Elecsys Anti-SARS-CoV-2 S

cobas®

REF		Σ	SYSTEM
09289267190	09289267501	200	**cobas e** 411 **cobas e** 601 **cobas e** 602
09289275190	09289275501	300	**cobas e** 801

English

For use in the USA only

System information

For **cobas e** 411 analyzer: test number 2550
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 71
For **cobas e** 801 analyzer: Application Code Number 10230

Warning

- For use under Emergency Use Authorization only.
- For prescription use only.
- For in vitro diagnostic use.
- The results of this semi-quantitative test should not be interpreted as an indication or degree of immunity or protection from reinfection.

Intended use

Elecsys Anti-SARS-CoV-2 S for use on the **cobas e** analyzers is an electrochemiluminescence immunoassay intended for qualitative and semi-quantitative detection of antibodies to SARS-CoV-2 in human serum and plasma (lithium heparin, dipotassium-EDTA, tripotassium-EDTA, and sodium citrate). The Elecsys Anti-SARS-CoV-2 S assay is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection. At this time, it is unknown for how long antibodies persist following infection and if the presence of antibodies confers protective immunity. The Elecsys Anti-SARS-CoV-2 S assay should not be used to diagnose or exclude acute SARS-CoV-2 infection.
Testing is limited to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. 263a, that meet requirements to perform moderate or high complexity tests.

Results are for the detection of SARS-CoV-2 antibodies. Antibodies to SARS-CoV-2 are generally detectable in blood several days after initial infection, although the duration of time antibodies are present post-infection is not well characterized. Individuals may have detectable virus present for several weeks following seroconversion.

Laboratories within the United States and its territories are required to report all results to the appropriate public health authorities. The sensitivity of the Elecsys Anti-SARS-CoV-2 S assay early after infection is unknown. Negative results do not preclude acute SARS-CoV-2 infection. If acute infection is suspected, direct testing for SARS-CoV-2 is necessary.

False positive results for Elecsys Anti-SARS-CoV-2 S assay may occur due to cross-reactivity from pre-existing antibodies or other possible causes.

The Elecsys Anti-SARS-CoV-2 S assay is only for use under the Food and Drug Administration's Emergency Use Authorization.

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

Summary

SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19), is an enveloped, single-stranded RNA Betacoronavirus. 7 coronaviruses have been identified as agents of human infection, causing disease ranging from mild common cold to severe respiratory failure.[1]

SARS-CoV-2 is transmitted primarily from person-to-person through respiratory droplets and aerosols.[2,3] The incubation period from infection to detectable viral load in the host commonly ranges from 2 to 14 days.[4,5] Detection of viral load can be associated with the onset of clinical signs and symptoms, although a considerable proportion of individuals remains asymptomatic or mildly symptomatic.[6,7,8] The interval during which an individual with COVID-19 is infectious has not yet been clearly established, however, transmission from symptomatic, asymptomatic, and pre-symptomatic individuals has been well described.[9,10,11]

Coronavirus genomes encode 4 main structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). The S protein is a very large transmembrane protein that assembles into trimers to form the distinctive surface spikes of coronaviruses. Each S monomer consists of an N-terminal S1 domain and a membrane-proximal S2 domain. The virus gains entry to the host cell through binding of the S protein to the angiotensin-converting enzyme 2 (ACE2), which is enzymatically active on the surface of numerous cell types including the alveolar type II cells of the lung and epithelial cells of the oral mucosa.[12,13] Mechanistically, ACE2 is engaged by the receptor-binding domain (RBD) on the S1 subunit.[14,15]

Upon infection with SARS-CoV-2, the host mounts an immune response against the virus, typically including production of specific antibodies against viral antigens. IgM and IgG antibodies to SARS-CoV-2 appear to arise nearly simultaneously in blood.[16] There is significant inter-individual difference in the levels and chronological appearance of antibodies in COVID-19 patients, but median seroconversion has been observed at approximately 2 weeks.[17,18,19,20]

Serologic assays can play an important role in understanding viral epidemiology in the general population. The Elecsys Anti-SARS-CoV-2 S assay uses a recombinant protein representing the RBD of the spike antigen in a double-antigen sandwich assay format. The Elecsys Anti-SARS-CoV-2 S assay detects antibodies to SARS-CoV-2 spike protein RBD.

Test principle

Double-antigen sandwich principle. The antigens within the reagent capture predominantly anti-SARS-CoV-2 IgG, but also anti-SARS-CoV-2 IgA and IgM. Total duration of assay: 18 minutes.

