PHE Public Health Microbiology Framework Agreement
Order Form

(in accordance with NHS Framework Agreement for the Supply of Goods (August 2014) – Appendix A – Call-off Terms and Conditions for the Supply of Goods / Services)

FROM

Participating Authority:	Public Health England (PHE), an executive agency of the Department of Health and Social Care.
Service address:	As per PHE official purchase order(s)
Invoice address:	PHE Accounts Payable Team Financial Accounting Services PHE Porton Down, Manor Farm Road Salisbury, Wiltshire SP4 0JG United Kingdom Email: [redacted]
PHE Procurement Lead:	[redacted]
PHE Project Manager for Implementation Phase:	[redacted]
PHE Supplier Relationship Manager (SRM):	[redacted]
PHE Internal Reference (if applicable)	To be quoted on all correspondence relating to this Order Form: Supply of Elecsys® Anti-SARS-CoV-2 COVID-19 antibody serology test to Public Health England.

TO

Supplier Details:	Roche Diagnostics Limited ("Roche") Charles Avenue Burgess Hill West Sussex RH15 9RY
Supplier Contact Details:	[redacted]

	[redacted]

1. CONTRACT DETAILS
(1.1) Contract Purpose: Pursuant to this Contract, Roche shall supply the Elecsys® Anti-SARS-CoV-2 COVID-19 antibody serology test and related consumables to PHE. This Contract shall also govern the use in connection with the performance of the Elecsys® Anti-SARS-CoV-2 COVID-19 antibody serology test.
(1.2) Contract Start Date (being the effective date from which this Contract commences as opposed to the date on which this Contract shall have been made. The date this Contract shall have been made is the date that the last party to sign shall have signed it, as set out in the signature block below)**: 18 May 2020**
(1.3) Contract Value (and breakdown if applicable): As set out in the table at Annex 3, subject to any increased requirement, as provided for in section 1.6 (c) below, the value of which is to be calculated at the price per test unit as also set out in the table at Annex 3.
(1.4) Contract End Date: A period of 6 months from the Contract Start Date subject to any permitted extensions as set out at 1.5 below.
(1.5) Contract Extension Options: The Contract shall be for a period of 6 months from the Contract Start Date ("Initial Term"), with an option to extend for an additional period of up to 6 months ("Extension Term"). Prior to the end of the Initial Term, Public Health England will give 45 calendar days' notice in writing on whether this Contract will come to an end or be extended, and if extended, the length of said extension.
(1.6) Deliverables - Goods: Pursuant to this Contract, Roche shall deliver the goods identified in Annex 1 ("the Goods"). **Timing of Delivery and Determination of Goods Allocation:** For the Initial Term and any subsequent Extension Term, the Goods are subject to the allocation process agreed between Roche and PHE, specifically: (a) Roche shall provide PHE with the 4 weekly forecast showing total number of tests available for distribution within the United Kingdom for that allocation cycle (such forecast being for volumes not less than the total minimum volume of tests which PHE has committed to purchase from Roche in the relevant period). (b) The table at Annex 3 sets out the total minimum volume of tests which PHE has committed to purchase from Roche within each period (as each such period is defined in column 2 of the table at Annex 3). (c) Where PHE determines that it has an increased requirement, it reserves the right to increase

the total minimum volume of tests which it has committed to purchase in any period starting after 30 June 2020 up to a maximum of 3 million tests in any such period. The Parties acknowledge that to the extent any allocation is required for testing under the 'Pillar 4' programme, they will discuss and agree how such Pillar 4 requirement will be implemented as against the provisions of this Contract. Any notice of increased requirement must be provided to Roche as part of the allocation information provided by PHE to Roche under subsection (d) below. The Parties acknowledge and agree that any PHE requirement over 3 million tests in any period will be subject to the agreement of both PHE and Roche and PHE acknowledge that Roche would, in such circumstances, require sufficient lead time to allow for increased production in any event.

(d) PHE shall provide Roche with the total number of tests to be allocated to each of the 21 networks as well as the Devolved Authorities and Crown Dependencies as outlined in Annex 2 for distribution within the United Kingdom for that allocation cycle. During the months of May and June, PHE shall instruct Roche with such information and a relevant reference number by no later than Monday at midday for each two week allocation cycle commencing on Monday 18 May 2020. For the month of July onwards, PHE shall instruct Roche with such information and a relevant reference number to be used in conjunction with the unique PO number (see section 1.10 below) monthly in advance by no later than the last Monday of the preceding month. For the avoidance of doubt, all instructions in respect of allocations should be sent by email addressed to [redacted]

(e) Upon receipt of the information and valid PO (bearing the unique PO number issued in accordance with section 1.10 below and the unique reference number for that particular order) regarding the number of tests to be allocated under subsection (d) above, Roche shall liaise with the Incident Management Lead at each network and by no later than midday the following day (Tuesday), Roche shall agree the number of tests to be delivered to each site in that given network and the timing of such delivery within the allocation period.

(f) Based on the confirmation email from the Incident Management Lead, Roche shall deliver the confirmed number of tests to the designated laboratory within 2 working days or as otherwise agreed between the parties.

The Parties reserve the right to modify this, by written agreement of both Parties, as necessary during the Term of this Contract.

(1.7) Instruments. For purposes of this Contract, PHE agrees that it shall use the existing installed instruments ("the Instruments") at sites within each of the networks including the Devolved Authorities and Crown Dependencies identified in Annex 2.

(1.8) Deliverables – Instrument Support: Not used

(1.9) Contract Price:

PHE shall pay to Roche the Contract Price as identified in Annex 3.

(1.10) PAYMENTS: Within five Working Days of receipt of your countersigned copy of this Contract, PHE will issue to Roche a unique PO Number. Roche must be in receipt of a valid PO

Number before submitting an invoice.

The unique PO Number will cover all the separate orders for Goods made under this Contract. However, for each such separate order, PHE will create a unique order reference number. That unique order reference number will be within the documentation returned to Roche requesting delivery of each agreed allocation. Each unique order reference number will cover all of the site locations to which Goods are to be delivered under that order period.

To avoid delay in payment it is important that the any invoice issued to PHE is compliant and that it includes a valid PO Number, order reference number and the details (name and telephone number) of your Buyer contact (i.e. Contract Manager).

If Roche have a queries regarding an outstanding payment please contact the PHE Accounts Payable section either by email to:

[redacted]
between 09:00-17:00 Monday to Friday.

2. ADDITIONAL REQUIREMENTS

(2.1) Supplemental requirements in addition to Call-off Terms and Conditions:

Exceptional circumstances as a result of the Covid-19 pandemic

2.1 Without prejudice to the Parties' obligations under the Contract (including but not limited to the Supplier's obligations under the Contract to supply the Goods, including as set out within the Order Form and the Roll-out Plan) the Parties recognise that the circumstances created as a result of the COVID-19 pandemic are exceptional and fast-moving. As a consequence, the Parties agree that they will act reasonably and in good faith together to seek to resolve any difficulties or challenges which may impact upon the manufacture and supply of Goods and in relation to the wider COVID-19 issues so as to ensure that public health is protected and preserved.

2.2 In this context:

2.2.1 the Supplier recognises that there may be a shortage of supply of Component Parts and accordingly, the Supplier shall take all reasonable steps to safeguard and protect all stocks of Component Parts held by it and its Group from time to time which may be required to manufacture the Goods;

2.2.2 the Supplier agrees to provide the Authority sufficient visibility of the Supplier's manufacturing processes and timelines for the manufacture and supply of Goods, in the form of its four week forecast, if so requested, to allow the Authority to plan an adjust order scheduling across the Authority's supply chain for products equivalent to or similar to the Goods;

2.2.3 the Supplier shall notify the Authority promptly of any exceptional events or circumstances which may impact upon the Supplier's ability to manufacture and supply Goods in accordance with this Contract and the Authority's requirements.

(2.2) Variations to Call-off Terms and Conditions for the Supply of Goods:

The Parties have agreed to certain amendments to the Call-Off Terms and Conditions for the Supply of Goods, as set out in Annex 4 to this Order Form.

Variations to Call-off Terms and Conditions for the Supply of Services: Not applicable.

2. 3. GOODS AND/OR SERVICES REQUIREMENTS

(3.1) Key personnel of the Supplier to be involved in the Services and deliverables:

[redacted]

(3.2) Specification/Quality/Performance standards:
According (as a minimum) to the published product specifications for Elecsys Anti-SARS-Cov-2 1FU E1G v1 and Elecsys Anti-SARS-Cov-2 E2G v1 at Annex 5 with the expectation of continued improvement in performance during the term of the Contract. For the purposes of this provision, "continued improvement" includes on-board stability, calibration performance, lot to lot variation or specific assay performance;

According with the findings of the published **Evaluation of Roche Elecsys Anti-Sars-CoV-2 serology assay for the detection of anti-SARS-CoV-2 antibodies** at Annex 6; and
C E Regulatory Certifications.

Once an established External Quality Assurance performance is live, the Goods supplied should meet national External Quality Assurance performance criteria and any nationally derived standard material in-line with Supplier-declared manufacturer performance.

(3.3) Location(s) at which the Services are to be provided:
Within the networks, Devolved Authorities and Crown Dependencies listed at Annex 2 the addresses of such sites being provided in the specific orders made under this Contract (as may be amended from time to time during the term of the Contract with the agreement of the Parties).

(3.4) Not used.

(3.5) Contract monitoring arrangements: As agreed by both parties in line with Schedule 8: Supplier Relationship Management of the Framework Agreement.

(**3.6) Management Information and meetings:** As agreed by both parties in line with Schedule 8: Supplier Relationship Management of the Framework Agreement.

