# Appendix 1
# National Microbiology Framework Agreement
# Order Form – Reference C110948
# Roche Diagnostics Limited

**FROM**

| | |
|---|---|
| **Authority:** | The Secretary of State for Health and Social Care as part of the Crown acting through the UK Health Security Agency of Nobel House, 17 Smith Square, London, SW1P 3HX (the **"Authority"**) |
| **Invoice address:** | Post: The UK Health Security Agency, Nobel House, 17 Smith Square, London, SW1P 3JR<br>Email: [redacted] |
| **Contract Manager:** | Name: [redacted] |
| **Secondary Contact: eg. business operational contact, project manager** | Name: [redacted] |
| **Procurement lead** | Name: [redacted] |
| **Name and address for notices:** | [redacted]<br>Address: UK Health Security Agency, Windsor House, 50 Victoria Street, London, SW1H 0TL |
| **Internal reference (if applicable):** | UKHSA CRE-ID 6242 |

**TO**

| | |
|---|---|
| **Supplier:** | Roche Diagnostics Limited, Charles Avenue, Burgess Hill, West Sussex, RH15 9RY |
| **Contract Manager:** | Name: [redacted] |
| **Secondary Contact:** | Name: [redacted] |
| **Name and address for notices:** | Name: [redacted] |

**Applicable terms and conditions**

The following terms and conditions are applicable to the Contract for this Order:

| | | |
|---|---|---|
| **Appendix A** | Call-off Terms and Conditions for the Supply of Goods and the Provision of Services | **Applicable to this Contract** |
| **Appendix B** | Optional Additional Call-off Terms and Conditions for Installation and Commissioning Services | ☐ **(only applicable if this box is checked)** |
| **Appendix C** | Optional Additional Call-off Terms and Conditions for Maintenance Services | ☐ **(only applicable if this box is checked)** |
| **Appendix D** | Optional Additional Call-off Terms and Conditions for Bespoke Research, Development and Manufacturing Requirements | ☐ **(only applicable if this box is checked and to the extent the applicable terms are included in Annex A (Order Specific Key Provisions))** |
| **Appendix E** | Optional Additional Call-off Terms and Conditions for Reagent Rental | ☐ **(only applicable if this box is checked)** |
| **Appendix F** | Optional Additional Call-off Terms and Conditions for Managed Equipment Services | ☐ **(only applicable if this box is checked)** |
| **Appendix G** | Optional Additional Call-off Terms and Conditions for Clinical Laboratory Diagnostic Testing Services | ☐ **(only applicable if this box is checked and to the extent the applicable terms are included in Annex A (Order Specific Key Provisions))** |
| **Appendix H** | Further Optional Additional Call-off Terms and Conditions<br>Each of the following clauses in Appendix H is only applicable to this Contract if the relevant box is checked: | **(only applicable if one or more boxes are checked)** |

| | |
|---|---|
| 1. TUPE applies at the commencement of the provision of Services | ☐ |
| 2. TUPE on exit | ☐ |
| 3. Different levels and/or types of insurance | ☐ |
| 4. Induction training for Services | ☐ |
| 5. Further Authority obligations | ☐ |
| 6. Assignment of Intellectual Property Rights in deliverables, materials and outputs of the Services | ☐ |
| 7. Inclusion of a Change Control Process | ☐ |

| | |
|---|---|
| 8. Authority step-in rights | ☐ |
| 9. Guarantee | ☐ |
| 10. Termination for convenience | ☒ |
| 11. Pre-Acquisition Questionnaire | ☐ |
| 12. Time of the essence (Goods) | ☐ |
| 13. Time of the essence (Services) | ☐ |
| 14. Specific time periods for inspection | ☐ |
| 15. Specific time periods for rights and remedies under Clause 3.6 of Schedule 2 of Appendix A | ☐ |
| 16. Right to terminate following a specified number of material breaches | ☐ |
| 17. Expert Determination | ☐ |
| 18. Consigned Goods | ☐ |
| 19. Improving visibility of Sub-contract opportunities available to Small and Medium Size Enterprises and Voluntary, Community and Social Enterprises | ☐ |
| 20. Management Charges and Information | ☐ |
| 21. COVID-19 related enhanced business continuity provisions | ☐ |
| 22. Buffer stock requirements | ☐ |
| 23. Modern slavery | ☒ |
| The additional Order Specific Key Provisions set out at Annex A (Order Specific Key Provisions) to this Order Form shall also apply to this Contract. | ☒ |

| 1. CONTRACT DETAILS |
|---|
| **(1.1) Commencement Date:** 18th January 2023 |
| **(1.2) Services Commencement Date (if applicable):**<br>N/A |