- 1st incubation: 20 µL of sample (**cobas e** 411, **cobas e** 601, and **cobas e** 602 analyzers) or 12 µL of sample (**cobas e** 801 analyzer), biotinylated SARS-CoV-2 S-RBD-specific recombinant antigen and SARS-CoV-2 S-RBD-specific recombinant antigen labeled with a ruthenium complex[a)] 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/ProCell M/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 reagent barcode or e-barcode.

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

Reagents - working solutions

cobas e 411, **cobas e** 601, and **cobas e** 602 analyzers:

The reagent rackpack is labeled as ACOV2S.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 12.0 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 SARS-CoV-2 S-Ag~biotin (gray cap), 1 bottle, 16 mL:
Biotinylated RBD domain of SARS-CoV-2 S as recombinant antigen < 0.4 mg/L; HEPES[b)] buffer 50 mmol/L, pH 7.4; preservative.

R2 SARS-CoV-2 S-Ag~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 16 mL:
RBD domain of SARS-CoV-2 S as recombinant antigen labeled with ruthenium complex < 0.4 mg/L; HEPES[b)] buffer 50 mmol/L, pH 7.4; preservative.

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

cobas e 801 analyzer:

Elecsys Anti-SARS-CoV-2 S

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The **cobas e** pack is labeled as ACOV2S.

M Streptavidin-coated microparticles, 1 bottle, 16 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 SARS-CoV-2 S-Ag~biotin, 1 bottle, 18.8 mL:
Biotinylated RBD domain of SARS-CoV-2 S as recombinant antigen < 0.4 mg/L; HEPES[b)] buffer 50 mmol/L, pH 7.4; preservative.

R2 SARS-CoV-2 S-Ag~Ru(bpy)$_3^{2+}$, 1 bottle, 18.8 mL:
RBD domain of SARS-CoV-2 S as recombinant antigen labeled with ruthenium complex < 0.4 mg/L; HEPES[b)] buffer 50 mmol/L, pH 7.4; preservative.

Calibrators are available separately. See Materials required (but not provided) section of this Method Sheet.

Precautions and warnings

For use under Emergency Use Authorization only.
This test has not been FDA-cleared or -approved; this test has been authorized by FDA under an Emergency Use Authorization (EUA) for use by laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. 263a, that meet requirements to perform high complexity tests.
This test has been authorized only for detecting antibodies against SARS-CoV-2, not for any other viruses or pathogens.
This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

For in vitro diagnostic use.
Do not use reagents beyond the labeled expiration date.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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 dust/fume/gas/mist/vapours/spray.

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.

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 in the kit have been assembled into a ready-for-use unit that cannot be separated.

cobas e 411, **cobas e** 601, and **cobas e** 602 analyzers:

All information required for correct operation is read in from the respective reagent barcodes.

cobas e 801 analyzer:

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 Elecsys reagent kit / **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the **cobas e** 411, **cobas e** 601 and **cobas e** 602 analyzers	14 days

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the **cobas e** 801 analyzer	14 days

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, dipotassium EDTA (K_2-EDTA), tripotassium EDTA (K_3-EDTA), and sodium citrate plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 1.00 ± 0.10 + bias at 0.8 U/mL ± 20 %.

For native samples collected in sodium citrated plasma: Slope 0.84 ± 0.10.

Results with sample materials other than serum were compared to serum results. Linear regression was performed for results obtained with the different sample materials, comparison of slope and bias verified comparability to serum results.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower values (U/mL) for individual patient specimens. In order to minimize dilution effects it is essential that respective sampling devices are filled completely according to manufacturer's instructions. For citrated plasma (1 part citrate solution + 9 parts blood), the dilution effect must be taken into account.

Stable for 3 days at 15-25 °C, 14 days at 2-8 °C, 3 months at -20 °C (± 5 °C). The samples may be frozen 3 times.

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.

Specimens should not be subsequently altered with additives (e.g. biocides, anti-oxidants or substances that could possibly change the pH or ionic strength of the sample) in order to avoid erroneous findings.

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

Do not use heat-inactivated samples.

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.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 09289291190, CalSet Anti-SARS-CoV-2 S, for 4 x 1.0 mL
- REF 09289313190, PreciControl Anti-SARS-CoV-2 S, 4 x 1.0 mL
- REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent (**cobas e** 411, **cobas e** 601, and **cobas e** 602 analyzers) or
- REF 05192943190, Diluent Universal 2, 2 x 36 mL sample diluent (**cobas e** 411, **cobas e** 601, and **cobas e** 602 analyzers) or
- REF 07299001190, Diluent Universal, 36 mL sample diluent (**cobas e** 801 analyzer)
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials for **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials for the **cobas e** 801 analyzer:

- 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

Additional material for all analyzers:

- REF 11298500160, 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.

cobas e 411, **cobas e** 601, and **cobas e** 602 analyzers:
Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers. Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer.

cobas e 801 analyzer:
Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager.

