Elecsys® Total-Tau CSF

Electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of total Tau in human Cerebrospinal fluid (CSF)

Indication
Tau (tubulin-associated unit) protein is one of the two hallmarks of Alzheimer's disease, besides β-Amyloid (1-42) (Abeta42). The Elecsys Total-Tau CSF assay is designed to detect the six human brain Tau isoforms or fragments in human CSF.

Numerous studies show that total Tau CSF (tTau) levels increase around 2 – 3 fold in mild-moderate AD patients compared to age-matched controls while CSF β-Amyloid (1-42) levels decrease to around half the level in controls.[1,2] CSF tTau has been shown to reflect the intensity of the neuronal and axonal damage and degeneration. High CSF tTau is also associated with a faster progression from MCI to AD.[3]

Intended use
The Elecsys Total-Tau CSF assay is an in vitro diagnostic immunoassay intended for the quantitative determination of the Total-Tau protein in human CSF.

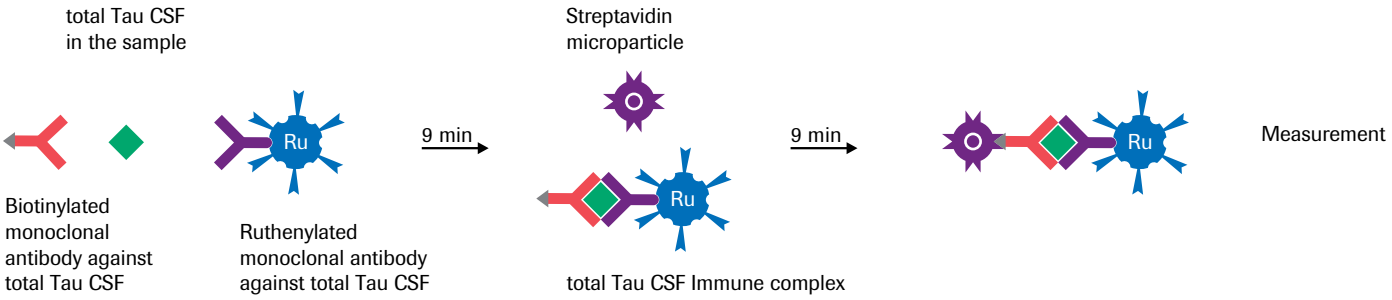
1. The Elecsys Total-Tau CSF assay is intended to be used alone or in combination with Elecsys β-Amyloid (1-42) CSF assay as a ratio in adult subjects with mild cognitive impairment (MCI) as an aid to identify subjects who are at lower vs. higher risk of cognitive decline as defined by change in a clinical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

Limitations of use
- The Elecsys Total-Tau CSF assay is an adjunct to other clinical diagnostic evaluations.
- A positive Elecsys Total-Tau CSF assay result and/or a positive Elecsys Total-Tau CSF to Elecsys β-Amyloid (1-42) CSF ratio result does not establish a diagnosis of AD or other cognitive disorder.
- The safety and effectiveness of the Elecsys Total-Tau 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 Elecsys and **cobas e** immunoassay analyzers.

NOT AVAILABLE FOR SALE IN THE US.

Test principle: 2-step sandwich assay



1st incubation (9 minutes)
50 µL of sample, two biotinylated monoclonal Tau-specific antibodies (5.28.464 and 4.35.411) and a monoclonal Tau specific antibody (PC1C6) labeled with a ruthenium complex[a)] react to form a sandwich complex.

2nd incubation (9 minutes)
After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

Measurement
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/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

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

Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

Elecsys® technology
ECL (Electrochemiluminescence) is Roche's technology for immunoassay detection. Based on this technology and combined with well-designed, specific and sensitive immunoassays, Elecsys delivers reliable results. The development of ECL immunoassays is based on the use of a ruthenium-complex and tripropylamine (TPA). The chemiluminescence reaction for the detection of the reaction complex is initiated by applying a voltage to the sample solution resulting in a precisely controlled reaction. ECL technology can accommodate many immunoassay principles while providing excellent performance.