**(1.3) Contract Price ((i) breakdown and (ii) payment profile):**

1.3.1 The total contract value shall be one million, six hundred and sixty six pounds and no pence (£1,666,000) (Excl. VAT) (the **"Total Contract Value"**)

1.3.2 This comprises of the supply of Roche COBAS e801 Reagents.

1.3.3 Following execution of this Contract, the Authority shall submit to the Supplier a purchase order for the Total Contract Value (the "**Purchase Order**"). The Purchase Order shall be for the Goods specified in Appendix A (the "**Goods**"):

1.3.4 Only orders placed directly by the Authority are binding under this Contract.

1.3.5 See Appendix A - Goods Information and Pricing for the price of the Goods.

1.3.6 The Supplier shall comply with the invoicing process and associated terms see Section 2 of Annex A (Order Specific Key Provisions), including the provision of monthly consolidated invoices.

1.3.7 Payment terms are net 30 days in arrears from the date the Authority receives valid consolidated invoices in accordance with this Contract.

1.3.8 The Purchase Orders issued by the Authority in respect of this Agreement do not form part of this Agreement.

**(1.4) Term of Contract:**

1.4.1 This Contract shall be deemed to have commenced on 18th January 2023 (the **"Commencement Date"**) and shall, unless terminated earlier, or extended, in accordance with its terms, expire on 30 November 2024 (the **"Term"**).

1.4.2 The Authority may terminate the Contract for convenience at any time pursuant to clause 10 (Termination for convenience) of Appendix H (Further Optional Additional Call-off Terms and Conditions) of this Contract provided the Authority gives the Supplier not less than 90 days written notice.

**(1.5) Break Clause options:**

1.5.1 The Authority may review the Contract as at 31st March 2023 and 31st March 2024 and shall advise the Supplier of any change to requirement by giving the Supplier written notice no later than 28th February 2023 and 28th February 2024.

## 2. GOODS REQUIREMENTS

**(2.1) Description of the Goods:**

| Material Number | Product Description |
|---|---|
| 9289275190 | Anti-SARS-CoV-2 S Elecsys® E2G 300 |
| 9203079190 | Anti-SARS-CoV-2 N Elecsys® E2G 300 |

2.1.1 The Authority may, but is not obliged to, order, and the Supplier shall provide, the Goods as specified in Appendix C (the "**Specification**") to be delivered and used within UKHSA laboratories over the Term (the "**Goods**").

2.1.2 Subject to Clauses of this Order Form, the Authority shall be entitled to order the Goods, and the Supplier shall provide the Goods.

**Ordering Procedure:**

2.1.3 The Authority may, but shall not be obliged to, provide the Supplier with call off orders for the Goods up to, but not exceeding, cumulatively the Contract Price.

2.1.4 The Authority shall place call off orders for the Goods on an ad-hoc basis. To assist the Supplier with their planning and expediting of the ad hoc orders, the Authority shall endeavour to place any new orders by 4pm each Monday.

2.1.5 The Supplier shall endeavour to deliver the Goods in accordance with the following estimated lead-times:

| Quantity of Kits: | Estimated Lead Time*: |
|---|---|
| Less than 20 kits | 7 Working Days |
| 20 kits or more | 14 Working Days |

*All estimated lead times are subject to confirmation based on the quantity being requested, the stock being held by the Supplier and the actual lead-time at the point of request.

2.1.6 The Supplier shall ensure the Goods delivered comply with the Specification and the Supplier's description of the Goods (which will contain any relevant technical information, quality standard, relevant testing and validation information and any relevant handling and storage information given).

2.1.7 The supplier warrants that any Goods that are shown to fail this Specification within the expiry date required for the goods are, at the Authority's sole discretion, either replaced or full credit given.