All analyzers: Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles/ **cobas e** pack.

Calibration

Traceability: This method has been standardized against the internal Roche standard for anti-SARS-CoV-2-S. This standard consists of an equimolar mixture of 2 monoclonal antibodies that bind Spike-1 RBD at 2 different epitopes. 1 nM of these antibodies correspond to 20 U/mL of the Elecsys Anti-SARS-CoV-2 S assay. No international standard is currently available for anti-SARS-CoV-2-S.

Note: The defined unit is specific for the Elecsys Anti-SARS-CoV-2 S assay and must not be used interchangeably with units of other assays.

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 since the same reagent kit 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:

- after 31 days when using the same reagent lot on the **cobas e** 411, **cobas e** 601 and **cobas e** 602 analyzers
- after 42 days when using the same reagent lot on the **cobas e** 801 analyzer
- after 14 days when using the same reagent kit or **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Anti-SARS-CoV-2 S. Please refer to the PreciControl Method Sheet for instructions for use, including description of the controls and the expected results.

In addition, other commercially available quality control material can be used that covers at least two levels of analyte.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit / **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Follow your laboratory's quality control procedures if the results obtained do not fall within the acceptable limits. Please refer to PreciControl instructions for use. 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 and accrediting group guidelines for quality control.

Calculation

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

Interpretation of the patient results

Result	Interpretation
< 0.80 U/mL	Negative for anti-SARS-CoV-2-S

Result	Interpretation
≥ 0.80 U/mL - ≤ 250 U/mL	Positive for anti-SARS-CoV-2-S, numeric value within the measuring interval
> 250 U/mL	Positive for anti-SARS-CoV-2-S, numeric value as "> 250 U/mL"

Note: Due to the diversity of the antibodies, the measured anti-SARS-CoV-2-S value can vary depending on the testing procedure used and the applied standard. Results obtained from a single sample using tests from different manufacturers can therefore differ. If there is a change in the assay procedure used to test the same patient then the anti-SARS-CoV-2-S values obtained upon changing over to the new procedure must be confirmed by parallel measurements with both methods. For citrated plasma (1 part citrate solution + 9 parts blood), the dilution effect must be taken into account.

Limitations

- Drug interferences are measured based on recommendations given in CLSI (Clinical and Laboratory Standards Institute) 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.
- Results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.
- This device should not be used to diagnose or exclude acute SARS-CoV-2 infection. Direct testing for SARS-CoV-2 with a molecular assay should be performed to evaluate acute infection in symptomatic individuals.
- The clinical applicability of semi-quantitative results is currently unknown and cannot be interpreted as an indication or degree of immunity nor protection from reinfection, nor compared to other SARS-CoV-2 antibody assays.
- Results obtained with this assay may not be used interchangeably with values obtained with different manufacturers' test methods.
- A positive result may not indicate previous SARS-CoV-2 infection. Consider other information including clinical history and local disease prevalence, in assessing the need for a second but different serology test to confirm an immune response.
- A negative result for an individual subject indicates the absence of detectable anti-SARS-CoV-2 antibodies. Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. A negative result can occur if the quantity of the anti-SARS-CoV-2 antibodies that are detected and are not present in the specimen is below the detection limits of the assay, or the antibodies that are detected are not present during the stage of disease in which a sample is collected.
- It is not known at this time if the presence of antibodies to SARS-CoV-2 confers immunity to re-infection.
- Not to be used to determine SARS-CoV-2 infection in donated blood units. This test should not be used for blood donor screening.
- The performance of this test has not been established in individuals that have received a COVID-19 vaccine. The clinical significance of a positive or negative antibody result following COVID-19 vaccination has not been established, and the result from this test should not be interpreted as an indication or degree of protection from infection after vaccination.
- The performance of this test was established based on the evaluation of a limited number of clinical specimens. Samples used to establish positive clinical agreement were collected between March and July 2020 in Switzerland, Germany, and Ukraine. The clinical performance has not been established in all circulating variants but is anticipated to be reflective of the prevalent variants in circulation at the time and location of the clinical evaluation. Performance at the time of testing may vary depending on the variants circulating, including newly emerging strains of SARS-CoV-2 and their prevalence, which change over time.

