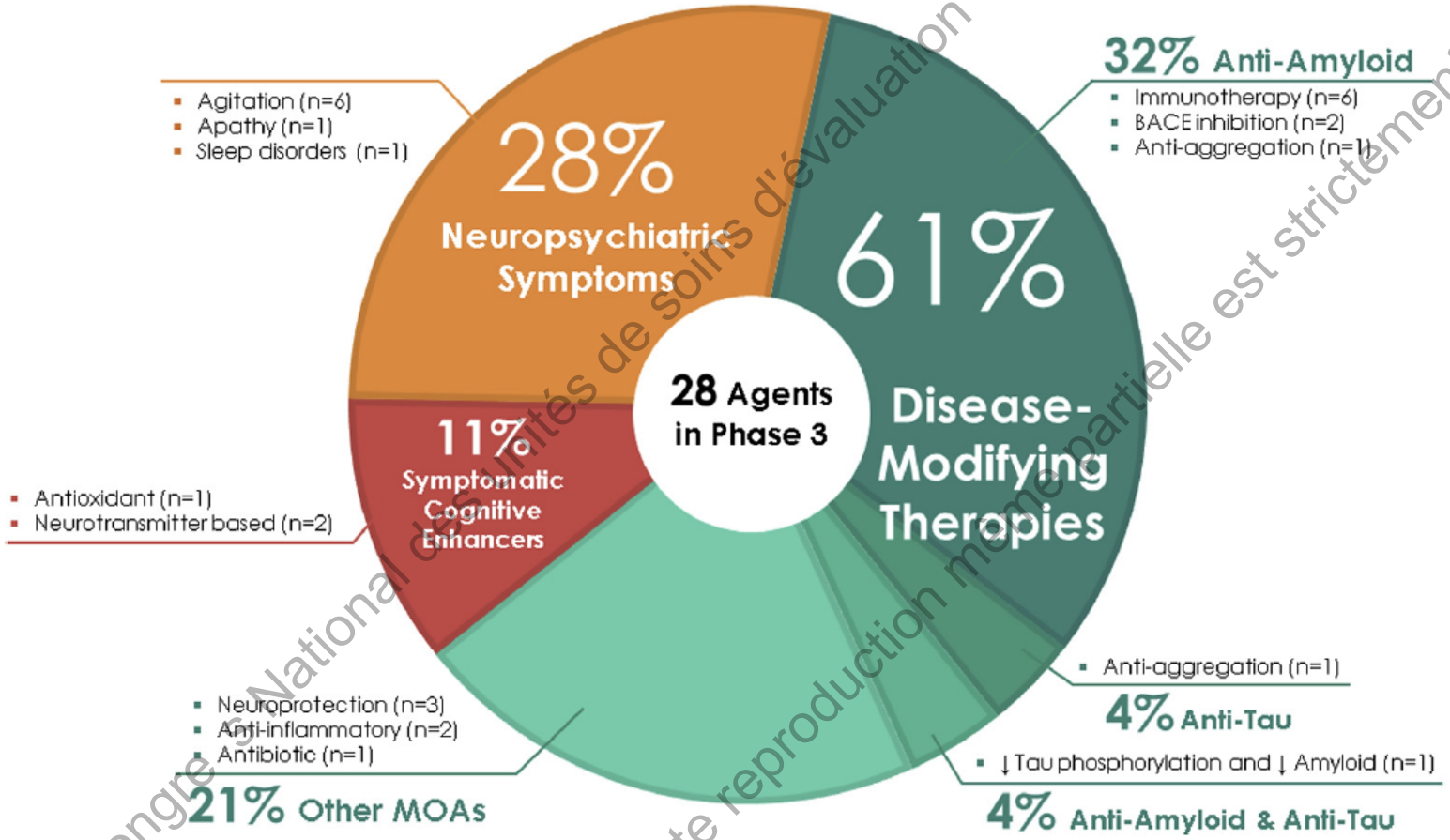
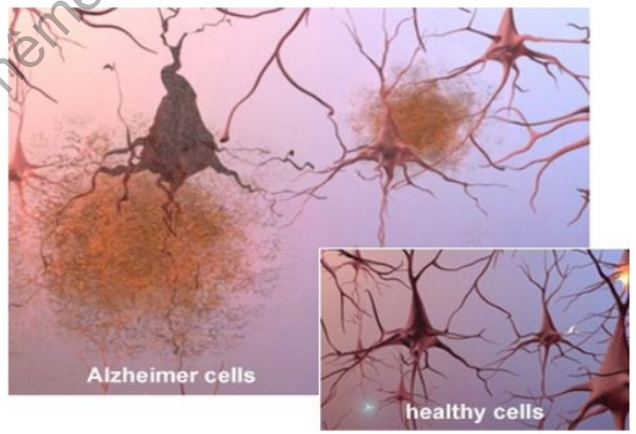


Fig. 2. Mechanisms of action of agents in phase 3.

