U.S. FOOD & DRUG ADMINISTRATION

CLIA Waiver by Application Approval Determination
Decision Summary

I. Document Number

CW240027

II. Parent Document Number

K243346

III. CLIA Waiver Type

Dual 510(k) and CLIA Waiver by Application (Dual Submission)

IV. Applicant

Roche Molecular Systems, Inc.

V. Proprietary and Established Names

cobas liat SARS-CoV-2 v2 nucleic acid test

VI. Measurand (analyte)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA. The assay targets both the ORF1 a/b non-structural region and membrane protein gene that are unique to SARS-CoV-2.

VII. Sample Type(s)

Nasopharyngeal Swabs (NPS) and anterior nasal swabs (NS)

VIII. Type of Test

This assay is a nucleic acid assay for the qualitative detection of SARS-CoV-2 RNA through nucleic acid extraction, amplification, and detection using real-time RT-PCR. All steps of the assay are automated within the cobas liat system, after scanning the specimen ID barcode, scanning the assay tube barcode, and the manual addition of sample into the assay tube.

IX. Test System Description

A Overview

cobas liat SARS-CoV-2 v2 nucleic acid test is an automated *in vitro* diagnostic test for the qualitative detection of SARS-CoV-2 RNA in nasopharyngeal swab (NPS) and anterior nasal swab (NS) specimens eluted in viral transport media.

The assay targets both the ORF1 a/b non-structural region and membrane protein gene that are unique to SARS-CoV-2. An Internal Control (IC) is also included. The IC is present to control for adequate processing of the target viruses and to monitor the presence of inhibitors in the sample preparation and RT-PCR.

The assay utilizes a single-use disposable cobas assay tube that holds the sample purification and PCR reagents and hosts the sample preparation and PCR processes. The cobas assay tube uses a flexible tube as a sample vessel. It contains all required unit dose reagents pre-packed in tube segments, separated by peelable seals, in the order of reagent use.

The cobas liat SARS-CoV-2 v2 nucleic acid test uses silica magnetic particle-based nucleic acid extraction and TaqMan probe-based real-time PCR amplification and detection. The cobas liat analyzer automates and integrates sample purification, nucleic acid amplification, and detection of the target sequence in biological samples. During the testing process, multiple sample processing actuators of the cobas liat analyzer compress the cobas liat assay tube to selectively release reagents from tube segments, move the sample from one segment to another, and control reaction volume, temperature, and incubation time. The cobas liat analyzer software controls and coordinates these actions to perform all required assay processes, including sample preparation, nucleic acid extraction, target enrichment, inhibitor removal, nucleic acid elution, and real-time PCR. All assay steps are performed within the closed and self-contained cobas liat SARS-CoV-2 v2 assay tube.

The cobas liat system was originally categorized as "waived" under K141338/CW140014 for the Liat Strep A Assay and six additional CLIA-waived assays have subsequently been implemented on the same instrument system (**Table 1**).

Table 1. Previously CLIA Waived tests for use with the **cobas** liat system

510(k) Number	CLIA Waiver	Device Name	Effective Date
K141338	CW140014	Liat Strep A Assay	05/15/2015
K111387	CW150003	cobas Liat Influenza A/B Nucleic acid test for use on the cobas Liat System	09/18/2015
K153544	CW150018	cobas Influenza A/B & RSV Nucleic acid test for use on the cobas Liat System	07/25/2016
K223591	CW220014	cobas SARS-CoV-2 & Influenza A/B Nucleic acid test for use on the cobas Liat System	07/27/2023
K223783	CW220015	cobas SARS-CoV-2 Nucleic acid test for use on the cobas Liat System	12/04/2023
K240197	CW240002	cobas liat CT/NG/MG nucleic acid test	01/16/2025

510(k) Number	CLIA Waiver	Device Name	Effective Date
K240217	CW240003	cobas liat CT/NG nucleic acid test	01/17/2025

B Test System Components

a. The cobas liat SARS-CoV-2 v2 kit includes:
- 20 cobas liat SARS-CoV-2 v2 assay tubes
- 2 cobas liat transfer pipette packs (12 pipettes/pack)
- 1 package insert barcode card.

b. The cobas liat SARS-CoV-2, Influenza A/B & RSV control kit is provided separately and includes:
- cobas liat SARS-CoV-2, Influenza A/B & RSV positive control (3 X 0.3 mL)
- cobas liat Neg Buf (negative control) (3 X 0.3 mL))
- 1 Control Kit Barcode Card.

