

**Category**

Best Medical Technology

**Drug / Device Name**

Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Phospho-Tau (181P) CSF (p-Tau181) assays

**Compound/ Tech Name**

N/A

**Trade Name**

N/A

**Date of Approval**

2022-12-08

**Indications**

The Elecsys  $\beta$ -Amyloid (1-42) CSFII and Elecsys Phospho-Tau (181P) CSF are in vitro electrochemiluminescence immunoassays for the measurement of the  $\beta$ -Amyloid (1-42) (Abeta42) and Phospho-Tau (181P) (pTau181) protein concentrations in cerebrospinal fluid (CSF) from adult patients aged 55 years and older being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment to generate a pTau181/Abeta42 ratio value. A negative result, defined as pTau181/Abeta42 ratio value below cut-off or an Abeta42 value above the measuring range, is consistent with a negative amyloid positron emission tomography (PET) scan result. A negative result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive result, defined as pTau181/Abeta42 ratio value above cut-off, is consistent with a positive amyloid PET scan result. A positive result does not establish a diagnosis of AD or other cognitive disorder. The pTau181/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations.

**Therapeutic Categories**

Alzheimer's Disease, diagnostics

**Background information and need for drug/device**

Alzheimer's Disease (AD) is one of the greatest health and societal challenges of our time and continues to intensify as populations age. Today in the US, one in three seniors die with dementia. By 2050, 140m people are projected to be living with the disease representing an economic burden of USD 17tn.<sup>1</sup> While dementia can be caused by multiple underlying causes, Alzheimer's disease is estimated to make up 60-80% of cases.<sup>2</sup> The Elecsys AD cerebrospinal fluid (CSF) assays fulfill a need for an accessible, affordable diagnostic solution for individuals with mild cognitive impairment (MCI) to enable appropriate treatment and care interventions, access to clinical trials and life/care planning.

Currently, the diagnosis of Alzheimer's is one of exclusion, largely based on various cognitive tests, routine laboratory tests and structural imaging (magnetic resonance imaging or computed tomography scan). Clinical criteria are limited and lead to an accurate diagnosis in only 70%-80% of

cases.<sup>3</sup> To increase diagnostic accuracy, an amyloid positron emission tomography (PET) scan, that measures the build-up of abnormal beta-amyloid protein in the brain, can be used as an adjunct to these evaluations.<sup>4</sup> However its use is limited due to high cost, scarcity and exposure to radioactivity. As an alternative, an Alzheimer's Association-sponsored working group has endorsed the use of CSF biomarkers for various clinical indications in the diagnosis of AD<sup>5</sup>. Importantly, CSF biomarker use has been recommended prior to initiation of treatment with lecanemab, in particular an increased pTau/Abeta42 ratio to establish the presence of amyloid. Lecanemab has been approved in the US for patients meeting the clinical criteria for mild cognitive impairment or mild AD dementia.<sup>6</sup>

The Elecsys AD CSF assays were developed to meet the need for an accessible, affordable, radiation-free diagnostic alternative that agrees highly with amyloid PET imaging. The test quantifies the levels of beta-Amyloid (1-42) peptide (Abeta42) and tau protein phosphorylated at amino acid 181 (p-Tau181). These molecules are modified versions of beta-Amyloid and tau proteins whose accumulation in brain tissue in extracellular amyloid plaques and intracellular neurofibrillary tangles are the hallmarks of AD. The Elecsys Abeta42 assay is traceable to reference materials ensuring accuracy of the Abeta42 ratio results.<sup>7</sup>

Both tests are immunoassays that make use of a two-step sandwich principle using a combination of biotinylated monoclonal antibodies and ruthenium complex-labeled monoclonal antibodies against the two targets, with reactions for the two targets performed separately. After addition of streptavidin-coated microparticles, the complexes become bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into a measuring cell where the microparticles are magnetically captured onto the surface of an electrode. After unbound particles are removed, voltage is applied to the electrode resulting in chemiluminescent emission which is measured by photomultiplier. Both assays are intended for use on the family of fully automated cobas e immunoassay analyzers. Results for each assay are determined by an analyte-specific calibration curve generated by 2-point calibration and a master curve provided by Roche. The ratio of these biomarkers (p-Tau181/Abeta42) is consistent with a negative amyloid PET scan if the result is less than or equal to the cutoff (negative), and with a positive amyloid PET scan if the result is above the ratio cutoff (positive, see History of Development section for further data).

#### Attached Files:

- Prix Galien USARocheBackground.pdf

#### History of the development of the drug/device

The Elecsys CSF AD assays were developed over a ten year journey that required discovery and innovation within Roche as well as collaboration with key partners in industry, academic medicine and patient advocacy groups, enabling the best science to be incorporated industry-wide and thereby helping to optimize care for all patients, regardless of which test they receive.

