Supplementary Material

Immunotherapies Targeting Amyloid and Tau Protein in Alzheimer's Disease: Should We Move Away From Diseases and Focus on Biological Targets? A Systematic Review and Expert Opinion

Arthur Esquer[1,5] · Frédéric Blanc[5,6]· Nicolas Collongues[1,2,3,4]

[1]Center for Clinical Investigation, INSERM U1434, Strasbourg, France.
[2]Department of Neurology, University Hospital of Strasbourg, Strasbourg, France.
[3]Biopathology of Myelin, Neuroprotection and Therapeutic Strategy, INSERM U1119, Strasbourg, France.
[4]Department of Pharmacology, Addictology, Toxicology, and Therapeutics, Strasbourg University, Strasbourg, France.
[5]Centre Mémoire de Ressources et de Recherche (CM2R), Geriatrics day hospital and cognitive-behavioral unit, Geriatrics Department, University Hospital of Strasbourg, Strasbourg, France.
[6]Strasbourg University and CNRS, ICube Laboratory UMR 7357 and FMTS (Fédération de Médecine Translationnelle de Strasbourg), IMIS team, Strasbourg, France.

Corresponding author : Nicolas Collongues - nicolas.collongues@chru-strasbourg.fr

Table S1 All anti-amyloid and anti-tau therapies with results in Phase 2 and Phase 3 trials in AD.

Target	Molecule	Study	Phase	Enrollment	Premature Stop	Arms	Age[1]	Primary endpoint	ARIA-H and/or siderosis N (%)	ARIA-E N (%)	SAE N (%)
Amyloid	Aducanumab	NCT02484547 EMERGE	III	1,643	Yes, Futility	Low dose	70.6 ± 7.4	CDR-SB (cognitive)	87 (16)	140 (26)	72 (13)
						High dose	70.6 ± 7.5		108 (20)	188 (35)	73 (13)
						PBO	*70.8 ± 7.4*		*37 (7)*	*13 (2)*	*81 (15)*
		NCT02477800 ENGAGE	III	1,653	Yes, Futility	Low dose	70.4 ± 7.0	CDR-SB (cognitive)	89 (16)	141 (26)	76 (14)
						High dose	70.0 ± 7.7		104 (19)	199 (36)	79 (14)
						PBO	*69.8 ± 7.7*		*34 (6)*	*16 (3)*	*70 (13)*
		NCT03639987 EVOLVE	II	52	Yes, lack of efficacy in other protocols	Surveillance 1	72.5 ± 7.17	Clinically impactful ARIA (safety)	2 (7.69)	NA	2 (7.69)
						Surveillance 2	73.3 ± 7.1		0 (0)	NA	0 (0)
	Bapineuzumab	NCT00996918 3002 (3000's extension)	III	198	Yes, lack of efficacy in other protocols	PBO + BAP 0.5	68.7	SAE (safety)	0 (0)	3 (7.7)	6 (15.4)
						PBO + BAP 1.0	68.9		0 (0)	6 (16.2)	1 (2.7)
						BAP 0.5 + BAP 0.5	71.4		1 (1.5)	2 (3.0)	10 (15.2)
						BAP 1.0 + BAP 1.0	70.6		3 (5.4)	3 (5.4)	11 (19.6)
		NCT00676143 3001 (APOE4 carriers)	III	1,100	Yes, lack of efficacy in other protocols	BAP 0.5	70.9	ADAS-Cog 11 (Cognitive)	11 (1.68)	109 (16.67)	137 (20.95)
						PBO	*70.2*		*7 (1.6)*	*9 (2.05)*	*77 (17.54)*
		NCT00998764 3003 (3001's extension)	III	494	Yes, lack of efficacy	BAP 0.5 + BAP 0.5	72.1	SAE (safety)	10 (3.6)	15 (5.5)	33 (12.0)
						PBO + BAP 0.5	71.4		23 (10.7)	20 (9.3)	35 (16.3)