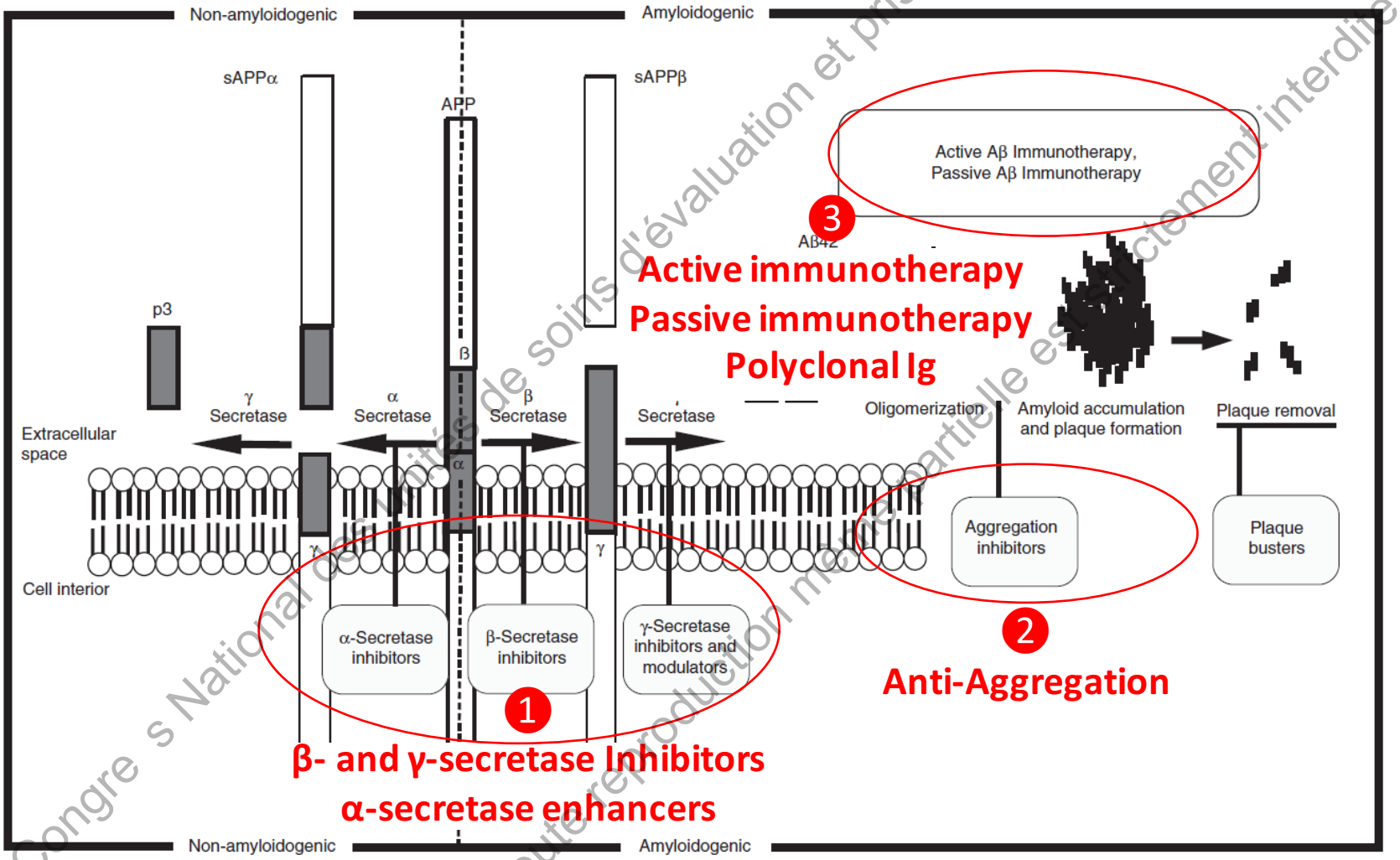
LA VOIE AMYLOÏDE



The amyloid hypothesis of Alzheimer's disease at 25 years

Dennis J Selkoe, John Hardy

DOI 10.15252/emmm.201606210 | Published online 29.03.2016 EMBO Molecular Medicine (2016) emmm.201606210



Hossein Samadi & David Sultzer. Solanezumab for Alzheimer's disease. Expert pinion on biological therapy 2011.

ANTICORPS MONOCLONAUX EN PHASE II/III

	Crenezumab[1]	Solanezumab[2,3]	Bapineuzumab[4]	BAN2401[5–7]	Aducanumab[8,9]	Gantenerumab[10,11]
Sponsor	Roche	Lilly	Pfizer	Eisai	Biogen	Roche
Epitope	Mid-domain	Mid-domain	N-Terminus	N-Terminus	N-Terminus	N-Term & Mid
Origine	Humanisé	Humanisé	Humanisé	Humanisé	Humain	Humain
Isotype	IgG4	IgG1	IgG1	IgG1	IgG1	IgG1
Cible	Toutes les formes de Aβ	Aβ soluble	Toutes les formes de Aβ	Aβ proto-fibrillaire	Oligomère et Aβ fibrillaire	Oligomère et Aβ fibrillaire
Status	• **Phase 2 en cours**	• **terminé**	• **terminé**	• **Phase 2 en cours**	• **terminé**	• **Phase 3 en cours**

Adapted from Neurimmune/Biogen presentation at AD/PD 2015, Nice, FR.

1. Adolfsson O, et al. *J Neurosci* 2012;32:9677-9689; **2.** Doody RS, et al. *NEJM;*2014:370:311-321; **3.** Yamada K, et al. *J Neurosci* 2009;29:11393-11398; **4.** Kerchner GA, Boxer AL. *Expert Opin Biol Ther* 2010;10:1121-1130; **5.** Kaplow JM, et al. *Alz Demen* 2013;9:807-808; **6.** Lai R, et al. *Alz Demen* 2014;10:689; **7.** Lannfelt L, et al. *Alz Res Ther* 2014;6:16 **8.** Hang Y, et al. *Neurodegener Dis* 2015;15:800; **9.** Sevigny J, et al. *Neurodegener Dis* 2015;15:311; **10.** Ostrowitzki S, et al. *Arch Neurol* 2012;69:198-207; **11.** Bohnmann B, et al. *J Alz Dis* 2012;28:49-69.

