Elecsys Phospho-Tau (181P) Plasma

cobas®

REF		Σ	SYSTEM
09697870190	09697870501	100	**cobas** e 801 **cobas** e 402

For use in the USA only

System Information

Short name	ACN (application code number)
pT181p	10258

Intended use

Elecsys Phospho-Tau (181P) Plasma is an in vitro **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay (ECLIA) intended for the measurement of the phosphorylated Tau 181 protein in human plasma on **cobas** e immunoassay analyzers.

The Elecsys Phospho-Tau (181P) Plasma assay result is intended to be used as an aid in the initial assessment for Alzheimer's disease and other causes of cognitive decline in adult patients aged 55 years and older, presenting with signs, symptoms, or complaints of cognitive decline. The result should be interpreted in conjunction with other clinical information.

A negative test result is consistent with a negative amyloid positron emission tomography (PET) scan result and reduced likelihood that a patient's cognitive impairment is due to amyloid pathology. These patients should be investigated for other causes of cognitive decline.

A positive test result may not be consistent with a positive amyloid PET scan result. Patients with an initial positive result should be further investigated to determine whether the amyloid pathology can be a cause of cognitive impairment.

Limitations of use

The Elecsys Phospho-Tau (181P) Plasma assay is not recommended for patients with signs, symptoms, or complaints of cognitive decline, who are already referred to the specialist.

The performance of Elecsys Phospho-Tau (181P) Plasma has not been established for:

- Predicting development of dementia or other neurologic conditions.
- Monitoring responses to therapies.

Summary

Tubulin-associated unit (Tau) is a structural microtubule-associated protein (MAP), primarily located in the axons of neurons within the central nervous system (CNS), where it plays a crucial role in stabilizing microtubules and supporting intracellular transport. Tau is found as 6 molecular isoforms in human brain. These isoforms are coded by the MAPT gene on chromosome 17 and generated by alternative splicing of its pre-mRNA.[1, 2, 3]

The most common post-translational modification of Tau proteins is phosphorylation. Tau phosphorylation decreases its binding to microtubules and reduces microtubule stability. The detached Tau undergoes self-aggregation, forming oligomers and higher-order Tau aggregates. As such, hyperphosphorylated Tau is the main component of neurofibrillary tangles (NFT), which is 1 of the 2 major hallmarks of Alzheimer's disease together with amyloid-β plaques.[1, 2, 3] Tau has a number of potential phosphorylation sites. The Elecsys Phospho-Tau (181P) Plasma assay is designed to detect the protein or fragments of Tau protein phosphorylated at threonine 181 (pTau181) in human plasma.

Clinical relevance

It has been demonstrated that Tau phosphorylation at threonine 181 occurs as a reaction to amyloid-β plaques and thus is closely linked to amyloid-β pathology.[4] Specifically, it has been shown that pTau181 levels rise close to the time when amyloid-β plaques become detectable by PET imaging.[5, 6, 7] Therefore, pTau181 has been proposed as a marker of amyloid-β proteinopathy.[8]

The use of biomarkers to diagnose Alzheimer's disease was included in the consensus research diagnostic criteria for Alzheimer's disease, mild cognitive impairment (MCI), and preclinical Alzheimer's disease, proposed by the National Institute on Aging (NIA) and the Alzheimer's Association.[8, 9] The use of blood biomarkers in the Alzheimer's disease diagnostic work-up was accounted for in subsequent revisions[10] and International Working Group (IWG) recommendations.[11]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- First incubation: 30 µL of sample, biotinylated monoclonal antibody specific for phosphorylation at threonine 181, and a monoclonal tau-specific antibody 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 which is instrument-specifically generated by 2-point calibration and a master curve provided via the cobas link.

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

Reagents

The **cobas** e pack is labeled as pT181p.

M	Streptavidin-coated microparticles, 1 bottle, 6.4 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
R1	Anti-pTau-Ab~biotin, 1 bottle, 7.0 mL: Biotinylated monoclonal anti-pTau antibody (mouse/human) 2.9 mg/L; HEPES[A)] buffer 50 mmol/L, pH 7.4; preservative.

A) HEPES = [4-(2-hydroxyethyl)-piperazine]-ethanesulfonic acid

R2	Anti-Tau-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 7.0 mL: Monoclonal anti-Tau antibody (mouse) labeled with ruthenium complex 4.5 mg/L; HEPES buffer 50 mmol/L, pH 7.4; preservative.

Warnings and precautions

For in vitro diagnostic use for healthcare 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: +1-800-428-2336

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

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas** e packs. All information required for correct operation is available via the **cobas** link.

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Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas** e pack **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

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

K_2-EDTA and K_3-EDTA plasma.

K_2-EDTA plasma tubes containing separating gel can be used.

Samples drawn in plasma separation tubes should be used immediately after sample processing and not be used after storage.

Criterion: Slope 0.90-1.10 + coefficient of correlation ≥ 0.95.

Stability: 2 days at 15-25 °C, 7 days at 2-4 °C, 3 months at -15 to -20 °C. Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing. Sample collection systems from various manufacturers may contain differing materials, which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

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

Do not use hemolyzed samples that are visibly colored red.

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, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Please always keep them capped if not in use.

Materials provided

For reagents, refer to the "Reagents" section.

Materials required (but not provided)

REF	Description
09697896190	CalSet Phospho Tau (181P) Plasma, for 4 x 1.0 mL
09697926190	PreciControl Phospho Tau (181P) Plasma, for 6 x 1.0 mL
	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
11298500160	ISE Cleaning Solution / Elecsys SysClean, 5 × 100-mL system cleaning solution

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Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

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.

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.

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using the relevant CalSet.

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

Use PreciControl Phospho Tau (181P) Plasma for routine quality control procedures.

Controls for the various concentration ranges should be run 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) Plasma target ranges provided, the user needs to ensure that the systematic bias with respect to the assigned target value is within ± 13 %, the intermediate precision CV is ≤ 10 % and the maximal total error is within ± 29.4 % (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.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

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

Expected values

A reference interval study was performed in accordance with the CLSI guideline EP28 A3c. The reference range was defined based on pTau181 levels in individuals (N = 174), aged 55 to 80, who were apparently cognitively normal based on their Quick Dementia Rating System (QDRS) score of zero. pTau181 levels were determined in K_2-EDTA on the **cobas** e 801 analyzer. The mean, median, 2.5th percentile, and 97.5th percentile of pTau181 for the reference population were calculated and listed below.

