Elecsys Phospho-Tau (181P) CSF

cobas®

Materials provided

REF		Σ	SYSTEM
08846715190	08846715500	100	**cobas** e 402 **cobas** e 801

For reagents, refer to the "Reagents" section.

Materials required (but not provided)

REF	Description
07357044190	CalSet Phospho Tau (181P), for 4 × 1.0 mL
07357052190	PreciControl Phospho Tau (181P), for 6 × 1.0 mL
63.614.625	2.5 mL Low bind False bottom tube, Sarstedt (for cerebrospinal fluid (CSF) collection)
	General laboratory equipment
	cobas e analyzer

Additional materials for **cobas** e 402 and **cobas** e 801 analyzers:

REF	Description
06908799190	ProCell II M, 2 × 2-L system solution
04880293190	CleanCell M, 2 × 2-L measuring cell cleaning solution
07485409001	Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
06908853190	PreClean II M, 2 × 2-L wash solution
05694302001	Assay Tip / Assay Cup tray, 6 magazines × 6 magazine stacks × 105 assay tips and 105 assay cups, 3 wasteliners
07485425001	Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution / Elecsys SysClean for Liquid Flow Cleaning Detection Unit
07485433001	PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution / Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
11298500316	ISE Cleaning Solution / Elecsys SysClean, 5 × 100-mL system cleaning solution

Note

The measured phosphorylated Tau (181P) (pTau) value in a given sample, determined with assays from different manufacturers, can vary due to differences in assay methods and reagent. Values determined in samples by different assay methods and on different **cobas** e platforms cannot be used interchangeably.

Please note that due to the sticky properties of the β-Amyloid (1-42) protein, the cutoff for the ratio pTau/Abeta42 (calculated based on results of the Elecsys Phospho-Tau (181P) CSF and the Elecsys β-Amyloid (1-42) CSF II assays) provided in this document is only valid if the required pre-analytical handling procedure (described in the section "Specimen collection and preparation" of the Elecsys β-Amyloid (1-42) CSF II assay Method Sheet) is strictly followed.

All analytical performance data were generated using frozen cerebrospinal fluid (CSF) material. A positive pTau result in CSF does not establish a diagnosis of Alzheimer's disease (AD) and should always be interpreted in conjunction with clinical information.

The cutoffs for the pTau/Abeta42 ratio (calculated based on results of the Elecsys Phospho-Tau (181P) CSF assay and the Elecsys β-Amyloid (1-42) CSF II assay) mentioned in the intended uses 1, 2, and 3 of this document differ from each other. For the intended uses 1 and 2, apply the amyloid cutoff. For intended use 3, apply the tau cutoff. The cutoff values are specified in the "Clinical performance data section" of this document.

System information

Short name	ACN (application code number)
pTau	10128

Intended use

The Elecsys Phospho-Tau (181P) CSF assay is an in vitro diagnostic immunoassay intended for the quantitative determination of the phosphorylated Tau protein in human CSF.

1. The Elecsys Phospho-Tau (181P) CSF assay is intended to be used alone or in combination with Elecsys β-Amyloid (1-42) CSF II assay as a ratio in adult subjects with mild cognitive impairment (MCI) as an aid to identify subjects who are at lower vs. higher risk of cognitive decline as defined by change in a clinical score within a 2 year period.

2. The Elecsys Phospho-Tau (181P) CSF assay is intended to be used in combination with Elecsys β-Amyloid (1-42) CSF II assay as a ratio in adult subjects with cognitive impairment being evaluated for AD and other causes of cognitive impairment wherein a positive and negative CSF result is concordant with positive and negative amyloid Positron Emission Tomography (PET) scan result, respectively.
3. The Elecsys Phospho-Tau (181P) CSF assay is intended to be used in combination with the Elecsys β-Amyloid (1-42) CSF II assay as a ratio in adult subjects with cognitive impairment being evaluated for AD and other causes of cognitive impairment. A negative result, defined as pTau/Abeta42 ratio value below cutoff, is consistent with a negative tau result based on the tau PET scan. A positive result, defined as pTau/Abeta42 ratio value above cutoff, is consistent with a positive tau result based on the tau PET scan.

Limitations of use

- The Elecsys Phospho-Tau (181P) CSF assay is an adjunct to other clinical diagnostic evaluations.
- A positive Elecsys Phospho-Tau (181P) CSF assay result and/or a positive Elecsys Phospho-Tau (181P) CSF to Elecsys β-Amyloid (1-42) CSF II ratio result does not establish a diagnosis of AD or other cognitive disorder.
- The safety and effectiveness of the Elecsys Phospho-Tau (181P) CSF assay have not been established for monitoring responses to therapies.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas** e immunoassay analyzers.