Aducanumab
EMERGE première étude positive (Oct 2019)

Primary endpoint of EMERGE (larger dataset)

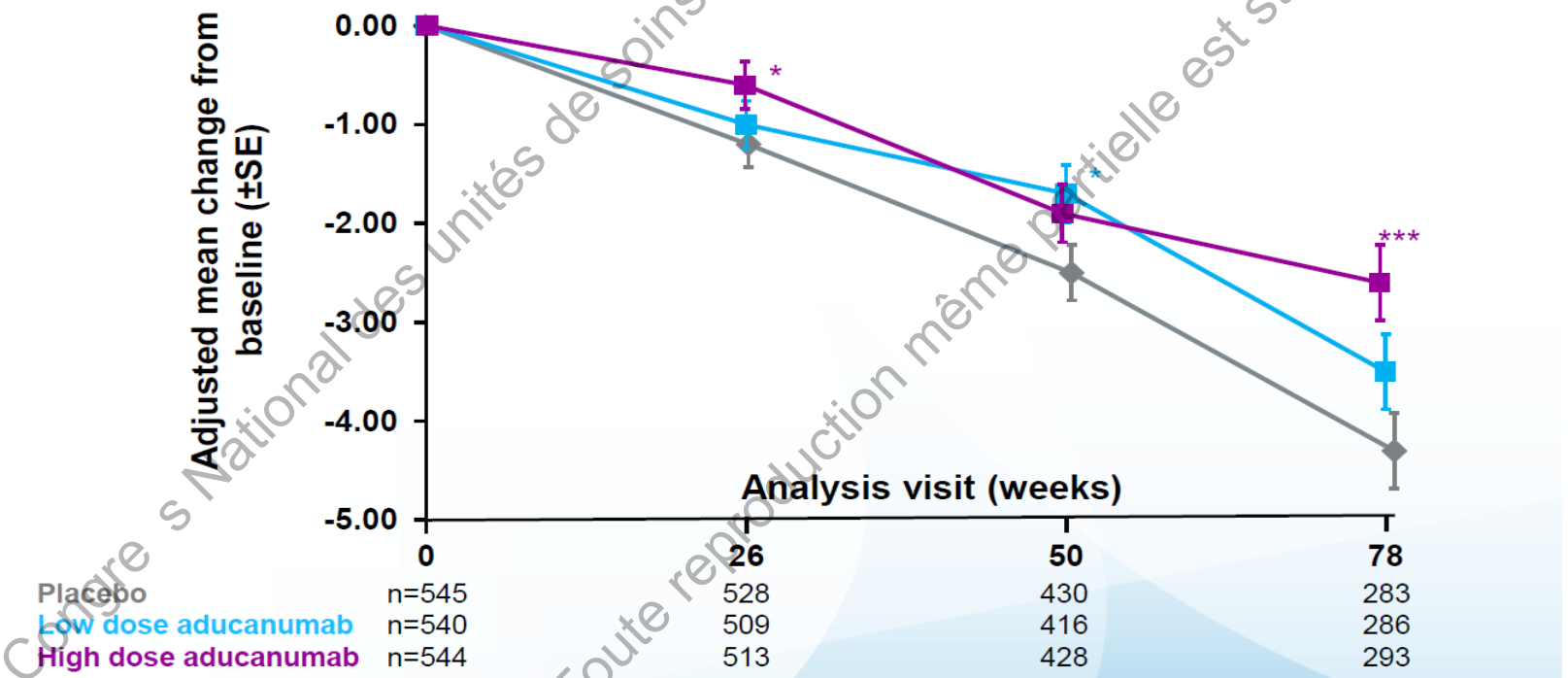
	ITT Population		OTC Population	
	% Reduction vs. Placebo[a] p-value		% Reduction vs. Placebo[a] p-value	
	Low dose (N=543)	High dose (N=547)	Low dose (N=329)	High dose (N=340)
CDR-SB	**-14%** 0.117	**-23%** 0.010	**-16%** 0.134	**-23%** 0.031

[a]: difference in change from baseline vs. placebo at Week 78. Negative percentage means less decline in the treated arm.

N: numbers of randomized and dosed subjects that were included in the analysis. Placebo = 548 (ITT) and 313 (OTC).