Assay	Mean	Median	2.5th percentile (90 % CI)	97.5th percentile (90 % CI)
pT181p [pg/mL]	0.774	0.658	0.323 (0.300-0.364)	1.91 (1.590-3.720)

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	Cognitively normal					
	Race[A]				Sex	
	White	Black	Asian	Other	Male	Female
N (%)	139 (79.9 %)	17 (9.8 %)	7 (4.0 %)	10 (5.7 %)	95 (54.6 %)	79 (45.4 %)
Mean (SD) [pg/mL]	0.805 (0.491)	0.697 (0.308)	0.650 (0.229)	0.581 (0.285)	0.836 (0.533)	0.699 (0.341)
Median [pg/mL]	0.667	0.594	0.668	0.484	0.701	0.594
Range [pg/mL]	0.300-3.72	0.300-1.59	0.300-0.979	0.320-1.18	0.300-3.72	0.300-1.94
2.5th Percentile [pg/mL], 97.5th Percentile [pg/mL]	0.358 - 1.94	N/A[B], N/A	N/A, N/A	N/A, N/A	0.342-1.96	0.300 - 1.91
N (%) > 0.722 [pg/mL]	58 (41.7%)	6 (35.3 %)	2 (28.6 %)	2 (20 %)	45 (47.4 %)	23 (29.1 %)

[A] No race reported for one subject with mean pTau181 of 0.559 pg/mL

[B] Results listed as not applicable (N/A) are due to an insufficient number of samples to properly calculate the value.

	Cognitively normal		
	All	Age Groups	
		55 to 70 years	71 to 80 years
N (%)	174 (100 %)	129 (74.1 %)	45 (25.9 %)
Mean (SD) [pg/mL]	0.774 (0.460)	0.703 (0.307)	0.976 (0.707)
Median [pg/mL]	0.658	0.631	0.718
Range [pg/mL]	0.300-3.72	0.300-1.94	0.300-3.72
2.5th Percentile [pg/mL], 97.5th Percentile [pg/mL]	0.323-1.91	0.323-1.52	0.358-3.43
N (%) > 0.722	68 (39.1 %)	46 (35.7 %)	22 (48.9 %)

Note: In this reference population, 61 % of the subjects were at or below the Elecsys Phospho Tau (181P) Plasma assay cutoff (0.722) for ruling out amyloid pathology and 39 % were above the cutoff. It has been recognized that neuropathologic changes such as amyloid plaques and Tau hyperphosphorylation are present in cognitively normal individuals.[11, 12]

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.

Interpretation of results

Results of the Elecsys Phospho Tau (181P) Plasma assay are reported by the instrument. The final result (negative or positive) must be interpreted by the laboratory professional according to the table below:

pT181p result	Interpretation
Negative (≤ 0.722 pg/mL)	A negative result is consistent with a negative amyloid PET scan result. These patients should be investigated for causes of cognitive decline other than amyloid pathology.
Positive (> 0.722 pg/mL)	A positive result may not be consistent with a positive amyloid PET scan result. Patients with an initial positive result should be further investigated to determine whether amyloid pathology can be a cause of cognitive impairment.

Performance Characteristics

Measuring range

0.300-10.0 pg/mL (defined by the Limit of Quantitation and the maximum of the master curve). Values below the Limit of Quantitation are reported as < 0.300 pg/mL. Values above the measuring range are reported as > 10.0 pg/mL.

Lower limits of measurement

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

Limit of Blank = [0.250 pg/mL]

Limit of Detection = [0.300 pg/mL]

Limit of Quantitation = [0.300 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 %.

Linearity

The linearity study for Elecsys Phospho Tau (181P) Plasma was assessed on the **cobas** e 801 analyzer; 3 independent dilution series covering the measuring range were prepared from human plasma samples. Linear regression was performed in accordance with CLSI EP06 Ed2. All deviations from linearity were within ± 10 %.

Assay	Range [pg/mL]	Slope	Intercept	R2
pT181p	0.248-10.9	0.998	0.0000	0.999

Linearity results support the measuring range claim of 0.300 pg/mL-10.0 pg/mL for Elecsys Phospho-Tau (181P) Plasma.

High-dose hook effect

High-dose hook effect was evaluated using 2 spiked plasma samples with analyte concentrations ≥ 150 pg/mL. Dilution series were measured with 1 lot on 1 **cobas** e 801 analyzer. There is no high-dose hook effect at pTau181 concentrations up to 150 pg/mL.

Interference

The effect on quantitation of analyte in the presence of endogenous interfering substances was determined on the **cobas** e 801 analyzer using human plasma. For each interfering substance a total of 4 plasma sample pools (low, high and 1 sample each slightly above or slightly below the cutoff) were prepared and tested in N = 5 determinations. The mean value was used to calculate the relative (%) or absolute (pg/mL) deviation from the reference sample.

Human anti-mouse antibodies (HAMAs) were tested at 1200.0 µg/mL in 5 replicates in the same run using 2 plasma sample pools.

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	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.310 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 2.0 g/dL
IgA	≤ 0.6 g/dL
IgM	≤ 0.35 g/dL
Albumin	≤ 7 g/dL

Criterion: Deviation within ± 0.1 pg/mL of initial value ≤ 1.0 pg/mL and within ± 10 % of initial value > 1.0 pg/mL

Pharmaceutical substances

The effect on quantitation of the pTau181 analyte in the presence of exogenous interfering substances using the Elecsys Phospho Tau (181P) Plasma assay was determined on the **cobas** e 801 analyzer. Pharmaceuticals were tested by spiking into 3 plasma sample pools (1 with low levels and 1 each slightly above or slightly below the cutoff). Each sample was tested in N = 5 determinations and the mean value was used to calculate the relative (%) or absolute (pg/mL) deviation from the reference sample.