Conditions of Authorization for the Laboratory

The Elecsys Anti-SARS-CoV-2 S assay Letter of Authorization, along with the authorized Fact Sheet for Healthcare Providers, the authorized Fact Sheet for Patients, and authorized labeling are available on the FDA website: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas. However, to assist clinical laboratories using the Elecsys Anti-SARS-CoV-2 S ("your product" in the conditions below), the relevant Conditions of Authorization are listed below:

- Authorized laboratories[c)] using your product will include with test result reports, all authorized Fact Sheets. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.
- Authorized laboratories using your product will use your product as outlined in the Instructions for Use. Deviations from the authorized procedures, including the authorized instruments, authorized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use your product are not permitted.
- Authorized laboratories that receive your product will notify the relevant public health authorities of their intent to run your product prior to initiating testing.
- Authorized laboratories using your product will have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.
- Authorized laboratories will collect information on the performance of your product and report to DMD/OHT7-OIR/OPEQ/ CDRH (via email: CDRH-EUA-Reporting@fda.hhs.gov) and Roche (1-800-428-2336) any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of your product of which they become aware.
- All laboratory personnel using your product must be appropriately trained in automated immunoassay techniques and use appropriate laboratory and personal protective equipment when handling this kit, and use your product in accordance with the authorized labeling. All laboratory personnel using the assay must also be trained in and be familiar with the interpretation of results of the product.
- Roche, authorized distributors, and authorized laboratories using your product will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

c) The letter of authorization refers to, "Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform moderate or high complexity tests" as "authorized laboratories".

Limits and ranges

Analytical measuring interval

The analytical measuring interval is 0.40-250 U/mL. Numeric values are interpreted as "negative" (< 0.8 U/mL) and as "positive" (≥ 0.80 U/mL). Please see Interpretation of the results section. When sample results exceed the upper limit of the analytical measuring interval, refer to the Dilution section below. Values above the measuring range are reported as > 250 U/mL (or up to 2500 U/mL for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.30 U/mL

Limit of Detection = 0.35 U/mL

Limit of Quantitation = 0.40 U/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 corresponds to the highest measurement result that is likely to be observed for analyte-free samples with a probability of 95 %. The Limit of Blank was estimated as the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank is 0.30 U/mL.

The Limit of Detection is the lowest concentration of antibodies to SARS-CoV-2 in a sample that can be detected with a probability of 95 %. The Limit of Detection was calculated based on the Limit of Blank and the

standard deviation of low concentration samples. The Limit of Detection is 0.35 U/mL.

The Limit of Quantitation is defined as the lowest amount of analyte in a sample that can be accurately quantified with a CV ≤ 20 %. It has been determined using low concentration of anti-SARS-CoV-2-S samples. The Limit of Quantitation is 0.40 U/mL.

Dilution

Samples with anti-SARS-CoV-2-S concentrations above the measuring range can be diluted with Diluent Universal or Diluent Universal 2. The recommended dilution is 1:10 up to 1:100.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Note: Antibodies to SARS-CoV-2 are heterogeneous. In some isolated cases, this may lead to non-linear dilution behavior.

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: 1 run per day with 5 replicates of each sample for 5 days. The following results were obtained:

Repeatability and Intermediate precision

cobas e 411 analyzer					
		Repeatability		**Intermediate precision[d)]**	
Sample N = 25	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.483	0.014	2.8	0.016	3.4
Human plasma 2	0.826	0.023	2.8	0.023	2.8
Human plasma 3	5.74	0.131	2.3	0.150	2.6
Human plasma 4	12.3	0.266	2.2	0.304	2.5
Human plasma 5	54.6	1.58	2.9	1.58	2.9
Human plasma 6	77.9	1.78	2.3	2.07	2.7
Human plasma 7	190	3.03	1.6	3.69	1.9
PC[e)] ACOV2S 1[f)]	< 0.40	-	-	-	-
PC ACOV2S 2	10.8	0.207	1.9	0.230	2.1

d) Intermediate precision includes repeatability and between-day/run components.

e) PC = PreciControl

f) PC ACOV2S 1 is free of analyte and therefore consistently resulted below the measuring range (< 0.40 U/mL) throughout the experiment, standard deviation and coefficient of variance could therefore not be determined (-).

