# Summary Basis for Regulatory Action

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| **Date:** | February 1, 2024 |
| **From:** | Nitin Verma, Ph.D.,<br>Chair of the Review Committee |
| **BLA/ STN#:** | 125799/0 |
| **Applicant Name:** | Roche Diagnostics Solutions<br>9115 Hague Road; Indianapolis, IN 46256 |
| **Date of Submission:** | April 14, 2023 |
| **MDUFA Goal Date:** | February 12, 2024 |
| **Proprietary Name:** | Elecsys Chagas<br>PreciControl Chagas<br>PreciControl Release Chagas |

**Established Name (common or usual name):** Elecsys Chagas test for use with **cobas pro** serology solution comprising of **cobas e** 801 analytical unit and **cobas pro** serology controller.

**Intended Use/Indications for Use:**

Elecsys Chagas is an in vitro immunoassay for the qualitative detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*, the causative agent of the Chagas disease) in human serum and plasma. Elecsys Chagas is intended to screen individual human donors, including volunteer donors of whole blood and blood components. The assay is also intended to be used to screen organ, tissue, and cell donors, when donor samples are obtained while the donor's heart is still beating. It is not intended for use on cord blood specimens.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use with **cobas pro** serology solution equipped with **cobas e** 801 analytical unit.

**Recommended Action:** The Review Committee recommends licensure of this product.

**Review Office Signatory Authority:** Anne Eder, MD, PhD; Director, Office of Blood Research and Review

**x I concur with the summary review.**

**☐ I concur with the summary review and include a separate review to add further analysis.**

**☐ I do not concur with the summary review and include a separate review.**

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The table below indicates the material reviewed when developing the SBRA.

**Table 1: Reviews Submitted**

| Document Title | Reviewer Name | Document Date |
|---|---|---|
| Product Review(s) (OBRR/DETTD)<br>• *Clinical*<br>• *Non-Clinical* | <br>Alain Debrabant<br><br>Virginie Dujols<br>Kavita Singh | <br>01/12 /2024<br><br>11/06/2023<br>12/26/2023 |
| Statistical Review(s)<br>• *Clinical and Non-Clinical (OBPV/DB/DNCE)* | Paul B. Hshieh | 09/18/2023 |
| CMC Review<br>• *CMC (OBRR/DETTD)*<br>• *Facilities Review (OCBQ/DMPQ)*<br>• *Microbiology Review (OCBQ/DBSQC)*<br>• *Establishment Inspection Report(s) (OCBQ/DMPQ)* | <br>Ranadhir Dey<br><br>Prajakta Varadkar<br><br>Seth Schulte<br><br>Prajakta Varadkar | <br>12/21/2023<br><br>01/18/2024<br><br>09/21/2023<br><br>07/13/2023 |
| Labeling Review(s)<br>• *OBRR*<br>• *APLB (OCBQ/APLB)* | <br>Nitin Verma<br><br>Sadhna Khatri | <br>01/26/2024<br><br>12/13/2023 |
| Lot Release Protocols/Testing Plans/Testing Panel (OCBQ/DBSQC) | Marie Anderson<br>Karen Smith | 12/13/2023<br>12/29/2023 |
| Bioresearch Monitoring Review (OCBQ/BIMO) | Kanaeko Ravenell<br>Yakubu Wangabi | 01/12/2024 |
| Software and Instrumentation (OBRR/DETTD) | Hongqiang Hu | 10/27/2023 |
| Other living donor (OTP/DHT) | Hanh Khuu | 01/02/2024 |

## 1. Introduction

The Elecsys Chagas assay is manufactured at the Roche Diagnostics Facilities located in Mannheim (b) (4) Germany. This biologics license application (BLA) for Elecsys Chagas assay from Roche Diagnostics Solutions, 9115 Hague Road Indianapolis, IN 46250, USA was received on April 14, 2023.

The application was assigned the number STN 125799/0 and granted a standard 10-month review status with a goal date of February 12, 2024. The application was filed May 22, 2023, and the mid-cycle meeting took place on September 13, 2023. The BLA application was preceded by pre-submission BQ170139/0 and a series of

five supplements BQ170139/1 to BQ170139/5, focused on the regulatory aspects related to software and instrumentation, pre-clinical studies as well as clinical studies for a group of Elecsys assays planned by Roche to be submitted to FDA for approval. The Elecsys assays are intended for use with the **cobas e** 801 analyzer and **cobas pro** serology solution. Due to commonalities between the technology and assay formats, an investigational new drug application (IND) 27257 was submitted collectively for all planned assays, followed by thirteen amendments; the last amendment was dated December 21, 2022.

**Table 2: Chronological Summary of Submission and FDA Interaction with Roche Diagnostics (RD)**

| Date | Action | Amendment to BL125799 |
|---|---|---|
| April 14, 2023 | BLA CBER receipt | /0 |
| April 17, 2023 | Acknowledgement letter | |
| May 05, 2023 | Amendment received for updating the serology controller software from version 1.0.3 to version 1.1.0 | /0/2 |
| May 17, 2023 | RD was requested to correct the FDA form 356h for FEI and DUNS numbers | |
| May 18, 2023 | RD submitted corrected FDA form 356h | /0/3 |
| May 22, 2023 | Filing Notification Letter | |
| June 08, 2023 | FDA IR – Request for Lot Release Template | |
| June 20, 2023 | Lot Release Template submitted by RD | /0/4 |
| June 29, 2023 | FDA IR – Analytical studies (acceptance criteria, LoB/LoD for serum and plasma, sample matrix used, COI deviations) | |
| July 10, 2023 | Response to FDA IR dated June 29, 2023 for the analytical studies | /0/6 |
| July 21, 2023 | FDA IR - Analytical studies (duplicate runs for PreciControls, LoB/LoD, acceptance criteria, serum/plasma comparison) | |
| July 27, 2023 | FDA IR – Endogenous interference due to Biotin | |
| July 31, 2023 | Response to FDA IR dated July 27, 2023 for the endogenous interference due to Biotin | /0/7 |
| July 31, 2023 | Response to FDA IR dated July 21, 2023 for the analytical studies | /0/8 |
| August 01, 2023 | Minor typographical error fixed to the response from Roche dated July 28, 2023, to the analytical studies IR dated July 21 2023 | /0/9 |
| August 08, 2023 | FDA IR for (b) (4) (b) (4) and Bioburden studies | |

