Cerebrospinal Fluid Biomarker Concordance with Amyloid PET in EMERGE and ENGAGE, Phase 3 Studies of Aducanumab in Patients with Early Alzheimer's Disease

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Disclosures

- LN, RM, TC, RR, GD, JB, PH, KH, and SBH are employees of Biogen and may be stockholders
- MV is an employee of Fujirebio Europe N.V.
- RD holds Lilly stock and Acumen stock options as a result of former employment and consultation services, respectively; he has also consulted for ADDF, Alexion Pharmaceuticals, Avid Radiopharmaceuticals, B2S Life Sciences, Biogen, C2N, Denali, Diadem, Ramon Health, TauC3 Biologics, and Weston Foundation

Statement on aducanumab

- Aducanumab is an investigational drug whose efficacy and safety have not yet been established. It is not approved for use in any country.
- Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and commercialization.
- As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally.

Forward-looking statements

- This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to additional results from the Phase 3 clinical studies of aducanumab; the potential clinical effects of aducanumab; the potential benefits, safety, and efficacy of aducanumab; potential regulatory discussions, submissions, and approvals and the timing thereof; clinical development programs, clinical trials, data readouts, and presentations related to aducanumab; the enrollment of any future clinical studies of aducanumab; the treatment of Alzheimer's disease; the potential of Biogen's commercial business and pipeline programs, including aducanumab; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai Co, Ltd; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later-stage or larger-scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

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EMERGE and ENGAGE were randomized, double-blind, placebo-controlled Phase 3 studies of aducanumab

Population	▪ Early Alzheimer's disease (mild cognitive impairment [MCI] due to Alzheimer's disease [AD] + mild AD dementia) ▪ Confirmed amyloid pathology (assessed by positron-emission tomography [PET; florbetapir, flutemetamol, and florbetaben] visual read)
Doses	▪ Two dosing regimens (low- and high-dose aducanumab) and placebo; randomized 1:1:1
Primary and secondary endpoints	▪ Primary: Clinical Dementia Rating–Sum of Boxes (CDR-SB) at 18 months ▪ Secondary: Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale 13-item (ADAS-Cog 13), and Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory mild cognitive impairment version (ADCS-ADL-MCI)
Sub-studies	▪ Amyloid PET ▪ Tau PET ▪ Cerebrospinal fluid (CSF) disease-related biomarkers

In EMERGE, **treatment with high-dose aducanumab resulted in statistically significant reduction in clinical decline** compared with placebo on the pre-specified primary and secondary endpoints; this finding was supported by biomarker results

ENGAGE **did not meet its primary endpoint**; however, participants who received adequate exposure to high-dose aducanumab **had outcomes similar to those** observed in EMERGE

AD; Alzheimer's disease; PET, positron-emission tomography.

Combined FDA and applicant PCNS Drugs Advisory Committee document. US Food and Drug Administration website. Published November 6, 2020. Accessed January 26, 2021; Budd Haeberlein S, et al. (2021). Manuscript submitted for publication; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed November 2019; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed November 2019.

Objectives

- Assess the use of CSF biomarkers ($A\beta_{42}$, $A\beta_{40}$, p-tau^{181} and t-tau) as an alternative to PET imaging for amyloid confirmation by conducting a concordance analysis using data from the EMERGE (NCT02484547) and ENGAGE (NCT02477800) studies
- Provide alternatives to the existing diagnostic tools to enable efficient patient screening for both clinical trials and clinical practice

Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography; p-tau^{181}, phosphorylated tau 181; t-tau, total tau.

Concordance analysis: comparison of CSF biomarkers with amyloid PET at screening

EMERGE and ENGAGE: Patients with early AD who consented to CSF substudy

Amyloid PET visual read

Lumbar puncture CSF collection per protocol

Lumipulse® G1200 automated immunoassay[1] (Fujirebio) at CCLS under GCLP

Concordance analysis between CSF biomarkers and amyloid PET

PET screening of Aβ (florbetapir, flutemetamol, and florbetaben)

CSF biomarkers ($A\beta_{42}$, $A\beta_{40}$, p-tau^{181} and t-tau)

Aβ, amyloid beta; AD; Alzheimer's disease; CCLS, Covance Central Laboratory Services; CSF, cerebrospinal fluid; GCLP, good clinical laboratory practice; PET, positron emission tomography; p-tau^{181}, phosphorylated tau 181; t-tau, total tau.