Summary

Tau (tubulin-associated unit) protein is one of the two hallmarks of AD, besides β Amyloid (1-42). Tau is found as 6 molecular isoforms in human brain. These isoforms are coded by a single gene on chromosome 17 and generated by alternative splicing of its pre-mRNA. The Tau from all these isoforms is called total Tau (tTau). The most common post-translational modification of Tau proteins is phosphorylation. Phosphorylation changes the shape of Tau molecule and regulates its biological activity. During neurodegeneration abnormal phosphorylation leads to formation of intracellular neurofibrillary tangles (NFTs) composed of the Tau protein that has undergone hyper-phosphorylation, and developed aggregates of hyper-phosphorylated Tau proteins called Phospho Tau (pTau).[1, 2]

The Elecsys Phospho-Tau (181P) CSF assay is designed to detect the protein or fragments of Tau protein phosphorylated at threonine 181 in human CSF.

Clinical relevance of pTau

In AD, numerous studies show that while CSF β Amyloid (1-42) levels decrease to around half the level in controls, CSF pTau 181 levels increase around 2-3 fold in mild moderate AD patients compared to age-matched controls.[3, 4] High CSF pTau levels are also associated with a faster progression from MCI to AD with more rapid cognitive decline in AD patients[5] and in mild AD dementia cases.[6]
CSF pTau biomarker might be useful in detecting the likely progression of MCI to AD[7] and has most power when used in combination with CSF β-Amyloid (1-42).

The extent and distribution of tau pathology can provide insights into diagnosis, disease severity and stage.[8, 9] Tau PET is an imaging technique that uses a radiotracer to detect and visualize tau protein deposits in the brain. While tau PET has potential for use in patients across the AD patient journey, its use in clinical routine is limited due to cost and accessibility constraints. Additionally, the variability in tau pathology patterns makes it challenging to establish a standardized interpretation of tau PET results.[10] The utilization of fluid biomarkers to identify tau pathology has the potential to address some of the limitations of PET imaging and enhance the diagnostic capabilities in the context of AD. Recent studies also show that the CSF pTau/Abeta42 ratio correlates with both amyloid and tau PET measures, highlighting the versatility of CSF biomarkers in reflecting amyloid and tau pathologies in the brain, increasing their diagnostic value.[11]

The use of biomarkers to diagnose AD was included in the diagnostic criteria established by consensus research for AD, mild cognitive impairment (MCI), and preclinical AD, proposed by the National Institute on Aging (NIA) and the Alzheimer's Association.[12, 13] The use of CSF biomarkers in the Alzheimer's disease diagnostic work-up was accounted for in subsequent revisions[14] and International Working Group (IWG) recommendations.[15]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- First incubation: 30 µL of sample, a biotinylated monoclonal antibody specific for phosphorylation at threonine 181 (11H5V1) and a monoclonal Tau-specific antibody (PC1C6) labeled with a ruthenium complex[a)] react to form a sandwich complex.
- Second incubation: After streptavidin-coated microparticles have been added, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell, where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission, which is measured by a photomultiplier.
- Results are determined via a calibration curve that is instrument-specifically generated by 2-point calibration and a leading calibration curve provided via **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents

The **cobas** e pack is labeled as pTau.

M	Streptavidin-coated microparticles, 1 bottle, 6.1 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

Elecsys Phospho-Tau (181P) CSF

R1 Anti-pTau Ab~biotin, 1 bottle, 6.8 mL:
Biotinylated monoclonal anti-pTau antibody (rabbit/mouse) 2.5 mg/L; Tris[A)] buffer > 14 mmol/L, pH 7.2; preservative.

A) Tris = Tris(hydroxymethyl)aminomethane

R2 Anti-Tau-Ab~Ru(bpy)$_3^{2+}$, 1 bottle, 6.8 mL:
Monoclonal anti-Tau antibody (mouse) labeled with ruthenium complex 2.0 mg/L; Tris buffer > 14 mmol/L, pH 7.2; preservative.

Warnings and precautions

For in vitro diagnostic use for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste

Warning: Handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards

Apply all relevant local disposal regulations to determine safe disposal.

The Safety Data Sheet is available for professional users on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing mist or vapours.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Hazardous components:

- 2-methyl-2H-isothiazol-3-one hydrochloride

Product safety labeling follows EU GHS guidance.

Contact phone for all countries: +49-621-7590

Avoid foam formation in all reagents and sample types (specimens, calibrators, and controls).