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| August 09, 2023 | FDA IR - Follow-up to the response dated July 31, 2023 regarding, LoB/LoD, matrix equivalency, number of replicates for PreciControls and Calibrators, Biotin interference | |
| August 18, 2023 | Response to FDA IR dated August 09, 2023 | /0/10 |
| August 18, 2023 | Response to FDA IR dated August 08, 2023 for [redacted] and Bioburden; RD informed that bioburden testing report will be provided by September 01, 2023 | /0/11 |
| September 01, 2023 | RD provided bioburden testing results | /0/12 |
| September 06, 2023 | FDA IR – related to the CMC – Source of the materials of human origin (CoA), target value assignment | |
| September 06, 2023 | FDA IR – related to Clinical study – CoA for the clinical sensitivity samples; modify inconclusive final status of endemic samples; separately demonstrate serum and plasma sensitivity data | |
| September 07, 2023 | Mid-cycle memo from BIMO – CBER requested inspection completion by October 26, 2023 for clinical study site at (b) (4) was inspected in April 2023 for Elecsys HIV Duo and Elecsys HTLV I/II, no form FDA 483 was issued | |
| September 08, 2023 | FDA IR – Discrepancy in the analytical study for naturally elevated Bilirubin interference | |
| September 12, 2023 | Response to FDA IR dated September 08, 2023 | /0/13 |
| September 12, 2023 | FDA IR – related to the CMC – Testing procedure- number of negative samples for the final QC kit release | |
| September 13, 2023 | Response to FDA IR (CMC) dated September 06 regarding origin of human source materials used in the preparation of controls and calibrators and test method used for the target value assignment for the controls and calibrators | /0/14 |
| September 13, 2023 | FDA IR – related to the bioburden testing | |
| September 15, 2023 | Updated the response dated September 13, 2023 by including a certificate of analysis for the source materials of human origin | /0/15 |

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| September 18, 2023 | Response to FDA IR (CMC) dated September 12 regarding number of unique negative samples used in the testing procedure | /0/16 |
| September 18, 2023 | FDA IR – related to CMC – Traceability of Elecsys Chagas assay | |
| September 20, 2023 | Response to FDA IR (Clinical) dated September 06 regarding CoA for the sensitivity samples; modification of table for the endemic test data; separate serum and plasma sensitivity data | /0/17 |
| September 20, 2023 | Response to FDA IR (Bioburden) dated September 13 | /0/18 |
| September 21, 2023 | Response to FDA IR (CMC) dated September 18; Traceability of Elecsys Chagas | /0/19 |
| September 27, 2023 | Confirmation of the shipping address of the firm to send the CBER blinded panels for Chagas | /0/20 |
| October 02, 2023 | FDA IR (Lot release) – related to the revisions to LRP template | |
| October 05, 2023 | FDA IR – related to Clinical study – Reason for the exclusion of endemic samples | |
| October 10, 2023 | Response to FDA IR (Clinical) dated October 05 – Reason for the exclusion of endemic samples | /0/21 |
| October 13, 2023 | Response to FDA IR (Lot release) – updated LRP template | /0/22 |
| October 16, 2023 | Follow up request (Lot release) – typographical error – change internal control sample numbers from 6 to 4 | |
| October 16, 2023 | Corrected a typo in the LRP template | /0/23 |
| November 07, 2023 | FDA IR – LRP template – specification in the testing procedure | |
| November 08, 2023 | Response to the FDA IR regarding LRP template – Roche submitted final LRP template | /0/24 |
| November 21, 2023 | Response to FDA IR – Roche submitted signed LRP template with test results generated using (b) (4) blinded panels with (b) (4) conformance lots | /0/25 |
| January 17, 2024 | FDA IR – Draft PI, carton label, and value sheet with comments communicated to RD | |
| February 2, 2024 | Response to FDA IR – RD submitted the final PI and outer box labels | /0/26 |

## 2. Background

The Elecsys Chagas is a qualitative serologic sandwich immunoassay intended for detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*) in human serum and plasma. The antibodies are detected using recombinant *T. cruzi* antigens derived from flagellar calcium binding protein (FCaBP), flagellar repetitive antigen (FRA), and cruzipain, and the detection is based on the electrochemiluminescence immunoassay (ECLIA) principle. Additional controls, calibrators and general use reagents are also required to perform the assay and described in the CMC section below.

This assay is designed to be performed on the **cobas e** 801 instrument, a high throughput, fully automated immunoassay analyzer that provides routine and priority processing while allowing continuous access and automated retesting. The **cobas e** 801 Immunoassay Analyzer Instrument incorporates a dedicated software package for instrument control, data collection, results analysis, calibration, quality control, and service software. Results are determined automatically by the Elecsys software based on the comparison of the electrochemiluminescence signal of the sample to the signal obtained by CHAGB calibration. The result of a sample measurement is given either as reactive or non-reactive, as well as in the form of a cutoff index (COI; signal sample/cutoff (S/CO)). Samples with a S/CO <1.00 are considered non-reactive for *T. cruzi* specific antibodies and do not need further testing. Samples with a S/CO ≥1.00 are considered initially reactive on the Elecsys Chagas. All initially reactive samples are automatically retested in duplicate using the Elecsys Chagas assay. Validation of all results is based on test result batches that are concluded by successful release control measurements.

The **cobas pro** serology solution is intended for use only with licensed blood screening assays by U.S. blood banks and plasma fractionators. It is intended for use only by personnel who are trained in its operation. Detailed device description is provided in the CMC and Software and Instrumentation sections below.