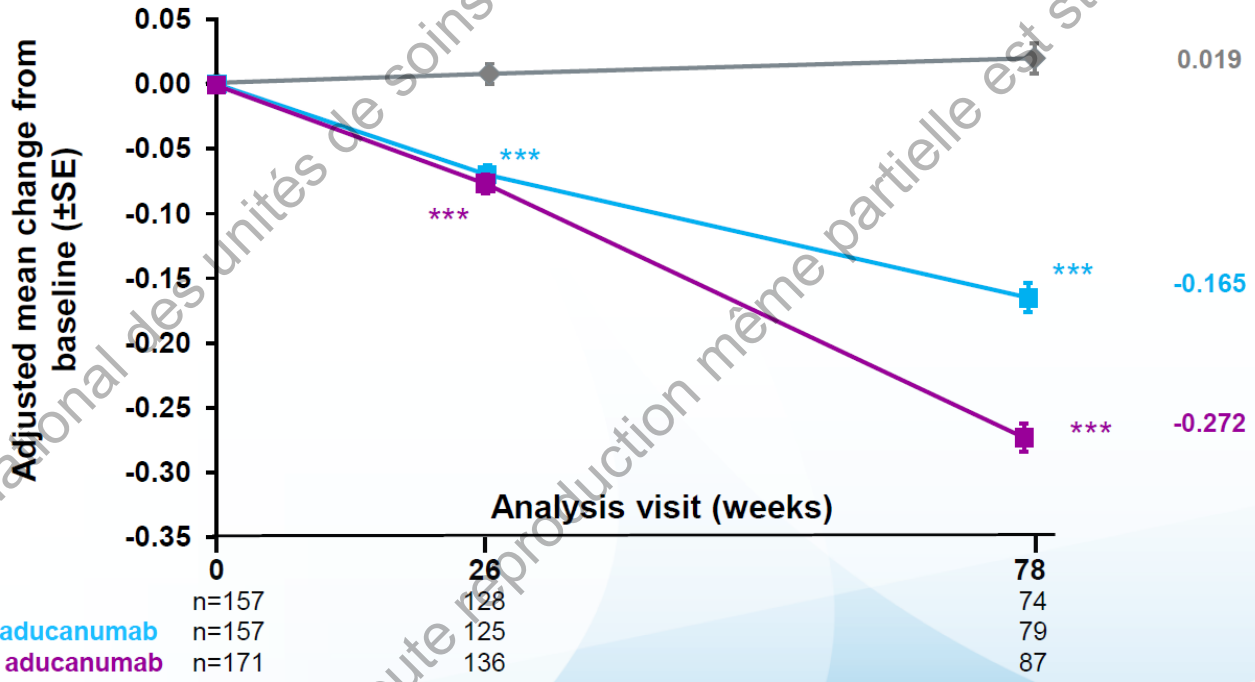
EMERGE : une action sur les ADL

EMERGE: Longitudinal change from baseline in ADCS-ADL-MCI



Des résultats concordants avec les biomarqueurs

EMERGE: Longitudinal change from baseline in amyloid PET SUVR

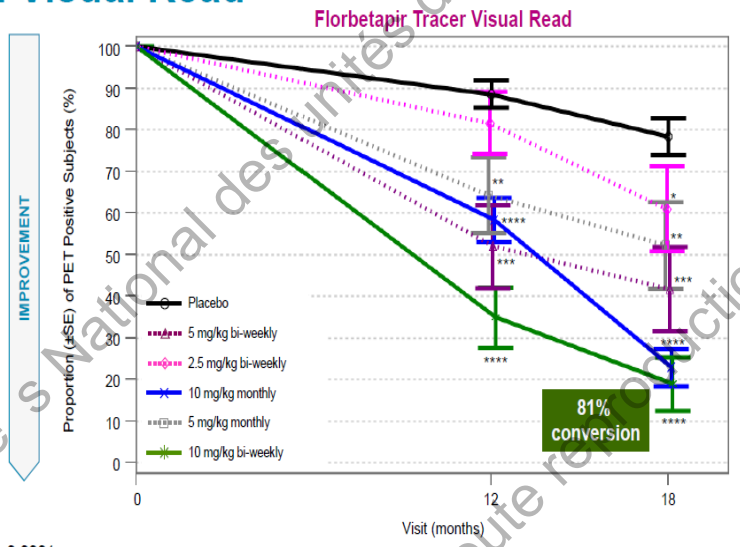


BAN2401

Une action sur l'amyloïde cérébrale avec 80% de « conversion »

Significant Conversion of Amyloid Positive to Negative With Visual Read

- Dose dependent conversion from amyloid positive to negative vs placebo
- BAN2401 significantly converted subjects from amyloid positive to negative across most doses



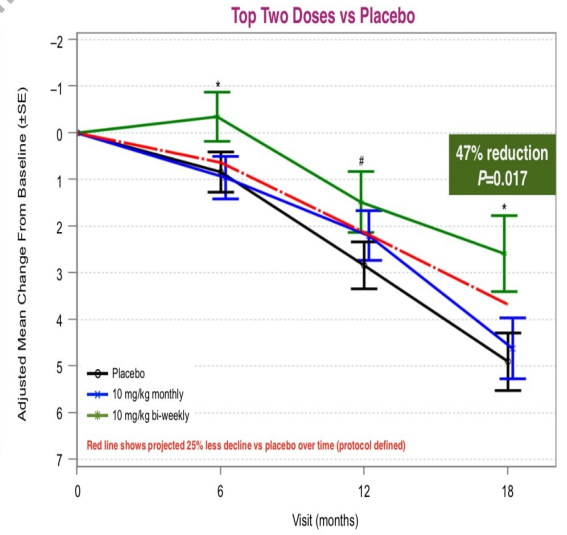
*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

Baseline images were read at time of inclusion; longitudinal 12 and 18 month reads were conducted after all subjects completed 18 months of treatment. Fisher's exact test was used to compare each dose vs placebo.

10

BAN2401 Slowed Cognitive Decline on ADAS-cog Over 18 Months

- Dose dependent reduction in decline on ADAS-cog over time, starting at 6 months
- Slower decline on ADAS-cog 10 mg/kg bi-weekly dose (**green**) vs placebo (**black**) across all time points

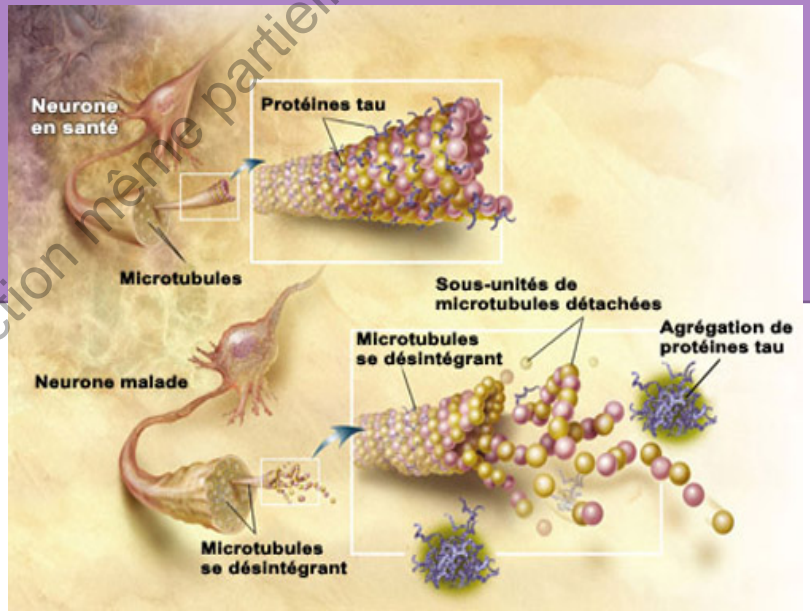


#P<0.1 (P=0.073), *P<0.05.