**(2.2) Premises and Location at which the Goods are to be delivered / provided:**

2.2.1 The supplier shall deliver the goods to the Premises and Location detailed in Appendix B – Delivery Location and such other locations as the Authority specifies from time to time.

2.2.2 The Supplier shall ensure that all products are labelled with product description, part number, volume, batch number, storage requirements and barcode.

2.2.3 All planned deliveries shall be pre-advised by the Supplier to the Authority's primary delivery contact stated below (individually or collectively be known as the "**Delivery Contact**") at least 48 hours prior to attendance:

2.2.4 Primary delivery contact: Business Operational Contact – [redacted]

E-mail: [redacted]

2.2.5 The Supplier shall provide the following data when notifying the Delivery Contact:

- Supplier name
- Authority's Order Number
- Item reference, Supplier's part code, description and quantity
- Item / pallet / carton reference for multi-pallet / carton shipments

2.2.6 The Delivery Contact will confirm:

- Booking reference number
- Date and time of service (where applicable); and
- Delivery address.

2.2.7 Delivery of the Goods shall be considered to have occurred when the Delivery Contact or other authorised representative of the Authority at the Authority's nominated location has signed the delivery note.

- The Supplier shall ensure that all Goods are packaged suitably so as not to cause loss or damage during shipment to a Delivery Location
- In the event that the Supplier is unable to deliver the agreed order in full, the Supplier shall inform the Authority of the actual number of Assays and/or Consumables to be shipped prior to shipment, explaining the reasons for non-compliance with the agreed order and inform the Authority of when such missing Goods will be delivered. The Supplier shall, using its best endeavours, deliver such missing Goods at the earliest possible time
- The Supplier shall ensure that all Goods are labelled with the product description, part number, volume, batch number, storage requirements and barcode.
- The Supplier shall inform the Authority of any requests, made directly to the Supplier, by the Delivery Locations, to vary the delivery and the Authority will approve or reject such requests.
- The Parties reserve the right to modify the above process, by written agreement of both Parties, as necessary during the Term of this Contract

2.2.8 The Supplier shall carry out deliveries within the ordinary working hours at the delivery location on the date specified.

**(2.3) Key personnel of the Supplier to be involved in the Goods:**

Name: [redacted]

**(2.4) Performance standards:**

2.4.1 The Supplier shall ensure the goods conform and perform to the Specification.

2.4.2 Timely delivery of the Services in accordance with section 2.6 below.

2.4.3 Proof of delivery of the Services to be supplied with each monthly consolidated invoice

**(2.5) Quality Standards & Warranty:**

2.5.1 Unless expressly agreed otherwise the Supplier shall ensure that the Goods have an expiry date of at least 4 weeks following the date of delivery by the Supplier, to allow the laboratories sufficient time to use the kit.

2.5.2 The Supplier warrants the Goods shall be fit for purpose and shall conform to the Specification for not less than four (4) weeks commencing from the date of delivery in accordance with Clause 10 of the Call-Off Terms and Conditions.

2.5.3 In the event that Goods are deemed to be Defective Goods by the Authority, the Authority, at its sole discretion, shall provide a written notice to the Supplier in accordance with Schedule 2, clause 3.6 of the Call-Off Terms and Conditions.

2.5.4 The quality assurance standards set out in the Supplier's Specification shall apply to the manufacture and supply of the Goods.

**(2.5.5) Return Conditions:**

For Goods that do not meet the quality and performance standards The Return Conditions will be as follows:

2.5.5.1 The Supplier is responsible for collecting the Goods.

2.5.5.2 The Supplier is responsible for the costs of returning/collecting the Goods.

2.5.5.3 Return Conditions shall be in accordance with Schedule 2 - clause 3 (Inspection, rejection, return and recall of the Goods) of the Call Off Terms and Conditions

**(2.6) Contract monitoring arrangements:**

2.6.1 The Authority Contract Manager (or their delegate) and the Supplier Contract Manager shall meet Monthly (or such other frequency as reasonably requested by the Authority) and no less than quarterly (unless otherwise notified by the Authority) to discuss the Supplier's performance and other matters connected to the delivery of the Contract.