Elecsys Total-Tau CSF assay characteristics

Testing time	18 min
Test principle	Sandwich principle
Calibration	2 point
Traceability	Tau(156-166)-Tau(192-202)-Tau(217-227) amid
Sample material	Human Cerebrospinal Fluid (CSF)
Sample volume	50 µL
LoB (Limit of Blank) LoD (Limit of Detection) LoQ (Limit of Quantitation) (Specification)	30 pg/mL 60 pg/mL 80 pg/mL
Measuring range	80 – 1,300 pg/mL (defined by the Limit of Quantitation and the maximum of the master curve). Values below the Limit of Quantitation are reported as <80 pg/mL. Values above the measuring range are reported as >1,300 pg/mL.
Intermediate precision	**cobas e** 411: 2.2 – 3.5 % (4.14 – 40.3 pg/mL) E170, **cobas e** 601, **cobas e** 602: 1.4 – 2.1 % (1.63 – 19.5 pg/mL)

Clinical values

1. Identification of patients at risk of cognitive decline

The ability of biomarker (BM) groups to predict changes in clinical scores; Clinical Dementia Rating Sum of Boxes (CDR-SB) and Mini Mental State Examination (MMSE) from baseline to 24 months were assessed in ADNI 1/GO/2 early and late mild cognitive impairment (MCI) cohort (N=619) based on the following:

Effect 1: no substantial changes in clinical scores (CDR-SB, MMSE) from baseline to 24 months in BM-negative patients.

Effect 2: a positive difference in changes of clinical scores (CDR-SB, MMSE) from baseline to 24 months between BM-positive and BM-negative patients.

Single marker tTau:
If tTau >300 pg/mL → test result positive.
If tTau ≤300 pg/mL → test result negative.

tTau/Abeta42 ratio
If tTau/Abeta42 ratio >0.28 → test result positive.
If tTau/Abeta42 ratio ≤0.28 → test result negative.

Clinical score	Biomarker	Effect (1) Estimate (95 % CI)[b)]	Effect (2) Estimate (95 % CI)
CDR-SB	tTau	0.56 (0.43, 0.69)	0.90 (0.68, 1.12)
	tTau/Abeta42	0.21 (0.07, 0.35)	1.41 (1.20, 1.62)
MMSE	tTau	-0.68 (-0.93, -0.43)	-1.40 (-1.81, -0.99)
	tTau/Abeta42	-0.13 (-0.40, 0.14)	-2.19 (-2.58, -1.79)

b) Confidence interval

2. Concordance with Amyloid Positron Emission Tomography (PET) visual read

Concordance between CSF biomarker test results and amyloid-PET visual read was assessed using CSF samples from the BioFINDER cohort of patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI) (N=277). The cut-off for the tTau/Abeta42 ratio was established as the value that optimized concordance with amyloid PET, then an adjustment factor was applied to obtain a cut-off valid for the pre-analytical handling procedure described in the section "Specimen collection and preparation" of the Elecsys β-Amyloid (1-42) CSF assay in its Method Sheet.

If tTau/Abeta42 ratio >0.28 → test result positive.
If tTau/Abeta42 ratio ≤0.28 → test result negative.

The agreement rates 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)

Note:
Due to the sticky properties of the β-Amyloid (1-42) protein, the Abeta42 concentration measured in a CSF sample is influenced by pre-analytical handling procedure. Accordingly, the provided cut-off value for the tTau/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 assay Method Sheet is used.

Material	Material number	Material configuration
Elecsys Total-Tau CSF	07356994-190	60 tests per rackpack
CalSet Total-Tau	07357010-190	4 × 1.0 mL
PreciControl Total-Tau	07357028-190	6 × 1.0 mL

References

1 *Mattsson, N., Zetterberg, H., Hansson, O. et.al. (2009).* ***JAMA 22,*** *302(4), 385-93.*

2 *Hampel, H., Blennow, K. (2004).* ***Dialogues Clin Neurosci,*** *6(4), 379-390.*

3 *Blom, ES., Giedraitis, V., Zetterberg, H. et al. (2009).* ***Dement Geriatr Cogn Disord,*** *27(5), 458-64.*

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