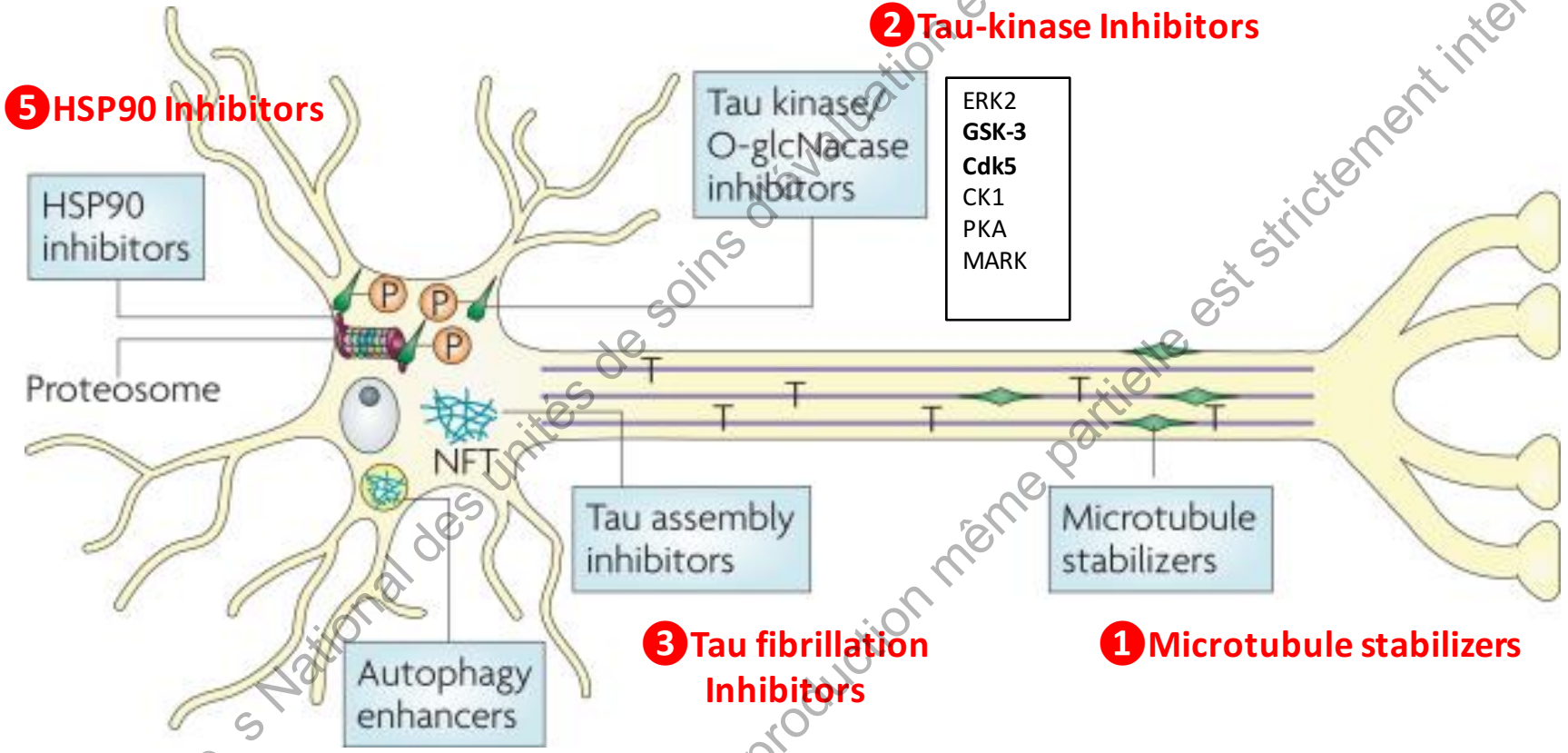
The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

9

LA VOIE DE LA PROTÉINE TAU



Tau and therapeutic targets



Brunden KR et al. Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies. Nat Rev Drug Discov. 2009 Oct;8(10):783-93.

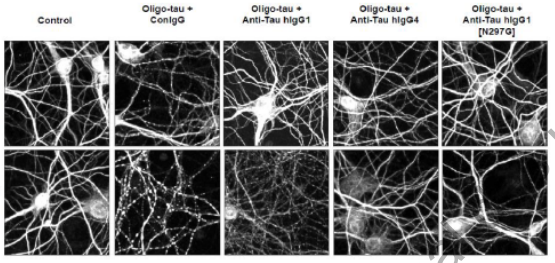
Immunothérapie anti-Tau

Anti-Tau antibody

Tau is a compelling target - passive anti-Tau immunotherapy shows efficacy

Protection against toxic oligomeric Tau

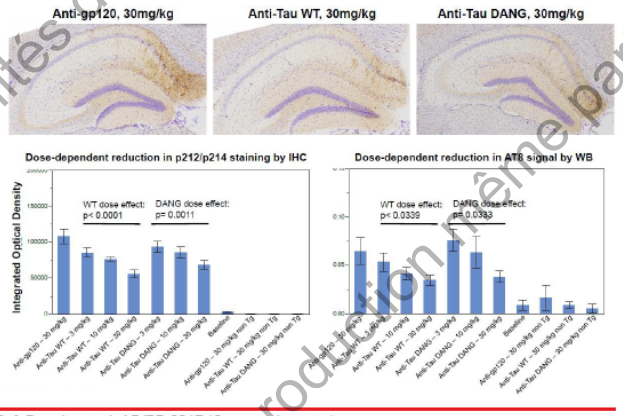
Reduced effector anti-tau is protective against Tau-mediated toxicity in the presence of microglia



Ref: Ayalon et al, AD/PD 2017 (Genentech oral presentation)

Dose-dependent inhibition of Tau spreading, independent of effector function

Dose-dependent efficacy shown for passive anti-Tau immunization, in the presence (WT) or absence (DANG) of IgG effector function



Ref: Brendza et al, AD/PD 2017 (Genentech poster)

Passive immunization with an anti-Tau antibody demonstrated dose-dependent efficacy, independent of antibody effector function, in support of the mechanism of action of targeting Tau spreading