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

Commonly used pharmaceuticals

Pharmaceutical	Concentration tested
Acetaminophen	156 mg/L
Acetylcysteine	150 mg/L
Acetylsalicylic acid	30 mg/L
Ampicillin-Na	75 mg/L
Ascorbic acid	52.5 mg/L
Cefoxitin	750 mg/L
Cyclosporine	1.8 mg/L
Doxycycline	18 mg/L
Heparin	3300 IU/L
Ibuprofen	219 mg/L
Itraconazole	30 mg/L
Levodopa	7.5 mg/L
Methyldopa	22.5 mg/L
Metronidazole	123 mg/L
Phenylbutazone	321 mg/L
Rifampicin	48 mg/L
Theophylline	60 mg/L

Criterion: Deviation within ± 0.1 pg/mL of initial value ≤ 1.0 pg/mL and within ± 10 % of initial value > 1.0 pg/mL

In addition, the following 26 special drugs were tested. No interference with the assay was found.

Special drugs

Pharmaceutical	Concentration tested
Esomeprazole	6.9 mg/L
Hydrochlorothiazide	1.128 mg/L
Lisinopril	0.246 mg/L
Metoprolol	1.5 mg/L
Atorvastatin	0.75 mg/L
Digoxin	0.039 mg/L
Rivaroxaban	2.7 mg/L
Escitalopram	0.192 mg/L
Clopidogrel	45 IU/L
Simvastatin	1.68 mg/L
Metformin	12 mg/L
Galantamine	250 mg/L
Rivastigmine	45 mg/L
Donepezil	30 mg/L
Furosemide	15.9 mg/L
Memantine	0.12 mg/L
Albuterol	0.045 mg/L
Formoterol	0.000273 mg/L
Fluticasone	0.00126 mg/L
Prednisone	0.1 mg/L
Montelukast	4.45 mg/L
Sitagliptin	1.15 mg/L
Insulin	111 mU/L

Losartan	3.24 mg/L
Amlodipine	0.08 mg/L
Adalimumab	240 mg/L

Criterion: Deviation within ± 0.1 pg/mL of initial value ≤ 1.0 pg/mL and within ± 10 % of initial value > 1.0 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.

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:

Elecsys Phospho-Tau (181) Plasma precision data

cobas e 402 analyzer					
		Within-run		Between-run	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.501	0.0202	4.0	0.00499	1.0
Human plasma 2	0.585	0.0215	3.7	0.00166	0.3
Human plasma 3	0.656	0.0198	3.0	0.00365	0.6
Human plasma 4	0.833	0.0257	3.1	0.000000	0.0
Human plasma 5	0.938	0.0256	2.7	0.0155	1.6
Human plasma 6	1.07	0.0239	2.2	0.0195	1.8
Human plasma 7	1.15	0.0248	2.2	0.0212	1.8
Human plasma 8	5.13	0.0685	1.3	0.0809	1.6
Human plasma 9	9.14	0.136	1.5	0.123	1.3
PC[A)] pT181p 1	0.627	0.0189	3.0	0.000000	0.0
PC pT181p 2	2.09	0.0321	1.5	0.0101	0.5

[A)] PC = PreciControl

Elecsys Phospho-Tau (181) Plasma precision data, continued

cobas e 402 analyzer					
		Between-day		Within Laboratory	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.501	0.0261	5.2	0.0334	6.7
Human plasma 2	0.585	0.0249	4.3	0.0329	5.6
Human plasma 3	0.656	0.0205	3.1	0.0287	4.4
Human plasma 4	0.833	0.0195	2.3	0.0323	3.9
Human plasma 5	0.938	0.0213	2.3	0.0367	3.9
Human plasma 6	1.07	0.0255	2.4	0.0400	3.7
Human plasma 7	1.15	0.0229	2.0	0.0399	3.5
Human plasma 8	5.13	0.000000	0.0	0.106	2.1
Human plasma 9	9.14	0.0849	0.9	0.202	2.2
PC pT181p 1	0.627	0.0228	3.6	0.0296	4.7
PC pT181p 2	2.09	0.0368	1.8	0.0499	2.4

Lot-to-lot precision

Elecsys Phospho-Tau (181P) Plasma

Lot-to-lot precision was determined using **cobas** e 801 analyzer, Elecsys reagents, plasma samples and controls in a protocol with the following experimental design: 3 lots of reagent at 1 site, 2 runs per day in triplicate each for 5 days (N = 90). The following results were obtained; which are representative of the performance expected on the **cobas** e 402 and **cobas** e 801 analyzers:

Elecsys Phospho-Tau (181) Plasma lot-to-lot precision data

cobas e analyzer					
		Within-run		Between-run	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.518	0.022	4.3	0.006	1.1
Human plasma 2	0.601	0.066	11.0	0.022	3.6
Human plasma 3	0.658	0.020	3.1	0.006	1.0
Human plasma 4	0.840	0.020	2.4	0.010	1.2
Human plasma 5	1.07	0.027	2.5	0.000	0.0
Human plasma 6	5.11	0.060	1.2	0.041	0.8
Human plasma 7	9.16	0.080	0.9	0.032	0.3
Human plasma 8	1.23	0.062	1.2	0.041	0.0
PC pT181p 1	0.626	0.020	3.2	0.011	1.8
PC pT181p 2	2.06	0.029	1.4	0.008	0.4

Elecsys Phospho-Tau (181) Plasma lot-to-lot precision data, continued

cobas e analyzer					
		Between-day		Between-lot	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.518	0.027	5.3	0.032	6.1
Human plasma 2	0.601	0.033	5.5	0.026	4.3
Human plasma 3	0.658	0.014	2.2	0.043	6.5
Human plasma 4	0.840	0.022	2.6	0.057	6.8
Human plasma 5	1.07	0.011	1.0	0.064	6.0
Human plasma 6	5.11	0.050	1.0	0.175	3.4
Human plasma 7	9.16	0.077	0.8	0.261	2.8
Human plasma 8	1.23	0.017	1.4	0.041	3.3
PC pT181p 1	0.626	0.014	2.3	0.053	8.5
PC pT181p 2	2.06	0.021	1.0	0.113	5.5

Elecsys Phospho-Tau (181) Plasma lot-to-lot precision data, continued

cobas e analyzer			
		Total	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.518	0.048	9.2
Human plasma 2	0.601	0.081	13.6
Human plasma 3	0.658	0.050	7.5
Human plasma 4	0.840	0.066	7.8
Human plasma 5	1.07	0.070	6.6
Human plasma 6	5.11	1.96	3.8
Human plasma 7	9.16	0.285	3.1

