Quality Management System

FRIZ Biochem GmbH

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Summary of Safety and Performance

1 Meta Information

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1.1 Purpose

This Summary of Safety and Performance (SSP) is intended to provide public access to an up-to-date summary of the main aspects of the safety and performance of the IVD medical device res4plex *direct* RT-PCR.

The SSP is not intended to replace the Instructions for Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users.

The information in the next section is intended for professional users. Please note that chapters/subchapters that are not applicable are indicated as such.

2 Summary of Safety and Performance (SSP) for professional users

2.1 Device identification and general information

Parameter	Value
Device trade name(s)	res4plex *direct* RT-PCR

Device reference number(s)	FBC107-Ax FBC107-Bx FBC107-Cx
Manufacturer´s name and address	FRIZ Biochem GmbH Floriansbogen 2-4 DE-82061 Neuried
Manufacturer´s single registration number (SRN)	DE-MF-000017533
Basic UDI-DI	426075389fbc107U6
European Medical Device Nomenclature (EMDN)	EMDN W0105: infectious diseases (W0105070302)
Risk class of the device	Class D according to rule 1, Rule 3c and Rule 3k
Indication whether it is a device for near-patient testing and/or a companion diagnostic	☐ Device for near-patient testing ☐ Companion Diagnostic (CDx) ☑ n.a.
Year when the first certificate was issued under Regulation (EU) 2017/746 covering the device	the device has not been certified under IVDR yet
Authorized representative, if applicable; name and the SRN	n.a.
NB's name (the NB that will validate the SSP) and NB's single identification number	TÜV SÜD Product Service GmbH NB 0123

2.2 Intended use of the device

2.2.1 Intended purpose

The res4plex *direct* RT-PCR test is an assay for in vitro examination of viral RNA in nasal, nasopharyngeal or oral/ oropharyngeal swabs to provide information to aid to diagnose symptomatic or asymptomatic patients under suspicion of respiratory diseases: SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus A/B (RSV A/B).

The IVD medical device detects the RNA of the aforementioned pathogens by qualitative measurements based on RT-qPCR and is intended for use in medical laboratories or health institutions by laboratory personnel specifically trained in RT-qPCR and *in vitro* diagnostic techniques. It has to be used in combination with conventional nucleic acid extraction systems for RNA extraction and RT-qPCR cyclers for detection and analysis.

2.2.2 Indication(s) and target population(s)

The target population encompasses subjects of all genders and ages. There are three different testing situations in which res4plex *direct* RT-PCR may be applied:

- The **first group** of persons to be tested are symptomatic persons. Infections with SARS-CoV-2, influenza or RSV show overlapping clinical presentations. The most common symptoms are rhinitis, cough (non-productive as well as productive, depending on disease progression), body/muscle aches and/or fever. In some cases may also nausea, vomiting and/or diarrhea occur. Infections with SARS-CoV-2, influenza or RSV present the full spectrum of being asymptomatic and requireing hospitalization in case of a severe disease progression (see State of the Art, SOTA_res4plex).
- The **second group** of persons to be tested are asymptomatic persons which have contact with other infected persons or if there are confirmed cases at institutions (e.g. schools, kindergarten, refugee center or retirement homes).
- The **third group** of persons shall be tested to prove that they are not infected, and thus, are allowed to enter a particular institution (e.g. hospitals).

For indications see Intended Purpose.

2.2.3 Limitation(s) and/or contra-indication(s)

No limitations and/or contra indications arise from the target population. High concentrations of blood in the specimen (> 1% (v/v)) may inhibit the RT-qPCR and a false-negative result could occur. For detailed limitation on limitations and/or contra indications arising from associated interferences, cross-reactions, etc. see Instructions for Use available at www.frizbiochem.de.

2.3 Device description

2.3.1 Description of the device

The res4plex *direct* RT-PCR test is a multiplex RT-qPCR test for the detection and differentiation of SARS-CoV-2, influenza A, B and RSV from RNA eluted from patient specimen. The RNA eluate is added to the ready-to-use reaction solution that contains all reagents necessary for RT-qPCR. RT-qPCR analysis can be performed on an qPCR cycler. A separate full process run control , previously added to each sample prior to RNA extraction, serves as control for nucleic acid isolation from the specimen as well as for RT-qPCR.

The res4plex direct RT-PCR test contains primer and probes specific for the targets SARS-CoV-2, influenza A, influenza B and RSV as well as the Internal Control. The probes are each labelled with fluorescent reporter dyes and a second dye that serves as a quencher and suppresses the fluorescence signals of intact probes. The analysis is performed by determining Ct (cycle threshold) values. The Ct value describes the cycle in which the signal rises above a certain threshold for the first time. The more target copies (here: virus RNA) are present in the sample, the lower the Ct value.

