Elecsys® β-Amyloid (1-42) CSF

ElectroChemiLuminescence Immunoassay (ECLIA) for the in vitro quantitative determination of ß-Amyloid (1-42) in human Cerebrospinal Fluid (CSF)

Indication

β-Amyloid (1-42) peptide deposition in the brain is one of the two hallmarks of AD, besides neurofibrillary tangles. Pathological changes in the β-Amyloid metabolism are the earliest alterations during AD development. These changes are reflected by the decrease in the CSF concentrations of β-Amyloid (1-42) as well as by the increase in the brain uptake of the specific tracers on the β-Amyloid PET[1]. Current clinical diagnostic criteria for Alzheimer disease require a patient to have dementia before a diagnosis can be made, and are largely based on the exclusion of other disorders. No clinical method is available for identifying prodromal AD in patients with mild cognitive impairment (MCI), as such individuals have only mild disturbances in episodic memory[2].

Intended use

Elecsys β-Amyloid (1-42) CSF is an in vitro diagnostic immunoassay intended for the quantitative determination of the β-amyloid (1-42) protein concentration in human cerebrospinal fluid (CSF).

1. The Elecsys β-Amyloid (1-42) CSF assay is intended to be used in adult subjects with cognitive impairment being evaluated for Alzheimer disease (AD) and other causes of cognitive impairment. Result above the cutoff is consistent with a negative amyloid positron emission tomography (PET) scan. Negative β-amyloid PET scans indicate sparse to no neuritic plaques and are inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD.
2. The Elecsys β-Amyloid (1-42) CSF assay is intended to be used in combination with Elecsys Phospho-Tau (181P) CSF or Elecsys Total-Tau 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 are concordant with positive and negative amyloid Positron Emission Tomography (PET) scan result, respectively.
3. Elecsys β-Amyloid (1-42) CSF assay is intended to be used alone or in combination with Elecsys Phospho-Tau (181P) CSF or Elecsys Total-Tau 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.

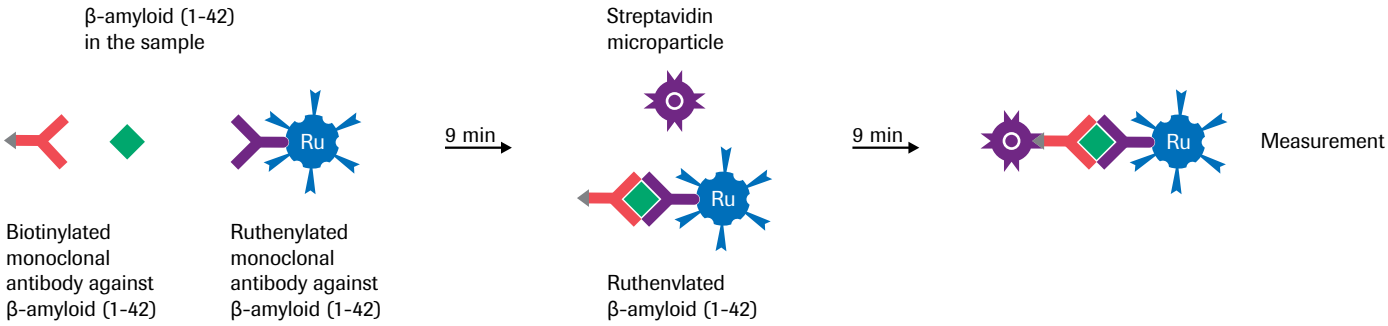
Limitations of use

- Elecsys β-Amyloid (1-42) CSF assay is an adjunct to other clinical diagnostic evaluations.
- A positive Elecsys β-Amyloid (1-42) CSF assay result and/or a positive Elecsys Phospho-Tau (181P) CSF or 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 β-Amyloid (1-42) 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: Total duration of assay: 18 minutes



1st incubation (9 minutes):
50 µL of sample, a biotinylated monoclonal β-Amyloid (1-42) specific antibody (21F12) and a monoclonal β-Amyloid (1-X) – specific antibody (3D6) labeled with a ruthenium complex[a)] are incubated and react to form a sandwich complex.

2nd incubation (9 minutes):
After addition streptavidin coated microparticles, the immunocomplex produced 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 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.