2.6.2 The Supplier shall provide any management information required on a monthly basis to include:

- 2.6.2.1 Performance against KPIs, delivery expectations, demand
- 2.6.2.2 Compliance to processes: Deliveries and Invoicing
- 2.6.2.3 Overview of any innovation, product performance/enhancement, service redesign, and horizon plans
- 2.6.2.4 Supplier input/issues on contract performance

**(2.7) Management information and meetings:**

2.7.1 At the Authority's request, within five (5) Working Days of such request, the Supplier shall provide such management information to the Authority as the Authority may reasonably request from time to time (including without limit any information about the Supplier's supply chain and its compliance in relation to sustainability requirements).

2.7.2 Performance and key performance indicators to be reported by the Supplier on a monthly basis include:

- 2.7.2.1 Quantity of delivery correct against the relevant Order as per Orders placed in accordance with Clause 2 of this Order Form
- 2.7.2.2 Quality of delivery in accordance with this Contract, including delivery presentation (the delivery must be presented in such a way that it can be unloaded safely and in a ready for use condition taking into consideration this Contract's requirements) and condition of the Goods (the Goods must be in a condition that is new and ready to use).
- 2.7.2.3 Timely and accurate administration (including booking/amending delivery times and Orders and invoices, delivery advice notes and labels being in accordance with the requirements of this Contract)
- 2.7.2.4 Establish any improvement action plans required
- 2.7.2.5 Corrective action notices

## 3. CONFIDENTIAL INFORMATION (if applicable)

**(3.1) The following information shall be deemed Confidential Information:**

- 3.1.1 Supplier pricing.
- 3.1.2 Contact details including, but not limited to, email addresses, landline / mobile phone numbers, etc. of Supplier representatives
- 3.1.3 Contact details including, but not limited to, email addresses, landline / mobile phone numbers, etc. of Authority's representatives

**(3.2) Duration that the information shall be deemed Confidential Information:**

- 3.2.1 For a period of three (3) years after the expiry or earlier termination of this Contract unless otherwise agreed in writing by the Parties.

## 4. DATA PROCESSING (if applicable)

**(4.1) Personal Data to be processed by the Supplier:**
In accordance with the Data Protection Protocol.

## 5. LEASE / LICENSE (if applicable)

**(5.1) The Authority is granting the following lease or licence to the Supplier:**

N/A

**Signature:**
**For and on behalf of the Authority**

[redacted]

Date Signed: 23/01/23

**Signature:**
**For and on behalf of the Supplier**

[redacted]

Date Signed: 23/01/2023

**Annex A**

**Order Specific Key Provisions**

**1. Delivery and Risk:**

1.1. The Supplier shall deliver the Goods to the location set out in Appendix B of this order form and such other locations as the Authority specifies from time to time.

1.2. The Supplier will ensure that the provision of the Goods is made in accordance with the terms of this Order Form including all Annexes, Appendices the Call-Off Terms and Conditions.

**2. Invoicing Process:**

2.1 Payment terms are net 30 days from receipt of a valid monthly invoice.

2.2 Within 10 Business Days of receipt of the Supplier's countersigned copy of the Contract, the Authority will send a unique purchase order ("PO") number. The Supplier must be in receipt of a valid PO number before submitting an invoice.

2.3 Notwithstanding submission of the Purchase Order to the Supplier, the Authority is only committed to purchasing such quantities of the Goods as it orders in accordance with this paragraph 2; and submission of the Purchase Order to the Supplier shall not constitute commitment on behalf of the Authority to purchase Goods up to the full Contract Price.

2.4 The Supplier shall provide a consolidated monthly invoice to the Authority for all Goods received and accepted by the Authority each month.

2.5 All invoices should be sent for approval and must include the proof of delivery to the Authority's designated finance mailbox e-mail [redacted] and their agreed representative (to be confirmed at first Supplier meeting) before being submitted for payment.

2.6 All invoices must be sent quoting a valid purchase order number. The Supplier shall provide a current statement of accounts on a monthly basis; this is a standard commercial process and should show all invoices raised and amounts outstanding.