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Calibration

Traceability: This method has been standardized against a purified reference material Tau(172-205)[pThr181]amide, absolutely quantified via amino acid analysis (AAA). Calibrator values are based on weighted pTau reference material, traceable to NIST amino acid reference calibrators.

The predefined leading calibration curve is adapted to the analyzer using the relevant calibrators.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e., not more than 24 hours after the reagent kit was registered on the analyzer).

The calibration interval may be extended based on acceptable calibration verification values determined by the laboratory.

Renewed calibration is recommended as follows:

- every 12 weeks when using the same reagent lot
- every 28 days when using the same **cobas** e pack on the analyzer
- as required, such as when quality control findings are outside the defined limits

Quality control

For routine quality control procedures, use PreciControl Phospho-Tau (181P) or other suitable controls.

It is recommended to run the controls for the various concentration ranges individually at least once every 24 hours when the test is in use, once per **cobas** e pack, and following each calibration.

Special care needs to be taken to ensure that the accuracy and precision of the testing stays within acceptable limits. Besides meeting the PreciControl Phospho-Tau (181P) target ranges provided, the user needs to ensure that the systematic bias with respect to the assigned target value is within ± 10 %, the intermediate precision CV is ≤ 10 % and the maximal total error is within ± 26.5 % (TE = |bias| + 1.65 × CV). It is recommended to use quality control rule software.

For those users who are not familiar with the special QC setup and application, detailed information is available in the brochure **"Guidance: Statistical Quality Control Rule Implementation"** in English language, which is available via navifyportal.roche.com. This brochure explains e.g. how to check if the maximal total error is within the allowed range based on the local QC results, besides other useful information.

Adjust the limits and control intervals based on the laboratory's individual requirements. If values fall outside the limits, each laboratory is advised to establish corrective measures.

Follow the applicable government regulations and local guidelines.

If necessary, repeat sample measurement.

Specimen collection and preparation

Only CSF collection and sampling tubes made of Polypropylene (PP) material should be used. Do not use tubes made of glass, Polystyrol (PS) or any other material.

In case the ratio pTau/Abeta42 is intended to be used with the provided cutoff, please follow the pre-analytical handling procedure for CSF sample collection and measurement, described in section "Specimen collection and preparation" of the Elecsys β-Amyloid (1-42) CSF II assay Method Sheet (REF 08821941190), otherwise the provided cutoff for ratio pTau/Abeta42 is not applicable. This restriction is not applicable for pTau as a single marker.

Stability of CSF samples: Stable for 5 days at 20-25 °C, 14 days at 2-8 °C, 8 weeks at -20 °C (± 5 °C).

Freeze only once.

Do not use hemolyzed CSF samples that are visibly colored red.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, analyze and measure samples and calibrators on the analyzers within 2 hours.

Please always keep them capped if not in use.

Test procedure

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via **cobas** link.

For optimum performance of the assay, follow the instructions given in this document for the corresponding analyzer. For analyzer-specific assay instructions, refer to the corresponding User Guide.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas** e pack on the reagent manager.

Avoid foam formation.

The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas** e pack.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in pg/mL.

Limitations and interferences

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations, and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 0.51 µmol/L or ≤ 0.03 mg/dL
Hemoglobin	≤ 0.0031 mmol/L or ≤ 5 mg/dL
Intralipid	≤ 10 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 4 IU/mL
IgG	≤ 0.02 g/dL
IgA	≤ 0.002 g/dL
IgM	≤ 0.0005 g/dL
Albumin	≤ 0.05 g/dL

Criterion: recovery within ± 3 pg/mL of initial value ≤ 25 pg/mL and within ± 10 % of initial value > 25 pg/mL.

There is no high-dose hook effect at pTau concentrations up to 300 pg/mL.

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

Commonly used pharmaceuticals

Pharmaceutical	Concentration tested mg/L
Acetaminophen	156
Acetylcysteine	150
Acetylsalicylic acid	30
Ampicillin-Na	75
Ascorbic acid	52.5
Cefoxitin	750
Cyclosporine	1.8
Doxycycline	18
Heparin	1100 IU/L
Ibuprofen	219
Itraconazole	0.06
Levodopa	7.5
Methyldopa + 1.5	22.5
Metronidazole	123
Phenylbutazone	107
Rifampicin	48
Theophylline	60

Criterion: recovery within ± 3 pg/mL of initial value ≤ 25 pg/mL and within ± 10 % of initial value > 25 pg/mL.