1. Fujirebio. https://www.fujirebio.com/en-us/products-solutions/lumipulser-g1200. Accessed January 28, 2021.

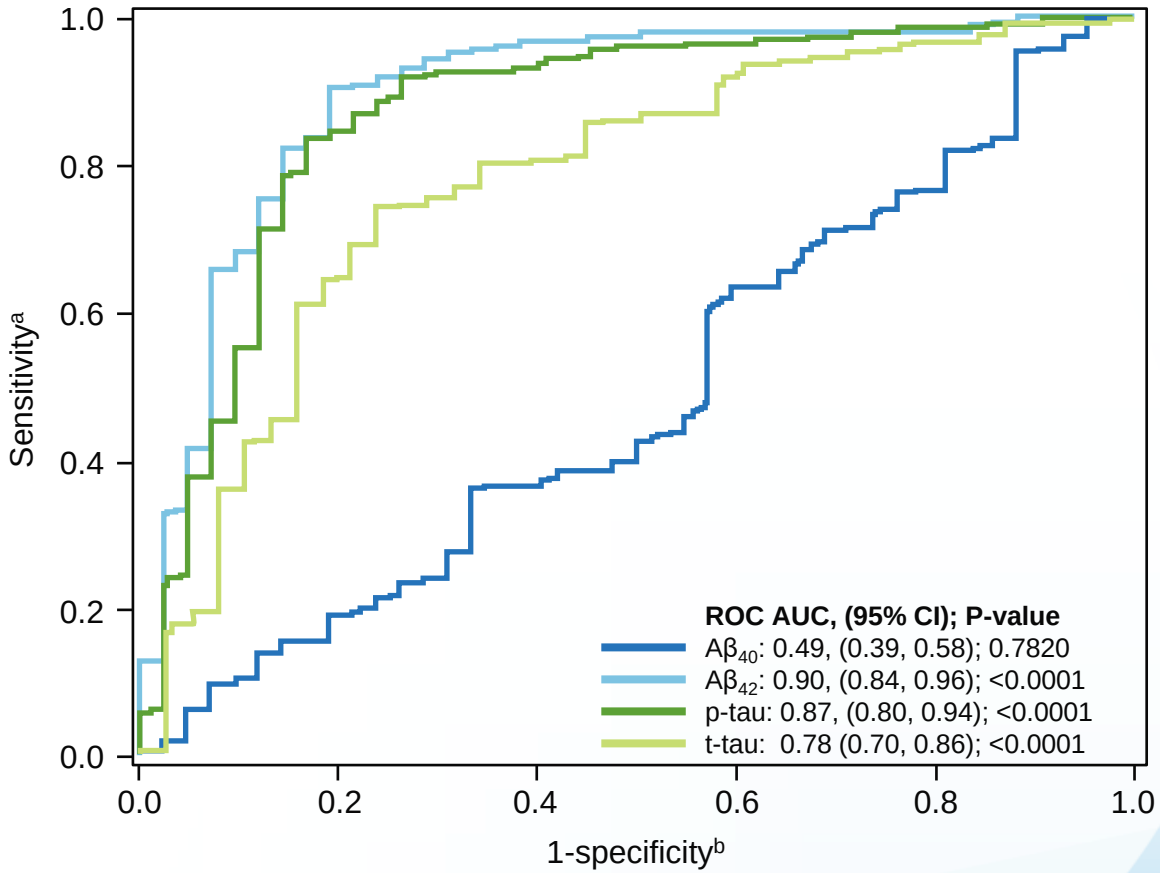
Baseline characteristics of cohort used for concordance analyses

	All patients (N=350)	Amyloid PET positive (N=308)	Amyloid PET negative (N=42)
Age, mean ± SD years	**69.6 ± 7.19**	**69.6 ± 7.25**	**69.4 ± 6.87**
Sex, n (%)			
Female	160 (45.7)	145 (47.1)	15 (35.7)
Male	190 (54.3)	163 (52.9)	27 (64.3)
Apolipoprotein E ε4, n (%)			
Carrier	221 (63.1)	212 (68.8)	9 (21.4)
Non-carrier	129 (36.9)	96 (31.2)	33 (78.6)
Clinical Stage, n (%)			
MCI due to AD	294 (84.0)	259 (84.1)	35 (83.3)
Mild AD	56 (16.0)	49 (15.9)	7 (16.7)