2.7 To avoid delay in payment the Supplier shall provide compliant invoices that includes, as a minimum, a valid PO number, PO line-item number (if applicable), PO line description, and the details (name and telephone number) of the Authority's authorised representative. Non – compliant invoices will be sent back to the Supplier, which may lead to a delay in a payment.

2.8 In support of Goods being delivered the Supplier shall provide to the Authority a signed delivery note confirming receipt of the Goods by email to [redacted]

2.9 If you have a query regarding an outstanding payment, please contact our Accounts Payable section by email to: [redacted]

# Appendix A
## Goods Information and Pricing

| Product Number | Product Description | Price Each |
|---|---|---|
| 9289275190 | Anti-SARS-CoV-2 S Elecsys® E2G 300 | [redacted] |
| 9203079190 | Anti-SARS-CoV-2 N Elecsys® E2G 300 | [redacted] |

# Appendix B
## Delivery Locations

The Supplier will be required to deliver to the following location.

Emerging Pathogen Serology
UK Health Security Agency
Porton Down
Salisbury
Wiltshire
SP40JG

# Appendix C
# Product Specifications

09289275500V4.0

# Elecsys Anti-SARS-CoV-2 S

cobas®

| REF | | Σ | SYSTEM |
|---|---|---|---|
| 09289275190 | 09289275500 | 300 | **cobas e** 402<br>**cobas e** 801 |

**English**

**System information**

| Short name | ACN (application code number) |
|---|---|
| ACOV2S | 10230 |

**Intended use**

Immunoassay for the in vitro quantitative determination of total antibodies to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spike (S) protein receptor binding domain (RBD) in human serum and plasma. The test is intended as an aid to assess the adaptive humoral immune response, including neutralizing antibodies, to the SARS-CoV-2 S protein after natural infection with SARS-CoV-2 or in vaccine recipients.

The **electro**chemiluminescence immuno**assay** "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 subunit and a membrane-proximal S2 subunit. The virus gains entry to the host cell through binding of the S protein to the angiotensin-converting enzyme 2 (ACE2), which is present 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 acts as the virus receptor and 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 against 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.[17,18,19,20,21] Also, titers after a resolved infection show considerable variance from patient to patient.[22]

Antibodies against SARS-CoV-2 with strong neutralizing capacity, especially potent if directed against the RBD, have been identified.[21,23,24] Competition of antibodies with binding of the RBD to ACE2 has been established as a reliable correlate for the assessment of the presence of neutralizing antibodies.[25] Numerous vaccines for COVID-19 are in development, many of which focus on eliciting an immune response to the RBD.[26,27,28]

Serologic assays can play an important role in understanding viral epidemiology in the general population and identifying individuals who are apparently naive and thus presumably susceptible to the virus.

The Elecsys Anti-SARS-CoV-2 S assay uses a recombinant protein representing the RBD of the S antigen in a double-antigen sandwich assay format, which favors the quantitative determination of high affinity antibodies against SARS-CoV-2. Quantification of the antibody response can help to determine the specific antibody titer and aid in longitudinal monitoring of the dynamics of the antibody response in individual patients. The Elecsys Anti-SARS-CoV-2 S assay shows good agreement with direct and surrogate virus neutralization assays.

**Test principle**

Double-antigen sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, 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 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 ACOV2S.

M Streptavidin-coated microparticles, 1 bottle, 16.0 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 buffer 50 mmol/L, pH 7.4; preservative.

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

**Precautions and warnings**

For in vitro diagnostic use.
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.

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.

# Elecsys Anti-SARS-CoV-2 S

cobas®

**Disposal:**

P501 Dispose of contents/container to an approved waste disposal plant.

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**

For professional use.

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

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.

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

Li-heparin, $K_2$-EDTA, $K_3$-EDTA and sodium citrate plasma.

Li-heparin and $K_2$-EDTA plasma tubes containing separating gel can be used.

Capillary blood collected in serum, Li-heparin plasma or $K_2$-EDTA plasma sampling tubes.

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.

For capillary blood derived samples: negative samples: < 0.4 U/mL, reactive samples: recovery within 70-130 % of serum value.

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.

Stable for 14 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.

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.

The performance of the Elecsys Anti-SARS-CoV-2 S assay has not been established with cadaveric samples or body fluids other than serum and plasma.