In addition, the following 15 special drugs were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested mg/L
Atorvastatin	0.75
Clopidogrel	0.3
Digoxin	0.039
Donepezil	30
Escitalopram	0.192
Esomeprazole	6.9
Furosemide	15.9
Galantamine	250
Hydrochlorothiazide	1.13
Lisinopril	0.246
Memantine	0.117
Metformin	12
Metoprolol	1.5
Rivastigmine	45
Simvastatin	1.68

Criterion: recovery within ± 3 pg/mL of initial value ≤ 25 pg/mL and within ± 10 % of initial value > 25 pg/mL.

Drug interferences are measured based on recommendations given in the CLSI guidelines EP07 and EP37 and in other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

In rare cases, interference caused by extremely high titers of antibodies to analyte-specific antibodies, streptavidin, or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, always assess the results in conjunction with the patient's medical history, clinical examination, and other findings.

Limits and ranges

Measuring range

8-120 pg/mL (defined by the Limit of Quantitation and the maximum of the master curve). Values below the Limit of Quantitation are reported as < 8 pg/mL. Values above the measuring range are reported as > 120 pg/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection, and Limit of Quantitation

Limit of Blank = 4 pg/mL

Limit of Detection = 8 pg/mL

Limit of Quantitation = 8 pg/mL

The Limit of Blank, the Limit of Detection, and the Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th-percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low-concentration samples. The Limit of Detection corresponds to the lowest analyte concentration that can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Specific performance data

Representative performance data on the analyzers is given below. Results obtained in individual laboratories may differ from the representative performance data.

Analytical specificity

The test is highly specific for human Phospho-Tau (181P). The following potential cross-reactivity was found:

Cross-reactant	Concentration tested pg/mL	Cross-reactivity %
Tau(172-205)amide	1300	0.9

Clinical performance data

Each laboratory is advised to investigate the transferability of the expected values to its own patient population and, if necessary, to determine its own reference ranges.

Note: Clinical performance data were generated using the Elecsys Phospho-Tau (181P) CSF assay (REF 07357036190) V1 that highly correlates with V2 of the Elecsys Phospho-Tau (181P) CSF assay (REF 08846693190). In an internal method comparison study (n = 129) the observed Pearson's correlation coefficient was 0.999.

Identification of patients at risk of cognitive decline

The ability of the single biomarker pTau as well as the biomarker ratio pTau/Abeta42 to identify patients at higher vs. lower risk of cognitive decline as defined by change in a clinical score within a 2-year period was assessed in a retrospective study (Roche study RD002530) based on samples from the ADNI1/GO/2 studies measured with the Elecsys Phospho-Tau (181P) CSF assay (REF 07357036190).[16] The primary analysis population included a total of 619 patients from the early (EMCI, 277) and late mild cognitive impairment (LMCI, 342) cohorts with baseline Elecsys CSF assay measurements available. For each of these patients also baseline assessments of the clinical scores Clinical Dementia Rating – sum of boxes (CDR-SB) and Mini-Mental State Examination (MMSE) were available. The average age of the 619 subjects was 72 years (range 54-91 years), 41 % / 59 % were female/male, the average education time was 16 years (range 6-20 years) and 51 % / 39 % / 11 % carried 0/1/2 ApoE4 alleles. The averages (standard deviation, SD) of clinical scores were as follows: CDR-SB, 1.5 (0.9) at baseline, 2.3 (2.1) at 2-year follow-up; MMSE, 27.7 (1.8) at baseline, 26.6 (3.3) at 2-year follow-up. The median (1.48 × median absolute deviation) of the Elecsys CSF marker concentrations at baseline were as follows: pTau, 24.0 (12.0) pg/mL; Abeta42, 837.7 (410.2) pg/mL. The ability of the biomarkers to separate patients at lower vs. higher risk of cognitive decline (as measured by change in CDR-SB or MMSE) within 2 years was assessed using linear mixed-effects models. The models were adjusted for age, sex, education time and baseline value of the respective clinical score. The cutoff values for pTau and pTau/Abeta42 were defined in study RD002145.

Due to different pre-analytic procedures between BIOFINDER and ADNI, a bridging study RD002475 was used to adjust the cutoffs from Biofinder to ADNI based on optimization for concordance with amyloid PET. Using the indicated cutoffs (see section below), the model-based average change in clinical scores (CDR-SB; MMSE) between baseline and 2 years in the negative group (effect (1)) and the difference in change in clinical scores between biomarker-positive and -negative groups (effect (2)) were as follows:

Clinical score	Biomarker	Effect (1) Estimate (95 % CI[A)])	Effect (2) Estimate (95 % CI)
CDR-SB	pTau	0.48 (0.34, 0.62)	1.00 (0.78, 1.21)
	pTau/Abeta42	0.17 (0.02, 0.32)	1.42 (1.21, 1.62)
MMSE	pTau	-0.43 (-0.69, -0.18)	-1.80 (-2.20, -1.40)
	pTau/Abeta42	-0.08 (-0.36, 0.20)	-2.17 (-2.56, -1.77)