## 3. Chemistry Manufacturing and Controls (CMC)

The manufacture of the Elecsys HIV Duo assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

### a) Manufacturing Summary

The Elecsys Chagas assay is manufactured at the Roche Diagnostics GmbH facilities in Germany located at (b) (4) Sandhofer Strasse 116, Mannheim, 68305, Germany. The third manufacturing site is located at (b) (4) (b) (4)

Elecsys Chagas test kit (List Number 09015582162) consists of 9 reagent cassettes (**cobas e** pack), each containing components M, R1, and R2, and two identical calibrator packs, each containing the components CHAGB Cal1 and CHAGB Cal2. The kit components are listed below:

- Component M: Streptavidin-coated microparticles for capturing biotin complex.
- Components R1 and R2: R1 (biotinylated-) and R2 (ruthenylated-) recombinant *T. cruzi* antigens, FCaBP, FRA, and Cruzipain
- CHAGB Cal1: Non-reactive calibrator 1, human serum negative for anti-*T. cruzi* antibodies
- CHAGB Cal2: Reactive calibrator 2, human serum positive for anti-*T. cruzi* antibodies

PreciControl Chagas (List Number 07092571162), supplied separately, is used for quality control of Elecsys Chagas. The control kit consists of the following components:

- PC CHAG1 B: Negative control, human serum non-reactive for antibodies to *T. cruzi*
- PC CHAG2 B: Positive control, human serum reactive for antibodies to *T. cruzi*

PreciControl Release Chagas (List Number 09367098190), identical to PC CHAG2B, supplied separately, is used as a release control, and consists of the human serum reactive for antibodies to *T. cruzi*.

Other general-purpose reagents and consumables for **cobas e** 801 analyzer used for processing all Elecsys assays are listed below:

- AssayTip/AssayCup tray (List Number 05694302001): Disposable pipetting tips and reaction vessels.
- CleanCell M (List Number 04880293190): Cleaning solution for the measuring cell.
- ISE Cleaning solution/Elecsys SysClean (11298500160): System cleaning solution.
- Liquid Flow Cleaning Cup (List Number 07485425001): Cups to supply ISE Cleaning Solution/Elecsys SysClean.
- PreClean II M (List Number 06908853190): Wash solution.
- PreWash Liquid Flow Cleaning Cup (List Number 07485433001): Cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit.
- ProCell II M (List Number 06908799190): System reagent for generating electrochemical signal.
- Reservoir cup (List Number 07485409001): Cups to supply ProCell II M and CleanCell M solutions.

**b) Testing Specifications**

The analytical methods and their validations and/or qualifications were reviewed for the Elecsys Chagas kit and found to be adequate for their intended use.

**c) CBER Lot Release**

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

**d) Facilities Review/Inspection**

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The activities and inspectional history for each facility involved in the manufacture of Elecsys Chagas are presented in the table below (Table 3) and summarized.

**Table 3: Manufacturing facilities for Elecsys Chagas**

| Name/Address | FEI Number | DUNS Number | Inspection / Waiver | Justification / Results |
|---|---|---|---|---|
| Roche Diagnostics GmbH<br>(b) (4)<br><br>*Manufacturing of Elecsys kit components and Control reagents Release testing of final device (assay)* | (b) (4) | (b) (4) | Waiver | CDER Pre-License Inspection<br>(b) (4) VAI<br><br>ORA Post-Market Approval Inspection<br>(b) (4) NAI |
| Roche Diagnostics GmbH<br>Sandhofer Strasse 116, 68305 Mannheim, Germany<br><br>*Labeling and final assembly of Elecsys Chagas kit and PreciControl. Manufacturing, labeling, and packaging of system reagents* | 3002806559 | 315028860 | Waiver | MRA Inspection Review by ORA/OPQO<br>(b) (4)<br>VAI<br><br>ORA For-Cause Inspection<br>(b) (4)<br>VAI<br><br>ORA Post-Market Approval Inspection<br>(b) (4) NAI |

CDER – Center for Drug Evaluation and Research; MRA – Mutual Recognition Agreement; NAI – No Action Indicated; ORA - Office of Regulatory Affairs; OPQO – Office of Pharmaceutical Quality Operations; VAI – Voluntary Action Indicated.

Roche Diagnostics GmbH, (b) (4) Germany

The Center for Drug Evaluation and Research conducted a pre-license inspection at Roche Diagnostics GmbH, (b) (4) Germany in (b) (4) The inspection covered Quality Control Laboratories associated with the subject BLA. All Form FDA-483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

Office of Regulatory Affairs (ORA) performed a post-market approval inspection at Roche Diagnostics GmbH, (b) (4) Germany in (b) (4) The inspection covered Elecsys assay kits. No FDA Form-483 was issued, and the inspection was classified as No Action Indicated (NAI).

Roche Diagnostics GmbH, Mannheim, Germany

The ORA/Office of Pharmaceutical Quality Operations performed a review of a GMP inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) (b) (4) under the Mutual Recognition Agreement. The firm's responses to the deviations identified were found acceptable. A GMP certificate is available in the European Union Drug Regulatory Authorities Network database. Based on review of the report, this inspection was classified by ORA as VAI.

ORA performed a for-cause inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) . All FDA Form-483 issues were resolved, and the inspection was classified as VAI.

ORA performed a post-market approval inspection at Roche Diagnostics GmbH, Mannheim, Germany in (b) (4) The inspection covered Elecsys assay kits. No FDA Form-483 was issued, and the inspection was classified as No Action Indicated (NAI).

**e) Environmental Assessment**

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

**f) Container Closure**

The assay components are packaged in plastic bottles with plastic snap caps. The calibrators and controls are packaged in glass bottles with rubber stoppers and plastic screw caps. The system reagents are packaged in either plastic bottles with plastic screw caps or dropper bottle with dropper and plastic screw cap.

Container closure integrity is not assessed as all products are manufactured as bioburden controlled and contain preservatives.

# 4. Software and Instrumentation

The following is a summary overview of software, instrumentation and risk management information provided to support a reasonable assurance that the device is safe and effective for its intended uses and conditions of use.

## a) Versioning

**cobas pro** serology controller version 1.1.0, **cobas pro** core software version 02-01, and **cobas pro** serology solution User Guide publication version 1.5.