					in other protocols						
		NCT00667810 3000 (APOE4 non-carriers)	III	901	Yes, lack of efficacy in other protocols	BAP 0.5	71.1	ADAS-Cog 11 (Cognitive)	2 (0.75)	13 (4.87)	32 (11.99)
						BAP 1.0	70.7		1 (0.38)	31 (11.79)	34 (12.93)
						PBO	*69.7*		*7 (2.03)*	*2 (0.58)*	*53 (15.41)*
		NCT00575055 301 (carriers)	III	1,121	No	BAP 0.5	72.0 ± 8.0	Cognitive and functional	NA	103 (15.3)	176 (26.2)
						PBO	*72.3 ± 8.4*		NA	*1 (0.2)*	*89 (19.9)*
		NCT00574132 302 (non-carriers)	III	1,331	No	BAP 0.5	73.1 ± 9.3	Cognitive and functional	NA	14 (4.2)	72 (21.4)
						BAP 1.0	73.5 ± 9.1		NA	31 (9.4)	76 (23.1)
						PBO	*71.9 ± 10.1*		NA	*1 (0.2)*	*108 (20.6)*
		NCT00606476 AAB-001-251 (102 (phase I) and 201 OLE)	II	194	Yes, lack of efficacy in other protocols	Study 102 + BAPI	70.4 ± 10.15	Safety and tolerability	2 (6)	5 (14)	13 (36)
						BAPI + BAPI	68.5 ± 9.19		1 (1)	6 (8)	35 (44)
						PBO + BAPI	67.8 ± 8.62		2 (3)	11 (14)	25 (32)
		NCT01254773 SUMMIT AD	II	146	No	20 mg/month	70.5 ± 8.68	Brain amyloid signal as SUVR using PET	0	1 (2.7)	4 (10.8)
						7 mg/month	74.1 ± 9.26		4 (11.1)	0	5 (13.9)
						2 mg/month	73.5 ± 8.34		0	1 (2.7)	6 (16.2)
						PBO	73.3 ± 8.79		0	0	3 (8.3)
		NCT00916617 (ext of 3026)	II	62	Yes, lack of efficacy in other protocols	BAPI 5 + 5	72.2 ± 8.92	Clinically significant MRI findings	0 (0)	3 (13.04)	4 (17.39)
						BAPI 10 + 10	74.0 ± 9.34		0 (0)	0 (0)	5 (23.82)
						PBO + BAPI 5	80.4 ± 5.54		1 (10)	2 (20)	7 (70)
						PBO + BAPI 10	70.3 ± 10.13		0 (0)	1 (14.29)	2 (28.57)
		NCT00112073 AAB-001-201	II	234	No	Bapineuzumab	70.1 ± 9.0	Safety assessments	NA	12 (9.7)	37 (30)

						PBO	67.9 ± 8.8		NA	0 (0)	22(20)
		NCT00663026	II	79	No	BAPI 5 mg	71.28 ± 8.73	AE, SAE (safety)	NA	2 (6.9)	2 (6.90)
						BAPI 10 mg	72.42 ± 8.83		NA	6 (19.35)	3 (9.68)
						PBO	*76.16 ± 8.6*		NA	*0 (0)*	*1 (5.26)*
	Crenezumab	NCT02670083 BN29552/CREAD	III	813	Yes, for futility	Crenezumab	71.0 ±7.9	CDR-SB (cognitive)	39 (9.8)	1 (0.3)	67 (16.6)
						PBO	*70. 3 ± 8.4*		*31 (7.8)*	*1 (0.3)*	*63 (15.6)*
		NCT03114657 BN29553/CREAD 2	III	806	Yes, for futility	Crenezumab	71.1 ± 7.5	CDR-SB (cognitive)	20 (5.0)	1 (0.3)	33 (8.3)
						PBO	*70.7 ± 7.9*		*23 (5.9)*	*0*	*42 (10.6)*
		NCT03491150 BN40031/CREAD OLE (extension of CREAD and CREAD2)	III	149	Yes, lack of efficacy in other protocols	Crene + Crene	72.0 ± 7.6	SAE (safety)	NA	NA	4 (5.48)
						PBO + Crene	73.8 ± 7.6		NA	NA	3 (3.95)
		NCT01723826 GN28525/OLE of ABBY and BLAZE	II	360	No	PBO + SC then IV	70.9 ± 7.4	AE (safety)	3 (6.38)	NA	9 (19.15)
						PBO + IV	71.9 ± 7.4		4 (6.35)	NA	14 (22.22)
						CREN SC + SC then IV	72.3 ± 7.2		3 (2.97)	NA	22 (21.78)
						IV + IV	72.2 ± 6.7		6 (4.03)	NA	35 (23.49)
		NCT01343966 ABE4869g/ABBY	II	448	No	300 mg SC Q2W	71.2 ± 6.3	ADAS-Cog (cognitive)	17 (13.9)	0	16 (13.1)
						SC PBO	*70.3 ± 7.2*		*11 (17.7)*	*0*	*6 (9.7)*
						15 mg/kg IV	70.9 ± 6.9		16 (9.7)	1 (0.6)	32 (19.4)
						IV PBO	*69.9 ± 7.1*		*11 (13.4)*	*0*	*11 (13.4)*
		NCT01397578 ABE4955g/BLAZE	II	91	No	300 mg SC Q2W	66.7 ± 9.5	Change in brain amyloid load (PET)	4 (15.4)	0	3 (11.5)
						SC PBO	*68.9 ± 8.3*		*0*	*0*	*1 (7.7)*