Elecsys Phospho-Tau (181P) Plasma

cobas e analyzer			
		Total	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**
Human plasma 8	1.23	0.051	4.2
PC pT181p 1	0.626	0.060	9.5
PC pT181p 2	2.06	0.119	5.8

Site-to-site reproducibility

Reproducibility was determined on a **cobas** e 801 analyzer with a panel of human plasma samples and 2 controls. Samples were measured in triplicate using 1 reagent lot in 2 runs for 5 days (N = 90) at 3 sites according to CLSI EP05 A3. The following results were obtained; which are representative of the performance expected on the **cobas** e 402 and **cobas** e 801 analyzers:

Elecsys Phospho-Tau (181) Plasma site-to-site reproducibility data

cobas e analyzer					
		Within-run		Between-run	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.462	0.015	3.2	0.007	1.6
Human plasma 2	0.540	0.020	3.6	0.007	1.2
Human plasma 3	0.623	0.016	2.6	0.006	1.0
Human plasma 4	0.790	0.021	2.7	0.000	0.0
Human plasma 5	1.02	0.024	2.4	0.000	0.0
Human plasma 6	4.94	0.048	1.0	0.047	0.9
Human plasma 7	8.94	0.086	1.0	0.032	0.4
Human plasma 8	1.15	0.026	2.3	0.017	1.5
PC pT181p 1	0.62	0.021	3.5	0.005	0.8
PC pT181p 2	2.03	0.031	1.5	0.000	0.0

Elecsys Phospho-Tau (181) Plasma site-to-site reproducibility data, continued

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		Between-day		Between-site	
Sample	**Mean [pg/mL]**	**SD [pg/mL]**	**CV %**	**SD [pg/mL]**	**CV %**
Human plasma 1	0.462	0.000	0.0	0.043	9.3
Human plasma 2	0.540	0.006	1.1	0.040	7.4
Human plasma 3	0.623	0.006	1.0	0.043	6.9
Human plasma 4	0.790	0.008	1.0	0.037	4.7
Human plasma 5	1.02	0.003	0.2	0.045	4.4
Human plasma 6	4.94	0.000	0.0	0.118	2.4
Human plasma 7	8.94	0.051	0.6	0.180	2.0
Human plasma 8	1.15	0.000	0.0	0.059	5.1
PC pT181p 1	0.62	0.010	1.7	0.010	1.7
PC pT181p 2	2.03	0.014	0.7	0.009	0.5

Elecsys Phospho-Tau (181) Plasma site-to-site reproducibility data, continued

Elecsys Phospho-Tau (181P) Plasma

cobas e analyzer			
		Total	
Sample	**Mean [pg/mL]**	**SD pg/mL**	**CV %**
Human plasma 1	0.462	0.046	9.9
Human plasma 2	0.540	0.045	8.4
Human plasma 3	0.623	0.047	7.6
Human plasma 4	0.790	0.044	5.5
Human plasma 5	1.02	0.051	5.0
Human plasma 6	4.94	1.36	2.7
Human plasma 7	8.94	0.208	2.3
Human plasma 8	1.15	0.067	5.8
PC pT181p 1	0.62	0.026	4.3
PC pT181p 2	2.03	0.035	1.7

Analytical specificity

The test is highly specific for human pTau181. The following potential cross-reactivity was found:

Cross-reactant	Concentration tested [pg/mL]	Cross-reactivity %
Non-phosphorylated Tau	60	0.04
pTau175	60	0.001

Clinical performance

A multicenter, prospective, non-interventional clinical study (Roche study RD006263) was conducted to evaluate the performance of Elecsys Phospho-Tau (181) Plasma.

The performance of Elecsys Phospho-Tau (181) Plasma was evaluated in 312 participants reflective of primary care, with respect to the following cutoff rule:

- If pT181p is > 0.722 pg/mL, the test result is positive.
- If pT181p is ≤ 0.722 pg/mL, the test result is negative.

This study population had an average age of 69.1 years (range 55-80 years) and presented with cognitive complaints or impairment, subjective or objective, of unknown cause, at 8 geographically diverse enrollment sites across the U.S. (n = 6) and Europe (n = 2). A total of 299 (95.8 %) subjects were enrolled at U.S. sites and 13 (4.17 %) at European sites.

The study population consisted of 40.7 % (127/312) males with a mean age of 69.1 years (range 57-80 years with a median age of 69 years), and 59.3 % females (185/312) with a mean age of 69.1 years (range 55-80 years with a median age of 69 years). In terms of race, 59.0 % were white, 34.0 % were black or African American, 1.6 % were Asian, 0.321 % were Middle Eastern, and 5.13 % identified as other. Regarding ethnicity, 66.3 % of participants were not Hispanic or Latino, 29.5 % were Hispanic or Latino, and for 4.17 % of the participants' information on ethnicity was missing. The study population included participants with comorbidities frequently encountered in clinical practice such as cardiovascular disease (56.1 %), diabetes (25.6 %), depression (19.9 %), kidney disease (2.24 %), or history of cerebrovascular accident (3.53 %) or cancer (12.5 %), among others.

Cognitive assessments [QDRS, Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR)], imaging [amyloid PET, magnetic resonance imaging (MRI)] and questionnaires (including medical history, medication, quality of life, physical activity, and socio-demographics) were collected from the enrolled participants.

The study participants were then categorized into 3 diagnostic groups by their physician, based on cognitive test results and clinical assessments: 41.0 % (128/312) subjective cognitive decline (SCD), 56.1 % (175/312) MCI, and 0.962 % (3/312) mild dementia. The diagnostic category was unknown in 6 subjects (1.92 %). The pre-dementia diagnostic groups (SCD and MCI) represented 97.1 % (303/312) of the study population.