2.3.2 Description of the components

Each kit contains the following vials which are sufficient for 96 reactions (see *Table 1*). Additionally, a quick start protocol is provided per kit.

Table 1: res4plex direct RT-PCR package content

Material	Lid colour	#vials; volume	#rxns.	Components

Solution A	green	1x; 1050 µL	96	Buffer, enzymes, primer and probes
Internal Control	blue	1x; 400 µL	96	Artificial nucleic acid target [1x10^7 cp/µL]
Positive Control	red	1x; 11 µL	1	Nucleic acids of SARS-CoV-2, influenza A, influenza B and RSV

2.3.3 Previous generation(s) or variants

The res4plex *direct* RT-PCR kit that is placed on the market under the IVDD is the predecessor product of the mentioned res4plex *direct* RT-PCR.

The res4plex *direct* RT-PCR shall be available in the following variants:

Table 2: res4plex direct RT-PCR configurations

Article number	Configuration	Target
FBC107-Ax	suitable for qPCR instrument with 5 detection channels (Cyan500/ FAM/HEX/Red610/Cy5)	Flu A; Flu B; SARS-CoV-2; RSV (A/B)
FBC107-Bx	suitable for use on a qPCR instrument with 5 detection channels (FAM/HEX/Red610/Cy5/Cy5.5)	Flu A; Flu B; SARS-CoV-2; RSV (A/B)
FBC107-Cx	suitable for use on a qPCR instrument with 4 detection channels (FAM/HEX/Red610/Cy5)	Flu A/B; SARS-CoV-2; RSV (A/B)

2.3.4 Accessories

The chapter is not applicable as no accessory is intended to be used in combination with the device.

2.3.5 Other devices and products to be used in combination

res4plex *direct* RT-PCR includes all substances and reagents needed for the *in vitro* diagnostic RT-qPCR reaction, however plastic consumables, RNA isolation kit and qPCR cycler is not included and must be provided by the user.

2.4 List of harmonized standards and common specifications (CS) applied

Standard	Edition	Title

EN ISO 13485	2016/A11:2021	Medical devices — Quality management systems — Requirements for regulatory purposes
EN ISO 14971	2012	Application of risk management to medical devices
EN ISO 15223	2021	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
EN ISO 23640:	2015	In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents
ISO/TR 20416	2020	Medical devices — Post-market surveillance for manufacturers
EN 13612	2002	Performance evaluation of in vitro diagnostic medical devices
EN ISO 17511	2021	In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples
EN ISO 18113-1	2022-10	In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions, and general requirements
EN ISO 18113-2	2022-10	In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 2: In vitro diagnostic reagents for professional use
ISO 5798	2022-04	In vitro diagnostic test systems - Requirements and recommendations for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by nucleic acid amplification methods
Common Specifications for certain class D devices	2022	European Commission, *COMMISSION IMPLEMENTING REGULATION (EU) of 4.7.2022 laying down common specifications for certain class D in vitro diagnostic medical devices in accordance with Regulation (EU) 2017/746 of the European Parliament and of the Council*. 2022.

2.5 Risks and warnings

2.5.1 Residual risks and undesirable effects

We successfully applied risk mitigation strategies. These measures reduced the probability category by at least one level without introducing new risks, thus we positively affected the benefit-risk ratio. Most important, the total number of inacceptable risks was reduced from two to zero. After measure implementation all individual residual risks are accepted and consequently the overall residual risk is acceptable.

The res4plex *direct* RT-PCR test fulfils the following parameters:

- compliance with the applicable general safety and performance requirements
- acceptable performance claims according to the state of the art and available diagnostic alternatives
- suitability of the device and its IFU for the intended users and use environment, including usability aspects

The residual risks are unlikely/moderate (probability/severity) or less.

Based on the pre-/clinical evidence and in alignment with the state of the art and the common specifications, res4plex direct RT-PCR achieves a clinical benefit by accurately detecting and differentiating RNA from SARS-CoV-2, Influenza A, Influenza B, and RSV A/B in human clinical specimens (i.e., nasopharyngeal and oropharyngeal swabs) and supporting diagnostic decision-making, taking into account additional clinical and laboratory information.

The clinical benefit is, to provide physicians with useful information with respect to patient management and therapy decisions, if applicable. This may help separate infected people from uninfected people and to isolate them from the rest of the population especially for high-risk patients. The overall residual risk is in line with the risk policy and acceptable.

The overall residual risk is in line with the risk policy and acceptable.