A) CI = confidence interval

Both the single marker pTau and the pTau/Abeta42 ratio separated patients at lower vs. higher risk of cognitive decline within 2 years. The pTau/Abeta42 ratio showed superior performance. For instance, change in CDR-SB and MMSE over 2 years between the biomarker-positive and -negative groups according to pTau/Abeta42 ratio differed by more than 1 and -2.5 units (lower confidence limit of effect (2)), respectively. Biomarker-negative patients did not show a change in CDR-SB and MMSE over 2 years more than 0.5 and -0.5 (upper confidence limit of effect (1)), respectively. These results did not change after additional adjustment for ApoE4 genotype (number of E4 alleles).

Model-based time course plot for change in CDR-SB over 2 years for pTau/Abeta42 ratio-based classification (without adjustment for ApoE4 genotype):

Elecsys Phospho-Tau (181P) CSF

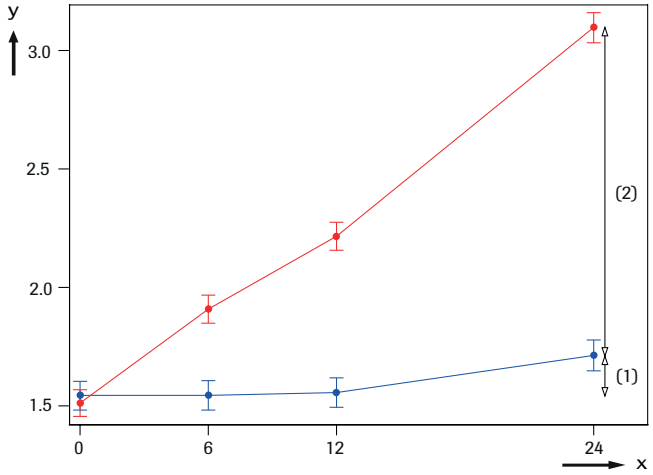

Figure: Model-derived average and standard error of CDR-SB in biomarker-positive (red) and -negative (blue) groups over follow-up time (x-axis; visit time point in months). Effects (1) and (2) as described above are symbolized by arrows.

x: Visit

y: CDR-SB

Concordance with amyloid PET visual read

Concordance with amyloid PET visual read was assessed in a retrospective study (Roche study RD002145) based on samples from the BioFINDER cohort.[17] The primary analysis population consisted of 277 mild cognitive symptoms (MCS) patients for whom CSF measurements and amyloid PET scan results were available (PET tracer: [18F] Flutemetamol). Of the 277 patients, 120 had subjective cognitive decline (SCD), 153 MCI and for 4 patients no assignment was available. The average age was 70 years (range 59-80 years), 42 % / 58 % of patients were female/male and 45 % / 54 % of patients were ApoE4 carriers/non-carriers. The median (1.48 × median absolute deviation) of the Elecsys markers at baseline was as follows: pTau, 20.0 (9.4) pg/mL; Abeta42, 1048 (593) pg/mL. The amyloid PET scans were read independently by 3 trained readers and majority voting was used to rate an image as positive or negative, resulting in 110 (40 %) positive and 167 (60 %) negative amyloid PET reads. The cutoffs for Abeta42 and the ratios pTau/Abeta42 and tTau/Abeta42 were established based on the amyloid PET visual read. The agreement rates for the Elecsys CSF markers with amyloid PET visual read were as follows:

	Agreement rates (%), (95 % CI)
Positive percentage agreement (PPA, “sensitivity”)	90.9 (83.9, 95.6)
Negative percentage agreement (NPA, “specificity”)	89.2 (83.5, 93.5)
Overall percentage agreement	89.9 (85.7, 93.2)