Essais en cours

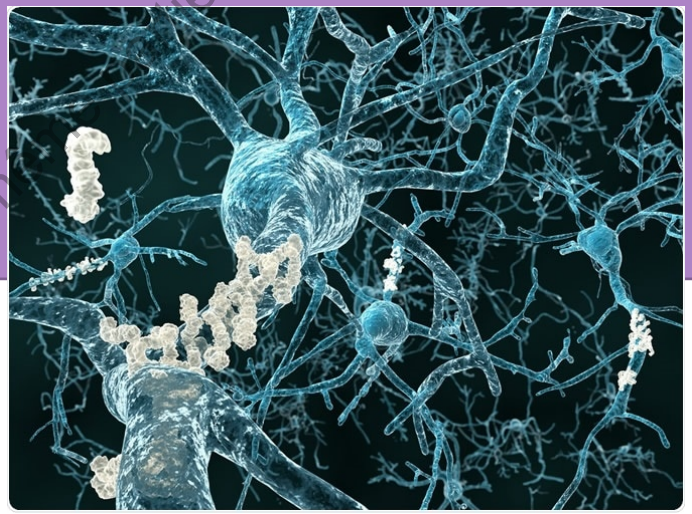
TANGO

Biogen

TAURIEL

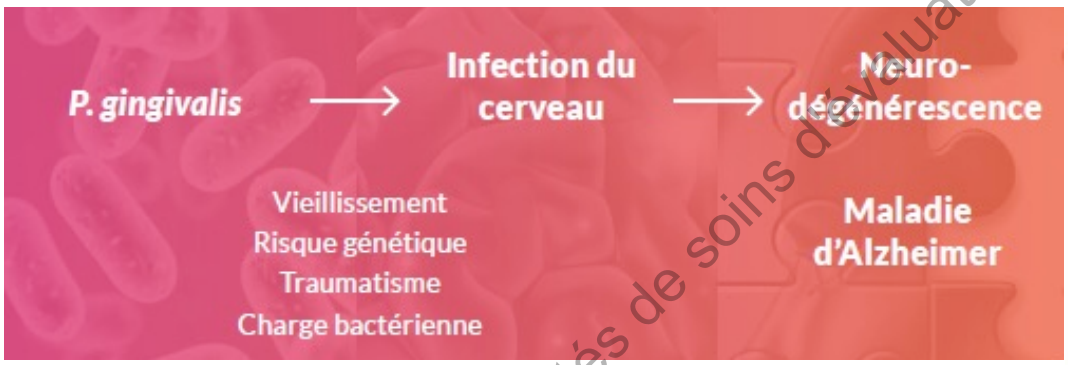
Genentech
A Member of the Roche Group

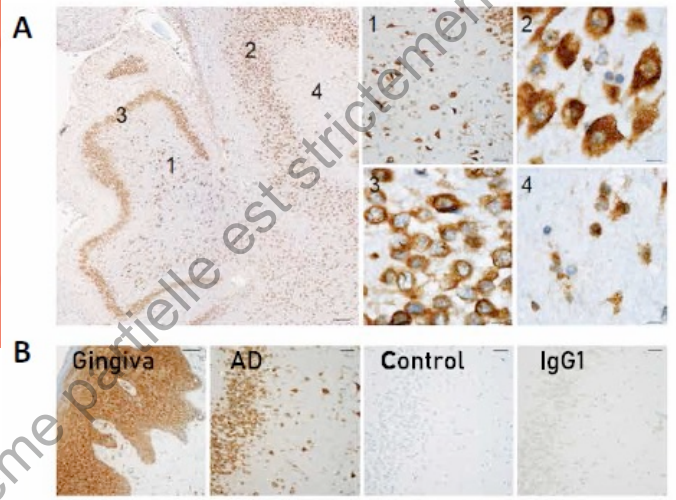
AUTRES VOIES THÉRAPEUTIQUES

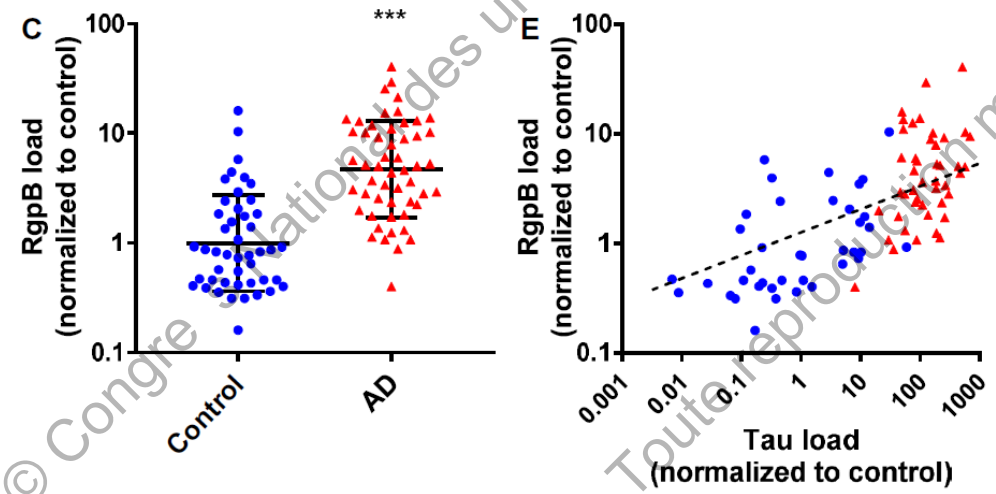


GAIN
Alzheimer's Trial

CORTEXYME

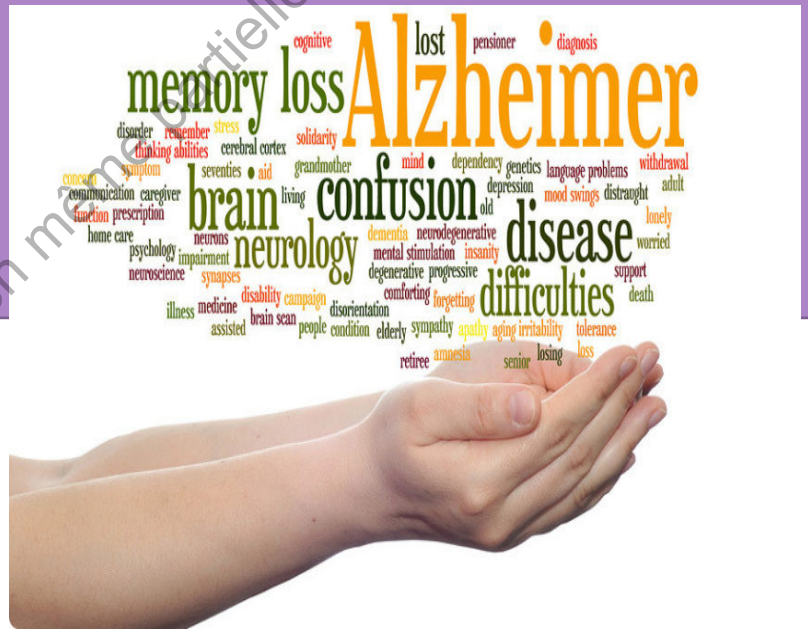






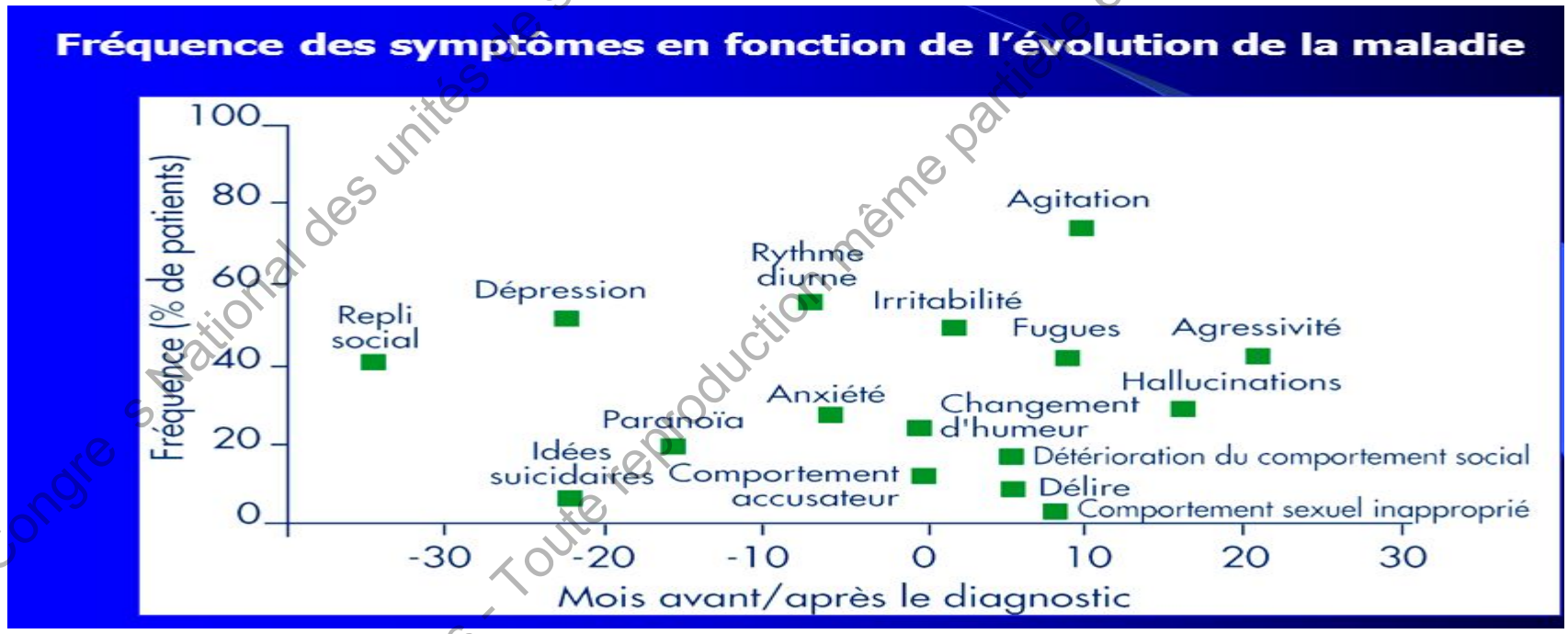
Dominy *et al.*, *Sci. Adv.* 2019; **5**

➢ LES TRAITEMENTS SYMPTOMATIQUES



DES SYMPTÔMES ET DES CIBLES DIVERS…

Troubles cognitifs
Altération de l'autonomie
Troubles psycho-comportementaux



A Phase 3 Study to Evaluate Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis: Study Population and Design

Foff,E[1]; Youakim,JM[1]; Owen,R[1]; Knowles,M[1]; Ballard,C[2]; Cummings,J[3]; Tariot,P[4]; Stankovic,S[1]

[1]ACADIA Pharmaceuticals Inc., [2]The University of Exeter Medical School, [3]Cleveland Clinic Lou Ruvo Center, Center for Neurodegeneration and Translational Neuroscience, Cleveland Clinic Lerner College of Medicine, [4]Banner Alzheimer's Institute, University of Arizona College of Medicine