2.5.2 Warnings and precautions

The res4plex *direct* RT-PCR test is intended for *in vitro* diagnostic use only. The test should only be performed by laboratory personnel specifically trained in RT-qPCR and *in vitro* diagnostic techniques. If the user makes substantial changes to the product or the application instructions, results may not correlate with the intended purpose.

- Before performing the test, read the entire instructions for use and follow them carefully.
  Deviations from the given test protocols can lead to invalid results.
- All patient samples must be treated as potentially infectious material.
- Discard sample and assay waste (that was in contact with patient material) according to your local, regional, or national safety regulations.
- The concentration specifications and incubation times of the manufacturers must be followed.
- Do not use the test beyond the expiration date.
- Do not use the test with opened or damaged packaging.
- Protect reagents from heat, moisture, and light.
- Do not replace or mix the reagents with reagents from other batches or other chemicals.
- Avoid contamination of the test by microorganisms and nucleases (DNases and RNases).
- Any carry-over of samples during handling and processing of the test may result in false positive test results.
- Good laboratory practice should be followed during the test.
- Use separated and segregated working areas for (1) sample preparation, (2) reaction setup and (3) amplification/detection activities. The workflow in the laboratory should proceed in unidirectional manner.
- Always wear disposable gloves in each area and change them before entering a different area.
- The test kits are intended for single use and must not be reused after performing qPCR reaction.
- If contamination of the qPCR cycler is suspected, cleaning and maintenance must be carried out according to the system´s manual.
- Safety Data Sheets (SDS) are available: for download via www.frizbiochem.de
- Pending EUDAMED entry, the Safety and Performance Summary (SSP) can be downloaded via http://www.frizbiochem.de

2.5.3 Other relevant aspects of safety

The chapter is not applicable as no field safety corrective actions (FSCA) and field safety notices (FSN) have been taken.

2.6 Summary of performance evaluation and post-market performance follow-up (PMPF)

2.6.1 Summary of scientific validity

To demonstrate the scientific validity of the res4plex *direct* RT-PCR test, the following data sources are used:

- The State-of-the-Art report
- scientific (peer-reviewed) literature.

We selected PubMed (MEDLINE database) as the source for the literature search. MEDLINE is compiled by the United States National Library of Medicine (NLM), is available online, and can be searched via PubMed. MEDLINE supports evidence-based medicine, and most of the systematic review articles published nowadays are based on extensive research in MEDLINE (Source: www.ncbi.nlm.nih.gov/pubmed).

The applied search strategy, the used search terms, and the respective metadata can be found in the literature search protocol.

A separate literature search was performed for each analyte (SARS-CoV-2, Influenza A, Influenza B, and RSV A/B). We defined the following exclusion criteria:

(1) The respective analyte was not considered (SARS-CoV-2 RNA, Influenza A RNA, Influenza B RNA or RSV A/B RNA).

(2) The relevant genes are not considered.

(3) No information on mutations, heterogeneity, or homology of the respective target genes was provided.

If the full texts were available in a language other than English, they were translated using DeepL (Source: https://www.deepl.com/de/translator) to gain an insight of the content.

The following Table 3 provides an overview of how many publications were excluded after abstract screening and after full-text screening and how many publications were considered for demonstration of scientific validity.

Table 3: Results of the literature searches

Analyte	Literature search results	Excluded after abstract screening	Excluded after full-text screening	Considered for scientific validity
SARS-CoV-2	55	24	8	23
Influenza A	44	21	7	16
Influenza B	26	17	3	6
RSV A/B	29	19	6	4

It could be shown that viral RNA detection is scientifically valid for detecting SARS-CoV-2, Influenza A, Influenza B, and RSV A/B. Furthermore, it could be confirmed that the chosen target genes underlying the res4plex *direct* RT-PCR test are appropriate targets for detecting SARS-CoV-2, Influenza A, Influenza B, and RSV A/B. Evidence was provided by PE-SV-report_res4plex Scientific Validity Report the fact that the N gene and the E gene of SARS-CoV-2, the M gene of Influenza A, the NS1 gene of Influenza B, and the N gene of RSV A/B are well-described targets for diagnostic tests. Moreover, these targets are used by various similar products.

In the next step, the selected individual target gene regions were evaluated regarding their scientific validity to detect the infection by SARS-CoV-2, Influenza A, Influenza B, and RSV A/B, respectively. The investigation was

focused on mismatches that could negatively affect the primer and/or probe binding. It was shown that most mismatches identified in the respective regions were outside of the primer and probe binding sites. For all mismatches that would affect the primer and/or probe binding, degenerated sequences are used to ensure efficient binding.