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision[d)]**	
Sample N = 25	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.441	0.007	1.6	0.016	3.7
Human plasma 2	0.933	0.014	1.5	0.022	2.3
Human plasma 3	5.60	0.102	1.8	0.181	3.2
Human plasma 4	12.0	0.189	1.6	0.334	2.8
Human plasma 5	53.2	0.761	1.4	1.46	2.7
Human plasma 6	75.5	1.55	2.1	2.70	3.6
Human plasma 7	183	3.31	1.8	5.13	2.8
PC ACOV2S 1[g)]	< 0.40	-	-	-	-
PC ACOV2S 2	10.5	0.118	1.1	0.341	3.3

g) PC ACOV2S 1 is free of analyte and therefore consistently resulted below the measuring range (< 0.40 U/mL) throughout the experiment, standard deviation and coefficient of variance could therefore not be determined (-).

cobas e 801 analyzer					
		Repeatability		**Intermediate precision[d)]**	
Sample N = 25	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.483	0.014	2.9	0.014	2.9
Human plasma 2	0.826	0.015	1.9	0.015	1.9
Human plasma 3	5.69	0.121	2.1	0.136	2.4
Human plasma 4	12.0	0.159	1.3	0.191	1.6
Human plasma 5	54.8	0.743	1.4	0.770	1.4
Human plasma 6	77.3	1.23	1.6	1.54	2.0
Human plasma 7	184	1.69	0.90	2.63	1.4
PC[e)] ACOV2S 1[g)]	< 0.40	-	-	-	-
PC ACOV2S 2	10.4	0.139	1.3	0.206	2.0

Precision study for evaluation of Lot-to-lot and Between-platform variability

An additional precision study for the estimation of lot-to-lot precision component was conducted with the design similar to the single-site precision study and with 2 additional lots.

Lot-to-lot precision

Lot-to-lot variability was evaluated for the **cobas e** 801 analyzer with 3 lots.

cobas e 801 analyzer					
		Repeatability		**Between-day**	
Sample N = 75	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.474	0.015	3.2	0.004	0.8
Human plasma 2a	0.824	0.018	2.2	0.003	0.4
Human plasma 2b	0.940	0.015	1.6	0.007	0.8
Human plasma 3	5.49	0.112	2.0	0.053	1.0
Human plasma 4	11.8	0.192	1.6	0.106	0.9
Human plasma 5	53.4	0.838	1.6	0.000	0.0
Human plasma 6	73.2	1.20	1.6	0.785	1.1
Human plasma 7	183	2.05	1.1	1.45	0.8
Human plasma 8	253	2.97	1.2	2.09	0.8

cobas e 801 analyzer					
		Between-lot		**Reproducibility**	
Sample N = 75	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.474	0.023	4.9	0.028	5.9
Human plasma 2a	0.824	0.052	6.3	0.055	6.7
Human plasma 2b	0.940	0.025	2.7	0.030	3.2
Human plasma 3	5.49	0.209	3.8	0.244	4.4
Human plasma 4	11.8	0.555	4.7	0.596	5.0
Human plasma 5	53.4	1.83	3.4	2.02	3.8
Human plasma 6	73.2	3.90	5.3	4.15	5.7
Human plasma 7	183	3.06	1.7	3.96	2.2
Human plasma 8	253	0.842	0.3	3.73	1.5

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Between-platform precision

Between-platform precision was evaluated as between different platform variability (1 **cobas e** 411, 1 **cobas e** 601, and 1 **cobas e** 801 analyzer).

cobas e 411, **cobas e** 601 and **cobas e** 801 analyzers					
		Repeatability		**Between-day**	
Sample N = 75	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.469	0.012	2.6	0.010	2.1
Human plasma 2a	0.812	0.020	2.4	0.017	2.1
Human plasma 2b	0.960	0.019	2.0	0.013	1.3
Human plasma 3	5.68	0.119	2.1	0.103	1.8
Human plasma 4	12.1	0.229	1.9	0.183	1.5
Human plasma 5	54.2	1.10	2.0	0.673	1.2
Human plasma 6	76.9	1.54	2.0	1.51	2.0
Human plasma 7	186	3.03	1.6	3.04	1.6
Human plasma 8	256	4.73	1.8	0.220	1.6

cobas e 411, **cobas e** 601 and **cobas e** 801 analyzers					
		Between-platform		**Reproducibility**	
Sample N = 75	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.469	0.024	5.1	0.028	6.0
Human plasma 2a	0.812	0.025	3.1	0.036	4.4
Human plasma 2b	0.960	0.023	2.4	0.032	3.4
Human plasma 3	5.68	0.050	0.9	0.165	2.9
Human plasma 4	12.1	0.124	1.0	0.319	2.6
Human plasma 5	54.2	0.777	1.4	1.51	2.8
Human plasma 6	76.9	0.970	1.3	2.36	3.1
Human plasma 7	186	3.16	1.7	5.33	2.9
Human plasma 8	256	2.71	1.1	6.89	2.7

