March 9, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 25, Medical Scope
Term Name	Endoscopic telescope Disease characteristic finding detection support software for endoscope (newly created)
Brand Name	nodoca
Applicant	Aillis, Inc.
Date of Application	June 4, 2021 (Application for marketing approval)

Results of Deliberation

In its meeting held on March 9, 2022, the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not designated as a medical device subject to a use-results survey and should be approved. The product is not classified as a biological product or a specified biological product.

Review Report

February 15, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 25, Medical Scope
Term Name	Endoscopic telescope Disease characteristic finding detection support software for endoscope (newly created)
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Applicant	Aillis, Inc.
Date of Application	June 4, 2021
Reviewing Office	Office of Software as a Medical Device, Office of Medical Devices I

Review Results

February 15, 2022

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Results of Review

A system called "nodoca" collectively analyzes information on medical questionnaires entered by users and information on pharyngeal image captured by a camera to detect characteristic signs and symptoms of influenza infection in the diagnosis of patients with suspected influenza infection. Two types of system are available for nodoca: A console system and a cloud system. The console system consists of a camera, camera stand, console, and accessories. The cloud system uses cloud system software (terminal software and server software) instead of the console of the console system. Both types have analysis software of the same program performance. A deep learning software based on patients' pharyngeal images and other data collected in clinical research (jRCTs032190120) is installed on nodoca. The concept of nodoca is to support physicians to diagnose patients during the early phase of influenza infection by detecting characteristic pharyngeal signs, including lymph follicles in the posterior pharyngeal wall.

The user inserts the camera, to the tip of which the "tongue spatula for camera" under notification (Notification No. 13BlX10294SC0001) is attached, into the patient's oral cavity to photograph the pharynx. Analysis starts once photographed pharyngeal images and information on a 26-item medical questionnaire are sent to the console placed within the medical institution, or the analysis server housed within the medical institution or an external institution. The analysis results are displayed on the console, or a generic tablet personal computer (PC) installed with the terminal software.

The applicant submitted non-clinical data supporting the electrical safety and electromagnetic compatibility, mechanical safety, performance, and software life cycle process of nodoca. The submitted data showed no particular problem.

The applicant submitted data from a clinical study conducted in 708 patients at 11 study sites in Japan using the previous generation model of nodoca (hereinafter referred to as "investigational device"). The safety of the investigational device was evaluated based on adverse events and malfunctions in safety analysis set (SAS) consisting of 706 patients excluding 2 patients with inadequate informed consent

process. The primary endpoint of the study was the "sensitivity and specificity of the investigational device in diagnosing influenza infection compared with polymerase chain reaction (PCR)." The primary endpoint was evaluated in full analysis set (FAS) consisting of 672 patients.

The lower limit of the 95% confidence interval (CI) in the clinical study was [redacted]% for sensitivity and [redacted]% for specificity. Although the specificity met the protocol-defined performance target of [redacted]%, sensitivity did not meet the predefined target of [redacted]%. In response to these results, the applicant modified the software program, camera, etc. in order to develop nodoca. The performance of nodoca was assessed in an additional study using patient data collected in the clinical study after excluding ineligible data that could not be analyzed, and the same endpoint as that of the clinical study ("additional study"). The lower limit of the 95% confidence interval in the additional study was 70.7% for sensitivity and 85.5% for specificity. Because nodoca met the protocol-defined respective performance targets, the efficacy of nodoca was considered to be demonstrated. However, the study failed to show the non-inferiority of nodoca to immunochromatography in sensitivity, which was a secondary endpoint of the study. The usefulness of nodoca over immunochromatography was not confirmed.

The safety of nodoca was evaluated based on adverse events and malfunctions reported in the clinical study because nodoca and the investigational device have no different features that may affect safety. In the clinical study, retching (vomiturition or vomiting reflex) was reported in 12 patients (1.7%) as an adverse event. All of the cases resolved quickly. No noteworthy adverse event was reported.

The clinical positioning of nodoca should be an aid to the diagnosis of influenza infection, and nodoca, alone, is not intended to make a definite diagnosis for the following reasons: nodoca does not directly confirm the presence of virus; and nodoca has not demonstrated its non-inferiority to immunochromatography. Therefore, information on precautions, etc. should caution that nodoca does not replace immunochromatography. At present, there is no finding that nodoca sufficiently differentiates influenza infection from other infectious diseases that present with lymph follicles in the posterior pharyngeal wall. This should also be cautioned in the information on precautions, etc.

PMDA concluded that there was no particular problem with the efficacy and safety of nodoca based on comprehensive evaluation of the submitted data and taking account of comments from the Expert Discussion.