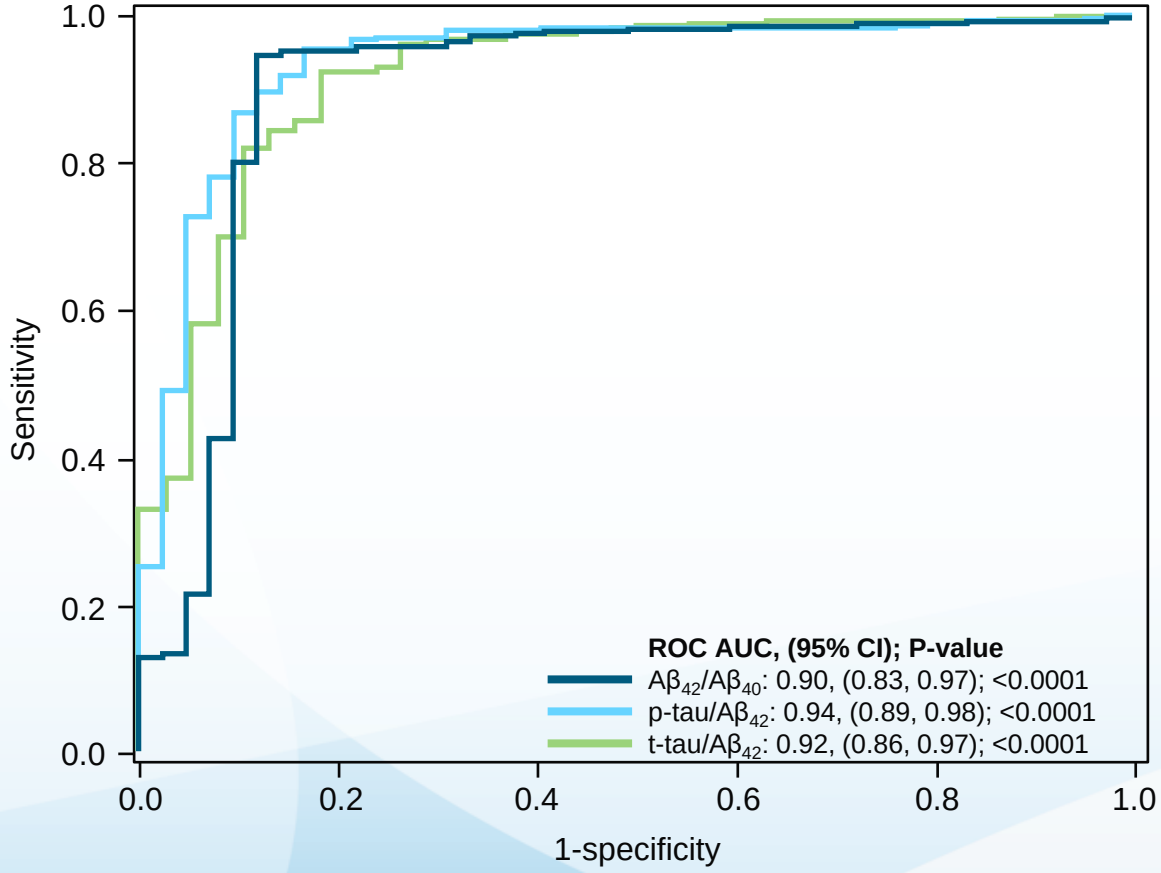
AD, Alzheimer's disease; MCI, mild cognitive impairment; PET, positron emission tomography; SD, standard deviation.