The demographic and clinical characteristics of the patients in the 3 diagnostic groups are presented according to amyloid PET scan results in the table below:

Elecsys Phospho-Tau (181P) Plasma

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	Diagnostic group				Amyloid PET visual read		
	SCD	MCI	Mild dementia	Missing	Positive	Negative	All
	(N=128, 41.0 %)	(N=175, 56.1 %)	(N=3, 0.962 %)	(N=6, 1.92 %)	(N=41, 13.1 %)	(N=271, 86.9 %)	(N=312, 100.0 %)
Age [years]							
55 to 70	89 (69.5 %)	81 (46.3 %)	1 (33.3 %)	4 (66.7 %)	12 (29.3 %)	163 (60.1 %)	175 (56.1 %)
71 to 80	39 (30.5 %)	94 (53.7 %)	2 (66.7 %)	2 (33.3 %)	29 (70.7 %)	108 (39.9 %)	137 (43.9 %)
Mean (SD)	66.6 (5.87)	70.9 (6.27)	68.7 (9.29)	69.3 (6.98)	73.5 (5.09)	68.4 (6.38)	69.1 (6.46)
Median	66.0	72.0	73.0	68.0	75.0	68.0	69.0
Q1 ... Q3	62.3 ... 71.0	67.0 ... 76.0	58.0 ... 75.0	62.8 ... 76.8	69.5 ... 78.0	63.0 ... 74.0	64.0 ... 75.0
Min ... Max	55.0 ... 80.0	56.0 ... 80.0	58.0 ... 75.0	62.0 ... 79.0	59.0 ... 80.0	55.0 ... 80.0	55.0 ... 80.0
Sex							
Male	53 (41.4 %)	73 (41.7 %)	1 (33.3 %)	0 (0 %)	20 (48.8 %)	107 (39.5 %)	127 (40.7 %)
Female	75 (58.6 %)	102 (58.3 %)	2 (66.7 %)	6 (100 %)	21 (51.2 %)	164 (60.5 %)	185 (59.3 %)
Race							
White	74 (57.8 %)	106 (60.6 %)	1 (33.3 %)	3 (50.0 %)	37 (90.2 %)	147 (54.2 %)	184 (59.0 %)
Asian	0 (0 %)	5 (2.86 %)	0 (0 %)	0 (0 %)	0 (0 %)	5 (1.85 %)	5 (1.60 %)
Black or African American	51 (39.8 %)	51 (29.1 %)	2 (66.7 %)	2 (33.3 %)	4 (9.76 %)	102 (37.6 %)	106 (34.0 %)
Middle Eastern	0 (0 %)	1 (0.571 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (0.369 %)	1 (0.321 %)
Other[A)]	3 (2.34 %)	12 (6.86 %)	0 (0 %)	1 (16.7 %)	0 (0 %)	16 (5.90 %)	16 (5.13 %)
Ethnicity							
Not Hispanic or Latino	69 (53.9 %)	132 (75.4 %)	2 (66.7 %)	4 (66.7 %)	32 (78.0 %)	175 (64.6 %)	207 (66.3 %)
Hispanic or Latino	58 (45.3 %)	31 (17.7 %)	1 (33.3 %)	2 (33.3 %)	4 (9.76 %)	88 (32.5 %)	92 (29.5 %)
Unknown	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Not Reported	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Missing	1 (0.781 %)	12 (6.86 %)	0 (0 %)	0 (0 %)	5 (12.2 %)	8 (2.95 %)	13 (4.17 %)
Body Mass Index (BMI) [kg/m^2]							
Mean (SD)	29.4 (5.61)	28.4 (5.21)	25.9 (4.83)	26.2 (3.68)	26.8 (4.11)	29.0 (5.49)	28.7 (5.37)
Median	28.5	27.5	24.8	27.1	25.8	28.3	27.8
Q1 ... Q3	25.7 ... 32.2	24.9 ... 31.2	21.8 ... 31.2	22.4 ... 29.2	23.9 ... 29.1	25.4 ... 31.8	25.2 ... 31.4
Min ... Max	16.5 ... 46.5	18.5 ... 48.8	21.8 ... 31.2	21.0 ... 30.6	20.7 ... 37.6	16.5 ... 48.8	16.5 ... 48.8
Quick Dementia Rating System (QDRS)							
Mean (SD)	3.03 (1.59)	4.40 (2.64)	5.17 (1.04)	4.58 (1.28)	3.91 (2.43)	3.84 (2.33)	3.85 (2.34)
Median	2.50	4.00	5.50	4.50	3.00	3.00	3.00
Q1 ... Q3	2.00 ... 3.50	2.50 ... 6.00	4.00 ... 6.00	3.38 ... 5.75	2.50 ... 4.75	2.00 ... 5.00	2.00 ... 5.00
Min ... Max	0.500 ... 10.5	0.500 ... 11.5	4.00 ... 6.00	3.00 ... 6.50	1.00 ... 11.5	0.500 ... 11.0	0.500 ... 11.5
Mini-Mental State Examination (MMSE)							
< 25	27 (21.1 %)	48 (27.4 %)	1 (33.3 %)	2 (33.3 %)	13 (31.7 %)	65 (24.0 %)	78 (25.0 %)
25-27	77 (60.2 %)	69 (39.4 %)	2 (66.7 %)	2 (33.3 %)	15 (36.6 %)	135 (49.8 %)	150 (48.1 %)
28-30	24 (18.8 %)	58 (33.1 %)	0 (0 %)	2 (33.3 %)	13 (31.7 %)	71 (26.2 %)	84 (26.9 %)
Mean (SD)	25.9 (1.89)	26.2 (2.42)	24.3 (2.89)	26.5 (3.02)	26.1 (2.51)	26.0 (2.19)	26.1 (2.23)
Median	26.0	26.0	26.0	27.0	26.0	26.0	26.0
Q1 ... Q3	25.0 ... 27.0	24.0 ... 28.0	21.0 ... 26.0	23.5 ... 29.3	24.0 ... 29.0	25.0 ... 28.0	24.3 ... 28.0
Min ... Max	21.0 ... 30.0	21.0 ... 30.0	21.0 ... 26.0	22.0 ... 30.0	21.0 ... 30.0	21.0 ... 30.0	21.0 ... 30.0
Clinical Dementia Rating (CDR) Global							