X. Specific Contents for CLIA Waiver

A Demonstrating "Simple":

- The cobas liat system automates all nucleic acid test (NAT) processes, including reagent preparation, target enrichment, inhibitor removal, nucleic acid extraction, amplification, real-time detection, and result interpretation in a rapid manner.
- The assay utilizes NPS and NS specimens collected in transport medium without the need for any specimen manipulation. A provided fixed volume pipette is used to transfer the sample to the assay tube. The tube is capped and remains closed for the entire test process. No further materials need to be added or removed from the tube.
- Running the assay requires no reagent manipulation. The assay tube contains all assay reagents pre-packed in tube segments separated by seals.
- The assay tube is designed such that it can only be inserted in the cobas liat analyzer in one direction.
- The test does not require any operator intervention during the analysis step.
- The cobas liat analyzer performs automated analysis of test results, which are reported on the cobas liat analyzer screen (i.e. reported in English as "[Target] Detected", "[Target] Not Detected", "[Target] Invalid", or "Aborted"), and requires no operator calibration, interpretation, or calculation.
- No technical or specialized training is required for troubleshooting or error code interpretation. If an error code is shown, simple on-screen instructions are provided to the operator for next steps.
- The system requires electronic or mechanical maintenance to be performed by the operator. The analyzer performs self-diagnostics during startup (initialization) and utilizes an advanced error diagnostics system to monitor the analyzer's performance during an assay. Under normal operation, the analyzer alerts the operator if a malfunction or error is detected.
- The Quick Reference instructions are written at a 7th grade comprehension level.

B Demonstrating "Insignificant Risk of an Erroneous Result"- Failure Alerts and Fail-Safe Mechanisms

1. Risk Analysis:
   Risk analysis was performed by the firm according to the principles of risk minimization as found in the standard EN ISO 14971 *Medical Devices – Application of risk management to medical devices*. Potential sources of errors that could adversely affect system performance were identified and mitigated first through system design and then through additional cautions in the labeling. All risks of harm to the patient or operator were mitigated to an acceptable level and were supported by flex studies and/or operator instructions.

2. Fail-Safe and Failure Alert Mechanisms:
   The cobas liat system is designed with a variety of fail-safe and/or failure alert mechanisms to prevent operator and instrument errors as described in **Table 2**.

   Table 2. Fail-safe and failure alert mechanisms the cobas liat SARS-CoV-2 v2 nucleic acid test

#	Description
1	Operator permissions restrict access to specific instrument functions/test capabilities.
2	On-screen instructions.
3	Use of barcodes to automate assay selection and provide traceability.
4	Lock-out feature to prevent use of expired or previously used reagents.
5	Controls to ensure correct tube insertion.
6	Sample volume detection.
7	Electronic error diagnostic and recovery to prevent out-of-specification operation.
8	System self-checks for instrument subsystems.
9	Auto-calibration and monitoring.
10	Automated data acquisition, analysis, and result interpretation.
11	System outputs results as a protected file so that results cannot be altered.
12	Internal Process Control to monitor the test procedure for each individual sample.
13	Mandatory "Add Lot" procedure for new reagent lots.
14	Software installations are protected by cryptographic methods that verify the origin and integrity.

3. Flex Studies:
   The cobas liat SARS-CoV-2 v2 is performed according to the same workflow as the previously cleared and CLIA waived tests on the liat system (e.g., cobas SARS-CoV-2 & Influenza A/B Nucleic acid test (K223591/CW220014), cobas Influenza A/B & RSV Nucleic acid test (K153544/CW150018), and Liat Step A Assay (K141338/CW140014)) and the physical properties of the liat analyzer are shared between all assays. Therefore, some of the previously conducted flex studies, considered not to be assay specific, demonstrating operational robustness of the cobas liat system, were not repeated and the previously generated data were leveraged for this application.

The following flex studies were conducted previously and may be referenced in the CLIA Waiver Decision Summaries for CW140014, CW150018 and CW220014:

a. Variation in operating temperature (environmental temperature above/below specified range).
b. Variation in humidity levels (environmental humidity above/below specified range).
c. Variation in altitude and atmospheric pressure (operation above specified altitude).
d. Operation of the instrument on non-level surface (instrument tilt (x-, y-tilt).
e. Movement of the liat analyzer during analysis.
f. Variable Sample Volume (input sample above/below the specified volume).
g. Assay tube orientation post sample addition.
h. Broken or compromised seals within the liat tubes (due to mishandling prior to testing).

Additional flex studies, deemed as assay specific, were performed to evaluate the robustness (i.e., risk of erroneous results) of the cobas liat SARS-CoV-2 v2 nucleic acid test when subjected to potential variations in workflow and control effectiveness that may reasonably be expected to occur with untrained operators in the intended use CLIA waived setting. Test conditions were designed based on a risk analysis of the complete test system and included conditions intended to verify the effectiveness of built-in controls. These studies are described below.

Flex studies were conducted using contrived samples consisting of inactivated SARS-CoV-2 (USA-WA1/2020) formulated at 3x LoD in simulated nasopharyngeal matrix (S-UTM). Equivalency between natural clinical and simulated matrices was demonstrated in a matrix equivalency study.

a. Internal Control (IC) Effectiveness

This study evaluated the effectiveness of the Internal Control (IC) to monitor the performance of the cobas liat SARS-CoV-2 v2 nucleic acid test sample processing and PCR amplification/detection under simulated process and reagent failures. IC effectiveness was demonstrated by testing a control condition and four (4) failure conditions with negative and positive samples comprised of inactivated SARS-CoV-2 diluted into simulated nasopharyngeal matrix (S-UTM) to approximately 3x LoD. Five replicates were tested per condition. Results were considered passing if the negative samples were negative for the control condition and negative and/or invalid for the failure conditions and the positive samples were positive for the control condition and positive and/or invalid for the failure conditions. All results were as expected as shown in **Table 3**, demonstrating that the internal control is effective to monitor the performance of sample preparation and PCR amplification/detection.