CSF biomarker ratios demonstrate robust concordance with amyloid PET results in EMERGE and ENGAGE

Individual biomarkers

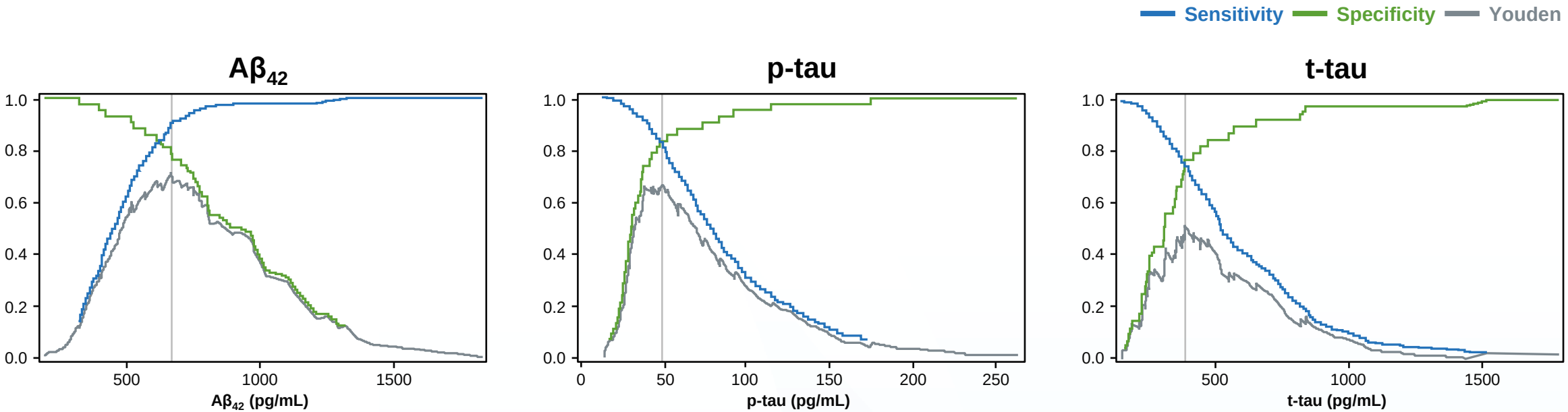


Biomarker ratios



[a] Sensitivity = positive percent agreement (PPA)
[b] Specificity = negative percent agreement (NPA)
Aβ, amyloid beta; AUC, area under the curve; CSF, cerebrospinal fluid; CI, confidence interval; PET, positron emission tomography; p-tau, phosphorylated tau 181; ROC, receiver operator characteristic; t-tau, total tau.

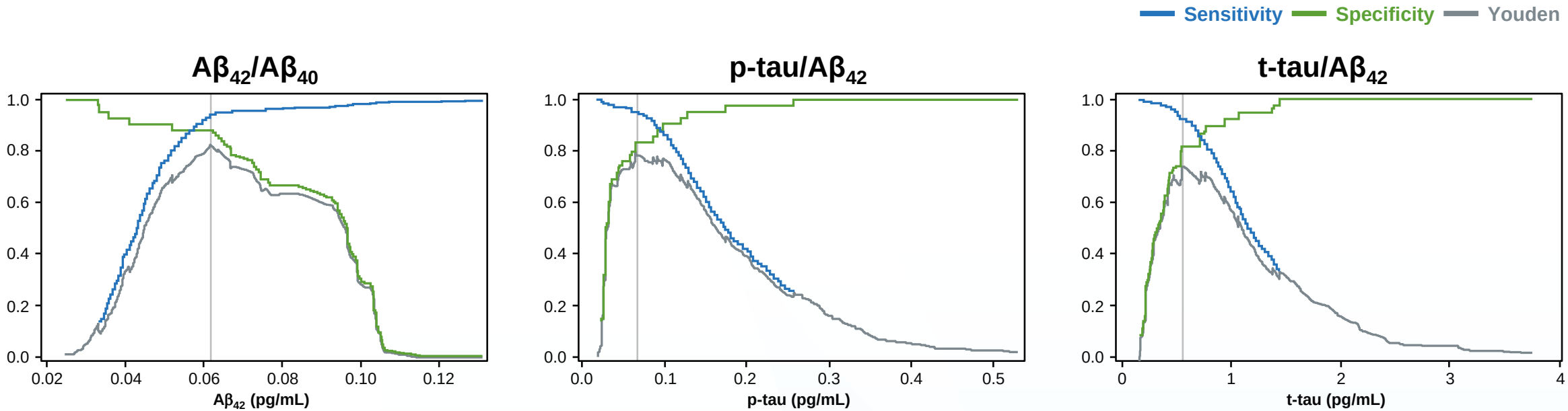
Sensitivity, specificity, and overall percent agreement (OPA) for CSF single biomarkers