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	Diagnostic group				Amyloid PET visual read		
	SCD	MCI	Mild dementia	Missing	Positive	Negative	All
	(N=128, 41.0 %)	(N=175, 56.1 %)	(N=3, 0.962 %)	(N=6, 1.92 %)	(N=41, 13.1 %)	(N=271, 86.9 %)	(N=312, 100.0 %)
0	15 (11.7 %)	3 (1.71 %)	0 (0 %)	0 (0 %)	3 (7.32 %)	15 (5.54 %)	18 (5.77 %)
0.5	111 (86.7 %)	165 (94.3 %)	0 (0 %)	0 (0 %)	34 (82.9 %)	242 (89.3 %)	276 (88.5 %)
1	2 (1.56 %)	7 (4.00 %)	3 (100 %)	0 (0 %)	2 (4.88 %)	10 (3.69 %)	12 (3.85 %)
1.5	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
2	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
2.5	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
3	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Missing	0 (0 %)	0 (0 %)	0 (0 %)	6 (100 %)	2 (1.48 %)	4 (1.48 %)	6 (1.92 %)
Clinical Dementia Rating Sum of Boxes (CDR-SB)							
Mean (SD)	1.86 (1.18)	2.18 (1.31)	5.00 (0.500)	NA (NA)	1.90 (1.58)	2.11 (1.25)	2.08 (1.30)
Median	2.00	2.00	5.00	NA	1.50	2.00	2.00
Q1 ... Q3	1.00 ... 2.50	1.00 ... 3.00	4.50 ... 5.50	NA ... NA	1.00 ... 2.50	1.00 ... 3.00	1.00 ... 3.00
Min ... Max	0 ... 7.50	0 ... 7.00	4.50 ... 5.50	Inf ... -Inf	0 ... 7.00	0 ... 7.50	0 ... 7.50
Missing (n, %)	13 (10.2 %)	4 (2.29 %)	0 (0 %)	6 (100 %)	2 (4.88 %)	21 (7.75 %)	23 (7.37 %)
Education [years]							
Mean (SD)	13.4 (3.37)	15.2 (3.59)	15.0 (2.65)	17.0 (2.10)	16.2 (3.34)	14.2 (3.55)	14.5 (3.58)
Median	12.0	15.0	16.0	17.0	16.0	14.0	14.0
Q1 ... Q3	12.0 ... 16.0	12.0 ... 18.0	12.0 ... 17.0	15.5 ... 18.5	14.0 ... 18.0	12.0 ... 16.0	12.0 ... 16.0
Min ... Max	5.00 ... 24.0	7.00 ... 37.0	12.0 ... 17.0	14.0 ... 20.0	10.0 ... 25.0	5.00 ... 37.0	5.00 ... 37.0
Mean (SD)	13.4 (3.37)	15.2 (3.59)	15.0 (2.65)	17.0 (2.10)	16.2 (3.34)	14.2 (3.55)	14.5 (3.58)
ApoE4 status[B)]							
Carrier	43 (33.6 %)	56 (32.0 %)	1 (33.3 %)	1 (16.7 %)	23 (56.1 %)	78 (28.8 %)	101 (32.4 %)
Non carrier	85 (66.4 %)	119 (68.0 %)	2 (66.7 %)	5 (83.3 %)	18 (43.9 %)	193 (71.2 %)	211 (67.6 %)
Collection site location							
Europe	1 (0.781 %)	12 (6.86 %)	0 (0 %)	0 (0 %)	5 (12.2 %)	8 (2.95 %)	13 (4.17 %)
U.S.	127 (99.2 %)	163 (93.1 %)	3 (100 %)	6 (100 %)	36 (87.8 %)	263 (97.0 %)	299 (95.8 %)

[A)] Including Native American, Alaska Native, and Native Hawaiian

[B)] Based on plasma ApoE4 levels (protein)

A total of 313 subjects underwent amyloid PET scans using FDA approved amyloid tracers (18F-Florbetapir, 18F-Florbetaben, or 18F-Flutemetamol). Amyloid PET scans were randomly assigned, read and interpreted by 3 trained readers out of a pool of 5, each reading independent of each other. Majority voting was used to classify each image as amyloid positive or negative, resulting in 41 (13.1 %) positive, and 271 (86.9 %) negative amyloid PET reads. The independent readers were blinded to all clinical information, including the patient's clinical status, diagnosis, and plasma and/or cerebrospinal fluid (CSF) biomarker measurements. Amyloid PET reads were conducted according to the approved instructions for use of the amyloid tracers. Positive concordance among readers occurred in 28 cases (8.95 %) and negative concordance occurred in 260 cases (83.1 %). Discordant positive readings occurred in 13 cases (4.15 %) and discordant negative readings occurred in 11 cases (3.51 %). There were no cases with 1 or 2 missing ratings, and only 1 case (0.319 %) had 3 missing ratings. The total available amyloid PET scans were 312.

The positive percent agreement (PPA) between readers was 81.6 % on average (range: 53.8 %-100 %), the negative percent agreement (NPA) was 97.1 % on average (range: 91.5 %-100 %), and the total percent agreement (TPA) was 94.9 % on average (range: 92.3 %-96.6 %). The time difference between blood collection and PET imaging exhibited a mean of 52.2 days (SD = 34.8), a median of 39 days, and ranged from -15 to 179 days. Timing was consistent between PET positive (mean = 45.8 days; SD = 29.9; median = 35 days; range: 8 to 112 days) and PET negative (mean = 53.1 days; SD = 35.5; median = 39 days, range: -15 to 179 days) participants.

The agreement of Elecsys Phospho-Tau (181P) Plasma with amyloid PET visual read classification at the Elecsys Phospho-Tau (181P) Plasma cutoff of 0.722 pg/mL is summarized in the table below:

Elecsys Phospho-Tau (181P) Plasma

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pT181p result	Amyloid PET visual read		Total
	Positive	Negative	
Positive (pT181p > 0.722 pg/mL)	38	132	170
Negative (pT181p ≤ 0.722 pg/mL)	3	139	142
Total	41	271	312

The prevalence of amyloid positivity based on amyloid PET was 13.1 % in the study population.