## b) Device Description

The **cobas pro** serology solution is a combination of the **cobas pro** serology controller (software), **cobas pro** integrated solutions (with up to four **cobas e** 801 analytical units with hardware and system software) and applicable licensed blood screening assays (**cobas e** flow and associated parameters and testing requirements for each assay). All software components of the Roche Serology Solutions meet the definition of Major Level of Concern due to their application in blood donor screening and the release of blood or blood components for transfusion or further manufacture. The **cobas pro** integrated solutions (**cobas pro**) is a fully automated system for the measurement of analytes in blood and its modular design allows for different combinations/ configurations of analytical units (e.g., **e** 801, **e** 602 or **e** 402).

The **cobas pro** automates electrochemiluminescence immunoassay test processing, result interpretation, and data management functions for screening of donations of whole blood and blood components using plasma or serum samples. For blood donor screening, each **cobas pro** integrated solutions configuration consists of up to four **cobas e** 801 analytical units. The **cobas e** 801 is a fully automated immunoassay analyzer intended to perform high throughput routine and priority testing (300 tests/hour) while allowing continuous access and automated retesting. The **cobas e** flow assay specific software modules, assay specific parameters included in the Application Code Numbers (ACN) and in the method sheets, control processing of each assay type on the **e** 801 analyzer. Positive sample ID is established and maintained with barcodes. Consumables are tracked for availability, stability and expiration using barcodes and RFID chips. The **cobas pro** serology solution interfaces with Laboratory Information Systems (LIS) for order and result reporting, it monitors the operation of up to four **cobas pro** integrated solution with **cobas e** 801 analyzers, validates results, stores, and archives data, and maintains assay calibration status. **cobas pro** serology solution also interfaces via **cobas** link for data transfer between the laboratory and the **cobas e**-library, to view and synchronize data from method sheets, value sheets for calibrators and controls, and other reagent documents, including test-specific system parameter files, lot-specific application parameter files, and calibrator and QC parameters files. This data is automatically downloaded to analyzers based on kit barcodes and RFID tags. Additional system functionalities and operation are described in the version-controlled user manual, method sheets and package inserts.

**c) Risk Management**

Risks related to donor test results, exposure of user to infectious disease agents, chemical, physical, and environmental hazards were evaluated. Major hazards include incorrect results, i.e., false positive and false negative donor test results, and moderate hazards include delayed results and physical hazards to the user/operator. The final risk profile of the **cobas e** 801 analyzer includes 0 red (unacceptable) risks, 15 yellow risks (that required assessment of acceptability), and 242 green (acceptable) risks. Of the 15 yellow risks, four are related to false negative results (due to wrong consumables placement, incorrect instrument processing, and non-conforming lab facilities), one is related to false positive results (due to incorrect instrument processing; for competitive assays only and irrelevant to the Elecsys Chagas test results) and 10 are related to a use of **cobas e** 801 analyzer (due to user exposure to infectious material, personal injury leading to delays/interruption). The final cybersecurity risk profile of the **cobas e** 801 analyzer includes 0 red risks, 19 yellow risks, and 79 green risks. The final risk profile of the **cobas pro** serology solution includes 0 red risks, 0 yellow risks and 24 green risks. The final cybersecurity risk profile of the **cobas pro** serology solution includes 0 red risks, 19 yellow risks, and 25 green risks. There were 0 red or yellow risks for the Elecsys Chagas assay, PreciControls and accessories needed to perform the assay.

The applicant stated that all risk control measures are implemented and verified, and that the labeling notifies the user of residual risks. Significant risk control measures include use of barcodes/RFID tags for sample and reagent tracking, automated checks for expiry of onboard assay reagents and QC reagents, maintenance procedures, labeling and user manuals, database management with automated scheduled data backups, and access controls with individual usernames and passwords, automated lock-out after periods of inactivity, firewalls and encryption, and configuration management, among others. The applicant concluded the overall residual risk of the **cobas pro** serology solution is acceptable. This assessment appears to be supported by the evidence provided.

**d) Unresolved Anomalies**

The **cobas pro** serology controller version 1.1.0 contains 45 non-safety-related open anomalies with minor severity and no patient risks identified, and 24 open anomalies assessed as causing minor user annoyance with minimal impact on testing. The **cobas pro e** 801 instrument software version 02-01 contains 43 non-safety-related open anomalies with minor severity and no patient risks identified.

**e) Testing**

Design verification was performed to confirm that the design elements meet the specified requirements and includes verification of the effectiveness of risk control measures for potential causes of failure modes. This included software verification, software validation, testing at the unit level for each functionality and detailed integration testing for all functions and system level integration. Test run results using representative assays and donor samples were provided. System integration testing confirmed that the **cobas pro** serology solution met requirements using

the Elecsys HBsAg and HTLV-I/II assay reagents and assay files, and instrument accessories.

### f) Development Management

The software development activities for each software component included establishing detailed software requirements, linking requirements with associate verification tests, verification and validation, defects tracking, configuration management, and maintenance activities to ensure the software conforms to user needs and intended uses.

**Review Note**: As agreed in BQ170139/1, the applicant submitted a software update for the Serology Controller software from version 1.0.3 to 1.1.0. The update includes automation of the onboard stability and usage tracking of calibrator/control material, and improvements from usability studies. The update does not change critical assay specific parameters such as volumes of reagents used, time for incubations, or time to signal readout. Thus, clinical data acquired using software version 1.0.3 and submitted for review in the current Elecsys Chagas BLA are not impacted by this update.