Table 3. IC Effectiveness

	3x LoD Replicates			Negative Replicates[a]		IC Results		
Condition Description	**Positive**	**Negative**	**Invalid**	**Negative**	**Invalid**	**Positive**	**Negative**	**Invalid**
Control (no simulated failures)	5	0	0	5	0	10	0	0
Failure to capture magnetic glass particles during nucleic acid extraction	0	0	4	0	5	0	10	0
Frangible seal break between the assay tube Sample Preparation segments	0	0	5	0	5	0	10	0
Deviation in PCR temperature	0	0	5	0	5	0	10	0
Frangible seal break between the assay tube PCR segments	0	0	5	0	5	0	0	10

[a] No SARS-CoV-2 positive results were generated in negative samples.

All control condition runs generated expected results. The IC responded correctly to all failure conditions and generated negative results. The built-in control measures/ fail-safe features were demonstrated to be effective.

b. External Control Effectiveness

External control effectiveness was demonstrated by testing a control condition and four (4) failure conditions with the Positive Control and five failure conditions for the Negative Control. Five (5) replicates were tested per condition and control. Results were considered passing if the Control replicates were valid for the control condition and invalid for the failure conditions. As shown in **Table 4**, all results were as expected showing that the external controls are effective to monitor the performance of an assay tube or to detect systematic errors.

Table 4. External Control Effectiveness

Condition Description	**Positive Control Replicates**		**Negative Control Replicates**	
	Valid	**Invalid**	**Valid**	**Invalid**
Control (no simulated failures)	5	0	5	0
Failure to capture magnetic glass particles during nucleic acid extraction	0	5	0	5
Frangible seal break between assay tube Sample Preparation segments	0	5	0	5

Condition Description	Positive Control Replicates		Negative Control Replicates	
	Valid	Invalid	Valid	Invalid
Deviation in PCR temperature	0	5	0	5
Frangible seal break between assay tube PCR segments	0	5	0	5
Run NC to simulate low level contamination (~3x LoD of SARS CoV-2)	n/a	n/a	0	5

n/a – not tested

c. Improper Assay Tube Storage (Incorrect Reagent Storage)

The purpose of this study was to test the effect of improper storage of the cobas liat SARS-CoV-2 v2 assay tube. Five (5) replicates of contrived positive samples comprised inactivated SARS-CoV-2 at 3x LoD in S-UTM were tested for each storage condition. Additionally, five (5) replicates of negative samples consisting of only S-UTM were tested for each condition. In order to pass the acceptance criteria, all positive replicates should be detected for SARS-CoV-2 and all negative replicates should be not detected for SARS-CoV-2. The assay tubes were stored at conditions shown in **Table 5**.

Table 5. Improper Assay Tube Storage Conditions

Test Condition #	Enclosed In Foil Pouch	Storage Temperature (°C)	Time point (Days)	Rationale
0	Yes	2-8°C	N/A	Control
1		-20°C	7	Simulates incorrect storage in freezer, or low temperature shipping excursion
2		30°C	14	Simulates extended storage at room temperature (15-30°C)
3		37°C	7	Simulates incorrect storage at high temperature, or higher temperature shipping excursion
4	No	-20°C	1	Simulates incorrect storage in freezer after opening packaging
5		2-8°C	1	Simulates incorrect storage in refrigerator after opening packaging
6		30°C	1	Simulates extended storage at room temperature after opening packaging
7		37°C	1	Simulates incorrect storage at high temperature, or higher temperature shipping excursion after opening packaging

As shown in **Table 6**, all positive and negative replicates met the acceptance criteria which demonstrated that the cobas liat SARS-CoV-2 v2 has robust performance when assay tubes are stored under improper conditions.

Table 6. Improper Assay Tube Storage Results Summary

Test Condition			Sample Type	n Detected/N Tested	
#	Temp.	Days		SARS-CoV-2	IC
0	2-8°C	N/A	3x LoD	5/5	5/5
			Negative	0/5	5/5
1	-20°C	7	3x LoD	5/5	5/5
			Negative	0/5	5/5
2	30°C	14	3x LoD	5/5	5/5
			Negative	0/5	5/5
3	37°C	7	3x LoD	5/5	5/5
			Negative	0/5	5/5
4	-20°C	1	3x LoD	5/5	5/5
			Negative	0/5	5/5
5	2-8°C	1	3x LoD	5/5	5/5
			Negative	0/5	5/5
6	30°C	1	3x LoD	5/5	5/5
			Negative	0/5	5/5
7	37°C	1	3x LoD	5/5	5/5
			Negative	0/5	5/5

d. Assay Tube Hold Time (Hold Time Post Sample Addition)

The purpose of this study was to test the effect of extended hold times between addition of the sample to the cobas liat SARS-CoV-2 v2 assay tube and initiation of the run on the cobas liat analyzer. Ten (10) replicates of contrived positive samples comprised of inactivated SARS-CoV-2 at 3x LoD in S-UTM were tested for each extended hold time condition. Additionally, ten (10) replicates of negative samples consisting of only S-UTM were tested for each condition. In order to pass the acceptance criteria, all positive replicates should be detected for SARS-CoV-2 and all negative replicates should be not detected SARS-CoV-2. The assay tubes test conditions are described in **Table 7**.