Elecsys Phospho-Tau (181) Plasma agreement rates percentages and likelihood ratios are summarized in the table below:

Study population	
N	**312**
Agreement Rates	
Amyloid PET visual read negative (% N) (95 % CI)	86.9 % (82.7 %-90.2 %)[A)]
Positive percent agreement (PPA) (n/N) (95 % CI)	92.7 % (38/41) (80.6 %-97.5 %)[A)]
Negative percent agreement (NPA) (n/N) (95 % CI)	51.3 % (139/271) (45.4 %-57.2 %)[A)]
Total percent agreement (TPA) (n/N) (95 % CI)	56.7 % (177/312) (51.2 %-62.1 %)[A)]
Positive predictive value (PPV) (n/N) (95 % CI)	22.4 % (38/170) (19.5 %-25.0 %)[B)]
Negative predictive value (NPV) (n/N) (95 % CI)	97.9 % (139/142) (94.5 %-99.3 %)[B)]
Likelihood ratios (95 % CI)	
Positive likelihood ratio (LR+)	1.90 (1.601-2.200)[C)]
Negative likelihood ratio (LR-)	0.143 (0.049-0.382)[C)]
Rule-out rate (n/N) (95 % CI)	45.5 % (142/312) (40.1 %-51.1 %)[A)]

[A)] 95 % CI are calculated using a Wilson score method for binomial proportions

[B)] 95 % CI are calculated using 95 % CI for the corresponding likelihood ratio and prevalence

[C)] 95% CI are calculated using an asymptotic method for ratios of two independent binomial proportions

Of the 41 subjects with a positive PET scan, 3 (7.3 %) had a false negative Elecsys Phospho-Tau (181P) Plasma result. The NPV was 97.9 %.
45.5 % (142/312) of all subjects received a negative Elecsys Phospho-Tau (181P) Plasma result.

The Elecsys Phospho-Tau (181) Plasma clinical performance stratified by clinical diagnosis is summarized in the table below:

N=306	SCD	MCI	Mild dementia
N (% Total)	128 (41.8%)	175 (57.2%)	3 (0.980%)
Amyloid PET visual read negative (% N) (95 % CI)	95.3 % (90.2 %-97.8 %)[A)]	81.1 % (74.7 %-86.2 %)[A)]	100 % (43.9 %-100 %) [A)]
PPA (n/N) (95 % CI)	83.3 % (5/6) (43.7%-97.0 %)[A)]	97.0 % (32/33) (84.7 %-99.5 %)[A)]	N/A[B)]

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N=306	SCD	MCI	Mild dementia
NPA (n/N) (95 % CI)	54.9 % (67/122) (46.1 %-63.5 %)[A)]	47.9 % (68/142) (39.8 %-56.1 %)[A)]	66.7 % (2/3) (20.8 %-93.9 %)[A)]
TPA (n/N) (95 % CI)	56.3 % (72/128) (47.6 %-64.5 %)[A)]	57.1 % (100/175) (49.7 %-64.2 %)[A)]	66.7 % (2/3) (20.8 %-93.9 %)[A)]
PPV (n/N) (95 % CI)	8.33 % (5/60) (4.4 %-10.8 %)[C)]	30.2 % (32/106) (26.5 %-34.0 %)[C)]	0 % (0/1) (0 %-79.3 %)[C)]
NPV (n/N) (95 % CI)	98.5 % (67/68) (95.1 %-99.7 %)[C)]	98.6 % (68/69) (93.0 %-99.70 %)[C)]	100 % (2/2) (34.2 %-100 %)[C)]
LR+ (95 % CI)	1.85 (0.94-2.47)[D)]	1.86 (1.55-2.20)[D)]	N/A
LR- (95 % CI)	0.303 (0.054-1.050)[D)]	0.0633 (0.011-0.324)[D)]	N/A
Rule-out rate (n/N) (95 % CI)	53.1 % (68/128) (44.5 %-61.6 %)[A)]	39.4 % (69/175) (32.5 %-46.8 %)[A)]	66.7% (2/3) (20.8%-93.9%)[A)]

[A)] 95 % CI are calculated using a Wilson score method for binomial proportions

[B)] Results listed as not applicable (N/A) are due to an insufficient number of samples to properly calculate the value.

[C)] 95 % CI are calculated using 95 % CI for the corresponding likelihood ratio and prevalence

[D)] 95% CI are calculated using an asymptotic method for ratios of two independent binomial proportions

The Elecsys Phospho-Tau (181P) Plasma clinical performance stratified by sex is summarized in the table below:

N=312	Male	Female
N (% Total)	127 (40.7 %)	185 (59.3 %)
Amyloid PET visual read negative (% N) (95 % CI)	 84.3 % (76.9 %-89.6 %)[A)]	 88.6 % (83.3 %-92.5 %)[A)]
PPA (n/N) (95 % CI)	90.0 % (18/20) (69.9 %-97.2 %)[A)]	95.2 % (20/21) (77.3 %-99.2 %)[A)]
NPA (n/N) (95 % CI)	53.3 % (57/107) (43.9 %-62.4 %)[A)]	50.0 % (82/164) (42.4 %-57.6 %)[A)]
TPA (n/N) (95 % CI)	59.1 % (75/127) (50.4 %-67.2 %)[A)]	55.1 % (102/185) (47.9 %-62.1 %)[A)]
PPV (n/N) (95 % CI)	26.5 % (18/68) (21.0 %-31.5 %)[B)]	19.6 % (20/102) (16.1 %-22.6 %)[B)]
NPV (n/N) (95 % CI)	96.6 % (57/59) (90.3 %-99.0 %)[B)]	98.8 % (82/83) (94.4 %-99.8 %)[B)]
LR+ (95 % CI)	1.93 (1.42-2.46)[C)]	1.90 (1.50-2.28)[C)]
LR- (95 % CI)	0.188 (0.052-0.578)[C)]	0.0952 (0.017-0.659)[C)]
Rule-out rate (n/N) (95 % CI)	46.5 % (59/127) (38.0 %-55.1 %)[A)]	44.9 % (83/185) (37.9 %-52.1 %)[A)]

A) 95 % CI are calculated using a Wilson score method for binomial proportions

B) 95 % CI are calculated using 95 % CI for the corresponding likelihood ratio and prevalence

C) 95% CI are calculated using an asymptotic method for ratios of two independent binomial proportions

The Elecsys Phospho-Tau (181P) Plasma clinical performance stratified by age group is summarized in the table below:

N=312	55 to 70 years	71 to 80 years
N (% Total)	175 (56.1 %)	137 (43.9 %)
Amyloid PET visual read negative (% N) (95 % CI)	93.1 % (88.4 %-96.0 %)[A)]	78.8 % (71.3 %-84.8 %)[A)]
PPA (n/N) (95 % CI)	100 % (12/12) (75.8 %-100 %)[A)]	89.7 % (26/29) (73.6 %-96.4 %)[A)]
NPA (n/N) (95 % CI)	63.8 % (104/163) (56.2 %-70.8 %)[A)]	32.4 % (35/108) (24.3 %-41.7 %)[A)]
TPA (n/N) (95 % CI)	66.3 % (116/175) (59.0 %-72.9 %)[A)]	44.5 % (61/137) (36.5 %-52.9 %)[A)]
PPV (n/N) (95 % CI)	16.9 % (12/71) (13.0 %-20.1 %)[B)]	26.3 % (26/99) (22.2 %-29.8 %)[B)]
NPV (n/N) (95 % CI)	100 % (104/104) (96.7 %-100 %)[B)]	92.1 % (35/38) (81.3 %-97.2 %)[B)]
LR+ (95 % CI)	2.76 (2.03-3.43)[C)]	1.33 (1.06-1.58)[C)]
LR- (95 % CI)	0 (0.000-0.383)[C)]	0.319 (0.107-0.855)[C)]
Rule-out rate (n/N) (95 % CI)	59.4 % (104/175) (52.0 %-66.4 %)[A)]	27.7 % (38/137) (20.9 %-35.8 %)[A)]

A) 95 % CI are calculated using a Wilson score method for binomial proportions

B) 95 % CI are calculated using 95 % CI for the corresponding likelihood ratio and prevalence

C) 95% CI are calculated using an asymptotic method for ratios of two independent binomial proportions

The Elecsys Phospho-Tau (181P) Plasma clinical performance stratified by race is summarized in the table below:

N=312	White	Asian	Black or African American	Other
N (% Total)	184 (59.0 %)	5 (1.60 %)	106 (34.0 %)	17 (5.45 %)
Amyloid PET visual read Negative (% N) (95 % CI)	79.9 % (73.5 %-85.0 %)[A)]	100 % (56.6 %-100 %)[A)]	96.2 % (90.7 %-98.5 %)[A)]	100 % (81.6 %-100 %)[A)]
PPA (n/N) (95 % CI)	94.6 % (35/37) (82.3 %-98.5 %)[A)]	N/A	75.0 % (3/4) (30.1 %-95.4 %)[A)]	N/A
NPA (n/N) (95 % CI)	44.9 % (66/147) (37.1 %-53.0 %)[A)]	40.0 % (2/5) (11.8 %-76.9 %)[A)]	56.9 % (58/102) (47.2 %-66.1 %)[A)]	76.5 % (13/17) (52.7 %-90.4 %)[A)]
TPA (n/N) (95 % CI)	54.9 % (101/184) (47.7 %-61.9 %)[A)]	40.0 % (2/5) (11.8 %-76.9 %)[A)]	57.5 % (61/106) (48.0 %-66.5 %)[A)]	76.5 % (13/17) (52.7 %-90.4 %)[A)]

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N=312	White	Asian	Black or African American	Other
PPV (n/N) (95 % CI)	30.2 % (35/116) (26.5 %-33.9 %)[B)]	0 % (0/3) (0 %-56.1 %)[B)]	6.38 % (3/47) (2.6 %-9.1 %)[B)]	0 % (0/4) (0 %-49.0 %)[B)]
NPV (n/N) (95 % CI)	97.1 % (66/68) (90.8 %-99.2 %)[B)]	100 % (2/2) (34.2 %-100 %)[B)]	98.3 % (58/59) (95.3 %-99.7 %)[B)]	100 % (13/13) (77.2 %-100 %)[B)]
LR+ (95 % CI)	1.72 (1.43-2.03)[C)]	N/A	1.74 (0.70-2.54)[C)]	N/A
LR- (95 % CI)	0.120 (0.0329-0.4012)[C)]	N/A	0.440 (0.079-1.270)[C)]	N/A
Rule-out rate (n/N) (95 % CI)	37.0 % (68/184) (30.3 %-44.1 %)[A)]	40.0 % (2/5) (11.8 %-76.9 %)[A)]	55.7 % (59/106) (46.2 %-64.8 %)[A)]	76.5 % (13/17) (52.7 %-90.4 %)[A)]

[A)] 95 % CI are calculated using a Wilson score method for binomial proportions

[B)] 95 % CI are calculated using 95 % CI for the corresponding likelihood ratio and prevalence

[C)] 95% CI are calculated using an asymptotic method for ratios of two independent binomial proportions

References

1 Chong FP, Ng KY, Koh RY, et al. Tau Proteins and Tauopathies in Alzheimer's Disease. Cell Mol Neurobiol 2018;38(5):965-980. https://doi.org/10.1007/s10571-017-0574-1

2 Smet-Nocca C. 1st Ed. Tau Protein: Methods and Protocols; Methods in Molecular Biology; Springer New York: New York, NY, 2017; Vol. 1523. https://doi.org/10.1007/978-1-4939-6598-4.

3 Wang Y, Mandelkow E. Tau in physiology and pathology. Nat Rev Neurosci 2016;17:22-35.

4 Pichet Binette A, Franzmeier N, Spotorno N, et al. Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. Nat Commun 2022;13(1):6635. https://doi.org/10.1038/s41467-022-34129-4

5 Barthélemy NR, Li Y, Joseph-Mathurin N, et al. Dominantly Inherited Alzheimer Network. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 2020;26(3):398-407. https://doi.org/10.1038/s41591-020-0781-z

6 Mattsson-Carlgren N, Andersson E, Janelidze S, et al. Aβ deposition is associated with increases in soluble and phosphorylated tau that precede a positive Tau PET in Alzheimer's disease. Sci Adv 2020;6(16), eaaz2387. https://doi.org/10.1126/sciadv.aaz2387

7 Therriault J, Vermeiren M, Servaes S, et al. Association of Phosphorylated Tau Biomarkers With Amyloid Positron Emission Tomography vs Tau Positron Emission Tomography. JAMA Neurol 2023;80(2):188-199. https://doi.org/10.1001/jamaneurol.2022.4485

8 Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024;20(8):5143-5169. https://doi.org/10.1002/alz.13859

9 Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270-279.

10 Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.Alzheimers Dement. 2011;7(3):257-262.

11 Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical- Biological Construct-An International Working Group Recommendation. JAMA Neurol 2024;81(12):1304-1311. https://doi.org/10.1001/jamaneurol.2024.3770.

12 The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12756

Additional information

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

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.

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