**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 07299001190, Diluent Universal, 36 mL sample diluent
- 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 the internal Roche standard for anti-SARS-CoV-2 S.

Subsequently, it could be shown that the First WHO International Standard for anti-SARS-CoV 2 immunoglobulin (human), NIBSC code: 20/136, behaves identically to the internal Roche standard, with a Pearson correlation coefficient r = 0.9996 between Limit of Quantitation and 1000 BAU/mL. Hence, the numeric results in U/mL of the Elecsys Anti-SARS-CoV-2 S assay and BAU/mL are equivalent (e.g. 1 U/mL of the Elecsys Anti-SARS-CoV-2 S assay corresponds to 1 BAU/mL).

Note: Although the defined unit for the Elecsys Anti-SARS-CoV-2 S assay is identical to the binding antibody unit (BAU) defined by the WHO standard, the defined unit for the Elecsys Anti-SARS-CoV-2 S assay must not be used interchangeably with units of other assays. See also the section "Interpretation of results".

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.

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:

- after 42 days when using the same reagent lot
- after 14 days when using the same **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.

In addition, other suitable control material can be used.

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.

09203079500V4.0

# Elecsys Anti-SARS-CoV-2

cobas®

| REF | | Σ | SYSTEM |
|---|---|---|---|
| 09203079190 | 09203079500 | 300 | **cobas e** 402<br>**cobas e** 801 |

**English**

**System information**

| Short name | ACN (application code number) |
|---|---|
| ACOV2 | 10226 |

**Intended use**

Elecsys Anti-SARS-CoV-2 is an immunoassay for the in vitro qualitative detection of antibodies (including IgG) to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in human serum and plasma. The test is intended as an aid in the determination of the immune reaction to SARS-CoV-2.

The electrochemiluminescence immunoassay "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 virus of the family Coronaviridae, genus Betacoronaviruses. Viruses of this family share similarities in their genome and organization, including the 4 structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). They cause diseases with symptoms ranging from those of a mild common cold to more severe ones such as the Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and COVID-19. Other coronaviruses known to infect humans include 229E, NL63, OC43 and HKU1. The latter are ubiquitous and infection typically causes common cold or flu-like symptoms.[1,2]

SARS-CoV-2 is mainly transmitted person-to-person primarily via respiratory droplets, but indirect transmission through contaminated surfaces is also possible.[3,4,5,6] The virus infects host cells via the angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the lungs.[7,8]

The incubation period for COVID-19 is thought to be within 14 days following exposure, with median incubation period being 4-5 days.[3,9,10] The interval during which an individual with COVID-19 is infectious has not yet been clearly established, however, transmission from both symptomatic and asymptomatic individuals has been described.[1,11,12,13,14,15] Those infected often exhibit fever and respiratory symptoms.[16,17,18] The spectrum of symptomatic infection ranges from mild to critical, with severe cases occurring predominantly in adults with advanced age or underlying medical comorbidities.[17,19,20]

Definite COVID-19 diagnosis entails direct detection of SARS-CoV-2 RNA by nucleic acid amplification technology (NAAT).[21,22,23] Serological assays, which detect antibodies against SARS-CoV-2, can contribute to identify individuals, which were previously infected by the virus, and to assess the extent of exposure of a population. They might thereby help to decide on application, enforcement or relaxation of containment measures.[24]

Upon infection with SARS-CoV-2, the host mounts an immune response against the virus, including production of specific antibodies against viral antigens. Understanding the dynamics of the antibody response to the virus is critical in establishing a relevant time window to use serology tests. Both immunoglobulin M (IgM) and G (IgG) have been detected as early as day 5 after symptom onset.[25,26] Median seroconversion has been observed at day 10-13 for IgM and day 12-14 for IgG[27,28,29], while maximum levels have been reported at week 2-3 for IgM, week 3-6 for IgG and week 2 for total antibody.[25,26,27,28,29,30,31] Whereas IgM seems to vanish around week 6-7[32,33] high IgG seropositivity is seen at that time.[25,32,33] While IgM is typically the major antibody class secreted to blood in the early stages of a primary antibody response, levels and chronological order of IgM and IgG antibody appearance seem to be highly variable for SARS-CoV-2.