Nevertheless, RNA viruses are prone to evolve drug resistance and escape immune surveillance. Thus, RNA viruses show a high mutation rate. For this reason, the scientific validity of the res4plex *direct* RT-PCR test shall be reviewed and updated regularly.

Eventually, the scientific validity for the res4plex *direct* RT-PCR test was demonstrated as the detection of the target gene regions of SARS-CoV-2, Influenza A, Influenza B, and RSV A/B RNA is verifiably associated with the infection of the respective pathogen.

2.6.2 Summary of performance data from equivalent device(s)

The chapter is not applicable as evidence of the underlying IVD medical device is not based on data from devices claimed to be equivalent to the device.

2.6.3 Summary of performance data from conducted studies prior to CE-marking

The chapter is not applicable as no performance studies have been conducted according to IVDR, Annex I, section 9 prior to CE-marking.

2.6.4 Summary of performance data from other sources

The chapter is not applicable as clinical evidence of the underlying IVD medical device is not based on data from other sources e.g., published experience gained by routine diagnostic testing.

2.6.5 Overall summary of the performance and safety

All experiments were conducted as planned in the performance evaluation plan(s).

2.6.5.1 Analytical performance

The res4plex *direct* RT-PCR test is performed with nucleid acid that has been extracted from nasopharyngeal or oropharyngeal specimen. Quality and yield of RNA is highly dependent on the RNA extraction method used. The performance is evaluated based solely on extracted RNA and thus independent of specimen collection, handling and stability.

To evaluate cross-reactivity as well as endogenous and exogenous interference, isolation of RNA from spiked samples in artificial nasopharyngeal fluid was needed. RNA was extracted according to the manufacturer's instructions. For all other parameters no sample preparation or pre-analytical processing was needed since quantified genomic RNA was directly used for RT-PCR.

RT-PCR data acquisition was performed according to Instructions for Use.

RT-PCR data were analysed using the Bio-Rad CFX Maestro 2.3 (Version 5.3.022.1030) or the LightCycler® 480 (release 1.5.1.62) software, respectively. A positive signal is characterized by a sigmoidal curve exhibiting both a lag phase and a logarithmic growth phase. Signals that do not exhibit this curve pattern, despite having a Ct value, are considered negative. It should be noted that in the case of low positive samples, the stationary phase might not be visible due to the cut off after 45 cycles. Thus, the presence of a stationary phase is not an essential requirement for defining a positive signal in such cases. Using the Bio-Rad CFX Meastro 2.3 software, the threshold was set within the logarithmic growth phase. Using the LightCycler® 480 Software, the threshold was set automatically.

The res4plex *direct* RT-PCR test shows analytical specificity, analytical sensitivity, and precision that are similar to competitor devices. All analytical performance claims were able to be proven.

Table 4: Overview of all applicable analytical performance parameters and the intended claims in comparison to the achieved results.

Analytical performance parameter	**Claim**	**Result/s**	**Requirement fulfilled**
Analytical sensitivity	see Limit of detection		☒ yes ☐ no
Analytical specificity	See Cross-reactivities, Endogenous and exogenous interference, Inclusivity, Competitive interference and Physical Interaction of primers and probes		☒ yes ☐ no
Cross-reactivities	Cross-reactivity was tested with in silico analysis as well as with wet-lab testing. For the in silico analysis, the following acceptance criterion was applied: the homology between the cross-reactive microorganism and the assay primers and probes is ≤ 80 %. Otherwise, the respective cross-reactant was also wet-lab tested.	From the wet-lab tested potentially cross-reacting organisms, none gave a false positive nor false negative result. Therefore, cross-reactivity can be excluded.	☒ yes ☐ no
Endogenous+exogenous interference	Both positive and negative samples regarding the test analytes (i.e., SARS-CoV-2, Influenza A, Influenza B, and RSV A/B) were tested with the spiked interfering substance. The following acceptance criteria were applied: No false positive test results for tests with negative samples regarding the test analytes. No false negative test results for tests with positive samples regarding the test analytes.	A high concentration of human blood in the sample (2% (v/v)) showed interference with the res4plex *direct* RT-PCR. Concentrations of human blood of ≤ 1% (v/v) as well as all other substances at indicated concentrations did not interfere with the test.	☒ yes ☐ no (Note in the IFU about interference of human blood)