As a result of its review, PMDA has concluded that nodoca may be approved for the intended use shown below and that the results should be presented to the Subcommittee on Software as a Medical Device for further deliberation.

Intended Use

nodoca photographs the patient's pharynx and collectively analyzes findings of the pharynx, such as the lymph tissue (including the tonsil and lymph follicles) on the pharyngeal images and patient's medical information to detect characteristic signs and symptoms of influenza infection. nodoca is used as an aid to the diagnosis of influenza infection. nodoca is not intended to make a definite diagnosis based on analysis results alone.

Review Report

February 15, 2022

Product for Review

Classification	Instrument & Apparatus 25, Medical Scope
Term Name	Endoscopic telescope Disease characteristic finding detection support software for endoscope (to be newly created)
Brand Name	nodoca
Applicant	Aillis, Inc.
Date of Application	June 4, 2021
Proposed Intended Use	nodoca is used as an aid to the diagnosis of influenza infection by photographing the pharynx and analyzing the photographed images.

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List of Abbreviations

AI	Artificial Intelligence
[redacted]	[redacted]
CPU	Central Processing Unit
FAS	Full Analysis Set
GPU	Graphics Processing Unit
JIS	Japanese Industrial Standard
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PC	Personal Computer
PCR	Polymerase Chain Reaction
PT	Preferred Term
QR	Quick Response
SAS	Safety Analysis Set
SOT	Standard of Truth
USB	Universal Serial Bus

I. Product Overview

A system called “nodoca” collectively analyzes information on medical questionnaires entered by users and information on pharyngeal image captured by a pharyngeal camera as shown in Figure 1 to detect characteristic signs and symptoms of influenza infection in the diagnosis of patients with suspected influenza infection.

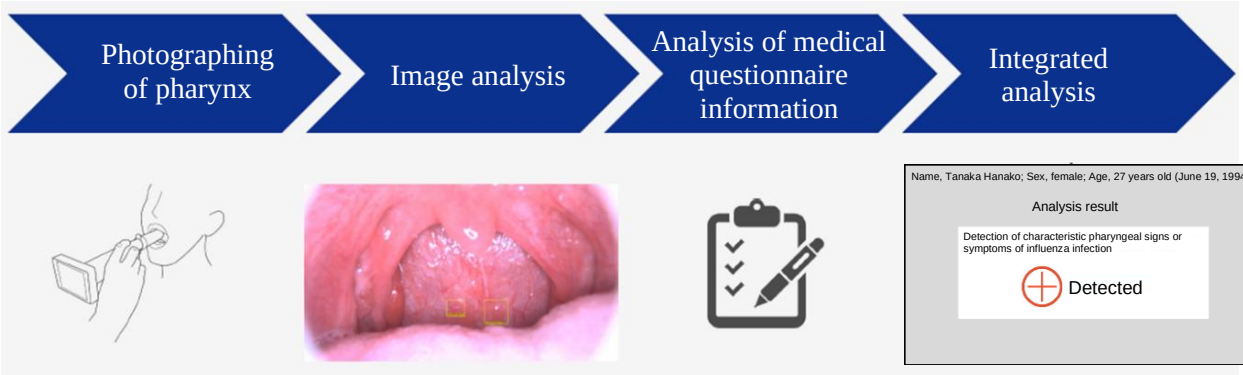


Figure 1. Flow from photographing the pharynx to outputting integrated analysis result

nodoca is intended to be used in patients with influenza-like symptoms. Analysis results of nodoca are used to aid the diagnosis of influenza infection, and nodoca is not intended to make a definite diagnosis based on its analysis results alone.

Two types of system are available for nodoca: A console system and a cloud system (Table 1). As shown in Figure 2, the console system consists of a camera, camera stand, console, and accessories (patient quick response [QR] code generator software and universal serial bus [USB] cable). The cloud system consists of a camera, camera stand, cloud system software, and accessories (patient QR code generator software and USB cable). The cloud system software consists of terminal software that displays analysis orders and analysis result and server software that analyzes data.

The following 2 types of cloud system are available: One in which cloud system software is provided by a recording medium and is installed on a server within the medical institution; and the other that uses cloud system software on a server outside of the institution. The program content used for display and data analysis in both systems is identical.