These assays were first released as research-use only tests to enable clinical studies that could advance our understanding of AD and to facilitate drug development. Other commercial and laboratory-developed investigational tests to measure CSF biomarkers in AD were also deployed, for similar purposes. While the importance of the CSF biomarker tests themselves became evident over time,

significant quantitative variability was observed between different investigational assays, as well as between laboratories for an individual assay, and within laboratories for individual specimens<sup>8</sup>. This quantitative discordance pointed to different sources of variability: the use of different, assay specific calibrators, which can be the source of considerable inter-assay variability, and pre-analytical parameters, which can cause inter- and intra-assay variability. Roche played a key role in developing solutions to both of these challenges.

The development of a certified reference material (CRM) that could be used for standardization of immunoassays performed on various platforms focused on Abeta42. The development of “gold standard” reference measurement procedures (RMPs) required for CRMs were undertaken through a joint effort between the Alzheimer Association-initiated Global Biomarker Standardization Consortium (GBSC) and the International Federation of Clinical Chemistry’s Working Group on CSF Proteins. Two liquid chromatography/mass spectrometry-based RMPs were developed<sup>9,10</sup> and qualified by the Joint Committee for Traceability in Laboratory Medicine as higher order reference methods suitable for use in quantifying CRMs. The availability of RMPs led to the development of three CRM preparations at three different concentrations that were shown to reduce quantitative bias between different Abeta42 assays<sup>11</sup>. Roche was the sole industry collaborator in RMP development<sup>10</sup> and a key industry collaborator in the development of CRMs<sup>11</sup>.

Roche also undertook an extensive investigation to identify pre-analytical parameters that affected biomarker measurement and to define a simplified protocol that could be easily incorporated into routine clinical practice to optimise test reproducibility. The adhesive property of Abeta42, particularly to non-polypropylene plastics, was identified as the major contributor to quantitative variability. Conditions for CSF collection, transport, handling/processing, and storage were defined that optimized Abeta42 recovery and ultimately improved test reproducibility. These findings were published<sup>12</sup> and were incorporated into international guidelines for pre-analytical handling of fresh and frozen CSF<sup>13</sup>, resulting from the work of a US Alzheimer’s Association-led collaborative consortium of investigators and industry partners, including Roche.

Clinical performance of the Elecsys AD test was determined for the first generation Elecsys AD assays through retrospective testing of CSF samples from two cohorts with available clinical status and amyloid PET results, considered to be the diagnostic gold standard for AD. The Swedish BioFINDER1 study cohort was used to obtain the p-Tau181/Abeta42 ratio that differentiates positive and negative results (“ratio cut-off”). The analysis population consisted of 277 participants with mild cognitive symptoms (120 had subjective cognitive decline, 153 had MCI, and for 4 patients no assignment was available). The Alzheimer’s Disease Neuroimaging Initiative (ADNI) studies ADNI-GO and ADNI2 were used to validate the cutoff ratio. The analysis population from the ADNI cohorts consisted of 646 participants (94 with significant memory concerns, 272 with early MCI, 152 with late MCI, and 128 with AD). Pre-analytical protocols for CSF handling differed between the BioFINDER1 and ADNI cohorts, necessitating a bridging study prior to cutoff validation in order to determine whether systematic differences in quantification occurred as a result of specimen handling disparities and to define a conversion factor that could be applied to measurements and to the cutoff ratio to account for quantification differences. The bridging study measured endogenous p-Tau181 and Abeta42 from CSF samples of patients suspected of normal pressure hydrocephalus as non-Alzheimer’s controls. CSF samples were handled according to BioFINDER1 and ADNI protocols and tested with the first generation Elecsys AD test. Meaningful systematic differences were observed for Abeta42 but not p-Tau181. A conversion factor to adjust ADNI results relative to BioFINDER1 results and a revised cutoff

to apply to the ADNI validation cohort results were defined. Using the revised cutoff, the agreements with amyloid PET classification were positive percent agreement = 88.2 (95% CI: 84.4 - 91.2); negative percent agreement = 92.6 (95% CI: 89.1 - 95.1). The ratio of p-Tau181/Abeta42 had concordant predictions for amyloid status in 583 of 646 individuals (90.25 %). The number of cases with discordant CSF status compared to amyloid PET assessments was 63 (9.75 %), consisting mainly of p-Tau181/Abeta42 negative and amyloid PET-positive cases. The validation met internally pre-defined acceptance criteria, with a final ratio cut-off of 0.22 for the first generation Elecsys AD assays.