Inclusivity	For inclusivity analysis, an in silico analysis was performed. The following acceptance criterion were applied: Frequency of sequences with exact match: at least 90%. Frequency of sequences with identical primer 3' end (first 5 nucleotides of 3' end position): at least 97%	The primer and probe sequences are suitable to detect the test analytes (i.e., SARS-CoV-2, Influenza A, Influenza B, and RSV A/B).	☒ yes ☐ no
Competitive interference	To analyse competitive interference, one test analyte was applied in a high concentration (10^6 copies/mL), whereas the other test analytes were applied in a low concentration (3x LoD). The following acceptance criterion was applied: No false negative test results for all test analytes.	In most cases, a high concentration of spiking analytes up to 10^6 cp/ml did not affect the detection of other analytes present at a low concentration. However, there were some exceptions. In the presence of 10^6 cp/ml SARS-CoV-2, Influenza A and RSVB at 3x LoD were not detectable. Similarly, in the presence of 10^6 cp/ml RSVA, Influenza A at 3x LoD could not be detected.	☒ yes ☐ no (Note in the IFU about competitive interference)
Physical Interaction of primers and probes	The physical interaction of the different assay primers and probes were investigated with an in silico analysis. The following acceptance criteria were applied: ΔG (kcal/mol) shall be > -9.0 and > -6.0 at 3´ complementary base pairs.	Potential dimers that do not fulfil the acceptance criteria were identified. Other parameters of the analytical performance studies show that potential dimers do not have an effect on the performance of the res4plex *direct* RT-PCR test.	☒ yes ☐ no
Accuracy	See Trueness and Precision		☒ yes ☐ no

Trueness (bias)	For the analyte SARS-CoV-2, an RNA standard from the joint research centre (European Commission) is available. For the other analytes, Influenza A, Influenza B, and RSV A/B, no certified reference materials or reference measurement procedures are available. Thus, the comparison to the current clinical standard practice is addressed within the clinical performance evaluation.	The used SARS-CoV-2 RNA was compared to the RNA standard from the joint research centre (European Commission). The deviation of the mean Ct values was below 0.4 or 1.5%, indicating that it is comparable to the European standard.	☒ yes ☐ no
Precision	See Repeatability and Reproducibility	In accordance with the acceptance criteria, the intra-assay CV values ranged between 0.57% and 1.15%, depending on the analyte and the inter-assay CV values ranged between 1.25% and 3.87%, depending on the analyte.	☒ yes ☐ no
Repeatability and Reproducibility	For precision estimation the agreement between different variation parameters (lot, instruments, operator) was evaluated. According to the Common Specifications for certain class D devices [1] and the technical specifications for in vitro diagnostics for SARS-CoV-2 [2] the following acceptance criteria were applied: No false positive test results. The agreement of test results between the different variation parameters is ≥ 99% for each test analyte in a concentration of 3x LoD. Intra-assay precision (repeatability): CV < 3% Inter-assay precision (reproducibility): CV < 5%		

Limit of detection	The limit of detection was determined for each analyte (SARS-CoV-2, Influenza A, Influenza B, and RSV A/B), separately. The following acceptance criteria were applied: The limit of detection is ≤ 10 copies/reaction for all analytes To verify the limit of detection that has been determined using a CFX Opus 96™ (Bio-Rad) cycler on a LightCycler® 480 II (Roche), at least 20 replicates of each target at 1x LoD were run on a LightCycler® 480 II. The following acceptance criteria were applied: At least 19/20 replicates are positive for each target analyte (≥ 95% agreement). For the Limit of Blank (LoB) The following acceptance criterion is applied: No false positive test results.	The limit of detection in copies/ reaction for the different analytes is: SARS-CoV-2: 2.84 (2.18 – 3.53) Influenza A H1N1 pdm09: 5.26 (3.42 – 7.51) Influenza A H3N2: 5.30 (3.85 – 6.87) Influenza B: 3.65 (2.88 – 4.52) copies/reaction RSV A: 3.54 (1.65 – 6.54) RSV B: 3.17 (2.45 – 3.94) LoD verification on a LightCycler480® II: At least 19/20 replicates are positive for each target analyte (≥ 95% agreement). Limit of blank: no false positive test results (96 samples analyzed)	☒ yes ☐ no
Robustness	See Precision, Stability, Carryover/Cross-contamination, and Whole system failure rate		☒ yes ☐ no
Stability	See Transport stability, Shelf life, and In-use stability		☒ yes ☐ no