Table 7. Assay Tube Hold Time (Hold Time Post Sample Addition) Test Conditions

Test Condition #	Temperature (°C)	Time from Sample Addition to Run	Rationale
0	20-25	Immediately	Control
1	20-25	2 hours	Simulated deviations from immediate processing.
2	20-25	4 hours	
3	20-25	6 hours	

Under Test Condition #3 (6-hour delay between sample addition and run), one (1) negative sample replicate was positive for SARS-CoV-2. The SARS-CoV-2 positive result was investigated and further confirmed by sequencing, and was attributed to sample contamination. Five (5) replicates of a new aliquot of the negative sample were re-tested under Test Condition #3 and all five (5) replicates generated negative (SARS-CoV-2 not detected) results as expected. All positive and negative replicates met the acceptance criteria which demonstrated that the cobas liat SARS-CoV-2 v2 nucleic acid test has robust performance when assay tubes are held for extended times after the sample has been added. The results are summarized in **Table 8**.

Table 8. Assay Tube Hold Time (Hold Time Post Sample Addition) Result Summary

Test Condition	Sample Type	n Detected/N Tested	
		SARS-CoV-2	IC
Immediately (Control)	3x LoD	10/10	10/10
	Negative	0/10	10/10
2 hours	3x LoD	10/10	10/10
	Negative	0/10	10/10
4 hours	3x LoD	10/10	10/10
	Negative	0/10	10/10
6 hours	3x LoD	10/10	10/10
	Negative[a]	1/15[b]	15/15

[a] Five additional negative replicates were tested due to the SARS-CoV-2 positive result.
[b] SARS-CoV-2 positive sample was confirmed positive by sequencing and attributed to sample contamination.

e. Improper Specimen Storage (Incorrect sample storage and delay in sample testing)
The purpose of this study was to test the stability of specimens following extended storage at different temperatures, as well as to test the effect of a delay in sample testing. Five (5) replicates of contrived positive samples comprised of inactivated SARS-CoV-2 at 3x LoD in S-UTM were tested for each sample storage condition. Additionally, five (5) replicates of negative samples consisting of only S-UTM were tested for each condition. In order to pass the acceptance criteria, all positive replicates should be detected for SARS-CoV-2 and all negative replicates should be not detected for SARS-CoV-2. The specimens were stored at conditions shown in **Table 9**.

Table 9. Improper Specimen Storage Test Conditions (Incorrect sample storage and delay in sample testing)

Test Condition #	Storage Temperature (°C)	Time	Rationale
0	2–8°C	1 Day	Control
1	20–25°C		Operator incorrectly stores specimen at room temperature.
2	37°C		Extreme high temperature condition. Operator incorrectly stores specimen at extreme high temperature.
3	-80°C		Control
4	-20°C		-20°C frozen storage condition. Operator incorrectly stores specimen in freezer rather than refrigerator.
5	20–25°C	2 days	Room temperature condition, delayed 2 days from recommended storage condition (15-30°C up to 4 hours).
6	2–8°C	4 days	Refrigerated temperature condition, delayed 1 day from recommended storage condition (2-8°C up to 72 hours)

As shown in **Table 10**, all positive and negative replicates met the acceptance criteria which demonstrated that the cobas liat SARS-CoV-2 v2 nucleic acid test has robust performance when specimens are stored under improper conditions.

Table 10. Improper Specimen Storage (Incorrect sample storage and delayed in sample testing) Result Summary

Test Condition	Sample Type	n Detected/N Tested	
		SARS-CoV-2	IC
1 day at 4°C (Control condition)	3x LoD	5/5	5/5
	Negative	0/5	5/5
1 day at 25°C	3x LoD	5/5	5/5
	Negative	0/5	5/5
1 day at 37°C	3x LoD	5/5	5/5
	Negative	0/5	5/5
1 day at -20°C	3x LoD	5/5	5/5
	Negative	0/5	5/5
1 day at -80°C	3x LoD	5/5	5/5
	Negative	0/5	5/5
2 days at 25°C	3x LoD	5/5	5/5

Test Condition	Sample Type	n Detected/N Tested	
		SARS-CoV-2	IC
	Negative	0/5	5/5
4 days at 4°C	3x LoD	5/5	5/5
	Negative	0/5	5/5

f. Bubbles in Sample Chamber

The purpose of this study was to test the effect of creating bubbles when transferring the sample to the sample chamber. Five (5) replicates of contrived positive samples comprised of inactivated SARS-CoV-2 at 3x LoD in S-UTM were tested in conditions with and without bubbles in the sample chamber. Additionally, five (5) replicates of negative samples consisting of only S-UTM were tested for each condition. In order to pass the acceptance criteria, all positive replicates should be detected for SARS-CoV-2 and all negative replicates should be not detected for SARS-CoV-2.