Table 1. Components of nodoca

Components		Console system	Cloud system	
			For internal server	For external server
Camera		○	○	○
Camera stand		○	○	○
Console		○	—	—
Cloud system software	Server software (for analysis)	—	○	— (Analysis by external server)
	Terminal software	—	○	○
Accessories		○	○	○

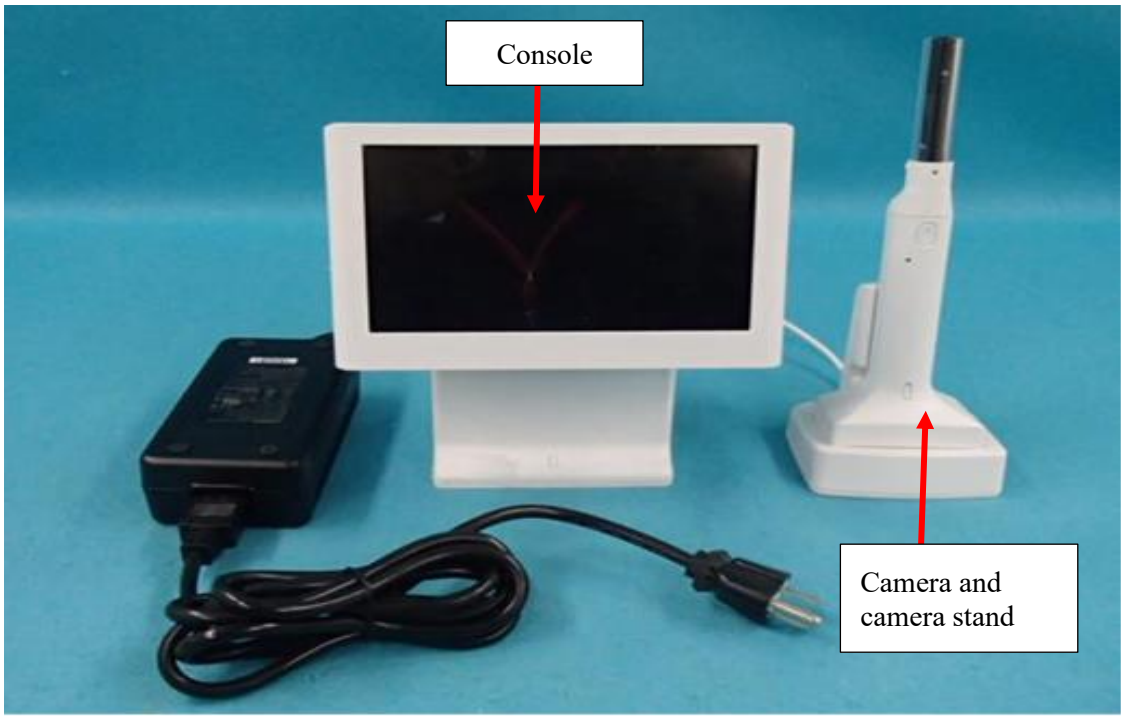


Figure 2. External appearance of nodoca (console system)

The user enters information obtained from the 26-item medical questionnaire shown in Table 2 and inserts the camera, to the tip of which the “tongue spatula for camera” under notification (Notification No. 13BlX10294SC0001) is attached, into the patient’s oral cavity.

Figure 4 illustrates the flow of analysis with nodoca up to displaying an analysis result. The analysis software starts pattern recognition processing and other analyses once pharyngeal image data captured by the camera and information on the medical questionnaire entered by the user are sent to the console placed within the medical institution, or the server housed within the medical institution or an external institution. The analysis results are displayed on the console of the console system, or a general-purpose tablet personal computer (PC) installed with the terminal software of the cloud system.

Table 2. Medical questionnaire information

	Parameter	Remarks
1	Name	Used for the identification of the patient
2	Sex	Input data, male or female
3	Date of birth	"Error" is displayed when age calculated from the input data is <6 years.
4	Body temperature at visit	Input range, 34.0°C-43.0°C
5	Peak body temperature after onset	Input range, 34.0°C-43.0°C
6	Date and time of onset	Time from onset is calculated from the input information.
7	Heart rate	Input unit, 6-120 bpm
8	Use of antipyretic (including marketed product) before visit	Input data, yes or no
9	Contact with a patient with fever or influenza infection in the last 3 days	Input data, yes or no
10	Joint pain	Input data, yes or no
11	Muscular pain	Input data, yes or no
12	Headache	Input data, yes or no
13	General malaise	Input data, yes or no
14	Appetite	Input data, yes or no
15	Chills	Input data, yes or no
16	Sweating	Input data, yes or no
17	Cough	Input data, yes or no
18	Sore throat	Input data, yes or no
19	Nasal discharge or nasal congestion	Input data, yes or no
20	Tonsillitis	Input data, yes or no
21	Digestive symptoms	Input data, yes or no
22	White film on tonsils	Input data, yes or no
23	Redness of tonsils	Input data, yes or no
24	Prior influenza vaccination	Input data, yes or no
25	Timing of last vaccination (Month)	Input range, January-December
26	Timing of last vaccination	Input data, early, mid, late in month, unknown