Transport stability	Before and after the transport simulation, negative and positive samples regarding the test analytes (i.e., SARS-CoV-2, Influenza A, Influenza B, and RSV A/B) were tested. The following acceptance criteria were applied: No false positive test results. The agreement of the test results before and after the transport simulation is ≤ 1 Ct value for each test analyte.	The Ct values did not deviate more than 1 after simulated transport. There were no false positive test results.	☒ yes ☐ no
Shelf life	The res4plex *direct* RT-PCR test shall have a shelf life of 12 months when stored between temperatures from -25 °C to -18 °C. Within the shelf-life study, positive and negative samples regarding the test analytes (i.e., SARS-CoV-2, Influenza A, Influenza B, and RSV A/B) were tested at 10 timepoints until 12 months. The following acceptance criteria were applied: No false positive test results. The agreement of the test results between T0 and a measurement test point is ≤ 10% for each test analyte.	The acceptance criteria were fulfilled for Solution A and Internal Control until 7 months storage and for the Positive Control until 4 months storage.	☒ yes ☐ no

In-use stability	The res4plex *direct* RT-PCR test should be able to be thawed and refrozen 6 times. The following acceptance criteria were applied: No false positive test results The agreement (ΔCt) of the test results between thawing cycle 1 and a later thawing cycle is ≤ 10% for each test analyte. Moreover, the res4plex *direct* RT-PCR shall have an in-use stability up to 8 hours in a temperature range from 2°C to 8°C. The following acceptance criteria were applied: No false negative test results with positive samples regarding the test analytes. The agreement of test results of the PC before and after storage at 4°C is ≤ 10% for each test analyte.	Solution A and Internal Control can be thawed and refrozen 4 times. After the 5th thawing, Ct values deviated more than 10% from thawing cycle 1. There were no false positive results. The res4plex *direct* RT-PCR kit can be stored at 4 °C for up to 8 hours before usage.	☒ yes ☐ no
Carryover/Cross-contamination	According to the Common Specifications for certain class D devices [1], at least five runs using alternating high positive and negative specimens regarding the test analytes (i.e., SARS-CoV-2, Influenza A, Influenza B, and RSV A/B) were performed. The following acceptance criteria were applied: No false negative test results. No false positive test results.	In line with the acceptance criteria, there were no false negative and no false positive test results.	☒ yes ☐ no

Whole system failure rate	According to the Common Specifications for certain class D devices [1], ≥ 100 samples with SARS-CoV-2 RNA at 3 × the 95 % positive cut-off concentration (3 x LOD) were tested within the precision study. The following acceptance criterion was applied: The detection rate for SARS-CoV-2 is ≥ 0.99.	Out of 106 tested samples that have been spiked with SARS-CoV-2 RNA at 3x LoD, 105 gave a positive result and 1 gave a negative result. Thus, the detection rate was ≥ 0.99, fulfilling the acceptance criterion.	☒ yes ☐ no

2.6.5.2 Clinical performance

For evidence of the clinical performance of the res4plex *direct* RT-PCR test, we evaluated the parameters according to Annex I, section 9.1 b) of the IVDR. The primary objective was to demonstrate, that the res4plex *direct* RT-PCR is at least clinically acceptable compared to the gold standard method. This is achieved when the following criteria are met.

Table 5: Overview of all applicable acceptance criteria

Clinical performance parameter	**Acceptance criteria**
Diagnostic sensitivity	For SARS-CoV-2, the diagnostic sensitivity is ≥ 95 %, > 76.0% for lower bound of 95% CI For Influenza A, the diagnostic sensitivity is ≥ 90 %, ≥ 80.0 % for lower bound of 95% CI For Influenza B, the diagnostic sensitivity is ≥ 90 %, ≥ 80.0 % for lower bound of 95% CI For RSV A/B, the diagnostic sensitivity is ≥ 90 %, ≥ 80.0% for lower CI of sensitivity
Diagnostic specificity	For SARS-CoV-2, the diagnostic specificity is ≥ 95 %., > 90.0 % for lower bound of 95% CI For Influenza A, the diagnostic specificity is ≥ 95 %, ≥ 90.0 % for lower bound of 95% CI For Influenza B, the diagnostic specificity is ≥ 95 %, ≥ 90.0 % for lower bound of 95% CI For RSV A/B, the diagnostic specificity is ≥ 95 %, ≥ 90.0 % for lower CI of specificity

In total 891 samples were analyzed. Due to a lack of positive Influenza B or RSV patient samples, INSTAND proficiency samples were analyzed in addition to left-over patient samples. Out of the total 891 samples, 696 were left-over patient samples, 54 were Influenza B proficiency samples, and 141 were RSV proficiency samples. From the tested samples, 105 were positive for SARS-CoV-2, 77 were positive for Influenza A, 54 were positive for Influenza B and 83 were positive for RSV. Diagnostic sensitivity and specificity were calculated using MedCalc®.

