Clinical Validation Report on IVD Reagents

Product name: 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography)

Model & specification: 20 tests/kit, each test strip packaged separately

Type of clinical trial: Clinical validation

Start date of clinical trial: Nov. 4, 2020

End date of clinical trial: Dec. 4, 2020

Testing agency: IPE Center for Medical Laboratory

Abstract

In order to evaluate the 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) (the “Test Kit” for short) producted by Beijing Lepu Medical Technology Co., Ltd. (“the Company” for short) that is applied in clinical practices for qualitative detection of 2019-nCoV neutralization antibody in the clinical samples (serum/plasma/whole blood), IPE Center for Clinical Laboratory conducted a clinical study on the test strip contained in the Test Kit. A total of 184 samples were clinically selected as the study objects, of which 72 were vaccinated and 112 were not. GenScript sVNT Kit was used as the Reference Kit. Based on the test result of the Reference Kit, the study objects were divided into neutralization antibody positive group and neutralization antibody negative group. At the same time, these samples were tested with the Test Kit, and the test results of the Test Kit and the Reference Kit were compared and statistically analyzed. The results showed that the diagnostic specificity of the Test Kit is 96.43%, the sensitivity 95.83%, and the total coincidence rate 96.20%. The above results show a good consistency between the Test Kit and the Reference Kit. The test kit is suitable for clinical diagnosis as an auxiliary means.

I. Introduction

Novel coronavirus (Corona Virus Disease 2019, COVID-19) has rapidly swept across many countries since its outbreak, and it continues to spread all over the world. All these countries are under great pressure for detection, prevention and treatment of COVID-19. The long-term solution against the COVID-19 epidemic is to successfully develop a safe and effective vaccine. However, some neutralization antibodies are present in those infected with 2019-nCoV, and these antibodies can prevent the virus from reinfecting healthy cells by binding the spike protein the virus surface. Therefore, how to quickly and accurately detect the novel coronavirus (2019-nCoV) neutralization antibody has become the top priority in accelerating the global anti-epidemic process.

Currently, the research and development on the Company's 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) has been completed. In order to validate its clinical suitability and accuracy, we are prepared to carry out clinical validation. Entrusted by Beijing Lepu Medical Technology Co., Ltd., IPE Center for Clinical Laboratory undertook the clinical trial on the 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) produced hereby in the clinical study.

II.Objective

To evaluate the suitability and accuracy of 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) produced by Beijing Lepu Medical Technology Co., Ltd. (“the Company” for short) for clinical application, its clinical performance should be investigated systematically.

The purpose of this clinical trial: to conduct comparative experimental investigation on the 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) (Test Kit) and GenScript sVNT Kit (Reference Kit) produced by GenScript Inc. using the same clinical samples. Statistical analysis was carried out on the test results to calculate the diagnostic specificity, the sensitivity and the total coincidence rate. According to the results of statistical analysis, it was validated that the Test Kit is equivalent to the Reference Kit, so as to prove the suitability and accuracy of the Test Kit for clinical auxiliary diagnosis.

The results of clinical trial are an important basis for evaluating the efficacy and safety of the Test Kit.

III. Test Management

1. Overview of management structure

This clinical trial was conducted by Beijing IPE Center for Medical Laboratory. As the applicant, Beijing Lepu Medical Technology Co., Ltd. was responsible for communication and contact during the clinical trial.

2. Quality control of the laboratory

1) All investigators participating in this clinical trial passed the qualification examination and had professional background and capacity related to clinical trial. Before clinical trial, all investigators had enough understanding and knowledge for specific contents of the clinical trial protocol and all indicators through training.
2) The quality control of the laboratory met the requirements of quality control of clinical laboratory to ensure the standardization of experimental operating instructions.
3) Quality control before the analysis: Check whether sample collection and processing met the requirements, and whether sample number and other information were correct.
4) Regularly inspect the implementation and completion of the clinical trial. Check the integrity and accuracy of clinical sample information and verify test results.