Elecsys Phospho-Tau (181P) CSF

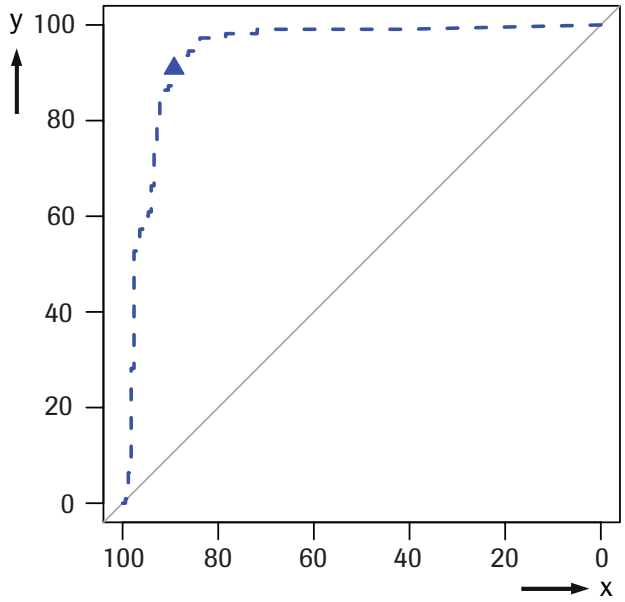

Figure: Receiver-operating characteristic curve of the pTau/Abeta42 ratio with outcome amyloid PET. Triangle denotes PPA and NPA at the cutoff; AUC: 94.4 % (91.5 %, 97.3 %).

x: NPA (specificity) (%)

y: PPA (sensitivity) (%)

Concordance with tau PET visual read

The concordance of the Elecsys CSF pTau/Abeta42 ratio with tau PET visual read as a reference method was assessed in a retrospective analysis using 2 independent cohorts.[18]

Cutoff determination was performed in a subset of 133 subjects from the ADNI-2/3[16] cohort, in subjects who had a clinical diagnosis of mild cognitive impairment (MCI) (n = 104; 78.2 %) or dementia due to AD (n = 29; 21.8 %), available Elecsys Phospho-Tau (181P) CSF assay and Elecsys β-Amyloid (1-42) CSF II assay measurements, and available tau PET scans. Tau PET scans were performed with [18F]-flortaucipir (FTP; TauvidTM, Eli Lilly, Utrecht, the Netherlands) and interpreted using the FTP visual-read methodology (tau-positive if visual read = AD+ or AD++, and tau-negative if visual read = AD–). In this cohort, 52 subjects (39.1 %) were tau-PET-positive and 81 (60.9 %) were tau-PET-negative. The average age was 70.9 years (range: 55.3-89.2 years), 56 patients (42.9 %) were female and 76 patients (57.1 %) were male; 63 (47.4 %) were APOE4 carriers and 56 (42.1 %) were non-carriers. APOE4 status was missing for 14 patients (10.5 %). For better comparability, CSF biomarker measurements of ADNI-2/3 were adjusted for the fresh routine-use pre-analytical procedure (described in the “Specimen collection and preparation” section) and the updated version II of the Abeta42 assay using results of the pre-analytical bridging study RD002842 published in Blennow et al., 2022.[19] The median values (1.48 × the median absolute deviation) of the Elecsys markers were as follows: Elecsys Phospho-Tau (181P) assay: 24.9 (11.2) pg/mL; Elecsys β-Amyloid (1-42) CSF II assay: 802.0 (453) pg/mL. A cutoff of 0.037 was selected as the best compromise between PPA and NPA. In the ADNI-2/3 cohort, this cutoff had PPA 88.5 % (77.0, 94.6), NPA 82.7 % (73.1, 89.4), and OPA 85.0 % (77.9, 90.0) (table 3 in Smith et al., 2025).

The cutoff was validated in an independent subset of 62 subjects from the Swedish BioFINDER-2 study (NCT03174938) assigned to either cohort C (SCD and MCI) or cohort D (AD dementia). The detailed inclusion and exclusion criteria for BioFINDER-2 are publicly available.[20] The analysis population consisted of subjects with MCI (n = 36; 58.1 %) and dementia due to AD (n = 26; 41.9 %), for whom Elecsys Phospho-Tau (181P) CSF assay and Elecsys β-Amyloid (1-42) CSF II assay measurements and tau PET scans were available (PET tracer: [18F]-RO948). The FTP visual read methodology was used for both tracers because [18F]-RO948 is structurally similar to FTP. [21, 22, 23] The tau PET status of the study subjects was derived based on the FTP visual read methodology performed by a single reader, resulting in 35 positive (56.5 %) and 27 negative (43.5 %) tau PET visual reads. The average age was 75.1 years (range: 54.5-87.4 years), 29 patients (46.8 %) were female and 33 patients (53.2 %) were male; 33 (53.2 %) were APOE4 carriers and 29 (46.8 %) were non-carriers. The median values (1.48 × the median absolute deviation) of the Elecsys markers were as follows: Elecsys Phospho-Tau (181P) CSF assay: 26.4 (13.9) pg/mL; Elecsys β-Amyloid (1-42) CSF II assay: 733.0 (307) pg/mL.