As shown in **Table 11**, all positive and negative replicates met the acceptance criteria which demonstrated that the cobas liat SARS-CoV-2 v2 nucleic acid test has robust performance when bubbles are introduced into the sample chamber.

Table 11. Bubbles in Sample Chamber Result Summary

Test Condition	Sample Type	n Detected/N Tested	
		SARS-CoV-2	IC
No Bubbles	3x LoD	5/5	5/5
	Negative	0/5	5/5
Bubbles in Sample Chamber	3x LoD	5/5	5/5
	Negative	0/5	5/5

Overall, based on flex studies previously performed for the cobas liat system and currently performed for the cobas liat SARS-CoV-2 v2 nucleic acid test specifically, the cobas liat SARS-CoV-2 v2 assay is robust to foreseeable user-dependent variations in the assay workflow. Additionally, built-in assay controls and fail-safe and/or failure alert mechanisms are effective in preventing the generation of erroneous results due to operator error and/or use of the cobas liat system outside the specified operating environmental conditions.

C Demonstrating "Insignificant Risk of an Erroneous Result" – Accuracy

1. Comparison Study

a. Study Design

i. Study Sites and Duration

Clinical performance characteristics of the cobas liat SARS-CoV-2 v2 nucleic acid test were evaluated in a multi-site prospective study during September 2023-March 2024 respiratory viral season in the U.S.. Fourteen (14) sites throughout the U.S. participated in the clinical study. The sites consisted of emergency rooms, urgent care clinics, outpatient clinics, and physicians' offices. All the sites were representative of CLIA waived intended use sites for this device.

ii. Operators
There were a total of 41 operators representative of intended CLIA waived users across the 14 clinical testing sites, with two (2) to five (5) operators per site. The participants were representative of operators at the CLIA waived sites. The test operators who participated in the study were untrained in the use of the cobas liat SARS-CoV-2 v2 nucleic acid test and none were trained laboratory technicians.

iii. Instructions for Use
The operators were provided the cobas liat SARS-CoV-2 v2 nucleic acid test Instructions for Use (IFU), the Quick Reference Instructions, and the cobas liat system User Guide. No other materials or instructions were provided and the operators received no training in the use of the test.

iv. Subjects (Patients)
The subjects were enrolled according to the study protocol Inclusion or Exclusion criteria from individuals with or without signs and symptoms of respiratory viral infection.

v. Samples
The clinical performance of the cobas liat SARS-CoV-2 v2 nucleic acid test was evaluated using prospectively collected specimens from all-comers with or without signs and symptoms of respiratory viral infection as described below.

One nasopharyngeal swab (NPS) and one nasal swab (NS) (either clinician-collected or self-collected under the supervision of the health care provider) were collected from each subject using standard collection methods and each eluted in UTM. Prospectively collected NPS and NS specimens were tested fresh at the clinical site with cobas liat SARS-CoV-2 v2 assay by the intended use operators following the product IFU and/or Quick Reference Instructions. The sample were tested on the comparator method following the products' IFU at the reference testing laboratory.

Subject matched paired NPS and NS samples were prospectively collected by 41 intended use operators from September 2023 to May 2024. In total, 4,446 prospectively collected paired NPS and NS specimens from individuals with or without signs and symptoms of respiratory viral infection were collected for the evaluation of cobas liat SARS-CoV-2 v2 nucleic acid test. Four (4) subjects were withdrawn due to not meeting the study eligibility criteria.

Symptomatic Cohort
In total, 1,730 prospectively collected paired NPS and NS specimens from symptomatic subjects were collected for the evaluation of cobas liat SARS-CoV-2 v2 nucleic acid test. One (1) subject was withdrawn due to not meeting the study

eligibility criteria. Of the 1,729 prospective symptomatic subjects enrolled, 1,705 NPS specimens were evaluable in the SARS-CoV-2 analysis, 19 were non-evaluable due to missing candidate test results due to protocol deviations, and five (5) were non-evaluable due to specimen handling issues. Of the 1,729 prospective symptomatic subjects enrolled, 1,706 NS specimens were evaluable in the SARS-CoV-2 analysis, 22 were non-evaluable due to missing or invalid candidate test results, and one (1) was non-evaluable due to specimen handling issues.