(3.7) Notices
For the purposes of this Contract, any contractual notice to be served, shall be sent to the persons named in this Order Form.

4. CONFIDENTIAL INFORMATION (if applicable)

(4.1) The following information shall be deemed Confidential Information:
All information regarding pricing and charges (Section 1.9 above) and existing installed base Annex 1-4) shall be considered Confidential.

For the avoidance of doubt, this restriction shall not prevent PHE from complying with its obligations by notifying under Contracts Finder or complying with its reporting obligations under regulation 84 of the Public Contracts Regulations 2015.

(4.2) Duration that the information shall be deemed Confidential Information:
Duration of the Contract plus ten (10) years from termination of the Contract.

Signature: DocuSigned by: [redacted] 973E0E3601F84BE...

For and on behalf of the Authority

Name: [redacted]

Job Title: [redacted]

Date: 21-May-2020

Signature: DocuSigned by: [redacted]

For and on behalf of the Supplier

Name: [redacted]

Job Title: [redacted]

Date: 20-mai-2020

Annex 1
Goods

Material Number	Material Description
9203095190	Elecsys SARS-Cov-2 200 tests
9203079190	Elecsys SARS-Cov-2 E2G 300 tests

Annex 2 – List of Networks, Devolved Authorities and Crown Dependencies

Region	Network	Name	Email
London	L1	[redacted]	
	L2		
	L3		
Midlands	ME 1	[redacted]	
	ME 2		
	ME 4	[redacted]	
East of England	ME 5		
	ME 6		
	ME 8	[redacted]	
South West	S1		
	S2		
	S3		
South East			
	S6	[redacted]	
	S7		
	N1		

North East and Yorkshire	N2	[redacted]
North West	N3	
	N4	
	N5	
North East and Yorkshire		
	N7	
North West	N8	
Northern Ireland		
Scotland		
Wales		
Guernsey		

Annex 3
Contract Price

Test	Period	Total Minimum Volume PHE committed to purchase during each Period (as Period stated in column 2 of this table)	Test Unit Price	Total
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**18/05/20-31/05/20**	[redacted]		
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**01/06/20-30/06/20**			
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**01/07/20-31/07/20**			
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**01/08/20-31/08/20**			
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**01/09/20-30/09/20**			
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**01/10/20-31/10/20**			
Elecsys SARS-CoV-2 ab assay Elecsys SARS-CoV-2 ab assay e801	**01/11/20-18/11/20**			
		[redacted]		**£13,464,000**

Annex 4

ADDITIONAL REQUIREMENTS (2.2 – Variations to Call-off Terms and Conditions)

Annex 5

Product specifications for Elecsys Anti-SARS-Cov-2 1FU E1G v1 and Elecsys Anti-SARS-Cov-2 E2G v1

Annex 6

Evaluation of Roche Elecsys Anti-Sars-CoV-2 serology assay for the detection of anti-SARS-CoV-2 antibodies

[redacted]

ANNEX 4 TO CONTRACT FOR THE SUPPLY GOODS RELATED TO TESTING FOR COVID-19

ADDITIONAL REQUIREMENTS (2.2 – Variations to Call-off Terms and Conditions)

SCHEDULE 2 of the Call-off Terms and Conditions

Clause 1.7 (Supply of Goods) shall be amended by the replacement of the cross-reference with the correct cross-reference to Clause 1.6.

Clause 2.3 shall be deleted and replaced by the following:

2.3 "The following details shall be shown on the outside of every package and within a delivery note which must accompany each package:

2.3.1 a description of the Goods which shall include, without limitation, the weight of the Goods where available and any order number allocated to the Goods by the Authority and/or Supplier;

2.3.2 the quantity in the package, where available;

2.3.3 any special directions for storage;

2.3.4 the expiry date of the contents, where applicable;

2.3.5 the batch number; and

2.3.6 the name and address of the manufacturer of the Goods and Supplier.

In addition, all Goods that customarily bear any mark, tab, brand, label, serial numbers or other device indicating place of origin, inspection by any government or other body or standard of quality must be delivered with all the said marks, tabs, brands, labels, serial numbers or other devices intact. Without prejudice to the generality of the foregoing, the Supplier shall label all Goods supplied to the Authority, and the packaging of such Goods, to highlight environmental and safety information as required by applicable Law."

Clause 9 (Price and Payment) shall be amended by the addition of the following:

"9.9 Where the Authority is entitled to receive any sums (including, without limitation, any costs, charges or expenses) from the Supplier under this Contract, the Authority may invoice the Supplier for such sums. Such invoices shall be paid by the Supplier within 30 days of the date of such invoice.

9.10 If a Party fails to pay any undisputed sum properly due to the other Party under this Contract, the Party due such sum shall have the right to charge interest on the overdue amount at a rate of 4% above Bank of England base rate, accruing on a daily basis from the due date up to the date of actual payment, whether before or after judgment."

Clause 10 (Warranties) shall be amended by the addition of the following clauses, as follows:

10.1.31 "it shall: (i) comply with all relevant Law and Guidance and shall use Good Industry Practice to ensure that there is no slavery or human trafficking in its supply chains; and (ii) notify the Authority immediately if it becomes aware of any actual or suspected incidents of slavery or human trafficking in its supply chains;

10.1.32 it shall at all times conduct its business in a manner that is consistent with any anti-slavery Policy of the Authority that is notified in writing to the Supplier and shall provide to the Authority any reports or other information that the Authority may request as evidence of the Supplier's compliance with this Clause 10.1.32 and/or as may be requested or otherwise required by the Authority in accordance with its anti-slavery Policy."

Clause 12 (Indemnity) shall be amended as follows:

Clause 12.1 shall be deleted and replaced by the following:

12.1 "The Supplier shall be liable to the Authority for, and shall indemnify and keep the Authority indemnified against, any loss, damages, costs, expenses (including without limitation legal costs and expenses), claims or proceedings in respect of:

12.1.1 any injury or allegation of injury to any person, including injury resulting in death;

12.1.2 any loss of or damage to property (whether real or personal); and/or

12.1.3 any breach of Clause 10.1.19 and/or Clause 11 of this Schedule 2 of these Call-off Terms and Conditions;

that arise or result from the Supplier's negligent acts or omissions or breach of contract in connection with the performance of this Contract including the supply of the Goods. The indemnity set out in this Clause 12.1 shall not apply to the extent that such loss, damages, costs, expenses (including without limitation legal costs and expenses), claims or proceedings have been caused by any act or omission by, or on behalf of, or in accordance with the instructions of, the Authority or a DHSC Authorised User of the Goods, including without limitation any use by the Authority or a DHSC Authorised User of the Goods either for a purpose not authorised by the Specification or in a manner which is inconsistent with the instructions set out or referred to in the Specification. For the purposes of this Clause 12, a DHSCn Authorised User of the Goods is a person to whom the Goods are made available by the Authority."

Clause 15 (Term and Termination) shall be amended as follows:

At clause 15.2.1 substitute “three (3) months” with “1 (one) month”; and

After clause 15.5.5 insert new clause 15.5.6 as follows:

“15.5.6 Upon the occurrence of any of the events in regulations 73(1)(a)-(c) of the Public Contracts Regulations 2015 (SI 2015/102).”

Clause 17 (Packaging, etc) shall be amended by the addition of the following to amend/replace the current provision as indicated:

17.2 *[to be inserted after current provision]* “and in relation to Goods imported into the United Kingdom for the purposes of the Producer Responsibility Obligations (Packaging Waste) Regulations 2007 and all applicable product and safety liability legislation in force in the United Kingdom from time to time, the Supplier shall assume all obligations for all activities performed outside the United Kingdom in relation to the Goods and the packaging, in addition to any other obligations the Supplier may have pursuant to such regulations and other legislation.”

17,4 *[to replace the current provision]* “The Supplier shall ensure that all Goods that are required by Law or Guidance to bear any safety information, environmental information, any mark, tab, brand, label, serial numbers or other device indicating place of origin, inspection by any government or other body or standard of quality at the point such Goods are delivered shall comply with such requirements at the point of delivery.”

Clause 18 (Coding requirements) shall be deleted and replaced by following:

18.1 “Unless otherwise confirmed and/or agreed by the Authority in writing the Supplier shall ensure full compliance with any Guidance issued by the Department of Health in relation to the adoption of GS1 and PEPPOL standards (to include, without limitation, any supplier compliance timeline and other policy requirements published by the Department of Health in relation to the adoption of GS1 and PEPPOL standards for master data provision and exchange, barcode labelling and purchase to pay transacting).

18.2 Once compliance with any published timelines has been achieved by the Supplier pursuant to the Order Form, the Supplier shall, during the Term, maintain the required level of compliance relating to the Goods in accordance with any such requirements and Guidance referred to as part of this Contract.

18.3 Once product information relating to Goods is placed by the Supplier into a GS1 certified data pool, the Supplier shall, during the Term, keep such information updated with any changes to the product data relating to the Goods.”

Clause 28 (Assignment, novation and subcontracting) shall be amended by deleting the following:

28.5 "…use its reasonable endeavours to…"

Clause 28.7 shall be deleted and replaced with the following:

28.7 "Neither Party may at any time transfer, assign, novate, subcontract or otherwise dispose of its rights and obligations under this Contract or any part of this Contract without the prior written consent of the other party, such consent not to be unreasonably withheld or delayed".

SCHEDULE 3 of the Call-off Terms and Conditions

Clause 2 shall be deleted, and replaced with the following:

"**2 Data Protection**

2.1 The Parties each acknowledge and agree that they may need to undertake Processing of Personal Data relating to each Party's representatives (in their respective capacities as Controllers) in order to (as appropriate):

(a) administer and provide the Goods;

(b) request and receive the Goods;

(c) compile, dispatch and manage the payment of invoices relating to the Goods;

(d) manage the Contract and resolve any disputes relating to it;

(e) respond and/or raise general queries relating to the Goods; and

(f) comply with their respective regulatory obligations.