Biomarker	Cutoff	Sensitivity[a]	Specificity[b]	OPA	Max. Youden J Index[c]
$A\beta_{42}$	664 pg/mL	90.5%	81.0%	89.4%	71.5%
p-tau	48.7 pg/mL	83.4%	83.3%	83.4%	66.8%
t-tau	390 pg/mL	74.3%	76.3%	74.6%	50.6%

[a] Sensitivity = positive percent agreement (PPA)
[b] Specificity = negative percent agreement (NPA)
[c] Youden J index = Sensitivity + Specificity − 1. Vertical reference indicates the biomarker value for which the maximum Youden J index is reached.
Aβ, amyloid beta; CSF, cerebrospinal fluid; OPA, overall percent agreement; p-tau, phosphorylated tau 181; t-tau, total tau.

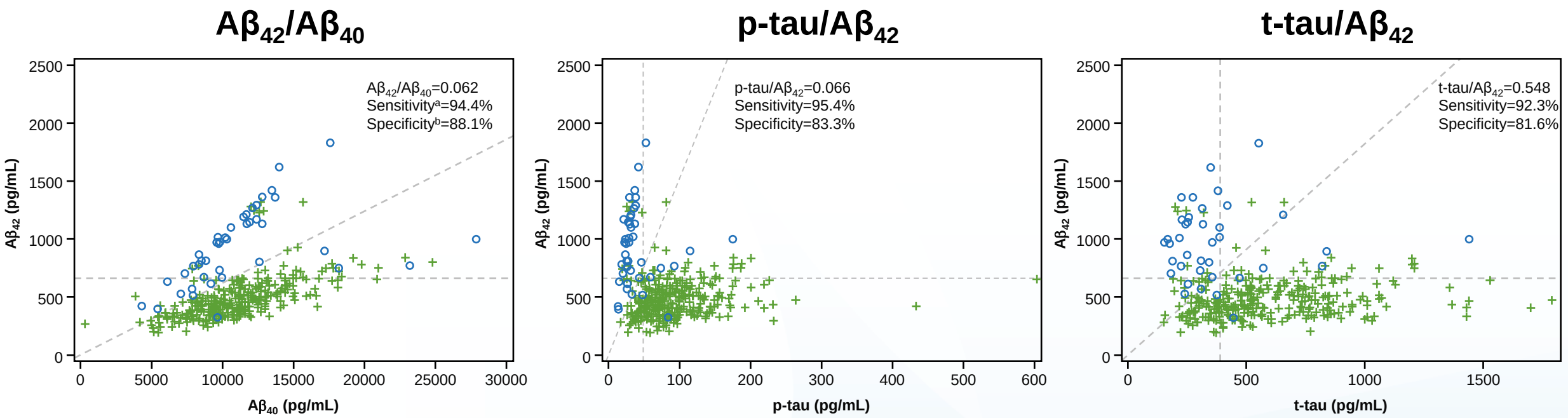
Sensitivity, specificity, and overall percent agreement (OPA) for CSF biomarker ratios



Biomarker Ratios	Cutoff	Sensitivity[a]	Specificity[b]	OPA	Max. Youden J Index[c]
$A\beta_{42}/A\beta_{40}$	0.062	94.4 %	88.1 %	93.7 %	82.5 %
p-tau/$A\beta_{42}$	0.066	95.4 %	83.3 %	94.0 %	78.8 %
t-tau/$A\beta_{42}$	0.548	92.3 %	81.6 %	91.1 %	73.9 %

[a] Sensitivity = positive percent agreement (PPA)
[b] Specificity = negative percent agreement (NPA)
[c] Youden J index = Sensitivity + Specificity − 1. Vertical reference indicates the biomarker value for which the maximum Youden J index is reached.
Aβ, amyloid beta; CSF, cerebrospinal fluid; OPA, overall percent agreement; p-tau, phosphorylated tau 181; t-tau, total tau.

CSF/PET concordance analyses in EMERGE and ENGAGE



Amyloid PET visual status at screening: ○ Negative + Positive

[a] Sensitivity = positive percent agreement (PPA)
[b] Specificity = negative percent agreement (NPA)
Aβ, amyloid beta; CSF, cerebrospinal fluid; OPA, overall percent agreement; PET, positron emission tomography; p-tau, phosphorylated tau 181; t-tau, total tau.