Reproducibility including Lot-to-lot and Between-platform variability

cobas e 411, **cobas e** 601 and **cobas e** 801 analyzers							
		Repeatbility		**Between-day**		**Between-lot**	
Sample N = 225	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.465	0.014	3.0	0.015	3.2	0.013	2.9
Human plasma 2a	0.818	0.018	2.2	0.022	2.7	0.039	4.7
Human plasma 2b	0.940	0.018	1.9	0.017	1.7	0.014	1.5
Human plasma 3	5.57	0.106	1.9	0.110	2.0	0.178	3.2
Human plasma 4	12.0	0.249	2.1	0.229	1.9	0.539	4.5
Human plasma 5	53.6	1.11	2.1	0.846	1.6	1.83	3.4
Human plasma 6	73.9	1.55	2.1	1.62	2.2	3.36	4.5
Human plasma 7	186	3.00	1.6	3.09	1.7	5.15	2.8
Human plasma 8	257	4.72	1.8	4.67	1.8	2.12	0.8

cobas e 411, **cobas e** 601 and **cobas e** 801 analyzers					
		Between-platform		**Reproducibility**	
Sample N = 225	Mean U/mL	SD U/mL	CV %	SD U/mL	CV %
Human plasma 1	0.465	0.016	3.4	0.029	6.3
Human plasma 2a	0.818	0.018	2.1	0.051	6.3
Human plasma 2b	0.940	0.021	2.2	0.035	3.7
Human plasma 3	5.57	0.102	1.8	0.256	4.6
Human plasma 4	12.0	0.246	2.0	0.682	5.7
Human plasma 5	53.6	0.900	1.7	2.47	4.6
Human plasma 6	73.9	1.62	2.2	4.35	5.9
Human plasma 7	186	5.02	2.7	8.38	4.5
Human plasma 8	257	4.91	1.9	8.52	3.3

Analytical specificity

1468 samples containing potentially cross-reacting analytes were tested with the Elecsys Anti-SARS-CoV-2 S assay. All samples were obtained before October 2019. No cross-reactivity was found. The resulting overall specificity was 100 %. Results are shown in the following tables:

SARS-CoV-2 related

Indication	**N**	**Reactive**	**Specificity %**
MERS CoV (anti-S1 IgG+)	51	0	100
Common Coronavirus panel[h)]	151	0	100

h) pre-pandemic samples, which showed serologic reactivity to at least one of the endemic Coronavirus HKU1, NL63, 229E, or OC43.

Infectious respiratory diseases

Indication	**N**	**Reactive**	**Specificity %**
Bordetella pertussis	39	0	100
Chlamydia pneumoniae	36	0	100
Common cold panel[i)]	21	0	100
Enterovirus	35	0	100
Haemophilus influenzae B	75	0	100
Influenza A	40	0	100
Influenza B	45	0	100
Influenza vaccines	25	0	100
Mycoplasma pneumoniae	46	0	100
Parainfluenza	82	0	100
Respiratory syncytial virus	51	0	100

i) 21 potentially cross-reactive samples from individuals with common cold symptoms, collected before October 2019

Other infectious agents or disease states

Indication	**N**	**Reactive**	**Specificity %**
Adenovirus	25	0	100
Borrelia spp.	6	0	100
Candida albicans	13	0	100
Chlamydia trachomatis	12	0	100
CMV acute (IgM+, IgG+)	86	0	100
E. coli (anti-E. coli-reactive)	10	0	100
EBV acute (IgM+, VCA IgG+)	106	0	100

Indication	N	Reactive	Specificity %
Gonorrhea	5	0	100
HAV acute (IgM+)	10	0	100
HAV late (IgG+)	15	0	100
HAV vaccines	15	0	100
HBV acute	12	0	100
HBV chronic	12	0	100
HBV vaccines	15	0	100
HCV	50	0	100
HEV	12	0	100
HIV	10	0	100
HSV acute (IgM+)	24	0	100
HTLV	6	0	100
Legionella (IgGAM+)	7	0	100
Listeria spp.	6	0	100
Measles	10	0	100
Mumps	14	0	100
Parvovirus B19	30	0	100
Plasmodium falciparum (malaria)	8	0	100
Rubella acute (IgM+, IgG+)	12	0	100
Toxoplasma gondii (IgM+, IgG+)	8	0	100
Treponema pallidum (syphilis)	62	0	100
VZV (varicella-zoster virus)	30	0	100

Autoimmune diseases

Indication	N	Reactive	Specificity %
AMA (anti-mitochondrial antibodies)	30	0	100
ANA (anti-nuclear antibodies)	17	0	100
Hemophiliacs	15	0	100
RA (rheumatoid arthritis)	10	0	100
SLE (systemic lupus erythematosus)	10	0	100