						15 mg/kg IV	71.4 ± 7.1		5 (13.9)	0	6 (16.7)
						IV PBO	*69.8 ± 7.7*		*2 (12.6)*	*0*	*3 (18.8)*
	Donanemab	NCT03367403 TRAILBLAZER-ALZ	II	272	No	Donanemab	75.0 ± 5.6	iADRS (cognitive + instrumental)	29 (22.1)	35 (26.7)	23 (17.6)
						PBO	75.5 ± 5.5		8 (6.4)	1 (0.8)	22 (17.6)
	Gantenerumab	NCT02051608 WN28745 + OLE	III	389	No	Gantenerumab	69.7 ± 8.9	AE, SAE (safety)	38 (19.79)	44 (22.92)	61 (31.77)
						PBO	*70.1 ± 8.6*		*30 (15.38)*	*34 (17.44)*	*53 (27.18)*
						Gantenerumab + Gantenerumab	71.43 (8.69)		25 (23.15)	31 (28.71)	41 (37.96)
						PBO + Gantenerumab	71.01 (9.31)		21 (17.95)	29 (24.79)	29 (24.79
		NCT01224106 Scarlet Road	III	799	Yes, for futility	105 mg	70.3 ± 70	CDR-SB (cognitive)	62 (22.9)	18 (6.6)	48 (17.7)
						225 mg	71.3 ± 7.1		42 (16.2)	35 (13.5)	46 (17.7)
						PBO	69.5 ± 7.5		35 (13.2)	2 (0.8)	55 (20.7)
		NCT01760005 DIAN-TU Master Protocol	Pivotal II/III	490	No	Gantenerumab	46.0 ± 10.8	DIAN-Multivariate Cognitive Endpoint (DIAN-MCE) (cognitive)	22 (33)	10 (19)	NA
						Solanezumab	42.5 ± 9.5		6 (12)	0 (0)	NA
						Shared Placebo	*44.2 ± 9.6*		*5 (13)*	*1 (3)*	*NA*
	Solanezumab	NCT00905372 EXPEDITION	III	1,000	No	Solanezumab	75.0 ± 7.9	ADAS-Cog11 (cognitive)	50 (4.9)	9(0.9)	261 (25.4)
						PBO	*74.4 ± 8.0*		*57 (5.6)*	*4 (0.4)*	*263 (25.6)*
		NCT01127633 EXPEDITION EXT (Extension of EXPEDITION AND EXPEDITION 2)	III	1,457	Yes, lack of efficacy in other protocols	Solanezumab	72.96 ± 7.766	AE, SAE (safety)	0 (0)	0 (0)	299 (40.74)
						PBO	73.10 ± 8.004		1 (0.14)	1 (0.14)	308 (42.60)
		NCT00904683 EXPEDITION 2	III	1,040	No	Solanezumab	72.5 ± 8.0		Not distinguished	Not distinguished from EXPEDITION	Not distinguished