The agreement rates for the ratio of the Elecsys Phospho-Tau (181P) CSF assay to the Elecsys β-Amyloid (1-42) CSF II assay with tau PET visual read were as follows:

Elecsys Phospho-Tau (181P) CSF

	Agreement rates (%), (95 % CI)
Positive percentage agreement (PPA, “sensitivity”)	85.7 (70.6, 93.7)
Negative percentage agreement (NPA, “specificity”)	70.4 (51.5, 84.1)
Overall percentage agreement	79.0 (67.4, 87.3)

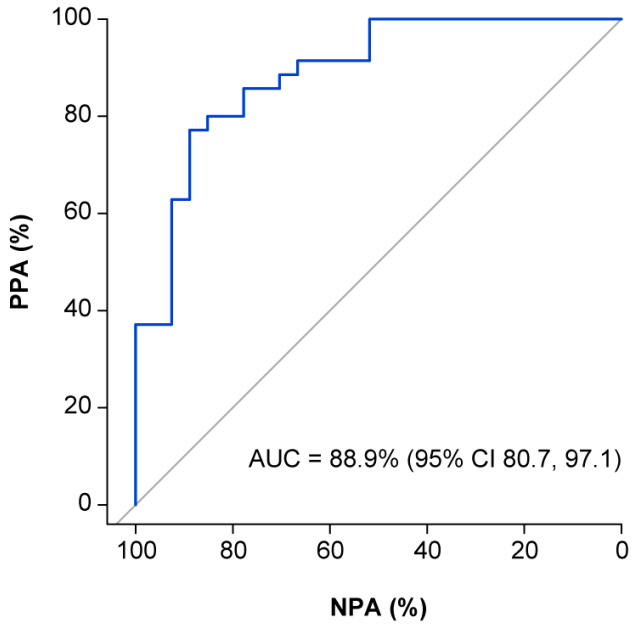

Figure: receiver operating characteristic (ROC) analysis using the tau PET visual read endpoint in the BioFINDER-2 cohort. AUC = area under the ROC curve, CI = confidence interval, NPA = negative percent agreement, PET = positron emission tomography, PPA = positive percent agreement

Cutoffs for PET concordance and cognitive decline

The influence of pre-analytical handling and assay versions on the measured pTau and Abeta42 levels was investigated in the study RD002842. The pTau values were not affected by the pre-analytical procedure and assay version. For Abeta42, systematic differences between the pre-analytical procedures and assay versions were observed.

The cutoff values for Abeta42 as single biomarker and for pTau/Abeta42 were adjusted according to the observed differences (please see below and Method Sheet of Elecsys β-Amyloid (1-42) CSF II assay REF 08821941190). Please note, that the provided cutoff value for the pTau/Abeta42 ratio is only valid if the pre-analytical handling procedure described in the section “Specimen collection and preparation” of the Elecsys β-Amyloid (1-42) CSF II assay Method Sheet (REF 08821941190) is used.

The cutoffs for cognitive decline are shown below:

If pTau > 27 pg/mL: test result positive If pTau ≤ 27 pg/mL: test result negative
If pTau/Abeta42 ratio* > 0.023: test result positive If pTau/Abeta42 ratio* ≤ 0.023: test result negative *The ratio should be rounded to 4 decimal places before comparing against 0.023. If the concentration of one of the analytes is outside the measuring range, the following rules apply: In cases Abeta42 < 150 pg/mL, Abeta42 > 2500 pg/mL, pTau > 120 pg/mL, pTau < 8 pg/m, the value should be set to the respective limit of the measuring range and the ratio should be calculated.

The cutoff for amyloid PET concordance is shown below:

If pTau/Abeta42 ratio* > 0.023: test result positive If pTau/Abeta42 ratio* ≤ 0.023: test result negative

*The ratio should be rounded to 4 decimal places before comparing against 0.023. If the concentration of one of the analytes is outside the measuring range, the following rules apply:
In cases Abeta42 < 150 pg/mL, Abeta42 > 2500 pg/mL, pTau > 120 pg/mL, pTau < 8 pg/m, the value should be set to the respective limit of the measuring range and the ratio should be calculated.

The new derived cutoff for tau PET concordance is shown below:

If pTau/Abeta42 ratio* > 0.037: test result positive

If pTau/Abeta42 ratio* ≤ 0.037: test result negative

*Round the ratio to 4 decimal places before comparing against 0.037. If the concentration of 1 of the analytes is outside the measuring range, the following rules apply:
If Abeta42 < 150 pg/mL, Abeta42 > 2500 pg/mL, pTau > 120 pg/mL, pTau < 8 pg/mL, set the value to the corresponding limit of the measuring range and calculate the ratio.