## 5. Analytical Studies

The analytical studies were conducted in compliance with 21 CFR Part 58 (Good Laboratory Practices or GLPs), as applicable and were performed at Roche Diagnostics GmbH, (b) (4)

### a) Precision Studies

Precision of the Elecsys Chagas assay was evaluated at one site with (b) (4) (b) (4) and one lot of Elecsys Chagas assay and one lot of PreciControl Chagas. The samples were tested over 21 days, with one run per day, using four replicates, yielding n=84 measurements per sample. The member panel included:

- (b) (4) *T. cruzi* antibody negative sample
- (b) (4) *T. cruzi* antibody (b) (4)-negative sample at target level S/CO (b) (4)
- (b) (4) *T. cruzi* antibody (b) (4) positive sample at the target S/CO (b) (4)
- (b) (4) *T. cruzi* antibody positive sample at the target S/CO (b) (4)
- (b) (4) *T. cruzi* antibody positive sample at the target S/CO (b) (4)
- PreciControl CHAG1 B at target level S/CO (b) (4)
- PreciControl CHAG2 B at approximate S/CO (b) (4)

**Table 4. Intermediate (Within-Laboratory) Precision for Elecsys Chagas**

| Sample | Mean S/CO | N | Repeatability | | Within-Laboratory Precision | |
|---|---|---|---|---|---|---|
| | | | SD [S/CO] | CV [%] | SD [S/CO] | CV [%] |
| HSP 1 | 0.093 | 84 | 0.001 | 1.4 | 0.001 | 1.5 |
| HSP 2 | 1.150 | 84 | 0.023 | 2.0 | 0.039 | 3.4 |
| HSP 3 | 2.674 | 84 | 0.052 | 1.9 | 0.096 | 3.6 |
| HSP 4 | 7.896 | 84 | 0.130 | 1.6 | 0.261 | 3.3 |
| HSP 5 | 0.768 | 84 | 0.010 | 1.3 | 0.023 | 3.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PC CHAG1 B | 0.102 | 84 | 0.001 | 1.2 | 0.002 | 1.7 |
| PC CHAG2 B | 4.031 | 84 | 0.037 | 0.9 | 0.121 | 3.0 |

* HSP = Human Specimens; PC = PreciControls; S/CO = signal to cut-off; N = number of replicates; CV = coefficient of variation expressed as a percentage (CVs are not meaningful when S/CO approaches zero); SD = standard deviation; PC CHAG1 B = Negative control, human serum non-reactive for antibodies to *T. cruzi*; PC CHAG2 B = Positive control, human serum reactive for antibodies to *T. cruzi*.

The data provided and reviewed demonstrate acceptable within-laboratory precision of the Elecsys Chagas assay.

**b) Limit of Detection**

(b) (4)

**c) Analytical Sensitivity**

(b) (4)

**d) Seroconversion Sensitivity**

The seroconversion sensitivity of the Elecsys Chagas assay was compared to the sensitivity of FDA-approved assays. For determination of seroconversion sensitivity, (b) (4) commercially available Chagas seroconversion panel and (b) (4) Chagas performance panels were tested. There were no panel members with discordant results between the Elecsys Chagas assay and the comparator assays. For all the (b) (4) panels, the first reactive time point for the Elecsys Chagas occurred at the same time as the first reactive time point for the comparator assay. The data

provided and reviewed demonstrate acceptable performance of the assay and there were no discrepant or the time to first reactive test result for the tested panels.

**e) Endogenous Interferences (Spiked)**

Assay performance was evaluated in samples with high levels of spiked interferants (hemoglobin, lipemia, bilirubin, and human serum albumin for total protein) using matched sets of analyte-negative, analyte low positive (b) (4) /CO) and positive (b) (4) /CO) donor serum specimens. (b) (4) The data demonstrate acceptable performance of the assay for both nonreactive and reactive samples, supporting the use of the Elecsys Chagas with donor specimens containing up to 500 mg/dL of hemoglobin, 2,000 mg/dL lipid, 44 mg/dL bilirubin, and 7 g/dL of total protein. In addition (b) (4) No interference was observed up to 1,200 ng/mL of biotin using the Elecsys Chagas assay.

**f) Endogenous Interferences (Native)**

Assay performance when used to test specimens containing naturally occurring elevated levels of hemoglobin, triglycerides, bilirubin, albumin, and rheumatoid factor were evaluated. A total of (b) (4) anti-*T. cruzi* negative serum specimens for each interferent were used. No false reactive results were obtained. The data demonstrate acceptable performance of the assay supporting the use of specimens that contain up to (b) (4) of hemoglobin (range tested (b) (4) ), up to (b) (4) of triglycerides (range tested (b) (4) ), up to (b) (4) (b) (4) of total bilirubin (range tested (b) (4) ), up to (b) (4) of albumin (range tested (b) (4) ), and up to (b) (4) rheumatoid factor (range tested (b) (4) ).

**g) Drug Interference**

Potential interference with the Elecsys Chagas assay from common therapeutic drugs was tested using anti-*T. cruzi* antibody negative and positive samples spiked individually with the following drugs: (b) (4) The data provided and reviewed demonstrate no interference in Elecsys Chagas assay from the drugs tested at concentrations of at (b) (4) times the highest drug concentration under therapeutic treatment (b) (4)

**h) Cross Reaction/Analytical Specificity**

Analytical specificity of the Elecsys Chagas assay was evaluated by testing specimens with conditions or disease states unrelated to *T. cruzi* infection. A total of 230 samples containing potentially interfering factors listed below were spiked individually with anti-*T. cruzi* antibodies ((b) (4) samples for each disease state or

condition) and the effect of potentially interfering factors was tested. The following specimens were used:

- Containing antibodies against HIV, HBV, HCV, HTLV- I/II, CMV, HSV IgG/IgM, and Dengue virus
- Positive for antibodies against Candida, Chlamydia, *E. coli*, Toxoplasma gondii, *Plasmodium*, Treponema pallidum (syphilis), and Leishmania
- Containing autoantibodies (ANA) and elevated titers of rheumatoid factor
- Containing heterophilic (EBV) or human anti-mouse antibodies (HAMA)
- After vaccination against influenza
- For Hyper-IgM/IgG interference
- From pregnant women and multiparous pregnancies

The obtained data demonstrated acceptable performance of the assay and indicate that the presence of potentially interfering substances or medical conditions included in the study has no effect on the detection of anti-*T. cruzi* antibodies. There was no significant effect on background signals in negative specimens (neat specimens).