2.2 Processing of Personal Data relating to each Party's representatives for the purposes set out in Clause 2.1 of this Schedule 3 of these Call-off Terms and Conditions shall only be done by each Party in accordance with their respective privacy policies. The Parties acknowledge that they may be required to share Personal Data with their affiliates, group companies and other relevant parties, within or outside of the country of origin, in order to carry out the activities listed in Clause 2.1 of this Schedule 3 of these Call-off Terms and Conditions, and in doing so each Party will ensure that the sharing and use of this Personal Data complies with applicable Data Protection Laws."

SCHEDULE 4 of the Call-off Terms and Conditions

Clause 1.1 of Schedule 4 of the Call-off Terms and Conditions shall be deleted, and replaced with the following:

"1.1 In this Contract the following words shall have the following meanings unless the context requires otherwise:

"Authority"	means the authority named on the Order Form;
"Authority's Obligations"	means the Authority's further obligations, if any, referred to in the Specification and Tender Response Document and/or the Order Form;
"Business Continuity Event"	means any event or issue that could impact on the operations of the Supplier and its ability to supply the Goods including an influenza pandemic and any Force Majeure Event;
"Business Continuity Plan"	means the Supplier's business continuity plan which includes its plans for continuity of the supply of the Goods during a Business Continuity Event;
"Business Day"	means any day other than Saturday, Sunday, Christmas Day, Good Friday or a statutory bank holiday in England and Wales;
"Call-off Terms and Conditions"	means these Call-off Terms and Conditions for the Supply of Goods (comprising of the front page of the document and the Schedules);
"Codes of Practice"	shall have the meaning given to the term in Clause 1.2 of Schedule 3 of these Call-off Terms and Conditions;
"Commencement Date"	means the date of the Order Form;
"Component Parts"	means the raw materials or any other constituent element of the Goods;
"Confidential Information"	means information, data and material of any nature, which either Party may receive or obtain in connection with the conclusion and/or operation of the Contract including any procurement process which is: (a) Personal Data or Sensitive Personal Data including without limitation which relates to any patient or other service user or his or her treatment or clinical or care history; (b) designated as confidential by either party or that ought reasonably to be considered as confidential (however it is conveyed or on whatever media it is stored); and/or (c) Policies and such other documents which the Supplier may obtain or have access to through the Authority's intranet;

"Contract"	means the Order Form, the provisions on the front page and all Schedules of these Call-off Terms and Conditions and the applicable provisions of the Framework Agreement;
"Contracting Authority"	means any contracting authority as defined in Regulation 2 of the Public Contracts Regulations 2015 (SI 2015/102) (as amended), other than the Authority;
"Contract Manager"	means for the Authority and for the Supplier the individuals specified in the Order Form or as otherwise agreed between the Parties in writing or such other person notified by a Party to the other Party from time to time in accordance with Clause 8.1 of Schedule 2 of these Call-off Terms and Conditions;
"Contract Price"	means the price exclusive of VAT that is payable to the Supplier by the Authority under the Contract for the full and proper performance by the Supplier of its obligations under the Contract calculated in accordance with the provisions of the Framework Agreement and as confirmed in the Order Form;
"Controller"	shall have the same meaning as set out in the General Data Protection Regulation (Regulation (EU) 2016/679);
COVID-19	means the coronavirus 2019;
"Data Protection Laws"	means (i) the Data Protection Act 2018 to the extent that it relates to processing of personal data and privacy; (ii) the General Data Protection Regulation (Regulation (EU) 2016/679), the Law Enforcement Directive (Directive (EU) 2016/680) and any applicable national implementing Law as amended from time to time; and (iii) all applicable Law about the processing of personal data and privacy;
"Defective Goods"	has the meaning given under Clause 4.6 of Schedule 2 of these Call-off Terms and Conditions;
"Dispute Resolution Procedure"	means the process for resolving disputes as set out in Clause 22 of Schedule 2 of these Call-off Terms and Conditions;

"DOTAS"	means the Disclosure of Tax Avoidance Schemes rules which require a promoter of tax schemes to tell HM Revenue and Customs of any specified notifiable arrangements or proposals and to provide prescribed information on those arrangements or proposals within set time limits as contained in Part 7 of the Finance Act 2004 and in secondary legislation made under vires contained in Part 7 of the Finance Act 2004 and as extended to National Insurance Contributions by the National Insurance Contributions (Application of Part 7 of the Finance Act 2004) Regulations 2012, SI 2012/1868 made under s.132A Social Security Administration Act 1992;
"Electronic Trading System(s)"	means such electronic data interchange system and/or world wide web application and/or other application with such message standards and protocols as the Authority may specify from time to time;
"Environmental Regulations"	shall have the meaning given to the term in Clause 1.2 of Schedule 3 of these Call-off Terms and Conditions;
"eProcurement Guidance"	means the NHS eProcurement Strategy available via: http://www.gov.uk/government/collections/nhs-procurement together with any further Guidance issued by the Department of Health in connection with it;
"Equality Legislation"	means any and all legislation, applicable guidance and statutory codes of practice relating to equality, diversity, non-discrimination and human rights as may be in force in England and Wales from time to time including, but not limited to, the Equality Act 2010, the Part-time Workers (Prevention of Less Favourable Treatment) Regulations 2000 and the Fixed-term Employees (Prevention of Less Favourable Treatment) Regulations 2002 (SI 2002/2034) and the Human Rights Act 1998;
"FOIA"	shall have the meaning given to the term in Clause 1.2 of Schedule 3 of these Call-off Terms and Conditions;

"Force Majeure Event"	means any event beyond the reasonable control of the Party in question to include, without limitation: (a) war including civil war (whether declared or undeclared), riot, civil commotion or armed conflict materially affecting either Party's ability to perform its obligations under this Contract; (b) acts of terrorism; (c) flood, storm or other natural disasters; (d) fire; (e) unavailability of public utilities and/or access to transport networks to the extent no diligent supplier could reasonably have planned for such unavailability as part of its business continuity planning; (f) government requisition or impoundment to the extent such requisition or impoundment does not result from any failure by the Supplier to comply with any relevant regulations, laws or procedures (including such laws or regulations relating to the payment of any duties or taxes) and subject to the Supplier having used all reasonable legal means to resist such requisition or impoundment; (g) compliance with any local law or governmental order, rule, regulation or direction that could not have been reasonably foreseen; (h) industrial action which affects the ability of the Supplier to supply the Goods, but which is not confined to the workforce of the Supplier or the workforce of any subcontractor of the Supplier; and (i) a failure in the Supplier's and/or Authority's supply chain to the extent that such failure is due to any event suffered by a member of such supply chain, which would also qualify as a Force Majeure Event in accordance with this definition had it been suffered by one of the Parties. but excluding, for the avoidance of doubt, the COVID-19 crisis and any related circumstances, events, changes or requirements;
"Framework Agreement"	means the Framework Agreement referred to in the Order Form;
"Fraud"	means any offence under any law in respect of fraud in relation to this Contract or defrauding or attempting to defraud or conspiring to defraud the government, parliament or any Contracting Authority;

"General Anti-Abuse Rule"	means (a) the legislation in Part 5 of the Finance Act 2013; and (b) any future legislation introduced into parliament to counteract tax advantages arising from abusive arrangements to avoid national insurance contributions;
"Good Industry Practice"	means the exercise of that degree of skill, diligence, prudence, risk management, quality management and foresight which would reasonably and ordinarily be expected from a skilled and experienced supplier engaged in the manufacture and/or supply of goods similar to the Goods under the same or similar circumstances as those applicable to this Contract, including in accordance with any codes of practice published by relevant trade associations;
"Goods"	means all goods, materials or items that the Supplier is required to supply to the Authority under this Contract (including, without limitation, as stated in the Order Form);
"Group"	means entities (other than the Supplier) within its corporate structure;
"Guidance"	means any applicable guidance, direction or determination and any policies, advice or industry alerts which apply to the Goods, to the extent that the same are published and publicly available or the existence or contents of them have been notified to the Supplier by the Authority and/or have been published and/or notified to the Supplier by the Department of Health, Monitor, NHS England, the Medicines and Healthcare Products Regulatory Agency, the European Medicine Agency the European Commission, the Care Quality Commission and/or any other regulator or competent body;
"Halifax Abuse Principle"	means the principle explained in the CJEU Case C-255/02 Halifax and others;
"Intellectual Property Rights"	means all patents, copyright, design rights, registered designs, trade marks, know-how, database rights, confidential formulae and any other intellectual property rights and the rights to apply for patents and trade marks and registered designs;
"Key Provisions"	means the key provisions set out in Schedule 1 of these Call-off Terms and Conditions and/or as part of the Order Form;
"KPI"	means the key performance indicators as set out in the Specification and Tender Response Document and/or the Order Form, if any;