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® β-Amyloid (1-42) CSF test characteristics

Testing time	18 min
Test principle	Sandwich principle
Calibration	2 point
Traceability	LC-MS/MS*
Sample material	Human Cerebrospinal Fluid (CSF)
Sample volume	50 µL
LoB (Limit of Blank) LoD (Limit of Detection) LoQ (Limit of Quantitation)	60 pg/mL 120 pg/mL 200 pg/mL
Measuring range	200 – 1,700 pg/mL (defined by the Limit of Quantitation and the maximum of the master curve) Values below the Limit of Quantitation are reported as <200 pg/mL Values above the measuring range are reported as >1,700 pg/mL
Intermediate precision	E170, **cobas e** 601, **cobas e** 602: 1.5 – 4.0 % (7.36 – 38.14 pg/mL)

** LC-MS/MS: Liquid chromatography-tandem mass spectrometry reference method*

Clinical values

1. Concordance with amyloid 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-offs for Abeta42 and the ratios pTau/Abeta42 and tTau/Abeta42 were established based on the amyloid PET visual read. As the BioFINDER study[3] (**B**iomarkers **F**or **I**dentifying **N**eurodegenerative **D**isorders **E**arly and **R**eliably) used different pre-analytical handling procedure from the one used by Roche, an adjustment factor was was used to "transfer" the cut-offs.

The resulting cut-offs after adjustment were as follows:

- If Abeta42 ≤1,000 pg/mL test result positive.
  If Abeta42 >1,000 pg/mL test result negative.
- If pTau/Abeta42 ratio >0.024 test result positive.
  If pTau/Abeta42 ratio ≤0.024 test result negative.
- 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)[a)]

	Abeta42	pTau/Abeta42	tTau/Abeta42
PPA[b)]	90.9 (83.9, 95.6)	90.9 (83.9, 95.6)	90.9 (83.9, 95.6)
NPA[c)]	72.5 (65.0, 79.1)	89.2 (83.5, 93.5)	89.2 (83.5, 93.5)
OPA[d)]	79.8 (74.6, 84.4)	89.9 (85.7, 93.2)	89.9 (85.7, 93.2)

a) Confidence interval. b) PPA = Positive percentage agreement (sensitivity). c) NPA = Negative percentage agreement (specificity). d) OPA = Overall percentage agreement

2. Identification of patients at risk of cognitive decline

The ability of the biomarkers to separate patients at lower vs. higher risk of cognitive decline as measured by change in Clinical Dementia Rating Sum of Boxes (CDR-SB)and Mini Mental State Examination (MMSE) within 2 years was assessed using linear mixed-effects model, using CSF samples from ADNI 1/GO/2[4] (**A**lzheimer's **D**isease **N**euroimaging **I**nitiative) early and late mild cognitive impairment (MCI) cohort (N=619).

- If Abeta42 ≤1,000 pg/mL test result positive.
  If Abeta42 >1,000 pg/mL test result negative.
- If pTau/Abeta42 ratio >0.024 test result positive.
  If pTau/Abeta42 ratio ≤0.024 test result negative.
- If tTau/Abeta42 ratio* >0.28 test result positive.
  If tTau/Abeta42 ratio* ≤0.28 test result negative.

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

Clinical score	Biomarker	Effect (1) Estimate (95% CI)	Effect (2) Estimate (95% CI)
CDR-SB	Abeta42	0.31 (0.16, 0.46)	1.10 (0.89, 1.31)
	pTau/Abeta42	0.17 (0.02, 0.32)	1.42 (1.21, 1.62)
	tTau/Abeta42	0.21 (0.07, 0.35)	1.41 (1.20, 1.62)
MMSE	Abeta42	-0.25 (-0.53, 0.04)	-1.79 (-2.19, -1.40)
	pTau/Abeta42	-0.08 (-0.36, 0.20)	-2.17 (-2.56, -1.77)
	tTau/Abeta42	-0.13 (-0.40, 0.14)	-2.19 (-2.58, -1.79)

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-offs for Abeta42 alone, pTau/Abeta 42 and tTau/Abeta42 ratios are only valid if the pre-analytical handling procedure described in the section "Specimen collection and preparation" of the Elecsys β-Amyloid (1-42) CSF assays Method Sheet is used

Material	Material number	Material configuration
Elecsys® β-Amyloid (1-42) CSF	06986811-190	60 tests per rackpack
CalSet β-Amyloid (1-42)	06986838-190	4 × 1 mL each of CalSet β-Amyloid (1-42) Level 1 and 2
PreciControl β-Amyloid (1-42)	06986846-190	6 × 1 mL each of PreciControl β-Amyloid (1-42) Level 1 and 2

References

1 *Lewczuk, P. et al. (2015).* ***Advances in Medical Sciences 60,*** *76-82.*

2 *Blennow, K.et al. (2010).* ***Nat. Rev. Neurol. 6,*** *131-144.*

3 *http://biofinder.se/the_biofinder_study_group/.*

4 *ADNI, http://www.adni-info.org/.*

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