Hepatic diseases

Indication	N	Reactive	Specificity %
Alcohol induced hepatitis/cirrhosis	13	0	100
Drug induced hepatitis/cirrhosis	10	0	100
Fatty liver	10	0	100
Liver cancer	10	0	100
Non-viral liver disease	15	0	100

Interfering substances

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	Interference (%)
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL	-1.4
Hemoglobin	≤ 1000 mg/dL or ≤ 10 g/L	-1.3
Intralipid	≤ 2000 mg/dL	2.9
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL	-2.3
Rheumatoid factors	≤ 1200 IU/mL	1.6
IgG	≤ 6.4 g/dL or ≤ 64 g/L	-9.8
IgA	≤ 1.6 g/dL or ≤ 16 g/L	-1.7
IgM	≤ 1.0 g/dL or ≤ 10 g/L	-3.0

Criterion: Deviation is ≤ 10 %

This assay has no biotin interference in serum concentrations up to 1200 ng/mL. Some studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after biotin ingestion for subjects consuming supplements of 20 mg biotin per day[21] and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin.[22]

No false negative results due to a high-dose hook effect were found with the Elecsys Anti-SARS-CoV-2 S assay but occurrence of high-dose hook effect cannot be completely excluded.

Commonly used pharmaceuticals

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found at 3x the daily dose, except for Itraconazole. The deviation for Itraconazole at 1.5x the daily dose is shown in the table below.

Drug	Concentration tested	Interference (%)
Acetylcysteine	150 mg/L	0.8
Acetylsalicylic acid	30 mg/L	2.7
Ampicillin	75 mg/L	3.5
Ascorbic acid	52.5 mg/L	2.8
Cefoxitin	750 mg/L	1.9
Doxycycline	18 mg/L	5.7
Heparin	3300 IU/L	3.3
Levodopa	7.5 mg/L	3.4
Methyldopa	22.5 mg/L	3.2
Metronidazole	123 mg/L	2.5
Rifampicin	48 mg/L	3.3
Acetaminophen	156 mg/L	-1.4
Cyclosporine	1.8 mg/L	-8.2
Ibuprofen	219 mg/L	-7.1
Theophylline	60 mg/L	-9.3
Phenylbutazone	321 mg/L	-6.1
Itraconazole	15 mg/L	-9.1

Special pharmaceuticals

In vitro tests were performed on 17 special pharmaceuticals. The deviation for the concentration tested is shown in the table below.

Drug	Concentration tested	Interference (%)
Zanamivir	0.006 mg/mL	-0.4
Oseltamivir	0.090 mg/mL	-0.1
Ceftriaxone	2.40 mg/mL	-3.3
Levofloxacin	0.300 mg/mL	1.2

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Drug	Concentration tested	Interference (%)
Meropenem	3.60 mg/mL	1.1
Ribavirin	0.720 mg/mL	3.8
Azithromycin	0.300 mg/mL	4.2
Lopinavir	0.720 mg/mL	-4.7
α-interferon 2b	3000 IU/mL	-0.9
Peramivir	0.360 mg/mL	-1.6
Tobramycin	0.360 mg/mL	2.1
Histamine Dihydrochl.	0.0006 mg/mL	1.1
Tocilizumab	0.384 mg/mL	0.8
α-interferon 2a	43200 IU/mL	2.2
Hydroxychloroquine sulfate C1	0.240 mg/mL	-4.0
Remdesivir	0.120 mg/mL	-1.4
Ritonavir	0.160 mg/mL	-7.6

Linearity

3 serum and 3 plasma (sodium citrate) samples containing high levels of SARS-CoV-2 antibodies were diluted with negative sample to prepare a dilution series comprised of 9 levels. Each level had 3 replicates. For serum samples, linearity was demonstrated for the interval of 0.26 U/mL to 346 U/mL with deviations from linearity within 15 %. For plasma samples, linearity was demonstrated for the interval of 0.29 U/mL to 304 U/mL with deviations from linearity within 15 %.

Taking into consideration the estimates of Limit of Blank, Limit of Detection, Limit of Quantitation, precision, and linearity, the analytical measuring interval is 0.40 U/mL to 250 U/mL.

Clinical agreement

Negative percent agreement

A total of 5991 serum samples were tested with the Elecsys Anti-SARS-CoV-2 S assay. All samples were obtained before October 2019. 1 false positive sample was detected.

The resulting overall negative percent agreement (NPA) in the internal study was 99.98 %. The lower 95 % confidence limit was 99.91 %.