"Law"	means: (a) any applicable statute or proclamation or any delegated or subordinate legislation or regulation; (b) any applicable European Union directive, regulation, decision or law; (c) any enforceable community right within the meaning of section 2(1) European Communities Act 1972; (d) any applicable judgment of a relevant court of law which is a binding precedent in England and Wales; (e) requirements set by any regulatory body; and (f) any applicable code of practice, in each case as applicable in England and Wales; and (g) any relevant collective agreement and/or international law provisions (to include, without limitation, as referred to in (a) to (f) above;
"Mediation Notice"	has the meaning given under Clause 22.5.1 of Schedule 2 of these Call-off Terms and Conditions;
"NHS"	means the National Health Service;
"Occasion of Tax Non-Compliance"	means: (a) any tax return of the Supplier submitted to a Relevant Tax Authority on or after 1 October 2012 is found on or after 1 April 2013 to be incorrect as a result of: (i) a Relevant Tax Authority successfully challenging the Supplier under the General Anti-Abuse Rule or the Halifax Abuse Principle or under any tax rules or legislation that have an effect equivalent or similar to the General Anti-Abuse Rule or the Halifax Abuse Principle; (ii) the failure of an avoidance scheme which the Supplier was involved in, and which was, or should have been, notified to a Relevant Tax Authority under the DOTAS or any equivalent or similar regime; and/or (b) any tax return of the Supplier submitted to a Relevant Tax Authority on or after 1 October 2012 gives rise, on or after 1 April 2013, to a criminal conviction in any jurisdiction for tax related offences which is not spent at the Effective Date or to a civil penalty for fraud or evasion;
"Order Form"	means the order form for the Goods, including its Annexes issued by the Authority and incorporated within the Contract;
"Party"	means the Authority or the Supplier as appropriate and Parties means both the Authority and the Supplier;

"Personal Data"	shall have the same meaning as set out in the General Data Protection Regulation (Regulation (EU) 2016/679);
"Policies"	means the policies, rules and procedures of the Authority as notified to the Supplier from time to time;
"Processing"	shall have the same meaning as set out in the General Data Protection Regulation (Regulation (EU) 2016/679);
"Product Information"	means information concerning the Goods as may be reasonably requested by the Authority and supplied by the Supplier to the Authority in accordance with Clause 20 of Schedule 2 of these Call-off Terms and Conditions for inclusion in the Authority's product catalogue from time to time;
"Rejected Goods"	has the meaning given under Clause 4.2 of Schedule 2 of these Call-off Terms and Conditions;
"Relevant Tax Authority"	means HM Revenue and Customs, or, if applicable, a tax authority in the jurisdiction in which the Supplier is established;
"Remedial Proposal"	has the meaning given under Clause 15.3 of Schedule 2 of these Call-off Terms and Conditions;
"Requirement to Recall"	has the meaning given under 4.9 of Schedule 2 of these Call-off Terms and Conditions;
"Schedule"	means the relevant part of the Call-off Terms and Conditions as per the headings within that document;
"Sensitive Personal Data"	means special categories of personal data as defined in the Data Protection Laws;
"Specification and Tender Response Document"	means the Specification and Tender Response Document set out in the Framework Agreement as supplemented by any further information set out and/or referred to in the Order Form and as amended and/or updated in accordance with this Contract ;
"Staff"	means all persons employed or engaged by the Supplier to perform its obligations under this Contract including any subcontractors and person employed or engaged by such subcontractors;
"Supplier"	means the supplier named on the Order Form;
"Term"	means the term as referred to in the Key Provisions and more particularly provided for within the Order Form;
"Third Party Body"	has the meaning given under Clause 8.5 of Schedule 2 of these Call-off Terms and Conditions; and

"VAT"	means value added tax chargeable under the Value Added Tax Act 1994 or any similar, replacement or extra tax.

Clause 1.4 of Schedule 4 of the Call-off Terms and Conditions shall be amended by the addition of references to "Annex".

09203079500V1.0

Elecsys Anti-SARS-CoV-2

cobas®

REF		Σ	SYSTEM
09203079190	09203079500	300	**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 **el**ectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

SARS-CoV-2 is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronaviruses. All coronaviruses share similarities in the organization and expression of their genome, which encodes 16 nonstructural proteins and the 4 structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). Viruses of this family are of zoonotic origin. They cause disease 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 Coronavirus Disease 2019 (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 transmitted person-to-person primarily via respiratory droplets, but also indirect transmission through contaminated surfaces is possible.[3,4,5,6] SARS-CoV-2 can be isolated from respiratory samples obtained via naso/oropharyngeal swabs or from sputum. The virus accesses host cells via the angiotensin-converting enzyme 2 (ACE2), which is the most abundant in the lungs.[7,8]

The incubation period for COVID-19 is thought to range from 2-14 days following exposure, with most cases showing symptoms approximately 4-5 days after exposure.[3,9,10] The interval during which an individual with COVID-19 is infectious has not yet been clearly established. Transmission from symptomatic individuals, the spread of virus to new hosts shortly before symptoms appear and asymptomatic transmission have all been described; however the evidence is not conclusive.[1,11,12,13,14]

Those infected may exhibit symptoms including fever, cough, fatigue, sputum production, loss of smell and shortness of breath.[15,16,17] The spectrum of symptomatic infection ranges from mild to critical, with most cases being non-severe. Severe illness is characterized by e.g. dyspnea, hypoxia, > 50 % lung infiltrates within 24 to 48 hours and occurs predominantly in adults with advanced age or underlying medical comorbidities such as hypertension, diabetes mellitus and cardiovascular disease. Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease. Critical cases are characterized by e.g. respiratory failure, shock and/or multiple organ dysfunction or failure. The proportion of severe or fatal infections vary greatly by location.[16,18,19]

Definite COVID-19 diagnosis entails SARS-CoV-2 detection by nucleic acid amplification technology (NAAT).[20,21,22] Although the underlying technology for NAAT is robust and shows excellent specificity, the outcome directly depends on the viral load acquired during sampling which, among others, can vary with time point of infection, individual patient, sampling method and position as well as sample preparation time.

Consequently, a non-negligible proportion of infected individuals may be missed by screenings based on symptoms and NAAT[23,24,25] and thus form an important source of continued viral spread. Serological assays can contribute to identify individuals exposed to the virus and assess the extent of exposure of a population, and might thereby help to decide on application, enforcement or relaxation of containment measures.[26]

Seroconversion has been observed as early as within 5 days after symptom onset for immunoglobulin M (IgM)[27] and within 5-7 days for IgG.[27,28] Based on still scarce data, anti-SARS-CoV-2 IgA seem to appear at around 3-6 days post-symptom onset.[25,29] Depending on the applied method, seroconversion is observed after a median of 10-13 days after symptom onset for IgM and 12-14 days for IgG.[23,30,31] Maximum seroconversion occurs at 2-3 weeks for IgM,[23,27,28,31,32] at 3-6 weeks for IgG,[23,27,28,33] and at 2 weeks for total antibodies.[31,34] Whereas IgM seems to vanish around week 6-7,[32,35] high IgG seropositivity is seen at that time.[27,32,35] Levels and chronological order of IgM and IgG antibody appearance are highly variable,[23,28,31,36] supporting detection of both antibodies simultaneously.

Neutralizing antibodies targeting spike and nucleocapsid proteins are formed as early as day 9 onwards, showing strong neutralizing response, thus seroconversion may lead to protection at a minimum for a limited time.[29,36,37,38,39] Cross-reactivity with SARS-CoV-2 induced neutralizing antibodies with SARS-CoV was observed, but not with other coronaviruses, suggesting that the vast majority of people are immunologically naive and thus susceptible to this virus.[25,29,36,37,40]

The Elecsys Anti-SARS-CoV-2 assay uses a recombinant protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2.

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); 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; preservative.

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

cobas®

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.[41,42]

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	72 hours

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	72 hours

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.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

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 3 days at 15-25 °C, 7 days at 2-8 °C, 28 days at -20 °C (± 5 °C). The samples may be frozen twice.

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 07299010190, Diluent MultiAssay, 45.2 mL sample diluent
- General laboratory equipment
- **cobas e** 801 analyzer

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
- 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.

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

No international standard is available for Anti-SARS-CoV-2.

Calibration frequency:

Calibration must be performed once per reagent lot using ACOV2 Cal1, ACOV2 Cal2 and 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 3 days when using the same reagent lot
- after 3 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 controls prepared as follows:

Negative control: Determine the COI of ACOV2 Cal1 by measuring it as a routine sample. Pool serum samples with a COI result of ≤ 150 % compared to the COI result of ACOV2 Cal1 (pooling of ≥ 5 non-reactive samples in this range is recommended). Mix carefully, avoiding foam formation. Prepare aliquots of at least 250 µL from this sample pool and store frozen at -20 °C (± 5 °C) or colder. Use these aliquots to perform regular quality control.
This negative control has a target value range of COI < 0.8 (qualitative assay result "non-reactive").

Positive control: Determine the COI of ACOV2 Cal2 by measuring it as a routine sample. Pool serum samples with a COI result that is higher than the COI result of ACOV2 Cal2 (pooling of ≥ 3 reactive samples in this range is recommended). Dilute the sample pool by adding pooled negative serum (pooling criterion see negative control) or Diluent MultiAssay to obtain a COI between 3 and 15. Mix carefully, avoiding foam formation. It is recommended to confirm calculated reactivity after dilution by a measurement. Prepare aliquots of at least 250 µL from this sample pool and store frozen at -20 °C (± 5°C) or colder. Use these aliquots to perform regular quality control. Upon first use of this control, determine the COI of the control by measurement of the control in triplicate and using a freshly opened **cobas e** pack.
The obtained median of these measurements serves as target value for this positive control. Subsequent measurements of all aliquots of this control material must match this target value ± 45 % (3SD = 45 %, 1SD = 15 %; qualitative assay result "reactive"). In case the quality control fails, thaw a new aliquot and re-assess the performance of the assay.
The target value of the positive control is lot specific and target value assessment as described above has to be performed for every assay lot.

After measurement, discard aliquots with a remaining volume of 250 µL or less, Aliquots with a remaining volume of more than 250 µL can be re-used if sealed tightly and stored immediately at 2-8 °C for max. 3 days. In case quality control fails for any reason, thaw a new control aliquot and re-assess the performance of the assay.