3. Statistics and data management

1) All selected cases were filled in the clinical outcome summary, including the subject number, age, gender, etc. Experimenters filled the test results of both the Reference Kit and the Test Kit in the clinical outcome summary.
2) After finishing data entry, main investigators, experimenters and Applicant reviewed the data together and locked data without any doubt.
3) The clinical outcome summary was then submitted to analysts for statistics and analysis. The obtained statics and analysis results were filled in corresponding parts of clinical report.

4. Data preservation

The Testing Agency and the Applicant kept one copy of clinical trial data respectively, including the following:

Clinical Test Agreement, Clinical Test Protocol, Clinical Trial Report, and Clinical Outcome Summary.

5. Problems found during investigation and measures

In clinical trials, when a small number of samples are tested, the results of the reference kit and the Test Kit may be inconsistent. In this case, the clinical quantitative data

of the samples involved in the test and the other common clinical trial reagents produced with the same principle are used for re-test.

IV. Test Design

1. Description of overall test design and protocol

With reference to the *Guideline of Clinical Study on In Vitro Diagnostic Reagents*, the appropriate study objects were selected and GenScript sVNT Kit produced by GenScript Inc. was used as the Reference Kit to conduct blinding simultaneous comparison, for analyzing the diagnostic specificity, sensitivity and the total coincidence rate of the Test Kit and the Reference Kit.

A total of 184 serum samples were clinically selected as the study objects. Based on the test result of the Reference Kit, the samples were divided into a positive group and a negative group. The samples were tested with the Test Reagent and the Reference Reagent, to compare the test results obtained with the two types of product. Statistical analysis was carried out on the test results to calculate the diagnostic specificity, the diagnostic sensitivity and the total coincidence rate. According to the results of statistical analysis, the suitability and accuracy of the Test Kit were judged, so as to determine whether the test result of the Test Kit is consistent with that of the Reference Kit.

2. Investigation method

1) Sample collection, storage and transportation methods

Please use the samples immediately after collection. The samples cannot be placed at room temperature for a long period of time. Serum should be separated as soon as possible to avoid hemolysis. Samples that have been hemolyzed cannot be used. The serum/plasma samples can be stored at 2-8℃ for 3 days. Freeze (-20℃) the samples and avoid repeated freezing and thawing in case of storage for a long time;

2) Determination of reference method

GenScript sVNT Kit produced by GenScript Inc. is 2019-nCoV neutralization antibody detection product early certified in the world, which is similar to 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) made by Beijing Lepu Medical Technology Co., Ltd. The product is therefore selected as a reference reagent for clinical study.

The samples with inconsistent test results in the test group and the control group can be compared and checked by clinical quantitative results and clinical diagnosis results.

3) Names, specifications, sources, lot number, expiry dates and preservation conditions of the products for clinical study

The product name for clinical study is 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography), and the specification is 20 tests/kit. The product is provided by Beijing Lepu Medical Technology Co., Ltd. The lot number is 20CG2601X, and its shelf-life is 12 months, and the storage condition is 4℃~30℃.

The reference reagent is GenScript sVNT Kit produced by GenScript Inc., of which the specification is 96 tests/kit and its shelf-life is 6 months and the storage condition is 2℃~8℃.

4) Methods of quality control

Regularly inspect the implementation and completion of the clinical trial. Check the integrity and accuracy of clinical sample information and verify test results.

5) Clinical trial method

After all the samples are tested with the Reference Kit and the Test Kit in synchronization respectively, and the test results of the two are compared. A statistical analysis on the recorded test result of the Test Kit and that of the Reference Kit is carried out after all the clinical samples are tested, followed by calculating the diagnostic specificity, the diagnostic sensitivity and the total coincidence rate, and evaluating whether both are equivalent according to these statistical indicators.

6) Statistical analysis methods for clinical study data

The diagnostic specificity, the diagnostic sensitivity and the total coincidence rate are obtained by calculating the test results of the Test Kit and the Reference Kit. The clinical suitability and accuracy of the product are validated by judging whether the indicators meet the clinical evaluation criteria, so as to calculate the test and statistical results of the Test Kit in testing different types of samples. Meanwhile, different types of samples are tested with the Test Kit and the Reference Kit in synchronization respectively, and the test results are compared. After all the clinical samples are tested, a statistical analysis on the recorded test results is carried out and followed by calculating the diagnostic specificity, the diagnostic sensitivity and the total coincidence rate, and evaluating whether both are equivalent according to these statistical indicators.

