Elecsys Phospho-Tau (181P) Plasma

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REF		Σ	SYSTEM
09697870190	09697870500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
pT181p	10258

Please note

The measured phosphorylated Tau (181P) 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 cannot be used interchangeably.

Intended use

Elecsys Phospho-Tau (181P) Plasma is an in vitro quantitative immunoassay intended for the determination of the phosphorylated Tau 181 protein in human plasma.

The Elecsys Phospho-Tau (181P) Plasma assay result is intended to be used for the early detection of amyloid pathology in adult subjects aged 55-80 years with subjective complaints or non-specific cognitive impairment (subjective cognitive decline) or whom their physician suspects of having mild cognitive impairment and who are being evaluated for Alzheimer's disease and other causes of cognitive decline in primary, secondary, or tertiary care settings.

A negative Elecsys Phospho-Tau (181P) Plasma assay result indicates a high likelihood of having a negative amyloid positron emission tomography / cerebrospinal fluid result and, therefore, a low likelihood of having amyloid pathology. Investigation is recommended for other potential causes of cognitive impairment.

Limitations of use

The Elecsys Phospho-Tau (181P) Plasma assay result must be considered as an aid in the diagnosis of Alzheimer's disease in conjunction with other clinical information.

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

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 in human plasma (pTau181).

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 closer to the time when amyloid-β plaques become detectable by positron emission tomography (PET) imaging than to the time when NFT are detectable.[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.[9,10] The use of blood biomarkers in the Alzheimer's disease diagnostic work-up was accounted for in subsequent revisions[8] and International Working Group (IWG) recommendations.[11]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st 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.
- 2nd incubation: After addition of streptavidin-coated microparticles, 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 - working solutions

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[b)] buffer 50 mmol/L, pH 7.4; preservative.

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.

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

Precautions and warnings

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 the safe disposal.

Safety data sheet available for professional user 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.

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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: all countries: +49-621-7590

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.

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.

Plasma tubes containing separating gel can be used.

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

Stability: 2 days at 20-25 °C, 7 days at 2-8 °C, 3 months at -20 °C (± 5 °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, i.e. not all available tubes of all manufacturers were tested. 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.

Always keep them capped when not in use.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 09697896190, CalSet Phospho-Tau (181P) Plasma, for 4 x 1.0 mL
- REF 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 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

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.

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 since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration 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: e.g. quality control findings 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.

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Limitations - interference

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

There is no high-dose hook effect at pTau concentrations up to 150 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
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

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 mg/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

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

In rare cases, interference due to 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, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

0.300-10 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 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, Limit of Detection and 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 which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable relative error of ≤ 20 %.

Linearity

The Elecsys Phospho-Tau (181P) Plasma assay is linear across the measuring range from 0.300 to 10 pg/mL. Samples were prepared according to CLSI EP06-Ed2 by diluting 3 plasma sample sets each with low samples in multiple steps ranging from > 10 pg/mL downwards to the Limit of Quantitation.

Expected values

The reference range was defined based on results from 174 apparently cognitively normal individuals aged 55 to 80 using the QDRS, with a score

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of zero. For each K_2-EDTA sample, the level of pTau181p was determined on the **cobas e** 801 analyzer. The mean, median, 2.5th percentile, and 97.5th percentile of pTau181p for the reference population are calculated and listed below.

Assay	Mean	Median	2.5th percentile (90 % CI)	97.5th percentile (90 % CI)
pT181p [pg/mL]	0.774	0.658	0.300 (0.300-0.364)	1.90 (1.590-3.720)

Note: In this reference population, 80 % of the subjects were below and 20 % were above the Elecsys Phospho-Tau (181P) Plasma assay cutoff for ruling out amyloid pathology. It has been recognized that neuropathologic changes such as amyloid plaques and Tau hyperphosphorylation are present in this proportion of cognitively normal individuals.[11,12]