Asymptomatic Cohort

In total, 2,716 prospectively collected paired NPS and NS specimens from asymptomatic subjects were collected for the evaluation of cobas liat SARS-CoV-2 v2 nucleic acid test. Three (3) subjects were withdrawn due to not meeting the study eligibility criteria. Of the 2,713 prospective asymptomatic subjects enrolled, 2,697 NPS specimens were evaluable in the SARS-CoV-2 analyses, 12 were non-evaluable due to missing candidate test results due to protocol deviations, one (1) sample observed a failed test, and three (3) were non-evaluable due to specimen handling issues. 2,700 NS specimens were evaluable in the SARS-CoV-2 analyses, ten (10) were non-evaluable due to missing or invalid candidate test results and three (3) were non-evaluable due to specimen handling issues.

An FDA cleared molecular assay that detects SARS-CoV-2 was used as the comparator method for evaluating the performance of the cobas liat SARS-CoV-2 v2 nucleic acid test. Performance for NPS was assessed against comparator results from testing an aliquot of the same NPS specimen and performance for NS was established against comparator results from testing an aliquot of the same NS specimen.

b. Results and Analysis

The clinical performance of the cobas liat SARS-CoV-2 v2 nucleic acid test, when used by untrained operators, testing NPS and NS specimens from patients with or without symptoms of respiratory tract infection is shown in **Tables 12 and 13,** respectively.

Table 12. Clinical Performance of cobas liat SARS-CoV-2 v2 nucleic acid test in Symptomatic Subjects

Specimen Type	Total (N)	Positive Percent Agreement			Negative Percent Agreement		
		a/ (a+c)	%	95% CI	b/ (b+d)	%	95% CI
NPS	1705	207/219[1]	94.5	90.7-96.8	1451/1486[2]	97.6	96.7-98.3
NS	1706	208/215[3]	96.7	93.2-98.4	1449/1491[4]	97.2	96.2-97.9

N = Total number of paired samples, CI = Confidence Interval, NPS = Nasopharyngeal swab, NS = Anterior Nasal Swab
Note: a = number of samples where both the cobas liat SARS-CoV-2 v2 nucleic acid test and the comparator tests are positive; b = number of samples where the cobas liat SARS-CoV-2 v2 nucleic acid test is positive and the comparator is negative; c = number of samples where the cobas liat SARS-CoV-2 v2 nucleic acid test is negative and the comparator is positive; d = number of samples where both the cobas liat SARS-CoV-2 v2 nucleic acid test and the comparator tests are negative.

[1] Of 12 NPS specimens negative for SARS-CoV-2 on cobas liat and positive on the comparator, eight (8) were positive for SARS-CoV-2 and four (4) were negative by an FDA cleared SARS-CoV-2 molecular test.

[2] Of 35 NPS specimens positive for SARS-CoV-2 on cobas liat and negative on the comparator, 12 were positive for SARS-CoV-2 and 23 were negative by an FDA cleared SARS-CoV-2 molecular test.

[3] Of seven (7) NS specimens negative for SARS-CoV-2 on cobas liat and positive on the comparator, six (6) were positive for SARS-CoV-2 and one (1) was negative by an FDA cleared SARS-CoV-2 molecular test.

[4] Of 42 NS specimens positive for SARS-CoV-2 on cobas liat and negative on the comparator, eight (8) were positive for SARS-CoV-2 and 34 were negative by an FDA cleared SARS-CoV-2 molecular test.

Table 13. Clinical Performance of cobas liat SARS-CoV-2 v2 nucleic acid test in Asymptomatic Subjects

Specimen type	Total (N)	Positive Percent Agreement			Negative Percent Agreement		
		a/ (a+c)	%	95% CI	d/ (b+d)	%	95% CI
NPS	2697	62/72[1]	86.1	76.3-92.3	2569/2625[2]	97.9	97.2-98.4
NS	2700	51/57[3]	89.5	78.9-95.1	2597/2643[4]	98.3	97.7-98.7

PPA = Positive Percent Agreement; CI = Confidence Interval; NPA = Negative Percent Agreement; NPS = Nasopharyngeal swab; NS = Nasal Swab.
Note: N = Total number of specimens; a = number of samples where both the cobas liat SARS-CoV-2 v2 nucleic acid test and the comparator tests are positive; b = number of samples where the cobas liat SARS-CoV-2 v2 nucleic acid test is positive and the comparator is negative; c = number of samples where the cobas liat SARS-CoV-2 v2 nucleic acid test is negative and the comparator is positive; d = number of samples where both the cobas liat SARS-CoV-2 v2 nucleic acid test and the comparator tests are negative.
[1] Of ten (10) NPS specimens negative for SARS-CoV-2 on cobas liat and positive on the comparator, six (6) were positive for SARS-CoV-2 and four (4) were negative by an FDA cleared SARS-CoV-2 molecular test.
[2] Of 56 NPS specimens positive for SARS-CoV-2 on cobas liat and negative on the comparator, 17 were positive for SARS-CoV-2 and 39 were negative by an FDA cleared SARS-CoV-2 molecular test.
[3] Of six (6) NS specimens negative for SARS-CoV-2 on cobas liat and positive on the comparator, three (3) were positive for SARS-CoV-2 and three (3) were negative by an FDA cleared SARS-CoV-2 molecular test.
[4] Of 46 NS specimens positive for SARS-CoV-2 on cobas liat and negative on the comparator, six (6) were positive for SARS-CoV-2 and 40 were negative by an FDA cleared SARS-CoV-2 molecular test.

i. Invalid Rate for Clinical Evaluation Samples

A total of 1724 tests were performed on NPS specimens from symptomatic subjects, of which 34 tests were initially non-evaluable (seven (7) were failed tests, eight (8) were invalid tests and 19 tests had protocol deviations) for an initial invalid rate of 0.46%. Upon repeat testing, 19 tests were non-evaluable (0 were failed tests, 0 were invalid tests and 19 tests had protocol deviations) and were not included in the final calculations. NPS specimens demonstrated a final invalid rate of 0%.