7) Final clinical evaluation

Compare with the reference kit officially marketed, the coincidence rate was calculated. The product performance shall meet the following requirements.

1) Diagnostic specificity: Namely the proportion of samples tested negative with the Test Kit and the Reference Kit in those tested negative with the Reference Kit. The diagnostic specificity should be greater than 90%.

2) Diagnostic sensitivity: Namely the proportion of samples tested positive with the Test Kit and the Reference Kit in those tested positive with the Reference Kit. The diagnostic sensitivity should be greater than 90%.

3) Total coincidence rate: Namely the proportion of samples with the same results tested with the Test Kit and the Reference Kit to the total samples. The total coincidence rate should be greater than 90%.

Diagnostic specificity and diagnostic sensitivity

		Reference system		Total
		Positive	Negative	
Test system	Positive	a	b	a + b
	Negative	c	d	c + d
Total		a+ c	b + d	a + b + c + d

In general, the formula for diagnostic specificity and diagnostic sensitivity are as follows:

Diagnostic sensitivity =a/(a + c)*100%

Diagnostic specificity =d/(b + d)*100%

Total coincidence rate = (a + d)/(a + c + b + d)*100%

The diagnostic specificity and diagnostic specificity meet the clinical requirements, and the two methods or products are considered to be equivalent; if the difference between diagnostic specificity and sensitivity is too large, the clinical trial protocol should be redesigned.

8) Modification of the protocol during the research

No modification.

V. Results and Analysis of Clinical Trial

A total of 184 samples were clinically selected as the study objects, of which 72 were vaccinated and 112 were not. All selected samples were tested.

The test results of 2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography) (Test Kit) produced by the Company and the Reference Kit were subjected to consistency statistics for analysis on the diagnostic sensitivity, diagnostic

specificity, and total coincidence rate, and summarizing in the form of four-fold table. The results are as follows:

Table 1: Test Results Obtained with the Test Kit and the Reference Kit

2019-nCoV Neutralization Antibody Test Kit	GenScript sVNT Kit	
	Positive	Negative
Positive	69	4
Negative	3	108
Sample Quantity	72	112

Table 2: Summary of Diagnostic Sensitivity and Specificity Results

Item	**Formula**	**Result**	95% CI
Diagnostic sensitivity (%)	a/(a + c) ×100%	95.83%	88.45% ~ 98.57%
Diagnostic specificity (%)	d /(b + d) ×100%	96.43%	91.18%~98.60%
Total coincidence rate (%)	(a + d) / (a + b + c + d) ×100%	96.20%	/

It can be seen from Table 1 that among the 72 samples in the positive group, 69 cases are positive and 3 cases are negative. Among the 112 samples in the negative group, 108 cases are negative and 4 cases are positive. The diagnostic specificity, diagnostic sensitivity and total coincidence rate are all greater than 90%, which indicates that the Test Kit has good diagnostic sensitivity and specificity, and is in good consistency with the Reference Kit.

VI. Discussion and Conclusion

(I) Discussion

The 2019-nCoV Neutralization Antibody Test Kit produced by Beijing Lepu Medical Technology Co., Ltd. contains the monoclonal antibody of 2019-nCoV spike protein (RBD) marked with colloidal gold pre-coated on the gold conjugate pad, the monoclonal antibody of mouse anti-human IgG antibody immobilized in the test area G and the corresponding antibody of mouse anti-human IgM antibody in the test area M and quality control area (C). The rapid detection of 2019-nCoV neutralization antibody in serum/plasma samples is used for auxiliary diagnosis of patients injected with 2019-nCoV vaccine. The purpose of the clinical trial is to evaluate the clinical performance of the product. The test can be summarized as follows:

The comparative analysis results between the Test Kit and GenScript sVNT Kit produced by GenScript Inc. are as follows:

Test results obtained with the Test Kit and the Reference Kit: The diagnostic specificity, diagnostic sensitivity and total coincidence rate are all greater than 90%, which indicates that the two systems are equivalent.