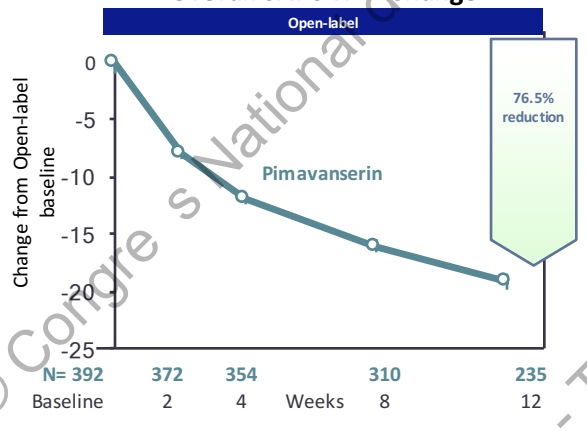
392 patients

Male or Female
50-90 yrs old

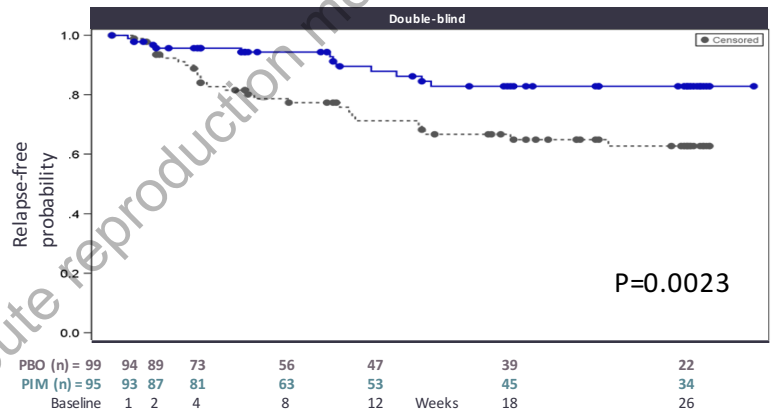
Primary endpoint
time to relapse in double-blind period

HARMONY

Overall SAPS-H+D Change



Patients on placebo are 2.8X more likely to experience a relapse of DRP



ACADIA® Pharmaceuticals

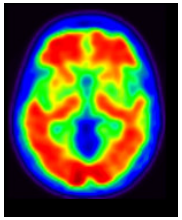
➢ LA PREVENTION

LES ESSAIS AU STADE PRÉSYMPTOMATIQUE

ÉTUDE	CRITÈRES D'INCLUSION	INTERVENTION	DURÉE	ENDPOINTS
Anti Amyloid treatment in Asymtomatic AD	Sujets normaux (CDR=0) Amyloïde +	Solanezumab	3 ans	Score cognitif composite
API-ADAD (Famille colombienne)	mutation autosomique dominante PS1	Crenezumab	5 ans	Score cognitif composite
API-APO	Asymptomatique APOE-4 homozygote	Immunothérapie active (CAD106) et BACE inhibiteur	5 ans	Score cognitif composite
Dominantly Inherited Alzheimer Network	Individus à risque d'une MA autosomique dominante	Solanezumab Gantenerumab	4 ans	Score cognitif composite Biomarqueurs (LCR et TEP)
Tomorrow study	APOE, âge, TOMM40	AD-4833 (pioglitazone, agoniste PPAR)	5 ans	Temps → MCI-AD

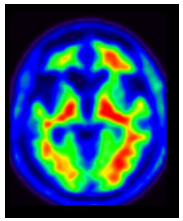
Les interventions non pharmacologiques
Results of MAPT-AV45

Amyloid positive group



Group	Mean change from baseline to 36 months (95% CI)	Mean difference (95% CI) vs placebo	P value (raw)	P value (Hochberg)
Omega3 + Multid.	**0.29 (0.02 ; 0.56)**	**0.72 (0.38 ; 1.04)**	**0.0004**	**0.0012**
Omega3	-0.23 (-0.44 ; -0.03)	0.18 (-0.09 to 0.46)	0.1356	0.1356
Multid.	**-0.05 (-0.17 ; 0.28)**	**0.47 (0.18 to 0.76)**	**0.0109**	**0.0218**

Amyloid Negative group



Group	Mean change from baseline to 36 months (95% CI)	Mean difference (95% CI) vs placebo	P value (raw)	P value (Hochberg)
Omega3 + Multid.	0.07 (-0.08 ; 0.21)	-0.08 (0.31 ; 0.16)	0.9222	0.9268
Omega3	0.08 (-0.11 ; 0.26)	-0.06 (-0.33 to 0.20)	0.9095	0.9268
Multid.	0.04 (-0.13 ; 0.20)	-0.10 (-0.35 to 0.14)	0.9268	0.9268

Positive effect of MI+omega-3 and MI alone in ITT, per-protocole and per-protocole adherence analysis

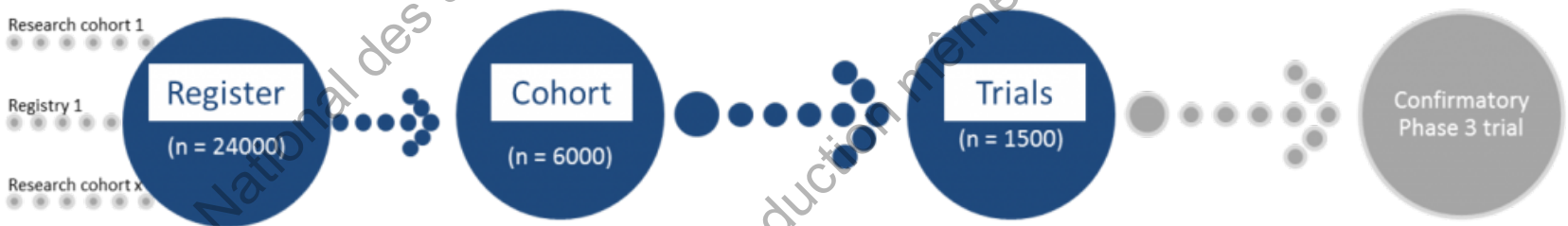
DELRIEU J et al., *Alzheimers Dement. 2019*

INITIATIVE EUROPÉENNE

Innovative Medicines Initiative

EPAD

European Prevention of Alzheimer's Dementia Consortium



Coordination Française : Toulouse GÉRONTOPÔLE

Collaboration Centres Académiques/Partenaires Industriels

efpia
European Federation of Pharmaceutical Industries and Associations

Conclusions

2019 : Une année charnière dans la recherche sur la maladie d'Alzheimer

- Le futur de la recherche :
  - Préciser le temps de l'intervention
  - Affiner les doses et les durées de traitements

- Inscription de la recherche dans le cadre des Gérosciences

The Inspire Bio-resource Research Platform for Healthy Aging & GeroSciences Biological age