Also pools of plasma samples with similar reactivity can be used, however re-clotting frequently occurs with plasma after thawing. If this occurs, either discard or centrifuge the aliquot before use. Do not mix serum samples and plasma samples to prepare a sample pool.

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.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. 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 guidelines for quality control.

Note: The controls should be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software. Only one target value and range for each control level can be entered in the analyzer. The reagent lot-specific target values have to be re-entered each time a specific reagent lot with different control target values and ranges is used. Two reagent lots with different control target values and ranges cannot be used in parallel in the same run.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of ACOV2 Cal1 and ACOV2 Cal2.

The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (COI; signal sample/cutoff).

Interpretation of the results

Results obtained with the Elecsys Anti-SARS-CoV-2 assay can be interpreted as follows:

Numeric result	Result message	Interpretation
COI < 1.0	Non-reactive	Negative for anti-SARS-CoV-2 antibodies
COI ≥ 1.0	Reactive	Positive for anti-SARS-CoV-2 antibodies

The magnitude of the measured result above the cutoff is not indicative of the total amount of antibody present in the sample.
The individual immune response following SARS-CoV-2 infection varies considerably and might give different results with assays from different manufacturers. Results of assays from different manufacturers should not be used interchangeably.

Limitations - interference

The effect of the following pharmaceutical compound on assay performance was tested. Interference was tested up to the listed concentration and no impact on results was observed.

Endogenous substance

Compound	Concentration tested
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL

Criterion: For samples with a COI ≥ 1.0, the deviation is ≤ 20 %. For samples with a COI < 1.0, the deviation is ≤ 0.2 COI.

Potential endogenous interferences e.g. hemolysis, bilirubin, rheumatoid factors and pharmaceutical compounds other than biotin have not been tested and an interference cannot be excluded.

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

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.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

A negative test result does not completely rule out the possibility of an infection with SARS-CoV-2. Serum or plasma samples from the very early (pre-seroconversion) phase can yield negative findings. Therefore, this test cannot be used to diagnose an acute infection. Also, over time, titers may decline and eventually become negative.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Specificity

A total of 5272 samples were tested with the Elecsys Anti-SARS-CoV-2 assay. All samples were obtained before December 2019. 10 false positive samples were detected.

The resulting overall specificity in the internal study was 99.81 %. The 95 % lower confidence limit was 99.65 %.

Elecsys Anti-SARS-CoV-2

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Cohort	N	Non-reactive	Reactive	Specificity, % (95 % CI[b])
Diagnostic routine	3420	3413	7	99.80 (99.58-99.92 %)
Blood donors	1772	1769	3	99.83 (99.51-99.97 %)
Common cold panel	40	40	0	100 (91.19-100 %)
Coronavirus panel[c]	40	40	0	100 (91.19-100 %)
Overall	**5272**	**5262**	**10**	**99.81 (99.65-99.91 %)**

b) CI = confidence interval

c) 40 potentially cross-reactive samples from individuals following an infection with Coronavirus HKU1, NL63, 229E or OC43, confirmed via PCR

Sensitivity

A total of 204 samples from 69 symptomatic patients with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys Anti-SARS-CoV-2 assay. 1 or more consecutive samples from these patients were collected after PCR confirmation at various time points.

Days post PCR confirm-ation	N	Reactive	Non-reactive	Sensitivity, % (95 % CI)
0-6	116	76	40	65.5 (56.1-74.1 %)
7-13	59	52	7	88.1 (77.1-95.1 %)
≥ 14	29	29	0	100 (88.1-100 %)

After recovery from infection, confirmed by a negative PCR result, 26 consecutive samples from 5 individuals were tested with the Elecsys Anti-SARS-CoV-2 assay.

Patient	Day of negative PCR*		Days after diagnosis with positive PCR						
			21-23	24-26	27-29	30-32	33-35	36-38	39-40
1	9	COI	24.7	-	27.4	31.7	38.9	56.0	-
2	12		28.8	29.8	30.6	32.7	35.7	-	-
3	17		-	46.5	53.6	-	67.1	73.7	77.0
4	21		24.1	29.8	40.7	51.2	61.5	67.5	-
5	24		-	0.990	1.12	1.55	-	1.66	1.97

* Day 0 represents 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).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Roche

09203095500V1.0

Elecsys Anti-SARS-CoV-2

cobas®

REF		Σ	SYSTEM
09203095190	09203095500	200	**cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 3000
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 737

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

Summary

SARS-CoV-2 is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronaviruses. All coronaviruses share similarities in the organization and expression of their genome, which encodes 16 nonstructural proteins and the 4 structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). Viruses of this family are of zoonotic origin. They cause disease 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 Coronavirus Disease 2019 (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 transmitted person-to-person primarily via respiratory droplets, but also indirect transmission through contaminated surfaces is possible.[3,4,5,6] SARS-CoV-2 can be isolated from respiratory samples obtained via naso/oropharyngeal swabs or from sputum. The virus accesses host cells via the angiotensin-converting enzyme 2 (ACE2), which is the most abundant in the lungs.[7,8]

The incubation period for COVID-19 is thought to range from 2-14 days following exposure, with most cases showing symptoms approximately 4-5 days after exposure.[3,9,10] The interval during which an individual with COVID-19 is infectious has not yet been clearly established. Transmission from symptomatic individuals, the spread of virus to new hosts shortly before symptoms appear and asymptomatic transmission have all been described; however the evidence is not conclusive.[1,11,12,13,14]

Those infected may exhibit symptoms including fever, cough, fatigue, sputum production, loss of smell and shortness of breath.[15,16,17] The spectrum of symptomatic infection ranges from mild to critical, with most cases being non-severe. Severe illness is characterized by e.g. dyspnea, hypoxia, > 50 % lung infiltrates within 24 to 48 hours and occurs predominantly in adults with advanced age or underlying medical comorbidities such as hypertension, diabetes mellitus and cardiovascular disease. Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease. Critical cases are characterized by e.g. respiratory failure, shock and/or multiple organ dysfunction or failure. The proportion of severe or fatal infections vary greatly by location.[16,18,19]

Definite COVID-19 diagnosis entails SARS-CoV-2 detection by nucleic acid amplification technology (NAAT).[20,21,22] Although the underlying technology for NAAT is robust and shows excellent specificity, the outcome directly depends on the viral load acquired during sampling which, among others, can vary with time point of infection, individual patient, sampling method and position as well as sample preparation time.

Consequently, a non-negligible proportion of infected individuals may be missed by screenings based on symptoms and NAAT[23,24,25] and thus form an important source of continued viral spread. Serological assays can contribute to identify individuals exposed to the virus and assess the extent of exposure of a population, and might thereby help to decide on application, enforcement or relaxation of containment measures.[26]

Seroconversion has been observed as early as within 5 days after symptom onset for immunoglobulin M (IgM)[27] and within 5-7 days for IgG.[27,28] Based on still scarce data, anti-SARS-CoV-2 IgA seem to appear at around 3-6 days post-symptom onset.[25,29] Depending on the applied method, seroconversion is observed after a median of 10-13 days after symptom onset for IgM and 12-14 days for IgG.[23,30,31] Maximum seroconversion occurs at 2-3 weeks for IgM,[23,27,28,31,32] at 3-6 weeks for IgG,[23,27,28,33] and at 2 weeks for total antibodies.[31,34] Whereas IgM seems to vanish around week 6-7,[32,35] high IgG seropositivity is seen at that time.[27,32,35] Levels and chronological order of IgM and IgG antibody appearance are highly variable,[23,28,31,36] supporting detection of both antibodies simultaneously.

Neutralizing antibodies targeting spike and nucleocapsid proteins are formed as early as day 9 onwards, showing strong neutralizing response, thus seroconversion may lead to protection at a minimum for a limited time.[29,36,37,38,39] Cross-reactivity with SARS-CoV-2 induced neutralizing antibodies with SARS-CoV was observed, but not with other coronaviruses, suggesting that the vast majority of people are immunologically naive and thus susceptible to this virus.[25,29,36,37,40]

The Elecsys Anti-SARS-CoV-2 assay uses a recombinant protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 20 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/ProCell 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 reagent rackpack (M, R1, R2) is labeled as ACOV2.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 12 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 SARS-CoV-2-Ag~biotin (gray cap), 1 bottle, 16 mL: Biotinylated SARS-CoV-2-specific recombinant antigen (E. coli); preservative.

R2 SARS-CoV-2-Ag ~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 16 mL: SARS-CoV-2-specific recombinant antigen labeled with ruthenium complex, preservative.

ACOV2 Cal1	Negative calibrator 1 (white cap), 1 bottle of 0.67 mL: Human serum, non-reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.
ACOV2 Cal2	Positive calibrator 2 (black cap), 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:

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.[41,42]

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

Reagent handling

For professional use.

The reagents in the kit are ready-for-use and are supplied in bottles compatible with the system.

cobas e 411 analyzer: The calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 4 calibration procedures per calibrator bottle set should be performed.

cobas e 601 and **cobas e** 602 analyzers: Perform only one calibration procedure per bottle.

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

Please note: Both the vial labels contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so that the barcode between the yellow markers can be read by the system. Place the vial on the analyzer as usual.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **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	72 hours
on the analyzers	72 hours

Stability of the calibrators	
unopened at 2-8 °C	up to the stated expiration date
or after opening at 2-8 °C	72 hours
on **cobas e** 411 at 20-25 °C	up to 3 hours
on **cobas e** 601 and **cobas e** 602 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.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

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 3 days at 15-25 °C, 7 days at 2-8 °C, 28 days at -20 °C (± 5 °C). The samples may be frozen twice.

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.