(II) Test conclusion

The comparative analysis results of the Test Kit and GenScript sVNT Kit produced by GenScript Inc. show that the diagnostic specificity of the Test Kit is 96.43%, the sensitivity 95.83%, and the total coincidence rate 96.20%. The above analysis results can demonstrate that the Test Kit is in good consistency with the Reference Kit, and the two systems are equivalent.

VI. Description of Exceptions in Clinical Investigation

There are no special circumstances to be stated in this clinical investigation.

Appendix I Instruction for Use of Reagent Used in the Clinical Trial

2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography)

[Product name]

2019-nCoV Neutralization Antibody Test Kit (colloidal gold immunochromatography)

[Model]

1 tests/kit, 5 tests/kit, 10 tests/kit, 20 tests/kit, 50 tests/kit (one test per bag for one person).

[Intended Use]

This product is used to qualitatively detect the 2019-nCoV neutralization antibodies in clinical samples (serum/plasma/whole blood).

[Summary]

Since the outbreak of novel coronavirus (2019-nCoV) has rapidly swept across many countries and continues to spread worldwide. All the countries are under tremendous pressure in the detection, prevention or treatment of 2019-nCoV. To cope with the epidemic situation, the only lasting solution is to successfully develop a safe and effective vaccine. In the process of vaccine development and marketing, the most important index to evaluate the effectiveness of the 2019-nCoV vaccine is the content of neutralizing antibody in subjects. So, the detection of 2019-nCoV neutralization antibodies is the top priority in accelerating the fight of global epidemic.

[Measurement Principle]

The product is based on the principle of antigen-antibody reaction and immunoassay technique. The test device contains colloidal gold labeled 2019-nCoV Spike Protein (RBD), mouse-anti human IgG antibody immobilized in G test area, mouse-anti human IgM antibody immobilized in M test area and the corresponding antibody in quality control area (C).

During the test, when the 2019-nCoV IgM neutralization antibody level in the sample is at or above the limit of detection of the test, the 2019-nCoV IgM neutralization antibody in the sample binds to the colloidal gold labeled 2019-nCoV Spike Protein (RBD) which is pre-coated on a gold label pad. The conjugates migrate upward through capillary effect and would be captured by mouse-anti human IgM antibody immobilized in M test area subsequently and this produces a purple-red band appears in the M test area. When the 2019-nCoV IgG neutralization antibody level in the sample is at or above the limit of detection of the test, the 2019-nCoV IgG antibody in the sample binds to the colloidal gold labeled 2019-nCoV Spike Protein (RBD) which is pre-coated on a gold label pad. The conjugates migrate upward through capillary effect and would be captured by mouse-anti human IgG antibody immobilized in G test area subsequently and this produces a purple-red band appears in the G test area. If it is a negative sample, there is not a purple-red band appeared in the M and G test area. Regardless of the presence or absence of the 2019-nCoV neutralization antibody in the sample, a purple-red band will appear in the quality control area (C). The purple-red band in the quality control area (C) is a criterion for judging whether there is enough sample and whether the chromatography process is normal. It also serves as the internal control standard for reagents.

[Component]

Model	Test cassette	Dropper	Instructions for use	Sample dilution
1 tests/kit	1 tests	10	1	1ml
5 tests/kit	5 tests	10	1	1ml
10tests/kit	10 tests	10	1	1.5ml
20 tests/kit	20 tests	20	1	2.5ml
50 tests/kit	50 tests	50	1	5ml
For each test, it contains one testing cassette and one package of desiccant.				

The test cassette is composed of test strip and test strip shell. The test strip is composed of one gold standard mat (containing colloidal gold labeled 2019-nCoV Spike Protein (RBD)), sample mat, cellulose nitrate membrane (containing mouse-anti human IgM antibody immobilized in M area, mouse-anti human IgG antibody immobilized in G area and goat anti-mouse antibody immobilized in C area), absorbing paper, plastic carrier board.