A total of 1728 tests were performed on NS specimens from symptomatic subjects, of which 42 tests were initially non-evaluable (nine (9) were failed tests, 12 were invalid tests and 21 tests had protocol deviations) for an invalid rate of 0.69%. Upon repeat testing, 22 tests were non-evaluable (0 were failed tests, one (1) was invalid test and 21 tests had protocol deviations) and were not included in the final calculations. NS specimens demonstrated a final invalid rate of 0.06%.

A total of 2710 tests were performed on NPS specimens from asymptomatic subjects, of which 35 tests were initially non-evaluable (14 were failed tests, seven (7) were invalid tests and 14 tests had protocol deviations) for an initial invalid rate of 0.26%. Upon repeat testing, 13 tests were non-evaluable (0 were failed test, 0 were invalid tests and 13 tests had protocol deviations) and were not included in the final calculations. NPS specimens demonstrated a final invalid rate of 0.0%.

A total of 2710 tests were performed on NS specimens from asymptomatic subjects, of which 29 tests were initially non-evaluable (12 were failed tests, eight (8) were invalid tests and 9 tests had protocol deviations) for an initial invalid rate of 0.30%. Upon repeat testing, ten (10) tests were non-evaluable (0 were failed tests, one (1) was invalid test and nine (9) tests had protocol deviations) and were not included in the final calculations. NS specimens demonstrated a final invalid rate of 0.04%

2. Device Performance with Analyte Concentrations Near the Cutoff

The performance of the cobas liat SARS-CoV-2 v2 assay with samples at virus concentration near the assay cutoff, was evaluated during a reproducibility study conducted in support of the 510(k) for this device, which included a sample with low concentration of SARS-CoV-2 (2x LoD) and a negative sample. The cobas liat SARS-CoV-2 v2 assay was evaluated at three CLIA waived sites. Two (2) operators at each of the three sites tested each panel member in triplicate on five different days across three (3) reagent lots, for a total of 540 tests (3 sites × 3 lots/site × 5 day/lot × 2 operators/day × 2 panel members/operator × 3 replicates/panel member), ~ 270 tests/panel member. Each site utilized a minimum of three liat analyzers.

The reproducibility panel samples were prepared by spiking inactivated SARS-CoV-2 (USA-WA1/2020) of known titer into negative simulated nasopharyngeal matrix (S-UTM). The low positive concentration used corresponded to 2x LoD. The negative sample was comprised of S-UTM.

Three (3) CLIA waived sites and six operators (two operators per site) participated in this reproducibility study. All operators had limited or no training or hands-on experience in conducting laboratory testing when the study initiated. The six operators at the three sites tested the members of the reproducibility panel in triplicate on five non-consecutive days. Three (3) cobas liat analyzers were used at each site for a total of nine cobas liat analyzers. Each site also used approximately equal amounts of three different lots of cobas liat SARS-CoV-2 v2 assay tubes. The results are presented in **Table 14.**

Table 14. Reproducibility Study- Qualitative Results

Target	Panel Conc.	% Agreement with Expected Results/ (n Agreement/N Tested) (95% CI)			
		Site 1	Site 2	Site 3	Overall
Negative	0	100% (86/86) (95.7-100)	100% (89/89) (95.9-100)	100% (90/90) (95.9-100)	100% (265/265) (98.6-100)
SARS-CoV-2[a]	Low Positive (2x LoD)	100% (90/90) (95.9-100)	100% (90/90) (95.9-100)	100% (90/90) (95.9-100)	100% (270-270) (98.6-100)
	Mod. Positive (5x LoD)	100% (88/88) (95.9-100)	100% (89/89) (95.9-100)	100% (90/90) (95.9-100)	100% (267/267) (98.6-100)

Mod = moderate, Conc= Concentration

[a] Inactivated virus

The total Ct variability, as measured by the standard deviation, was less than or equal to 1.18. These results, shown in **Table 15**, indicate that the reproducibility of the cobas liat SARS-CoV-2 v2 nucleic acid test is acceptable.