								ADAS-Cog14 (cognitive)	from EXPEDITION		from EXPEDITION
						PBO	*72.4 ± 7.8*		Not distinguished from EXPEDITION	Not distinguished from EXPEDITION	Not distinguished from EXPEDITION
		NCT01900665 EXPEDITION III	III	2,129	No	Solanezumab	72.7 ± 7.8	ADAS-Cog14 (cognitive)	37 (3.5)	NA	175 (16.6)
						PBO	73.3 ± 8.0		30 (2.8)	NA	202 (18.9)
		NCT02760602 EXPEDITION PRO	III	26	Yes, terminated due to lack of evidence	Solanezumab	73.46 ± 6.01	ADAS-Cog14 (cognitive)	NA	NA	2 (15.38)
						PBO	75.62 ± 4.93		NA	NA	1 (7.69)
		NCT00329082	II	25	No	100 mg Q4W	71.2 ± 9.2	Safety and tolerability	NA	0	8 (32)
						400 mg Q4W					
						100 mg QW					
						400 mg QW					
						PBO					
Amyloid	Lecanemab	NCT03887455 CLARITY-AD	III	1,906	No	Lecanemab	71.4 ± 7.9	CDR-SB (cognitive)	155 (17.3)	113 (12.6)	126 (14.0)
						PBO	71.0 ± 7.8		81 (9.0)	15 (1.7)	101 (11.3)
		NCT01767311 BAN2401-G000-201	II	856	No	10 mg/kg Q2W	73 (51-88)	ADCOMS (cognitive)	11 (6.8)	16 (9.9)	25 (15.5)
						10 mg/kg Q1M	71 (53-90)		28 (11.1)	25 (9.9)	31 (12.3)
						5 mg/kg Q2W	72 (52-87)		17 (18.5)	3 (3.3)	16 (17.4)
						5 mg/kg Q1M	71 (55-84)		7 (13.7)	1 (2.0)	4 (7.8)
						2.5 mg/kg Q2W	71 (50-86)		2 (3.8)	1 (1.9)	10 (19.2)
						PBO	71 (50-89)		13 (5.3)	2 (0.8)	43 (17.6)
	Ponezumab	NCT00722046	II	198	No	Part A : 1.0 mg/kg	72.2 ± 8.4	AE, SAE (safety)	1 (4.00)	0	7 (28.00)
						Part A : 0.5 mg/kg	71.9 ± 9.4		6 (24.00)	1 (4.00)	8 (32.00)

						Part A : 0.1 mg/kg	70.8 ± 8.2		4 (16.00)	0	7 (28.00)
						Part A : PBO	70.0 ± 7.8		6 (25.00)	0	3 (12.50)
						Part B : 8.5 mg/kg	71.8 ± 7.3		7 (22,58)	0	10 (32.26)
						Part B : 3.0 mg/kg	70.5 ± 8.9		3 (9.39)	0	7 (21.88)
						Part B : PBO	70.4 ± 10.3		5 (15.63)	0	3 (9.38)
Tau	Gosuranemab	NCT03352557 TANGO	II	654	Yes, lack of efficacy following the placebo-controlled period readout	PC 2000 mg Q4W	69.4 ± 7.11	AE, SAE (safety)	NA	NA	25 (11.68)
						PC 600 mg Q4W	69.7 ± 6.66		NA	NA	13 (12.26)
						PC 375 mg Q12W	70.3 ± 6.79		NA	NA	6 (10.34)
						PC 125 mg Q4W	70.4 ± 6.80		NA	NA	6 (10.34)
						PC PBO	69.8 ± 6.63		NA	NA	26 (12.15)
						LTE 2000 mg Q4W	69.4 ± 7.11		NA	NA	10 (5.95)
						LTE 600 mg Q4W	69.7 ± 6.66		NA	NA	9 (10.11)
						LTE 375 Q12W	70.3 ± 6.79		NA	NA	1 (2.04)
						LTE 125 mg Q4W	70.4 ± 6.80		NA	NA	5 (11.11)
						LTE PBO + 2000 mg Q4W	69.8 ± 6.63		NA	NA	13 (7.88)
	Tilavonemab	NCT02880956 M15-566	II	453	No	2000 mg Q4W	29 (25.7%) < 65 years 84 (74.3%) ≥ 65 years	CDR-SB (cognitive)	3 (2.65)	NA	17 (15.04)
						1000 mg Q4W	17 (14.7%) < 65 years		6 (5.17)	NA	22 (18.97)