[Storage and Stability]

It should be stored at 4℃ ~ 30℃, be kept dry and away from sunlight. The shelf life is 12 months.

For per test cassette, it should be used within 1 hour after unsealing.

Production Date and Expiration date are shown in the package label.

[Sample Requirements]

The test can be performed with serum/plasma/whole blood.

The blood should be collected by professional medical staff, and it is advised of detecting serum/plasma in priority, and under emergency conditions or special conditions, the whole blood of patients can be used for rapid testing.

After collection of samples, it should be tested immediately. It is forbidden for long time placement of the sample under room temperature. For whole blood sample, if it can not be tested in time, it can preserve for 24 hours between 2 and 8℃. Serum/plasma samples can be preserved for 3 days under temperature between 2 and 8℃, and for long time storage, they should be stored under -20℃, and it should avoid repeated freeze-thaw cycles.

Before testing, the sample must be restored to room temperature, ready for application only after homogeneity.

The sample must be returned to room temperature before testing, and should be used after mixing.

Do not use samples with severe hemolysis, severe lipids, and jaundice.

[Test Method]

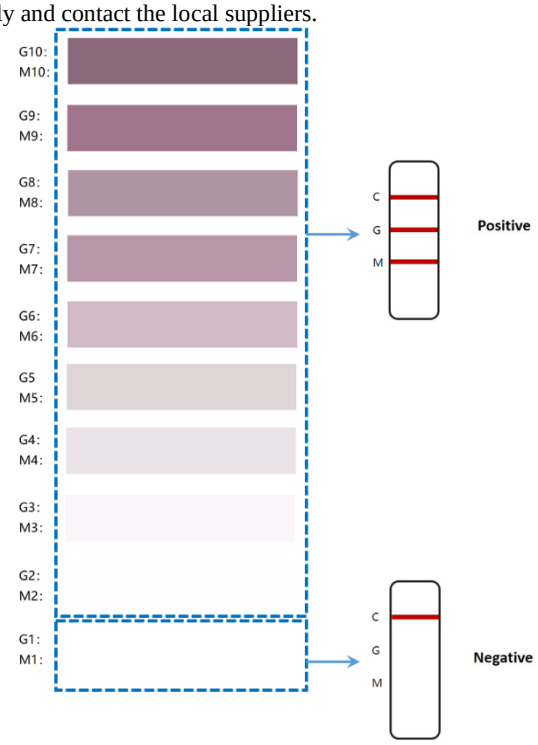
Please read the instruction for use carefully before performing the test. Before testing, restore the reagents and blood sample to room temperature.

1. Remove the test cassette from the packaging reagent bag and use it within 1 hour, especially in an environment with room temperature higher than 30 ℃ or in high humidity.
2. Place the kit on a clean platform.
   - Serum or plasma sample: Add one drop (about 10 μL) of serum or plasma sample to well A with a dropper, and then add two drops (about 80 μL) of sample dilution to well B, and start timing.
   - Whole blood sample: Add two drops (about 20 μL) of whole blood sample to sample well A with a dropper, and then add two drops (about 80 μL) of sample dilution to sample well B, and start timing.
3. Wait for the fuchsia band to appear. The test results should be read at 15 minutes. Do not read the results after 20 minutes.

[The Explanation of the Testing Results]

A Color Card is provided in this test kit. The test results need to be compared with the color card for judgment. The specific determination methods are as follows:

- Positive (+): The purple red band appears in quality control area (C) and M/G test area. In comparison with the Color Card, the chroma of purple red band should be equal to or better than G2/M2 of Color Card.
- Negative (-): The purple red band only appears in quality control area (c). There is no purple red band in the M/G test area or the chroma of purple red in M/G test area is weaker than G2/M2 of Color Card.
- Invalid: There is no purple stripe in the quality control area (C), indicating incorrect operating procedures or the test strip has already deteriorated. Under this conditions, it must read the instruction for use again carefully, and then use the new test strips to test again. If the problem still exists, stop using this lot number immediately and contact the local suppliers.