Precision

Precision was determined using Elecsys reagents, samples, and controls based on a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day, in duplicate each, for 21 days (n = 84). The following results were obtained:

cobas e 402 and cobas e 801 analyzers					
		Repeatability		Intermediate precision	
Sample	**Mean pg/mL**	**SD pg/mL**	**CV %**	**SD pg/mL**	**CV %**
Human CSF 1	15.5	0.161	1.0	0.238	1.5
Human CSF 2	20.8	0.268	1.3	0.441	2.1
Human CSF 3	26.1	0.269	1.0	0.343	1.3
Human CSF 4	30.3	0.314	1.0	0.428	1.4
Human CSF 5	56.0	0.734	1.3	1.02	1.8
Human CSF 6	111	1.45	1.3	2.86	2.6
PreciControl pTau 1	13.8	0.202	1.5	0.238	1.7
PreciControl pTau 2	47.4	0.524	1.1	0.717	1.5

Method comparison

A comparison of the Elecsys Phospho-Tau (181P) assay, REF 08846715190 (**cobas** e 402 analyzer; y), with the Elecsys Phospho-Tau (181P) assay, REF 08846715190 (**cobas** e 801 analyzer; x), gave the following correlations (pg/mL):

Number of samples measured: 127

Passing/Bablok[24]	Linear regression
y = 1.04x – 0.119	y = 1.04x – 0.172
τ = 0.976	r = 1.00

The sample concentrations were between 8.34 and 117 pg/mL.

Additional information

For further information, refer to the appropriate User Guide for the corresponding analyzer, to the corresponding application sheets, and to the Method Sheets of all necessary components.

Additions, deletions, or changes are indicated by a change bar in the margin.

A point (period/stop) is always used in the English version of a Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. The translated Method Sheets use decimal commas. Labels only use the decimal point as separator. Separators for thousands are not used.

Report any serious incident that has occurred in relation to the device to the manufacturer and the competent authority of the member state in which the user and/or patient is established.

Symbols

In addition to the ISO 15223-1 standard, Roche Diagnostics uses the following symbols and signs:

Elecsys Phospho-Tau (181P) CSF

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CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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Elecsys Phospho-Tau (181P) CSF

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Changelog

For this document version only:

Due to technical reasons, changes that have been made since the last version of this document are listed in the following table instead of indicated by change bars in the margin.

Section headers are indicated in bold letters.

In addition to the changes listed in the table below, this method sheet version contains several editorial and layout updates.

Section	Current version	Previous version
Note	**Note** All analytical performance data were generated using frozen cerebrospinal fluid (CSF) material. Section updated	**Please note** All performance data were generated using frozen cerebrospinal fluid (CSF) material.
Intended use	Section updated	
Summary	Section updated	
Quality control	Follow the applicable government regulations and local guidelines.	Follow the applicable government regulations and local guidelines for quality control.
Warnings and precautions	**Warnings and precautions**	**Precautions and warnings**
Warnings and precautions	laboratory	health care
Warnings and precautions	Hazardous components: • 2-methyl-2H-isothiazol-3-one hydrochloride	
Calibration	every	after
Quality control	Use PreciControl Phospho-Tau (181P) or other suitable controls for routine quality control procedures.	For quality control, use PreciControl Phospho-Tau (181P).
Quality control	Follow the applicable government regulations and local guidelines.	Follow the applicable government regulations and local guidelines for quality control.
Specimen collection and preparation	Stability of CSF samples: Stable for 5 days at 20-25 °C, 14 days at 2-8 °C, 8 weeks at -20 °C (± 5 °C). Freeze only once.	Stability of CSF samples: Stable for 8 weeks at -15 to -25 °C (one freeze/thaw cycle),14 days at 2-8 °C, 5 days at 20-25 °C.
Specimen collection and preparation	Centrifuge samples containing precipitates and thawed samples before performing the assay.	Centrifuge samples containing precipitates before performing the assay.
Test procedure	**Test procedure**	**Reagent handling** **Assay**
Limitations and interferences	**Limitations and interferences**	**Limitations - interference**
Specific performance data	**Clinical performance data** Each laboratory is advised to investigate the transferability of the expected values to its own patient population and, if necessary, to determine its own reference ranges. Section updated	**Clinical performance** Each laboratory should investigate the transferability of the expected values to its own patient population.

Elecsys Phospho-Tau (181P) CSF

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Section	Current version	Previous version
References	New references: 8-24	
Additional information	A point (period/stop) is always used in the English version of a Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. The translated Method Sheets use decimal commas. Labels only use the decimal point as separator. Separators for thousands are not used.	A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the boundary between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.
Symbols	Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:	Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):