**i) Prozone (Hook Effect)**

Assay performance was evaluated using high-titer, anti-*T. cruzi* antibody positive samples (from S/CO (b) (4) to S/CO (b) (4)) undiluted and diluted, with a dilution factor ranging from (b) (4) . The data provided and reviewed demonstrate acceptable performance of the assay as all high titer specimens tested reactive. No false negative results were obtained due to hook effect.

**j) Serum and Plasma Comparison**

The impact of anticoagulants on the performance of the Elecsys Chagas assay was evaluated using (b) (4) matched serum and plasma specimens collected from individual donors. Reactive samples and near cut-off non-reactive samples were contrived by collecting (b) (4) individual non-reactive donor samples and spiking each with material from individual reactive donor samples collected from (b) (4) unique reactive samples at a ratio ranging from (b) (4) volume of the reactive material in the final sample to achieve a range of (b) (4) S/CO to (b) (4) S/CO. (b) (4) negative samples were tested from unique native samples.

The assay performance when used with samples anticoagulated with Lithium heparin, Sodium citrate, di-Potassium EDTA, tri-Potassium EDTA and citrate phosphate dextrose (CPD) was compared to the performance demonstrated when testing serum specimens. In addition, the suitability of different blood collection tubes was evaluated by testing samples collected with serum-, $K_2$-EDTA- and Lithium heparin separation tubes. The data provided and reviewed demonstrate acceptable performance of the assay with specimens collected in the anticoagulants and tube types listed above supporting the use of specimens collected in these anticoagulants and tube types.

**k) Specimen Storage**

Assay performance with serum and plasma specimens collected in $K_2$-EDTA, Sodium citrate, Lithium heparin and CPD stored at various temperatures for different periods of time was evaluated. The target analyte concentrations ranged from (b) (4) to (b) (4) S/CO for negative and (b) (4) to (b) (4) S/CO for anti-*T. cruzi* positive samples.

The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of serum and plasma specimens that were stored at 15 to 30°C for up to 7 days, 2 to 8°C for up to 14 days, -20°C or colder for up to 12 months, and up to (b) (4) freeze/thaw cycles. These data support the storage claims in the package insert.

**l) Specimen Processing**

Assay performance with centrifuged non-frozen and previously frozen specimens was evaluated using (b) (4) serum specimens – anti-*T. cruzi* antibody negative (n= (b) (4) or spiked with anti-*T. cruzi* antibody (n= (b) (4) (b) (4) positive, and with anti-*T. cruzi* antibody (n= (b) (4) (b) (4) positive - compared to the uncentrifuged, homogenized reference. The target concentrations ranged from (b) (4) to (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use with non-frozen and previously frozen serum specimens for 10 to 15 minutes at 2000 to 4000 RCF (relative centrifugal force = x g).

**m) On-clot Specimen Processing**

Assay performance with serum and plasma (di-Potassium EDTA, Sodium citrate, and Lithium heparin) specimens after storage on-clot was evaluated using (b) (4) specimens across all specimen types – anti-*T. cruzi* antibody negative (n= (b) (4) and anti-*T. cruzi* antibody (b) (4) positive (n= (b) (4) and compared to specimens stored at unstressed conditions. The target concentrations ranged from (b) (4) to (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use with samples stored on-clot for 7 days at 15 to 30°C and 14 days at 2 to 8°C.

**n) Kit Lot Calibration and On-Board Calibration Stability**

Calibration of the Elecsys Chagas assay must be performed once per reagent lot using CHAGB Cal1, CHAGB Cal2 and fresh reagents. Lot calibration stability was validated using Elecsys Chagas kit of the same lot stored at 2 to 8°C up to (b) (4) using the initial calibration. A total of (b) (4) serum specimens – anti-*T. cruzi* antibody negative (n= (b) (4) and anti-*T. cruzi* antibody (b) (4) positive (n= (b) (4) at analyte level range (b) (4) S/CO to (b) (4) S/CO along with (b) (4) PreciControls - were tested in duplicate and compared to unstressed reagents of the same lot measured using the initial calibration. The data provided and reviewed demonstrate acceptable performance of the assay supporting a Lot Calibration stability of up to 12 weeks. In addition, the same panel and acceptance criteria was utilized to test stability of the Elecsys Chagas kit components stored on-board a **cobas e** 801 analyzer for (b) (4) (b) (4) with panel test results obtained using the initial calibration. Acceptable performance was observed, supporting the On-Board stability of up to 28 days using the initial calibration.

**o) Reagent Stability Studies**

Reagent real time stability was validated using (b) (4) Elecsys Chagas kit lots stored at 2 to 8°C up to (b) (4) compared to t = 0 months. A total of (b) (4) serum specimens - anti-*T. cruzi* antibody negative (b) (4) and anti-*T. cruzi* antibody (b) (4) (b) (4) positive (b) (4) at the reactivity range (b) (4) S/CO to (b) (4) S/CO along with (b) (4) PreciControls - were tested in (b) (4) and compared to unstressed reagents. The data provided and reviewed demonstrate acceptable performance of the assay supporting a reagent stability claim of up to (b) (4) at 2 to 8°C.

In addition, the same panel, was utilized to evaluate on-board stability of the Elecsys Chagas kit components when stored at (b) (4) for (b) (4) Transport stability was evaluated at (b) (4) for (b) (4) when compared to unstressed kits stored at 2 to 8°C to evaluate stability during shipping. Acceptable performance was observed, supporting an on-board stability claim of up to 16 weeks at (b) (4) and a transportation claim of up to (b) (4)

**p) Temperature Effects on Samples, Calibrators and PreciControls Prior to Measurement**

Assay performance with specimens, calibrators, and controls directly after storage at 2 to 8°C was evaluated using (b) (4) serum specimens— anti-*T. cruzi* antibody negative (n (b) (4) and one each of anti-*T. cruzi* antibody (b) (4) positive — compared to samples that were equilibrated at (b) (4) for (b) (4) The target concentrations obtained ranged from (b) (4) (b) (4) (b) (4) S/CO. The data provided and reviewed demonstrate acceptable performance of the assay supporting the use of specimens and kit components without first equilibrating for (b) (4) (b) (4)

**q) Calibrator Stability**

Calibrators are supplied ready-for-use in vials compatible with the system. Stability of calibrators was evaluated by measuring them in (b) (4) storage under various conditions. The data provided and reviewed demonstrate acceptable performance of calibrators supporting stability claims of storage for up to 5 hours at 20 to 25°C, and up to 16 weeks at 2 to 8°C.