[Limitation of Procedure]

1. The test results of this product should be comprehensively judged by the physician in combination with other clinical information, and should not be used as the only criterion;
2. The product is used to test the 2019-nCoV neutralization antibody of the tested sample.

[Product Performance Index]

1 Analytical Specificity

1.1 Cross-reactivity: This test device has no cross reactivity with endemic human coronavirus OC43 antibody, endemic human coronavirus HKU1 antibody, endemic human coronavirus NL63 antibody, endemic human coronavirus 229E antibody, influenza A virus antibody, influenza B virus antibody, respiratory syncytial virus antibody, adenovirus antibody, rhinovirus antibody, enterovirus antibody, EB virus antibody, measles virus antibody, cytomegalovirus antibody, rotavirus antibody, norovirus antibody, mumps virus antibody, varicella-zoster virus antibody, and mycoplasma pneumoniae antibody.

1.2 Interfering substances:

The test results do not be interfered with the substance at the following concentration:

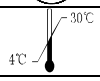
bilirubin concentration ≤250 μmol/l; triglycerides concentration≤15 mmol/l; hemoglobin concentration ≤10 g/dL; rheumatoid factor concentration≤80RU/ml; anti-mitochondrial antibody concentration≤80 U/mL; antinuclear antibody concentration ≤80U/mL; the total IgG concentration ≤14g/L.

The test results do not be influenced by the following substance:α-interferon, zanamivir, ribavirin, oseltamivir, and paramivir, Lopinavir, ritonavir, abidol, levofloxacin, azithromycin, ceftriaxone, meropenem, tobramycin, histamine hydrochloride, phenylephrine, oxymetazoline, sodium chloride (containing Preservatives), beclomethasone, dexamethasone, flunisolide, triamcinolone, budesonide, mometasone and fluticasone.

[Precautions]

1. The test is only suitable for professionals to use *in vitro* auxiliary diagnosis. Do not use expired products.
2. Do not freeze or use after the expiration date (see the packaging for the expiration date).
3. Avoid excessive temperature and humidity in the experimental environment. The reaction temperature should be 15-30°C and the humidity should be below 70%.
4. The package bag contains desiccant, and it should not be taking orally.
5. It is recommended to use fresh blood for the sample collection. It is not recommended to use high-fat chyle, jaundice, and high rheumatoid factor samples. Do not use hemolyzed samples.
6. When testing, please wear protective clothing, medical mask, gloves and goggles.
7. Do not use the test card with broken single packaging, unclear marks, and past the expiration date.
8. Dispose of used specimens, test cards and other waste in accordance with relevant local laws and regulations.

[Explanation of Symbols]

	DO NOT USE IF PACKAGE IS DAMAGED		CONSULT INSTRUCTIONS FOR USE
	DO NOT REUSE		EXPIRY DATE
	TEMPERATURE LIMIT		DATE OF MANUFACTURER
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	KEEP AWAY FROM SUNLIGHT		KEEP DRY
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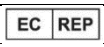	AUTHORIZED REPRESENTATIVE IN THE EUROPEAN COMMUNITY		

Beijing Lepu Medical Technology Co., Ltd.
Floor 3 Building 7-1 No.37 Chaoqian Road, Changping District, Beijing, 102200, P.R. China
Floor 5 Building 7-1 No.37 Chaoqian Road, Changping District, Beijing, 102200, P.R. China
Tel: +86-10-80123964
Email: lepuservice@lepumedical.com
Web: en.lepumedical.com

Lepu Medical (Europe) Cooperatief U.A.
Abe Lenstra Boulevard 36, 8448 JB, Heerenveen,The Netherlands
Tel: +31-515-573399 Fax: +31-515-760020

Appendix II Clinical Trial Data

Sample No.	Test results of Test Kit	Test results of Reference Kit
1	Positive	Positive
2	Negative	Negative
3	Negative	Negative
4	Negative	Negative
5	Positive	Positive
6	Positive	Positive
7	Positive	Positive
8	Negative	Negative
9	Positive	Positive
10	Negative	Negative
11	Positive	Positive
12	Positive	Positive
13	Negative	Negative
14	Negative	Negative
15	Negative	Positive
16	Negative	Negative
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