Anti-SARS-CoV-2 IgM and IgG often appear simultaneously, and some cases have been reported where IgG appears before IgM, limiting its diagnostic utility.[26,27,29,34,35]

After infection or vaccination, the binding strength of antibodies to antigens increases over time - a process called affinity maturation.[36] High-affinity antibodies can elicit neutralization by recognizing and binding specific viral epitopes.[37,38] While correlates of immunity/protection to SARS-CoV-2 still need to be identified, neutralization of the virus is presumed to be an important role of antibodies.[39] In SARS-CoV-2 infection, antibodies targeting both the spike and nucleocapsid proteins, are formed as early as day 9 onwards, which correlates with a strong neutralizing response, suggesting seroconversion may lead to protection for at least a limited time.[34,40,41,42,43] However, more scientific evidence will be necessary to determine if neutralizing antibodies against SARS-CoV-2 confer long-term immunity.

The Elecsys Anti-SARS-CoV-2 assay uses a recombinant protein representing the nucleocapsid (N) antigen in a double-antigen sandwich assay format, which favors detection of high affinity antibodies against SARS-CoV-2. Elecsys Anti-SARS-CoV-2 detects antibody titers, which have been shown to positively correlate with neutralizing antibodies in neutralization assays.[44,45]

**Test principle**

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, biotinylated SARS-CoV-2-specific recombinant antigen and SARS-CoV-2-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 II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

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

**Reagents - working solutions**

The **cobas e** pack (M, R1, R2) is labeled as ACOV2.

M Streptavidin-coated microparticles, 1 bottle, 16.0 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 SARS-CoV-2-Ag-biotin, 1 bottle, 18.8 mL:
Biotinylated SARS-CoV-2-specific recombinant antigen (E. coli) < 0.5 mg/L; HEPES[b)] buffer 50 mmol/L, pH 7.7; preservative.

R2 SARS-CoV-2-Ag-$Ru(bpy)_3^{2+}$, 1 bottle, 18.8 mL:
SARS-CoV-2-specific recombinant antigen labeled with ruthenium complex < 0.5 mg/L; HEPES buffer 50 mmol/L, pH 7.7; preservative.

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

ACOV2 Cal1 Negative calibrator 1, 1 bottle of 0.67 mL:
Human serum, non-reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.

ACOV2 Cal2 Positive calibrator 2, 1 bottle of 0.67 mL:
Human serum, reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.

**Precautions and warnings**

For in vitro diagnostic use.
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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

# Elecsys Anti-SARS-CoV-2

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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: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-SARS-CoV-2 (ACOV2 Cal2) was heat-inactivated for 30 minutes at 56 °C.

However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[46,47]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

**Reagent handling**

For professional use.

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

*Calibrators:*

The calibrators are supplied ready-for-use in bottles compatible with the system.

Store the calibrators at 2-8 °C for later use.

Perform **only one** calibration procedure per bottle.

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

| Stability of the calibrators: | |
|---|---|
| unopened at 2-8 °C | up to the stated expiration date |
| after opening at 2-8 °C | 31 days |

| Stability of the calibrators: | |
|---|---|
| on the analyzers at 20-25 °C | use only once |

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

**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, $K_2$-EDTA and $K_3$-EDTA plasma.

Li-heparin and $K_2$-EDTA plasma tubes containing separating gel can be used.

Capillary blood collected in serum, Li-heparin or $K_2$-EDTA sampling tubes.

Criterion: Absolute deviation of negative samples ± 0.3 COI (cutoff index) from serum value; reactive samples: recovery within 70-130 % of serum value.

Stable for 7 days at 15-25 °C, 14 days at 2-8 °C, 28 days 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 or systems 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/collection system 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.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

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

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.

The performance of the Elecsys Anti-SARS-CoV-2 assay has not been established with cadaveric samples or body fluids other than serum and plasma.

**Materials provided**

See "Reagents – working solutions" section for reagents.

**Materials required (but not provided)**

- REF 09216928190, PreciControl Anti-SARS-CoV-2, 4 x 1.0 mL
- REF 07299010190, Diluent MultiAssay, 45.2 mL sample diluent
- 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