							99 (85.3%) ≥ 65 years				
						300 mg Q4W	24 (22.22%) < 65 years 84 (77.8%) ≥ 65 years		2 (1.85)	NA	19 (17.59)
						PBO	15 (12.9%) < 65 years 101 (87.1%) ≥ 65 years		4 (3.45)	NA	26 (22.41)
		NCT03712787 Extension of M15-566	II	364	Yes, lack of efficacy in other protocols	2000 mg + 2000 mg	14 (15.9%) < 65 years 74 (84.1%) ≥ 65 years	AE, SAE (safety)	NA	NA	12 (13.64)
						1000 mg + 1000 mg	11 (11.3%) < 65 years 86 (88.7%) ≥ 65 years		NA	NA	11 (11.34)
						300 mg + 1000 mg	8 (9.2 %) < 65 years 79 (90.8%) ≥ 65 years		NA	NA	16 (18.39)

						PBO + 2000 mg	10 (11%) < 65 years 81 (89%) ≥ 65 years		NA	NA	10 (10.99)
	Semorinemab	NCT03289143 Tauriel	II	457	No	8100 mg	§9.4 ± 6.8	CDR-SB (cognitive)	8 (6.9)	0	16 (17.8)
						4500 mg	69.0 ± 7.1		8 (6.1)	1 (0.8)	17 (12.9)
						1500 mg	70.3 ± 6.8		5 (5.6)	0	17 (19.1)
						PBO	69.8 ± 7.3		10 (7.7)	1 (0.8)	14 (10.8)
		NCT03828747 PC + OLE	II	272	No	Semorinemab	71.6 ± 8.2	ADAS-Cog11 (cognitive)	NA	NA	22 (16.30)
						PBO	73.1 ± 8.0)				22 (16.67)
						Semorinemab (OLE)	72.3 ± 8.1				14 (7.22)
	Zagotenemab	NCT03518073	II	360	No	5600 mg	75.70 ± 5.49	ADCS-iADL (instrumental)	NA	NA	19 (16.38)
						1400 mg	75.10 ± 5.33				22 (17.46)
						PBO	75.30 ± 5.22				14 (11.86)

PBO placebo; [1]mean (standard deviation); *No peer-reviewed results available; only those communicated by the company are shown here; *D/P* drug/placebo % ratio;"/" in D/P drug/placebo % ratio is on placebo lines; where the formula would be placebo/placebo; *ARIA-H* Amyloid related imaging abnormalities-Hemorrhage; *ARIA-E* Amyloid related imaging abnormalities-Edema; *AE* adverse effect; *SAE* Severe adverse effect; *TEAE* Treatment emergent adverse effect; *CDR-SB* Clinical dementia rating-sum of boxes; *ADAS-Cog 11/14* Azheimer's Disease Assessment Scale Alzheimer's-cognitive subscale 11/14 items version; *DAD* Disability Assessment for Dementia; *iADRS* Integrated Alzheimer's Disease Rating Scale; *NA* Not available; *DIAN MCE* Dominantly Inherited Alzheimer Network-Multivariate Cognitive Endpoint; *ADCL-ADL* Alzheimer's Disease Cooperative Study - Activities of Daily Living; *C-SSRS* Columbia-Suicide Severity Rating Scale; *MRI* Magnetic resonance imaging; *SUVR* Standardized uptake value ratio; *PET* positron emission tomography; *ADCOMS* Alzheimer's disease composite score.