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

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls 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 03609987190, Diluent MultiAssay, 2 x 16 mL sample diluent
- 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 all analyzers:

- 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. 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. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calibrators:

Place the calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (**cobas e** 601 and **cobas e** 602 analyzers).

Calibration

No international standard is available for Anti-SARS-CoV-2.

Calibration frequency: Calibration must be performed once per reagent lot using ACOV2 Cal1, ACOV2 Cal2 and fresh reagent (i.e. not more than 24 hours since the 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 3 days when using the same reagent lot
- after 3 days when using the same reagent kit on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use controls prepared as follows:

Negative control: Determine the COI of ACOV2 Cal1 by measuring it as a routine sample. Pool serum samples with a COI result of ≤ 150 % compared to the COI result of ACOV2 Cal1 (pooling of ≥ 5 non-reactive samples in this range is recommended). Mix carefully, avoiding foam formation. Prepare aliquots of at least 250 µl from this sample pool and store frozen at -20 °C (± 5 °C) or colder. Use these aliquots to perform regular quality control.

This negative control has a target value range of COI < 0.8 (qualitative assay result "non-reactive")

Positive control: Determine the COI of ACOV2 Cal2 by measuring it as a routine sample. Pool serum samples with a COI result that is higher than the COI result of ACOV2 Cal2 (pooling of ≥ 3 reactive samples in this range is recommended). Dilute the sample pool by adding pooled negative serum (pooling criterion see negative control) or Diluent MultiAssay to obtain a COI between 3 and 15. Mix carefully, avoiding foam formation. It is recommend to confirm calculated reactivity after dilution by a measurement.

Prepare aliquots of at least 250 µl from this sample pool and store frozen at -20 °C (± 5 °C) or colder. Use these aliquots to perform regular quality control. Upon first use of this control, determine the COI of the control by measurement of the control in triplicate and using a freshly opened reagent rack pack.

The obtained median of these measurements serves as target value for this positive control. Subsequent measurements of all aliquots of this control material must match this target value ± 45 % (3SD = 45 %, 1SD = 15 %; qualitative assay result "reactive"). In case the quality control fails, thaw a new aliquot and re-assess the performance of the assay.

The target value of the positive control is lot specific and target value assessment as described above has to be performed for every assay lot.

After measurement, discard aliquots with a remaining volume of 250 µl or less. Aliquots with a remaining volume of more than 250 µl can be re-used if sealed tightly and stored immediately at 2-8 °C for max. 3 days.

In case quality control fails for any reason, thaw a new control aliquot and re-assess the performance of the assay.

Also pools of plasma samples with similar reactivity can be used, however re-clotting frequently occurs with plasma after thawing. If this occurs, either discard or centrifuge the aliquot before use. Do not mix serum samples and plasma samples to prepare a sample pool.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

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, and following each calibration.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note: The controls should be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software. Only one target value and range for each control level can be entered in the analyzer. The reagent lot-specific target values have to be re-entered each time a specific reagent lot with different control target values and ranges is used. Two reagent lots with different control target values and ranges cannot be used in parallel in the same run.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of ACOV2 Cal1 and ACOV2 Cal2.

The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (COI; signal sample/cutoff).

Interpretation of the results

Results obtained with the Elecsys Anti-SARS-CoV-2 assay can be interpreted as follows:

Numeric result	Result message	Interpretation
COI < 1.0	Non-reactive	Negative for anti-SARS-CoV-2 antibodies
COI ≥ 1.0	Reactive	Positive for anti-SARS-CoV-2 antibodies

The magnitude of the measured result above the cutoff is not indicative of the total amount of antibody present in the sample.
The individual immune response following SARS-CoV-2 infection varies considerably and might give different results with assays from different manufacturers. Results of assays from different manufacturers should not be used interchangeably.

Limitations - interference

The effect of the following pharmaceutical compound on assay performance was tested. Interference was tested up to the listed concentration and no impact on results was observed.

Elecsys Anti-SARS-CoV-2

cobas®

Endogenous substance

Compound	Concentration tested
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL

Criterion: For samples with a COI ≥ 1.0, the deviation is ≤ 20 %. For samples with a COI < 1.0, the deviation is ≤ 0.2 COI.

Potential endogenous interferences e.g. hemolysis, bilirubin, rheumatoid factors and pharmaceutical compounds other than biotin have not been tested and an interference cannot be excluded.

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

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.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

A negative test result does not completely rule out the possibility of an infection with SARS-CoV-2. Serum or plasma samples from the very early (pre-seroconversion) phase can yield negative findings. Therefore, this test cannot be used to diagnose an acute infection. Also, over time, titers may decline and eventually become negative.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Specificity

A total of 5272 samples were tested with the Elecsys Anti-SARS-CoV-2 assay. All samples were obtained before December 2019. 10 false positive samples were detected.

The resulting overall specificity in the internal study was 99.81 %. The 95 % lower confidence limit was 99.65 %.

Cohort	N	Non-reactive	Reactive	Specificity, % (95 % CI[b])
Diagnostic routine	3420	3413	7	99.80 (99.58-99.92 %)
Blood donors	1772	1769	3	99.83 (99.51-99.97 %)
Common cold panel	40	40	0	100 (91.19-100 %)
Coronavirus panel[c]	40	40	0	100 (91.19-100 %)
Overall	**5272**	**5262**	**10**	**99.81 (99.65-99.91 %)**

b) CI = confidence interval

c) 40 potentially cross-reactive samples from individuals following an infection with Coronavirus HKU1, NL63, 229E or OC43, confirmed via PCR

Sensitivity

A total of 204 samples from 69 symptomatic patients with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys Anti-SARS-CoV-2 assay. 1 or more consecutive samples from these patients were collected after PCR confirmation at various time points.

Days post PCR confirm-ation	N	Reactive	Non-reactive	Sensitivity, % (95 % CI)
0-6	116	76	40	65.5 (56.1-74.1 %)
7-13	59	52	7	88.1 (77.1-95.1 %)
≥ 14	29	29	0	100 (88.1-100 %)

After recovery from infection, confirmed by a negative PCR result, 26 consecutive samples from 5 individuals were tested with the Elecsys Anti-SARS-CoV-2 assay.

Patient	Day of negative PCR*		Days after diagnosis with positive PCR						
			21-23	24-26	27-29	30-32	33-35	36-38	39-40
1	9	COI	24.7	-	27.4	31.7	38.9	56.0	-
2	12		28.8	29.8	30.6	32.7	35.7	-	-
3	17		-	46.5	53.6	-	67.1	73.7	77.0
4	21		24.1	29.8	40.7	51.2	61.5	67.5	-
5	24		-	0.990	1.12	1.55	-	1.66	1.97

* Day 0 represents 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).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE

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www.roche.com

Roche

DS DS MC

Public Health England

Protecting and improving the nation's health

Evaluation of Roche Elecsys Anti-Sars-CoV-2 serology assay for the detection of anti-SARS-CoV-2 antibodies

Diagnostics and Genomics Technology (D&G Tech)
Diagnostic Support (DSP)
Rare and Imported Pathogens Laboratory (RIPL)

Public Health England, Porton Down, Salisbury, SP4 0JG

Executive summary

This document sets out an evaluation of the Roche Elecsys Anti-SARS-CoV-2 serology assay for the detection of anti-SARS-CoV-2 in serum samples.

The evaluation was conducted by the Diagnostic Support Group (DSP) at PHE Porton Down between 4 and 7 May 2020. 100 serum samples from convalescent patients and 472 negative samples were included in the evaluation.

All negative samples tested negative by the assay, giving an assay specificity of 100%.

The sensitivity of the assay ranged from 42.9% to 100%. Assay sensitivity increased when the time between symptom onset and the time when the sample was taken (the interval) increased. Samples taken with an interval between 0 and 10 days gave the lowest sensitivity, whilst samples taken with an interval of >40 days were detected with 100% sensitivity. The sensitivity of the assay at 21 days post-symptom onset is 84.4%. This is in line with the information supplied by Roche, the manufacturer, and is in line with other antibody ELISA tests that have been assessed.

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PHE supports the UN Sustainable Development Goals

Contents

Introduction

Elecsys Anti-SARS-CoV-2 is intended for the detection of IgM and IgG antibodies to SARS-CoV-2 in human serum and plasma.

The assay is an **e**lectro**c**hemi**l**uminescent **i**mmuno**a**ssay (ECLIA). The ECLIA assay is intended for use on the Roche cobas® E immunoassay analysers.

This report details an evaluation of the ECLIA assay conducted at PHE Porton Down between 4-7 May 2020 to inform a decision by the Department of Health and Social Care on potential use of the assay by NHS laboratories for the detection of anti-SARS-CoV-2 antibodies in patient samples.

Roche Elecsys Anti-Sars-CoV-2 Assay

The Elecsys Anti-SARS-CoV-2 assay is an ECLIA assay manufactured by Roche Diagnostics GmbH. The assay is listed as CE marked.

As per the manufacturer's information, the assay uses a recombinant protein representing the nucleocapsid (N) protein of SARS-CoV-2.

Test Principle

The assay is a sandwich immunoassay with a total duration of 18 minutes from start to result per sample. There are four main steps in the assay which are:

- 1st incubation. 12 µL of sample, biotinylated SARS-CoV-2-specific recombinant antigen and SARS-CoV-2-specific recombinant antigen labelled with a ruthenium complex* 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 cut off value previously obtained by calibration.

  * Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy))

Interpretation of the result

The kits contain two controls ACOV2 Cal1 containing human serum, non-reactive for anti-SARS-CoV-2 antibodies and ACOV Cal2 containing human serum reactive for anti-SARS-CoV-2 antibodies. The analyser automatically calculates the cut off based on the measurement of ACOV2 Cal1 and ACOV2 Cal2. The result of a sample is given either as reactive or non-reactive as well as in the form of a cut off index (COI; signal sample/cut off). The results can be interpreted as follows:

Numeric Result	Result Message	Interpretation
COI <1.0	Non-reactive	Negative for anti-SARS-CoV-2 antibodies
COI >1.0	Reactive	Positive for anti-SARS-CoV-2 antibodies

Table 1: Manufacturer's interpretation of the results

Manufacturer's listed limitations

The following limitations of the assay are:

- The magnitude of the measured result above the cut-off is not indicative of the total amount of antibody in the sample.
- The individual immune response following SARS-CoV-2 infection varies considerably and might give different results with assays from different manufacturers. Results from different manufacturers should not be used interchangeably.
- For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.
- A negative test result does not completely rule out the possibility of an infection with SARS-CoV-2. Serum or plasma samples from the very early (pre-seroconversion) phase can yield negative findings. Therefore, this test cannot be used to diagnose an acute infection. Also, over time, titres may decline and eventually become negative.

Manufacturer's performance characteristics

Sensitivity and specificity

A total of 204 samples from 69 symptomatic patients with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys Anti-SARS-CoV-2 assay. 1 or more consecutive samples from these patients were collected after PCR confirmation at various time points.

Days post PCR confirmation	N	Reactive	Non-reactive	Sensitivity, % (95% CI)
0-6	116	76	40	65.5 (56.1-74.1%)
7-13	59	52	7	88.1 (77.1-95.1%)
≥ 14	29	29	0	100 (88.1-100%)

Table 2: Sensitivity of the assay according to the manufacturer

A total of 5272 samples were tested with the Elecsys Anti-SARS-CoV-2 assay. All samples were obtained before December 2019. 10 false positive samples were detected. The resulting overall specificity in the internal study was 99.81 %. The 95 % lower confidence limit was 99.65 %.

Interferences

Interference was tested with the endogenous substance biotin up to a concentration of 4912 nmol/L or 1200 ng/mL. No impact on results was observed. Potential endogenous interferences e.g. haemolysis, bilirubin, rheumatoid factors and pharmaceutical compounds other than biotin were not tested and an interference cannot be excluded.

Testing of Elecsys Anti-SARS-CoV-2 Assay by PHE

Three kits of the Elecsys Anti-SARS-CoV-2 (Lot 49025901, exp 31/05/20) were obtained from Roche on 4th May 2020. Two further kits were delivered on 7th May 2020 and will be used for precision testing.

Procedure for testing

Research operators from DSP and RIPL performed testing of kits using the following sample sets. All testing was performed per the manufacturer's instructions on a Roche cobas® e 411 instrument.

- Positive samples. 100 convalescent samples defined by a positive PCR from a swab sample for that patient. The samples were previously analysed for anti-SARS-CoV-2 antibodies using the EUROIMMUN anti-SARS-CoV-2 IgG assay (EI 2606-9601 G). The interval (symptom onset date to sample collection date) is known for 84 samples. Two of these samples had an interval of ≤ 14 days. The remaining 14 samples, the interval is the patient admitted to hospital to sample collection date so the interval for these samples is artificially low.
- Confounder negative samples. 50 samples from the Sero-Evaluation Unit (SEU), Manchester that are rheumatoid factor (12 samples), CMV (6 samples), EBV (19 samples) or VZV (13 samples) positive. All but one were negative using the Euroimmun IgG assay.
- Porton negative samples. 35 samples from the RIPL 2015 Lyme disease negative sample collection.
- Manchester negative samples. 387 historic samples from the Seroepidemiology Unit (SEU).

Testing results

Sensitivity

Total number of convalescent samples (n)	**Reactive**	**Non-reactive**	**Sensitivity**
100	79	21	79% (69.7-86.5)

Table 3: Overall sensitivity of the assay from the PHE evaluation

Please note that the sensitivity of the assay according to different intervals (date of symptom onset to sample collection) is not given here, as this data was missing from 14 samples. Of the remaining samples, only 2 had an interval of ≤ 14 days.

The number of positive samples based on interval is given in table 4 below.

Group (based on interval)	Reactive	Non-reactive	% Positive
<= date from admission	10	4	71.4%
11 to 20	3	4	42.9%
21 to 30	29	8	78.4%
31 to 40	28	4	87.5%
41 to 50	8	0	100%
miss	1	2	50%
From 21 days	**65**	**12**	**84.4%**

Table 4: % positivity based on interval

The data accords with the manufacturer's supplied data and the % positive sera increases as the interval increases, with 100% positivity seen at over 40 days since symptom onset. The samples in the first row had an unclear interval, as the date from admission into hospital was supplied rather than the date of symptom onset but appears to align with a symptom onset around 20 days.

Specificity

Three sample sets were used to determine the specificity of the assay, 50 confounder samples, 35 RIPL Lyme disease negative samples and 387 negative historical samples.

Category	n	Reactive	Non-reactive	Specificity (95% CI)
Total	472	0	472	100% (94.2-100)
Confounder + RIPL samples	85	0	85	100% (95.8-100.0)
Negative samples	387	0	387	100% (99.8-100.0)

Table 5: Specificity of the assay from the PHE evaluation

Statistical Analysis

Results by group: The scatterplot in Figure 1 shows the distribution of the samples by group (convalescent, confounder + RIPL samples and negative samples). There is very little variation with the negative samples, that pool around the COI 0.1 mark, with a few high negative values. The convalescent samples are much more widely distributed with some samples pooling with the high negatives just below the cut-off of COI 1.0.

Results by time since onset: Figure 2 shows a scatterplot analysis of samples according to their time since symptom onset. For this analysis, 14 samples that did not have an accurate time since onset (the dates supplied were the admission to hospital dates rather than the time since symptom onset) were not included in the analysis.

Assay cut-off: Figure 3 shows the distribution of antibodies against the manufacturer's cut-off of COI 1.0. The results indicate a heavy tail to the negative distribution. In order to assess the cut-off for the assay the distribution of the assay units in the negative samples are assessed (see Figure 4). It is usually desirable that a cut-off is set at least about 3 standard deviations (SD) above the mean of the negatives. This calculation assumes the negative samples are normally distributed (usually on a log-scale) but for the COVID-19 assays it is apparent that the negative distribution is often positively skewed. In addition, some negatives are clearly outliers from the main negative distribution so should be excluded. Therefore, to identify a +3SD cut-point clear outliers were dropped (clearly above assay cut-offs if any existed) and the only the right-hand tail of the negative distribution used to fit a half-normal distribution using all results above an appropriate cut-point that ideally gives a reasonable fit for the half-normal. This can then be used to identify a 3SD cut-point from this distribution as well as obtain a z-score and theoretical specificity of the manufacturer cut-off. Looking at those with results <2 the mean was 0.086 (-1.06 log10) and the half-normal standard deviation was 0.258 (log10) (right hand part of the distribution above the mean). Mean + 2.58 SD = 0.399 and mean + 3SD = 0.519. So, a cut-off of mean + 3 SD of 0.519 is well below the manufacturer's cut-off. This gives a theoretical specificity of 100%.