Optimal cutoff value of $A\beta_{42}/A\beta_{40}$ ratio in EMERGE and ENGAGE is similar to other studies using the LUMIPULSE® platform[1]

CSF Biomarker	EMERGE and ENGAGE	Alcolea et al.[2]	Moon et al.[3]
$A\beta_{42}$	≤ 664 pg/mL	≤ 916 pg/mL	≤ 642 pg/mL
p-tau	≥ 48.7 pg/mL	≥ 63 pg/mL	≥ 36.0 pg/mL
t-tau	≥ 390 pg/mL	≥ 456 pg/mL	≥ 337 pg/mL
$A\beta_{42}/A\beta_{40}$	≤ 0.062	≤ 0.062	≤ 0.060
p-tau/$A\beta_{42}$	≥ 0.066	≥ 0.068	≥ 0.051
t-tau/$A\beta_{42}$	≥ 0.548	≥ 0.62	≥ 0.315

Aβ, amyloid beta; CSF, cerebrospinal fluid; p-tau, phosphorylated tau 181; t-tau, total tau.

1. Fujirebio. https://www.fujirebio.com/en-us/products-solutions/lumipulser-g1200. Accessed January 28, 2021; 2. Alcolea D, et al. *Ann Clin Transl Neurol*. 2019;6:1815–1824; 3. Moon S, et al. *Alzheimers Res Ther*. 2021;13:22.

Agreement between CSF biomarker ratios and amyloid PET in EMERGE and ENGAGE is similar to other studies using the LUMIPULSE® platform[1]

CSF Biomarker	EMERGE and ENGAGE			Alcolea et al.[2]			Moon et al.[3]		
	Sensitivity[a]	Specificity[b]	OPA	Sensitivity	Specificity	OPA	Sensitivity	Specificity	OPA
$A\beta_{42}$	91%	81%	89%	95%	51%	79%	80%	88%	--
p-tau	83%	83%	83%	80%	83%	81%	80%	79%	
t-tau	74%	76%	75%	75%	83%	78%	59%	89%	
$A\beta_{42}/A\beta_{40}$	94%	88%	94%	88%	77%	84%	85%	92%	
p-tau/$A\beta_{42}$	95%	83%	94%	93%	80%	88%	85%	93%	
t-tau/$A\beta_{42}$	92%	82%	91%	81%	83%	82%	85%	88%	

[a] Sensitivity = positive percent agreement (PPA)
[b] Specificity = negative percent agreement (NPA)
Aβ, amyloid beta; CSF, cerebrospinal fluid; OPA, overall percent agreement; PET, positron emission tomography; p-tau, phosphorylated tau 181; t-tau, total tau.

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Summary

- In patients from the EMERGE and ENGAGE Phase 3 trials of aducanumab, **robust concordance between CSF biomarkers of amyloid confirmation and amyloid PET** results at screening was demonstrated
- CSF biomarker ratios had higher concordance with amyloid PET than single CSF biomarkers
- For the CSF $A\beta_{42}/A\beta_{40}$ ratio, the observed sensitivity of 94%, specificity of 88%, and OPA of 94% in EMERGE and ENGAGE were comparable to approved PET tracers (sensitivity, 88%-98%; specificity, 80%-95%)[1-3]
- Optimal cutoff values of CSF biomarkers from assessing the screening samples in EMERGE and ENGAGE were similar to other studies using the LUMIPULSE® platform[4]

Aβ, amyloid beta; CSF, cerebrospinal fluid; OPA, overall percent agreement; PET, positron emission tomography.

1. Avid Radiopharmaceuticals. Amyvid (Florbetapir F 18 Injection). U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202008Orig1s000LBL.pdf. Accessed January 28, 2021; 2. GE Healthcare, Inc. Vizamyl (Flutemetamol F 18). U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203137Orig1s000Lbl.pdf. Accessed January 28, 2021; 3. Piramal Imaging SA. Neuraceq (florbetaben F18) Injection. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204677Orig1s000Lbl.pdf. Accessed January 28, 2021; 4. Fujirebio. https://www.fujirebio.com/en-us/products-solutions/lumipulser-g1200. Accessed January 28, 2021.

Acknowledgments

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