The FDA-cleared Elecsys  $\beta$ -Amyloid (1-42) CSF II assay is the second generation test that incorporates standardization with the above described CRMs and the new routine-use pre-analytical protocol for CSF handling. To address systematic differences between results generated with the first and second assay generation, a second bridging study, requiring additional CSF samples, was performed<sup>14</sup>. Similar to the first bridging study (but in different specimens), endogenous p-Tau181 and Abeta42 were measured in CSF specimens from patients suspected of normal pressure hydrocephalus. CSF samples were prepared according to the BioFINDER protocol and measured using the first generation assays. The BioFINDER cohort was utilized for cutoff setting. The values were compared with the values in CSF samples prepared according to the new routine use pre-analytical protocol and measured with the second generation of the two assays. The CSF biomarker percentage measurements were highly correlated. No meaningful differences were obtained for p-Tau181. The mean percentage difference for Abeta42 was -6.32 % (95 % CI: -8.73 % to -3.90 %). The inverse value of the conversion factor ( $1/0.9368$ ) was used for the adjustment of p-Tau181/Abeta42 ratio cut-off defined in the BioFINDER<sup>1</sup> cohort. The adjusted ratio cut-off for the second generation test is  $0.022 \times 0.9368^{-1} = 0.023$ .

Attached Files:

- Prix Galien USA Roche History.pdf

### **Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition**

The innovation of the Elecsys AD CSF test lies in the clinical robustness of the biomarker combination, p-Tau181 and Abeta42, along with the fully automated instrument on which testing is performed. The ratio of p-Tau181/Abeta42 can discriminate amyloid PET-positive from amyloid PET-negative patients with sufficiently high accuracy that a gray zone around the test cutoff is not required<sup>15,16,17</sup>, which is clinically advantageous because all test results are usable for diagnostic purposes, in combination with additional clinical information and provided that quality control specifications are met. Tests with lower diagnostic accuracy, such as those that employ Abeta42/Abeta40 ratios from measurement of Abeta42 and Abeta40 levels in CSF, require gray zones around the test cut-off due to overlapping results of individuals with amyloid PET-positive and amyloid PET-negative results within a range of results above and below the cutoff.<sup>16,18</sup> Results within the gray zone are likely positive and have increased diagnostic uncertainty compared to amyloid PET. This could pose a number of diagnostic challenges including continued uncertainty for the patient and healthcare provider, the potential need for and cost of additional diagnostic testing, as well as a delay in diagnosis.

The Elecsys AD CSF test is also innovative because it facilitates a shift in the AD testing paradigm from the esoteric testing laboratory (scarce, specialized instruments with limited menu) to routine daily testing on common laboratory analyzers, enabling broad access to AD testing and improving time to diagnosis. The test is designed to run on a commonly available (>3600 placed in the US) family of fully

automated (sample-in/answer-out), random access analyzers with rapid time-to-result, that are workhorses in US core chemistry laboratories due to the large, comprehensive menu of available assays (>100).

The Elecsys AD CSF test has the potential to enable research when deployed in the conduct of clinical trials. For example, it could be useful for enrollment, particularly in studies of pathophysiology or treatment of pre-clinical stages, when only biomarkers or PET have utility, for study execution, because accessibility allows testing to be performed at diverse sites, and for data interpretation since CSF biomarker results can be compared across all testing sites due to the incorporation of an optimized pre-analytical protocol into the test procedure and calibrators for Abeta42 that are traceable to international standards. When used in clinical trials as an alternative to amyloid PET, the Elecsys CSF AD test has the potential to enable many different avenues of AD research that could be beneficial to the human condition including research on AD as a disease entity, particularly factors associated with disease progression, on therapeutics that slow, stop or reverse AD progression, and on non-invasive digital biomarkers and minimally invasive laboratory-based AD diagnostics, such as plasma-based biomarker tests, which will allow for the identification of the future wave of patients who will benefit from care and treatment.

Finally, the Elecsys CSF AD test has the potential to improve the lives of people with dementia by improving their care in a number of different ways. Given the rising prevalence of dementia, it can help meet the increased need for diagnostic testing that amyloid PET cannot. It could help provide more rapid, accurate diagnosis compared to the use of clinical criteria alone which is difficult and often erroneous. Timely diagnosis is especially important for AD patients with MCI who benefit from early patient/caregiver education, care planning, and interventions that can preserve cognitive function such as lifestyle changes and treatment with disease modifying therapies such as lecanemab which was recently approved for use in these patients.

Attached Files:

- Prix Galien USA Roche Innovation.pdf

### **Please provide appropriate references (ie Pubmed links)**

References for the entire submission appears below. Note we included a PDF for each section that includes the references and maintains the web links (although, reference numbering changes in the PDFs due to segmenting the overall submission)

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