**r) PreciControl Stability**

The PreciControl Chagas is supplied as ready-for-use in vials used for monitoring the accuracy of the Elecsys Chagas assay. Stability of PreciControl (PC) CHAG1 B and PC CHAG2 B was evaluated after storage under various conditions compared to t = 0 by (b) (4) measurements. The data provided and reviewed demonstrate acceptable performance of PreciControls supporting stability claims of storage for up to 5 hours at 20 to 25°C, up to (b) (4) at 2 to 8°C, and up to (b) (4) at 2 to 8°C after first opening. Multiple-use stability data were acceptable for up to (b) (4) quality control procedures when stored at 20 to 25°C.

**s) Within-Assay Carryover**

Sample to sample carryover was evaluated using a panel of (b) (4) positive and (b) (4) negative samples run (b) (4) times on (b) (4) **cobas e** 801 analyzers. (b) (4) assay

was used as a surrogate because (b) (4) could be generated. Every negative sample was exposed to potential carryover (b) (4) times. After sample processing, all negative samples were retested and yielded concentrations below the (b) (4) assay (b) (4) No sample-to-sample carryover was detected.

**t) Cadaveric Studies**

No cadaveric claims were sought by sponsor in this BLA.

**Review Note:** Roche stated that (b) (4) (b) (4)

**u) Microbial Challenge**

The analytical methods and their validations and/or qualifications reviewed for the Elecsys Chagas kit were found to be adequate for their intended use.

## 6. Clinical Studies

Clinical studies were conducted to evaluate assay specificity, sensitivity, and reproducibility to demonstrate performance in the intended use population of the Elecsys Chagas assay. Testing was performed at three blood donor testing laboratories and confirmatory testing was conducted at one additional site. (b) (4) lots of the Elecsys Chagas Reagent Kit, and (b) (4) lot each of the PreciControl Chagas, and the PreciControl Chagas Release Kit were used for the studies at each of the testing sites.

**a) Clinical Specificity**

A prospective multicenter study was conducted to evaluate the clinical specificity of the Elecsys Chagas assay on the **cobas e** 801 analyzer and using an FDA licensed comparator assay by testing a total of 7,578 specimens. All donors enrolled were evaluated and no donation was excluded.

Of the 7,578 specimens tested, 3,754 fresh serum and 3,824 fresh plasma samples from voluntary whole blood donors collected at three blood donation centers spread across 21 sites, were tested at three (b) (4) sites. The specimens were collected from donors that had not been screened on a previous donation using an FDA licensed test for antibodies to *T. cruzi* (i.e., first time donors). The initial and repeat reactive rates for the serum specimens were 0.05% (2/3,754). Out of two repeat reactive serum samples, the follow-up sample for only one specimen could be obtained. That follow-up sample also was repeat reactive on the Elecsys Chagas assay. The supplemental testing using an FDA-licensed assay results for both initial and follow-up samples were non-reactive, indicating that the two repeatedly reactive samples using Elecsys Chagas assay were false positive results. The initial and repeat reactive rates for the plasma specimens were 0.00% (0/3,824). Overall, the initial and repeat reactive rate for the Elecsys Chagas assay was 0.026% (2/7,578).

The specificity of the Elecsys Chagas assay relative to the final anti-*T. cruzi* antibody status in whole blood donors was calculated to be 99.97% (7,576/7,578) with a 95% Confidence Interval (CI) of 99.90% to 99.99%.

**Table 5: Elecsys Chagas Clinical Study. Specificity of the Elecsys**

| Specimen Category | N | IR (% of Total) | RR (% of Total) | Number Positive by Supplemental Testing (% of RR) | Specificity (%)[a] (95% CI) |
|---|---|---|---|---|---|
| Volunteer Blood Donors – Serum | 3,754 | 2 (0.05) | 2 (0.05) | 0 (0.00) | 99.95<br>3,752/3,754<br>(99.81 – 99.99) |
| Volunteer Blood Donors – Plasma | 3,824 | 0 (0.00) | 0 (0.00) | 0 (0.00) | 100.00<br>3,824/3,824<br>(99.90 – 100.00) |
| Total Volunteer Blood Donors | 7,578 | 2 (0.03) | 2 (0.03) | 0 (0.00) | 99.97<br>7,576/7,578<br>(99.90 – 99.99) |

N = Number tested; IR = initially reactive; RR = repeatedly reactive; CI = confidence interval.
[a] Based on supplemental test results for the 2 repeatedly reactive specimens (both serum).

## b) Clinical Sensitivity

Elecsys Chagas assay sensitivity was established by analyzing test results for 372 specimens that were identified as *T. cruzi* positive. Testing was performed at three clinical sites. Elecsys Chagas repeatedly reactive specimens were confirmed with supplemental testing using an FDA-licensed assay.

Of 372 tested specimens, 102 were *T. cruzi* PCR positive, and 270 were serology positive. For the evaluation, 371 specimens were used; one known *T. cruzi* serology positive sample tested non-reactive with the comparator assay and was excluded. Overall sensitivity was determined to be 100% (371/371) with a 95% confidence interval of 99.98% to 100% as presented in Table 6.