The parameters sensitivity and specificity were calculated as follows:

		Status according to CP/RP	

		positive	negative	
Results from IP	positive	True Positive (TP)	False Positive (FP)	Sensitivity = TP/(TP+FN)
	negative	False Negative (FN)	True Negative (TN)	Specificity = TN/(FP+TN)

The results are summarized in the following:

		SARS-CoV-2 samples		
		positive	negative	
res4plex	positive	104	1	Sensitivity: 99.1% (94.8 - 100.0)
	negative	1	744	Specificity: 99.9% (99.3 - 100.0)
		Influenza A samples		
		positive	negative	
res4plex	positive	73	1	Sensitivity: 94.8% (87.2 - 98.6)
	negative	4	680	Specificity: 99.9% (99.2 - 100.0)
		Influenza B samples		
		positive	negative	
res4plex	positive	54	0	Sensitivity: 100.0% (93.4 - 100.0)
	negative	0	725	Specificity: 100.0% (99.5 - 100.0)
		RSV samples		
		positive	negative	

res4plex	positive	83	1	Sensitivity: 100.0% (95.7 - 100.0)
	negative	0	667	Specificity: 99.9% (99.2 - 100.0)

The diagnostic sensitivity and specificity data of the res4plex *direct* RT-PCR test fulfil the acceptance criteria. In conclusion, the clinical performance data demonstrate the clinical evidence of the res4plex direct RT-PCR test.

2.6.6 Ongoing or planned post-market performance follow-up (PMPF)

We use a Post-Market Performance Follow-Up (PMPF) Plan to define PMPF measures to be taken for the res4plex *direct* RT-PCR in order to keep the performance evaluation continually updated. The results of the PMPF activities are summarized and evaluated in the post-market performance follow-up report.

PMPF activities are grouped as follows:

General methods

- Collecting experiences gained from the (clinical) routine use of the IVD medical device at the EU reference laboratory (class D product)
- Obtaining feedback from users
- Proactively continuously reviewing the scientific literature and other sources for relevant (clinical) performance and scientific data
- Continuous monitoring of relevant clinical guidelines from professional (medical) societies
- Proactive verification of the performance data of equivalent and similar products, including searches in safety databases

Specific methods

- Interlaboratory comparisons; further quality assurance programs
- Epidemiological studies
- Evaluation of patient and disease registers
- Evaluation of genetic databases
- Post-market clinical performance studies (PMPF studies)

2.7 Metrological traceability of assigned values

The res4plex *direct* RT-PCR kit contains an internal control which is based on an artificial sequence. No suitable reference materials or reference measurement procedures of higher metrological order are available.

2.7.1 Explanation of the unit of measurement

The chapter is not applicable as no suitable reference materials or reference measurement procedures of higher metrological order are available.

2.7.2 Applied reference materials and/or reference measurement procedures

The chapter is not applicable as no suitable reference materials or reference measurement procedures of higher metrological order are available.

2.8 Suggested profile and training for users

Based on the characterization of users in the intended purpose description we define the following user groups:

Table 5: res4plex direct User Groups

No.	Name of the User Group	Short Description
1	Laboratory Personnel	primary user: uses the res4plex *direct* RT-PCR for in vitro diagnostic analysis in a medical laboratory.
2	Laboratory Specialist	primary user: responsible for evaluation and release of the results

Table 6: User group "Laboratory Personnel"

User group:	**Laboratory Personnel**
Typical job title(s):	medical/biological-laboratory assistant, laboratory technician
Demographic characteristics (age, sex, language, specific physical attributes):	no specific gender typical age: between 20 and 67 years not necessarily a native speaker, but knows the required technical terminology
Expected qualification (education, degree, training):	education as medical/biological-laboratory assistant or laboratory technician
Expected job experience (related to the product, similar products):	No specific job experience related to the product required
Typical work environment (physical and rganizational/ social):	medical laboratory
Use scenarios (general description):	1. Receive the specimen
	2. Register the patient/specimen
	3. Perform nucleic acid extraction according to the laboratory's standard
	4. Perform the res4plex *direct* RT-PCR test using an qPCR cycler
	4. Recognize and interpret results.

Typical equipment (used during performance of the tasks):	qPCR cycler; disposable protective gloves; PCR reaction tubes/microtiter plate plus lids/adhesive optical film ; Pipettes; Pipette tips with filter (DNase/ RNase-free); Table centrifuge; RNA isolation kit
Expected product training (with regard to the device)	Training in RT-qPCR and *in vitro* diagnostic techniques

Table 7: User group "Laboratory Specialist"

User group:	**Laboratory Specialist**
Typical job title(s):	specialist in laboratory medicine
Demographic characteristics (age, sex, language, specific physical attributes):	no specific gender typical age: between 30 and 67 years not necessarily a native speaker, but knows the required technical terminology
Expected qualification (education, degree, training):	university degree, specialist training for laboratory medicine
Expected job experience (related to the product, similar products):	specialist training in infectious respiratory diseases
Typical work environment (physical and organizational, social):	medical laboratory
Use scenarios (general description):	Analyze and release the diagnostic report
Typical equipment (used during performance of the tasks):	qPCR cycler with corresponding software; LIMS software
Expected product training (with regard to the device)	Software training

3 Summary of Safety and Performance (SSP) for patients/lay persons

Information presented below is intended for patients or lay persons. A more extensive summary of the safety and performance prepared for healthcare professionals is found in section 2.