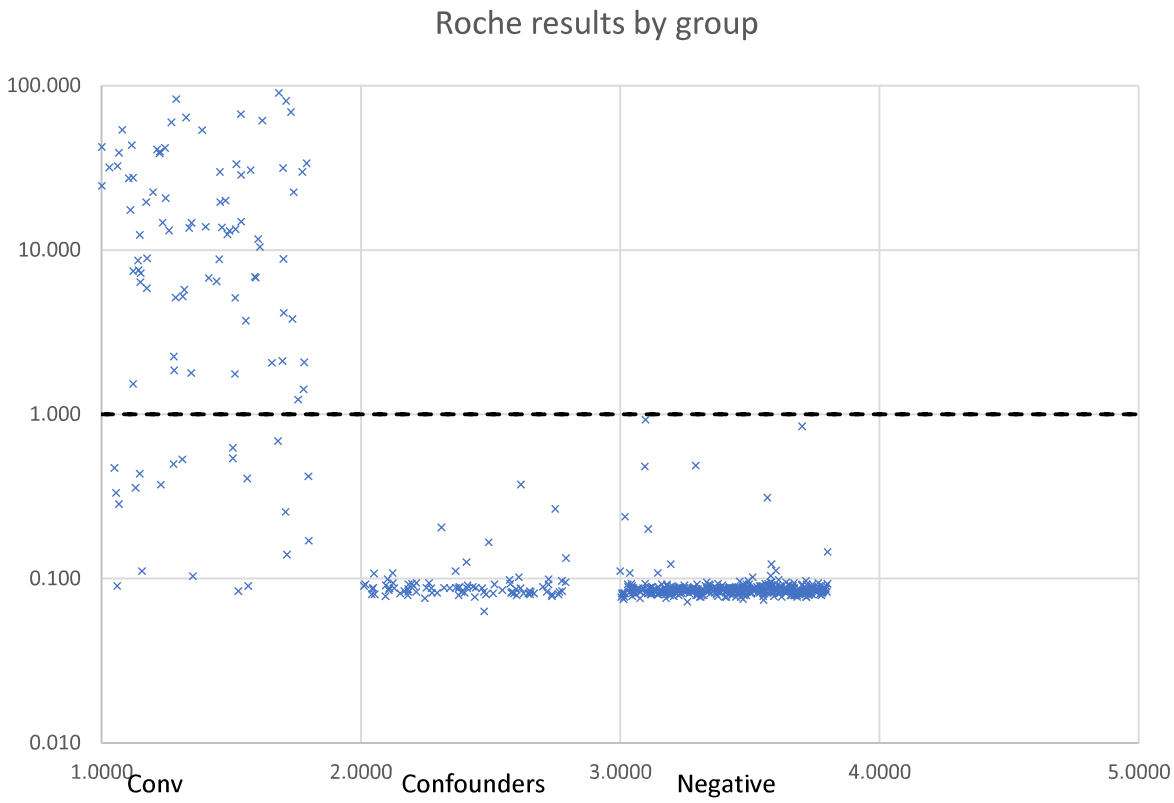

Figure 1: Scatterplot of results by sample category

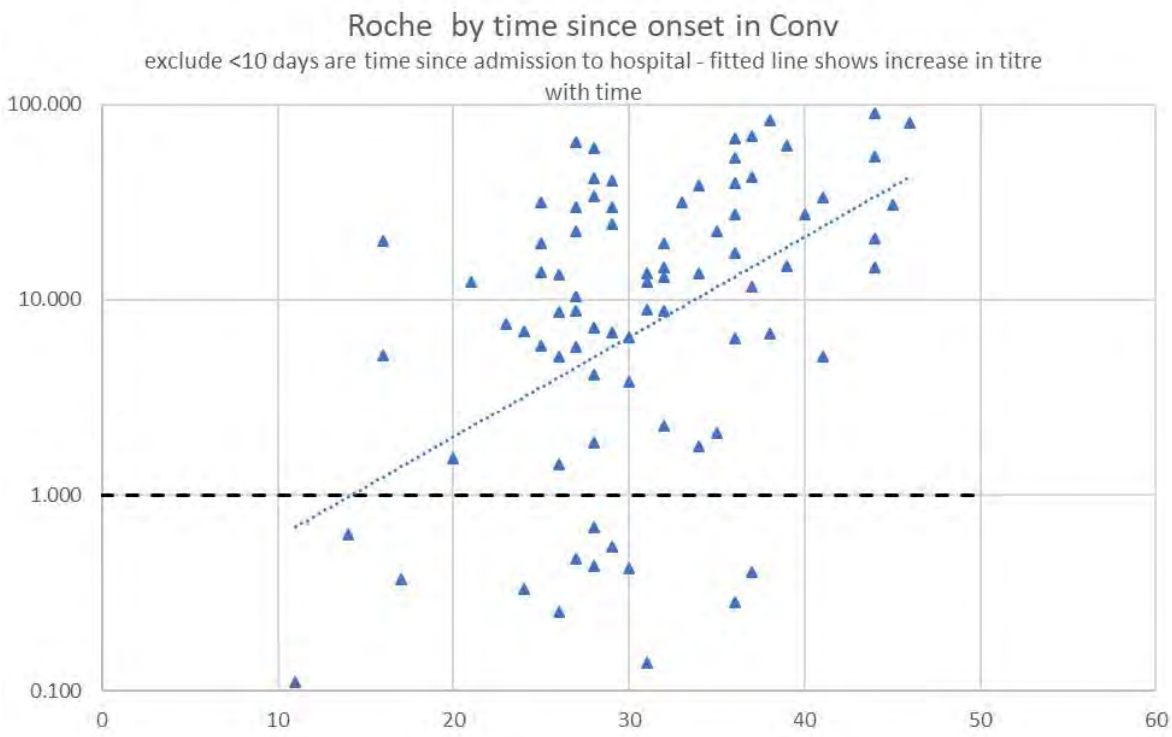

Figure 2: Scatterplot of time since symptom onset (excluding 14 samples that did not have an accurate time since symptom onset)

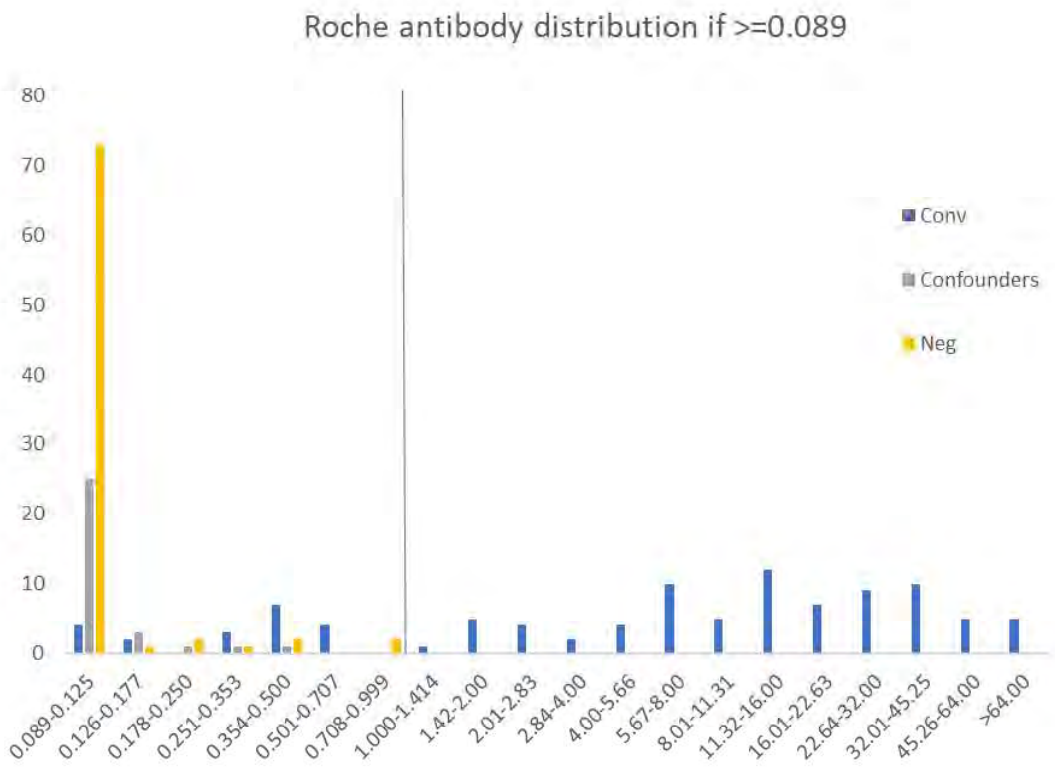

Figure 3: Antibody distribution on a logarithmic scale. The light blue line denotes the manufacturer's cut-off at a value of COI 1.0.

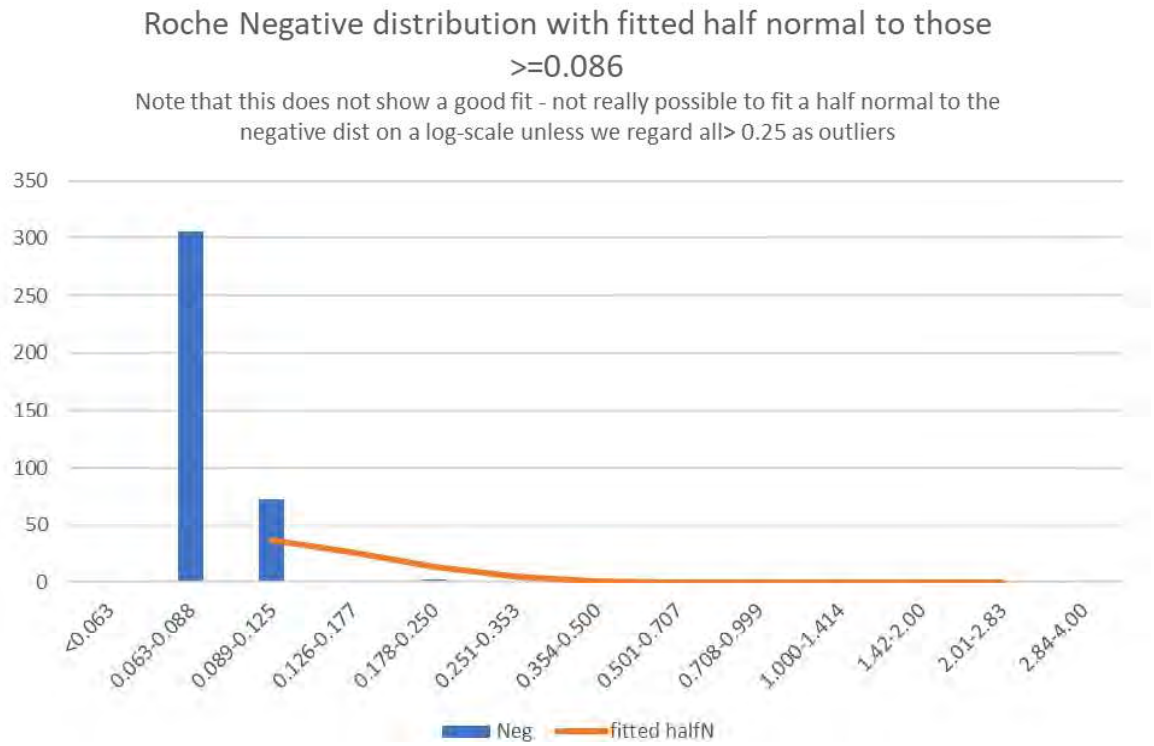

Figure 4: Negative distribution with a fitted half normal

Conclusion

In conclusion, the Elecsys Anti-SARS-CoV-2 assay is a very highly specific assay with a specificity of 100%.

The sensitivity of the assay varied over time, increasing from 42.9% for an interval of 0-10 to 100% sensitivity after 40 days symptom onset. The sensitivity of the assay at 21 days post symptom onset is 84.4%.

This is in line with the sensitivity data supplied by the manufacturer and in line with the sensitivity over time seen in other SARS-CoV-2 antibody assays. The cut-off used by the manufacturer was found to be on the high side and could be reduced with very little loss in specificity.