Cohort	N	Reactive	NPA %	95 % lower confidence limit, %	95 % upper confidence limit, %
Diagnostic routine (Europe)	2528	0	100	99.85	100
Blood donors (USA)	2713	1	99.96	99.79	100
Blood donors (Africa)	750	0	100	99.51	100
Overall	**5991**	**1**	**99.98**	**99.91**	**100**

Positive percent agreement

A total of 1485 sodium citrate plasma samples from 331 symptomatic patients (including 172 samples from 172 hospitalized patients) with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys Anti-SARS-CoV-2 S assay. 1 or more sequential samples from these patients were collected at various time points after PCR confirmation. Positive percent agreement (PPA) was correlated with days post PCR specimen collection, and the results are shown for the first bleed per time bin.

First bleed

233 of the tested samples had a sampling date of 15 days or later after diagnosis with PCR. 225 of these 233 samples were determined with ≥ 0.8 U/mL in the Elecsys Anti-SARS-CoV-2 S assay and hence considered positive, resulting in a PPA of 96.6 % (95 % CI: 93.35-98.51 %) in this sample cohort.

Days after PCR positive result	Number tested	Pos	Neg	PPA (%)	95 % CI[j] (%)
0-7	32	29	3	90.6	(74.98 - 98.02)
8-14	77	67	10	87.0	(77.41 - 93.59)
≥ 15	233	225	8	96.6	(93.35 - 98.51)

j) CI = confidence interval

Titer development was investigated with the Elecsys Anti-SARS-CoV-2 S assay with sequential samples from individual patients ranging up to 126 days following reactive PCR result. None of the samples showed a decline of titers below the reactive range.

Titer development over time for patient samples ranging ≥ 100 days following a reactive PCR result is shown below. At this time, it is unknown for how long antibodies persist following infection and if the presence of antibodies confers protective immunity.

Donor	Day* U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL
1	20 20.4	23 22.2	27 30.5	33 47.4	36 51.7	61 73.5	82 87.7	103 114
2	21 36.1	24 44.3	31 32.4	34 48.5	37 51.4	62 63.1	83 73.2	104 71.9
3	26 139	34 223	38 186	41 153	45 150	67 198	87 147	106 155
4	21 32.3	30 95.3	33 151	36 315	41 374	62 293	83 244	107 214
5	30 33.0	35 29.5	38 31.2	42 41.2	112 59.9	-	-	-
6	20 7.88	30 32.6	38 26.6	62 39.2	71 35.7	76 40.3	86 36.0	107 42.1
7	19 20.7	22 40.4	25 101	29 149	39 115	48 97.7	59 115	104 175
8	15 22.1	22 14.2	30 37.1	37 166	40 136	55 226	79 124	107 96.9
9	34 181	41 148	45 148	52 165	67 152	74 154	87 125	106 119
10	26 4.42	29 4.79	32 4.83	35 5.21	42 4.67	52 5.95	73 7.28	103 7.69
11	16 305	42 296	78 371	106 408	-	-	-	-
12	28 139	31 162	40 114	44 166	47 141	62 93.0	86 69.5	103 59.1
13	24 33.9	31 45.6	38 63.7	46 53.4	59 47.4	74 41.8	92 41.9	102 42.8
14	25 79.8	28 86.4	33 120	41 117	47 103	59 108	76 97.1	109 105
15	36 255	52 165	68 126	77 94.8	92 122	96 107	106 141	126 162
16	30 425	44 246	51 379	58 298	73 215	85 169	90 173	104 147
17	29 220	32 205	40 177	48 141	55 136	76 122	95 116	101 101
18	31 63.6	39 66.9	43 53.4	53 43.4	64 57.3	68 48.9	92 69.7	102 58.8
19	32 94.5	46 79.5	53 84.3	60 71.8	68 92.1	74 73.6	94 78.9	102 75.8
20	38 56.4	46 84.2	68 104	74 106	82 114	99 141	106 152	110 146

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Donor	Day* U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL	Day U/mL
21	31 9.4	38 10.1	48 8.7	52 9.0	57 8.0	71 8.8	92 10.4	106 10.4
22	44 54.3	49 51.0	61 59.2	70 56.9	117 99.8	-	-	-
23	35.0 524	42.0 451	55.0 416	74.0 386	81.0 392	109 345	-	-
24	44 669	48 685	51 584	58 605	63 582	73 562	90 591	104 570
25	36 64.0	49 83.5	56 78.6	69 83.9	82 100	89 103	105 121	-

* Days after initial positive PCR.

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

Symbols

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CONTENT	Contents of kit
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REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

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