3.1 Device identification and general information

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.2 Intended use of the device

3.2.1 Intended purpose

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.2.2 Indication(s)

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.2.3 Contra-indication(s) and/or limitation(s)

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.3 Device description

3.3.1 General device description

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.3.2 How the device is achieving its intended purpose

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.3.3 Accessories or other devices/equipment to be used in combination

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.4 Risks and warnings

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.4.1 Control and management of potential risks

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.4.2 Remaining risks and undesirable effects

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.4.3 Warnings and precautions

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.4.4 Other relevant aspects of safety

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.5 Summary of performance evaluation and post-market performance follow-up (PMPF)

3.5.1 Summary of scientific validity

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.5.2 Summary of performance data

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.5.3 Ongoing or planned post-market performance follow-up (PMPF)

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

3.6 Suggested profile and training for users

Chapter not applicable as underlying IVD medical device is not a device for self-testing.

4 Annex

4.1 Terms and Abbreviations

The following table lists document-specific abbreviations and definitions:

Term	Description	Reference
CDx	Companion diagnostic	n. a.
Companion diagnostic	Device which is essential for the safe and effective use of a corresponding medicinal product to: - identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or - identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product	IVDR, Art. 2
Contra-indication	Specific medical reasons for not using a particular IVD medical device in the usual way (e. g. a virus infection that interferes with the biomarker analysis, a urinary tract infection that affects the results of a urine test).	internal definition
DI	Device Identifier	n. a.
EMDN	European Medical Device Nomenclature	n.a.

EUDAMED	European Database on Medical Devices	n.a.
FSCA	Field Safety Corrective Action; Corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market	IVDR, Art. 2
FSN	Field Safety Notice; Communication sent by a manufacturer to users or customers in relation to a field safety corrective action	IVDR, Art. 2
IFU	Instructions For Use; Information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken	IVDR, Art. 2
Intended purpose	Use for which the IVD medical device is intended according to the data supplied by the manufacturer on the label, the IFU, or in promotional and sales materials and as specified by the performance evaluation.	IVDR, Art. 2
IVD	In Vitro Diagnostic	n. a.
IVDD	Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices	n. a.
IVDR	European Regulation 2017/476 on in vitro diagnostic medical devices	n. a.
Kit	Set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic examination, or a part thereof	IVDR, Art. 2
Lay person	Individual who does not have formal education in a relevant field of healthcare or medical discipline	IVDR, Art. 2
Limitation	A situation/factor that (may) affect the results of an in-vitro diagnostic test (e.g. running a marathon before Ca^{2+}-measurement due to untypically high Ca^{2+}-level) or for which the test has not been clinically validated (e.g. usage for children, usage during pregnancy).	internal definition
MDSW	Medical device software	MDCG 2019-11
n. a.	not applicable	n. a.

NB	Notified Body; conformity assessment body designated in accordance with this Regulation	IVDR, Art. 2
Near-patient testing	Any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional	IVDR, Art. 2
PEP	Performance evaluation plan	n. a.
PER	Performance evaluation report	n. a.
Performance of a device	Ability of a device to achieve its intended purpose as claimed by the manufacturer. It consists of the analytical and, where applicable, the clinical performance supporting that intended purpose	IVDR, Art. 2
PMPF	Post-Market Performance Follow-up	n. a.
Scientific validity	Association of an analyte with a clinical condition or a physiological state	IVDR, Art. 2
Self-testing	Any device intended by the manufacturer to be used by lay persons, including devices used for testing services offered to lay persons by means of information society services	IVDR, Art. 2
SRN	Single Registration Number	n. a.
SSP	Summary of Safety and Performance	n. a.
SVR	Scientific validity report	n. a.
TD	Technical documentation	n. a.
UDI	Unique Device Identification; Series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market	IVDR, Art. 2

4.2 Revision history

SSP revision number	Date issued	Change description	Revision validated by the Notified Body	
20240228	2024-02-28	Initial creation	☑	Yes Validation language: ENG
			☐	No (*see note)