**Table 6: Elecsys Chagas Clinical Study. Overall Sensitivity Summary**

| Specimen Category | N | Number Positive | Number RR (% of Tested) | Number RR that were Positive by Supplemental Testing (% of RR) | Sensitivity (%) (95% CI) |
|---|---|---|---|---|---|
| Samples known to be PCR positive for *T. cruzi* | 102 | 102 | 102<br>(100) | 102<br>(100) | 100%<br>102/102<br>(96.37 – 100.00) |
| Samples known to be positive for antibodies to *T. cruzi* | 269 | 269 | 269<br>(100) | 269<br>(100) | 100%<br>269/269<br>(98.59 – 100.00) |

| Specimen Category | N | Number Positive | Number RR (% of Tested) | Number RR that were Positive by Supplemental Testing (% of RR) | Sensitivity (%) (95% CI) |
|---|---|---|---|---|---|
| Total | 371 | 371 | 371 (100) | 371 (100) | 100% 371/371 (98.98 – 100.00) |

N = number tested; RR = Repeatedly Reactive.

### c) Reactivity in Increased Risk Populations and Endemic Areas

Elecsys Chagas performance in an untested increased risk population and individuals from endemic areas was evaluated using a total of 912 specimens including 110 samples from Mexico. There were 642 specimens non-reactive by Elecsys Chagas with a specimen status of negative and 267 samples repeatedly reactive by Elecsys Chagas assay. Two specimens were repeat reactive on the comparator test and non-reactive on Elecsys Chagas assay. One of the repeat reactive specimens tested reactive on the FDA licensed test and the final status of this sample was confirmed reactive. The second repeat reactive specimen on the comparator assay, and as well as a specimen that tested repeat reactive on Elecsys Chagas and non-reactive on the comparator assay, produced an inconclusive result using an FDA-licensed assay and were removed from the evaluation. Table 7 below summarizes the study data.

**Table 7. Elecsys Chagas Testing in Increased Risk Cohorts and Endemic Areas**

| Sample Group | Number Tested Initial Draw | Initially Reactive (% of Tested) | Repeatedly Reactive (% of Tested) | Confirmed Positive n (% of RR) |
|---|---|---|---|---|
| Individuals from Endemic Areas - multiple countries* | 802 | 268 (33.42) | 268 (33.42) | 267 (99.63) |
| Individuals from Endemic Areas - Mexico | 110 | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| Total | 912 | 268 (29.39) | 268 (29.39) | 267 (99.63) |

* Individuals from Chagas endemic areas included specimens from the following countries: El Salvador (200), Argentina (72), Uruguay (158), Paraguay (125), Bolivia (96) and Chile (151).

### d) Reproducibility Studies

Reproducibility of the Elecsys Chagas assay was evaluated at three sites with (b) (4) (b) (4) per site using three lots each of the Elecsys Chagas assay and (b) (4) (b) (4) each of PreciControl Chagas as per CLSI EP05-A3. The panels were tested in random access mode for five days in two runs per day with three replicates per run using three lots of the Elecsys Chagas kits yielding 270 test results per panel member (2 runs/day x 5 days x 3 replicates/concentration x 3 sites x 3 reagent lots). The member panel included:

- (b) (4) low anti-*T. cruzi* antibody sample at the target S/CO (b) (4)
- (b) (4) high anti-*T. cruzi* antibody sample at target S/CO (b) (4)

Additionally, three lots of PreciControls were tested as samples:

- PreciControl CHAG1 B at target level S/CO (b) (4)
- PreciControl CHAG2 B at target level S/CO (b) (4)

All test results, for all panel members, met target specifications and were used to calculate repeatability and reproducibility of the Elecsys Chagas assay. The results of the reproducibility panel and control testing demonstrate that Elecsys Chagas assay is reproducible across three sites and three lots of reagents across a range of reactivity, as presented in Table 8.

**Table 8. Overall Repeatability and Reproducibility for Elecsys Chagas**

| Sample | Mean | N | Repeatability | | Between Run | | Between Day | | Intermediate precision | | Between Site | | Between Lot | | Reproducibility | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | SD | % CV | SD | % CV | SD | % CV | SD | % CV | SD | % CV | SD | % CV | SD | % CV |
| High *T. cruzi* Antibody | 10.1 | 270 | 0.179 | 1.77 | 0.116 | 1.15 | 0.089 | 0.88 | 0.231 | 2.29 | 0.035 | 0.34 | 0.348 | 3.45 | 0.419 | 4.15 |
| Low *T. cruzi* Antibody | 1.86 | 270 | 0.027 | 1.42 | 0.017 | 0.89 | 0.016 | 0.84 | 0.035 | 1.88 | 0.012 | 0.64 | 0.028 | 1.51 | 0.047 | 2.50 |
| PC CHAG1B | 0.111 | 270 | 0.002 | 1.59 | 0.001 | 1.19 | 0.003 | 2.34 | 0.003 | 3.07 | 0.001 | 1.31 | 0.006 | 5.10 | 0.007 | 6.09 |
| PC CHAG2B | 3.84 | 270 | 0.069 | 1.80 | 0.088 | 2.30 | 0.037 | 0.95 | 0.118 | 3.07 | 0.000 | 0.00 | 0.090 | 2.36 | 0.149 | 3.87 |

### e) BIMO – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for three clinical investigator study sites that participated in the conduct of Protocol RD005615. The inspections did not reveal significant problems that impacted the data submitted in this original Biologics License Application (BLA).

### f) Pediatrics

N/A

### g) Other Special Populations

N/A

## 7. Advisory Committee Meeting

N/A

## 8. Other Relevant Regulatory Issues

N/A

## 9. Labeling

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed, instructions for use, package, and container labels on December 13, 2023, and found them acceptable from a promotional and comprehension perspective.

## 10. Recommendations and Risk/ Benefit Assessment

### a) Recommended Regulatory Action

The Review Committee reviewed the original submission and related Amendments. All review issues have been resolved; therefore, the Review Committee recommends licensure of the Elecsys Chagas assay.

### b) Risk/Benefit Assessment

The risk/benefit analysis demonstrates that the benefit of the Elecsys Chagas assay outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 100% (95% CI of 98.98% – 100.00%), indicating a low probability of a false negative result. Among 7,578 first time blood donors tested with the Elecsys Chagas assay, the assay specificity of 99.97% (95% CI of 99.90 – 99.99%) in clinical trials suggests a low probability of a false positive result.

### c) Recommendation for Post-marketing Activities

No post-marketing activities have been proposed for this application.