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

Specific performance data

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

Precision

Precision was determined using Elecsys reagents, samples and controls in 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 801 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human plasma 1	0.545	0.0258	4.7	0.0263	4.8
Human plasma 2	0.622	0.0324	5.2	0.0324	5.2
Human plasma 3	0.624	0.0248	4.0	0.0271	4.3
Human plasma 4	0.828	0.0262	3.2	0.0300	3.6
Human plasma 5	0.972	0.0287	2.9	0.0334	3.4
Human plasma 6	1.02	0.0321	3.1	0.0412	4.0
Human plasma 7	1.09	0.0349	3.2	0.0390	3.6
Human plasma 8	5.19	0.0849	1.6	0.105	2.0
Human plasma 9	9.22	0.146	1.6	0.202	2.2
PC[c)] pT181p 1	0.543	0.0281	5.2	0.0296	5.5
PC pT181p 2	1.95	0.0372	1.9	0.0477	2.4

c) PC = PreciControl

cobas e 402 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human plasma 1	0.543	0.0239	4.4	0.0294	5.4
Human plasma 2	0.627	0.0248	4.0	0.0276	4.4
Human plasma 3	0.620	0.0197	3.2	0.0281	4.5
Human plasma 4	0.830	0.0274	3.3	0.0325	3.9
Human plasma 5	0.962	0.0224	2.3	0.0326	3.4
Human plasma 6	1.01	0.0232	2.3	0.0320	3.2
Human plasma 7	1.08	0.0287	2.7	0.0332	3.1
Human plasma 8	5.14	0.0536	1.0	0.0869	1.7
Human plasma 9	9.21	0.117	1.3	0.176	1.9
PC pT181p 1	0.549	0.0254	4.6	0.0275	5.0
PC pT181p 2	1.96	0.0393	2.0	0.0506	2.6

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 %**
Non-phosphorylated Tau	60	0.04
conc. pTau175	60	0.001

Method comparison

A comparison of the Elecsys Phospho-Tau (181P) Plasma assay, REF 09697870190 (**cobas e** 402 analyzer; y), with the Elecsys Phospho-Tau (181P) assay, REF 09697870190 (**cobas e** 801 analyzer; x), gave the following correlations (pg/mL):

Number of samples measured: 124

Passing/Bablok[13]
y = 0.969x + 0.0353
r = 0.999

The sample concentrations were between 0.0480 and 9.79 pg/mL.

Clinical performance

Ruling out amyloid pathology (as determined based on amyloid PET visual read)

The clinical performance of the Elecsys Phospho-Tau (181P) Plasma assay with amyloid PET visual read as a reference method was assessed in a prospective multicenter study (Roche study RD006263), in which subjects were enrolled at 18 clinical sites in the US, Europe, and Australia. The study included subjects with cognitive complaints or objective memory impairment of unknown etiology being evaluated for Alzheimer's disease and other causes of cognitive decline, or in need of referral for further cognitive evaluation. Participants with potential comorbidities other than active delirium or encephalopathy were not excluded unless they presented any condition that, in the opinion of the investigator, could interfere in the

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proper execution of the study procedures and/or in their future permanence in the study.

In a prior analysis, the Elecsys Phospho-Tau (181P) Plasma assay cutoff had been established at 0.934 pg/mL. The cutoff was validated in an analysis population derived from the study described here, which consisted of 650 participants with subjective cognitive decline (n = 265), MCI (n = 345), or mild dementia (n = 30), for whom amyloid PET scan results were available (PET tracer: 18F-florbetapir, 18F-florbetaben or 18F-flutemetamol). Cognitive stage was unknown in 10 participants.

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 146 (22.5 %) positive and 504 (77.5 %) negative amyloid PET reads.

The average age was 69.3 years (range: 55-80 years), 56 % of patients were female, 44 % of patients were male. The median of the Elecsys Phospho-Tau (181P) Plasma assay baseline was 0.850 pg/mL. The predictive values and agreement rates for the Elecsys Phospho-Tau (181P) Plasma assay with amyloid PET visual read were as follows:

	Agreement rates (%) (95 % CI)
Negative predictive value	93.8 (91.3, 95.6)
Positive predictive value	46.6 (42.7, 50.5)
Positive percentage agreement (PPA, “sensitivity”)	83.6 (76.7, 88.7)
Negative percentage agreement (NPA, “specificity”)	72.2 (68.2, 76.0)
Overall percentage agreement	74.8 (71.3, 78.0)

Cutoff for ruling out amyloid pathology

If pT181p is > 0.934 pg/mL, the test result is positive.

If pT181p is ≤ 0.934 pg/mL, the test result is negative.

References

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For further information, please refer to the appropriate user guide or operator’s manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

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.

CE 0123

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