Table 15. Reproducibility Study- Ct Analysis Results

Viral Target	Panel Member Conc.	n/N[a]	Mean Ct	Between Sites		Between Lots		Between Days		Between Operators		Within-Run (Residual)		Total	
				SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
SARS-CoV-2[b]	2x LoD	270/270	33.8	0.00	0.0	0.38	1.1	0.17	0.5	0.36	1.1	1.03	3.0	1.16	3.4
SARS-CoV-2[b]	5x LoD	267/267	32.4	0.13	0.4	0.54	1.7	0.27	0.8	0.00	0.0	1.00	3.1	1.18	3.6

Ct = cycle threshold; LoD = Limit of Detection; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2; SD = standard deviation; CV% = percent coefficient of variation.
[a] n is the number of positive tests, which contribute Ct values to the analysis. N is the total number of valid tests for the panel member.
[b] Inactivated virus

3. Operator Questionnaire

Upon completion of the Clinical and Near the Cutoff Studies (Reproducibility), the operators at each site were asked to complete an Operator Questionnaire that asked them to rate the ease of use of the test procedure and answer proficiency questions related to cobas liat SARS-CoV-2 v2 assay result interpretation. The proficiency potion of the questionnaire included 19 images of a cobas liat system display and asked if the result for SARS-CoV-2 was positive, negative, or could not be assessed, as well as four (4) assay interpretation images for invalid or aborted tests (23 total points possible). The ease of use questionnaire asked the operators to reply to a series of eight (8) statements using an agreement scale (1= strongly disagree to 5= strongly agree).

Of the 41 operators who participated in the clinical study, there were two (2) individuals who were no longer employed by the clinical sites at the time the questionnaire was given, so only 39 operators provided responses. **Table 16** shows the results of the proficiency questions by operator. The combined score for the proficiency portion of the questionnaire was 99.8% (895/897 correct responses).

Table 16. Study Operator Proficiency Test Results - Interpretation of Results

Site ID[a]	Operator	% Correct (n Correct/N Total)		Overall Score
		SARS-CoV-2	Assay Result[b]	
1	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
2	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)

Site ID[a]	Operator	% Correct (n Correct/N Total)		Overall Score
		SARS-CoV-2	Assay Result[b]	
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
3	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
4	1	94.7% (18/19)	100.0% (4/4)	95.7% (22/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
6	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
7	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
8	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
9	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
10	1	100.0% (19/19)	75.0% (3/4)	95.7% (22/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	4	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	5	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)

Site ID[a]	Operator	% Correct (n Correct/N Total)		Overall Score
		SARS-CoV-2	Assay Result[b]	
11	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
12	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	4	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
13	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	4	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
14	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	3	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
15	1	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
	2	100.0% (19/19)	100.0% (4/4)	100.0% (23/23)
Mean Score	**Overall**	**99.9% (740/741)**	**99.3% (155/156)**	**99.8% (895/897)**

[a] No operators from Site 5 tested samples from the prospective study.
[b] Assay results were evaluated when invalid results or aborted tests were obtained.

The operators' average scores indicating their agreement with the statements in the ease of use questionnaire are shown in **Table 17**. The average agreement with the statement ranged from 4.5 (4 being Agree) to 5 (5 being Strongly Agree). The overall score for the ease of use questions was 4.9 out of 5, indicating the operators agreed the device was easy to use overall.

Table 17. Operators Post Study Ease-of-Use Questionnaire Results

Statement	Average Agreement with Statement Score[a] (1 = Strongly Disagree, 5 = Strongly Agree)
The instructions to add lot and perform controls were easy to follow.	4.8
The instructions to test specimens were easy to follow.	5.0
It was easy to load the sample into the liat assay tube.	5.0
It was easy to start the assay on the liat analyzer.	5.0
It was easy to read the test results.	4.8
It was easy to understand the test results.	4.8
The Instructions For Use and Quick Reference Instructions clearly explain what to do if a test result is invalid.	4.5
I did not need help when I tested samples using the liat assay.	5.0
Overall Score	**4.9**

[a] Statements were scored as follows: 1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree.

D Labeling for Waived Devices

1. The labeling consists of:

    a. **cobas** liat SARS-CoV-2 v2 nucleic acid test Instructions for Use

    b. **cobas** liat SARS-CoV-2 v2 nucleic acid test Quick Reference Instructions

    c. **cobas** liat system User Guide

2. The following elements are appropriately present:

    - The cobas liat system User Guide specifies the environmental operating conditions under which testing may be performed.
    - The cobas liat system User Guide and cobas liat SARS-CoV-2 v2 nucleic acid test Instructions for Use are clear and easy to understand.
    - The cobas liat SARS-CoV-2 v2 nucleic acid test Instructions for Use and Quick Reference Instructions identify the test as CLIA Waived.
    - The cobas liat SARS-CoV-2 v2 nucleic acid test Instructions for Use:
        - Indicate that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test.
        - Include step-by-step instructions for performing the test.
        - Include safety considerations applicable for untrained users.
        - Specify the actions to be taken if an invalid test result is obtained.
        - Include a summary of the studies performed to support CLIA Waiver.

- Include appropriate warnings and/or limitations pertaining to clinical interpretation of test results.
- Include recommendations for Quality Control testing including the source of appropriate control materials and the frequency of testing.

- The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

XI. Conclusion

The submitted information in this CLIA waiver application supports a CLIA waiver approval decision.