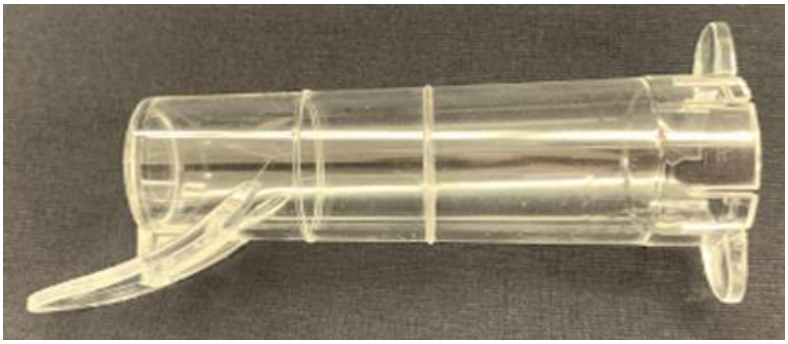


Figure 3. Tongue spatula for camera

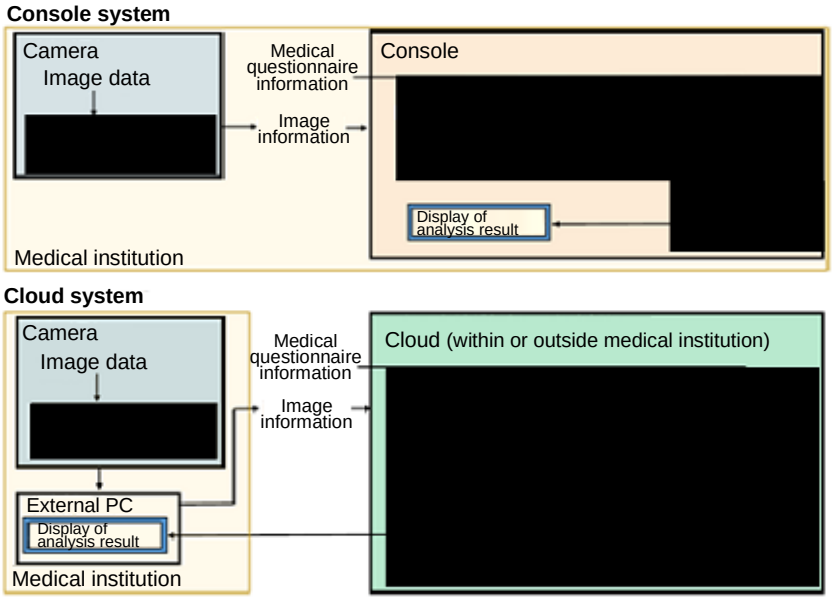


Figure 4. Flow chart up to outcome assessment

The analysis software installed on nodoca was constructed by deep learning of patients' data collected in clinical research (jRCTs032190120) shown in Table 3. As shown in Table 4, the data used in deep learning were [redacted] image data from [redacted] patients that were extracted in view of avoiding overemphasis on PCR results, [redacted], and presence or absence of [redacted].

Table 3. Summary of clinical research (jRCTs032190120)

Title of research	Data collection research on influenza follicles
Type of research	Specified clinical research
Research objective	Clinical information are collected from subjects with suspected influenza infection, and the posterior pharyngeal wall are photographed using the camera for the posterior pharyngeal wall (under development), console, and tongue spatula. Then, the above data are studied for differences in the distribution and shape of follicles between subjects with and without influenza infection, as well as variations of follicles. Learning data and verification data are collected for the future development of an influenza diagnosis support AI program.
Research period	[redacted], 20[redacted] to [redacted], 20[redacted]
Number of sites	64
Number of subjects	9,047
Number of images	[redacted]

Table 4. Data for learning

Parameter	Category	Number of patients
PCR result	Positive	[redacted]
	Negative	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
Total number of patients		[redacted]
Total number of images		[redacted]

Figure 5 shows the assessment algorism of the analysis software installed on nodoca. First, [redacted] is calculated. The presence or absence is assessed [redacted].

As shown in Figure 6, the analysis result, whether "characteristic pharyngeal signs or symptoms of influenza infection" are "⊕Detected" or "⊖Not detected," is presented to the user. When analysis fails, an alert pops up to prompt the user to photograph the pharynx again.

nodoca is not intended to improve its performance through additional learning in a post-marketing setting.

Figure 5. Flow of assessment algorism

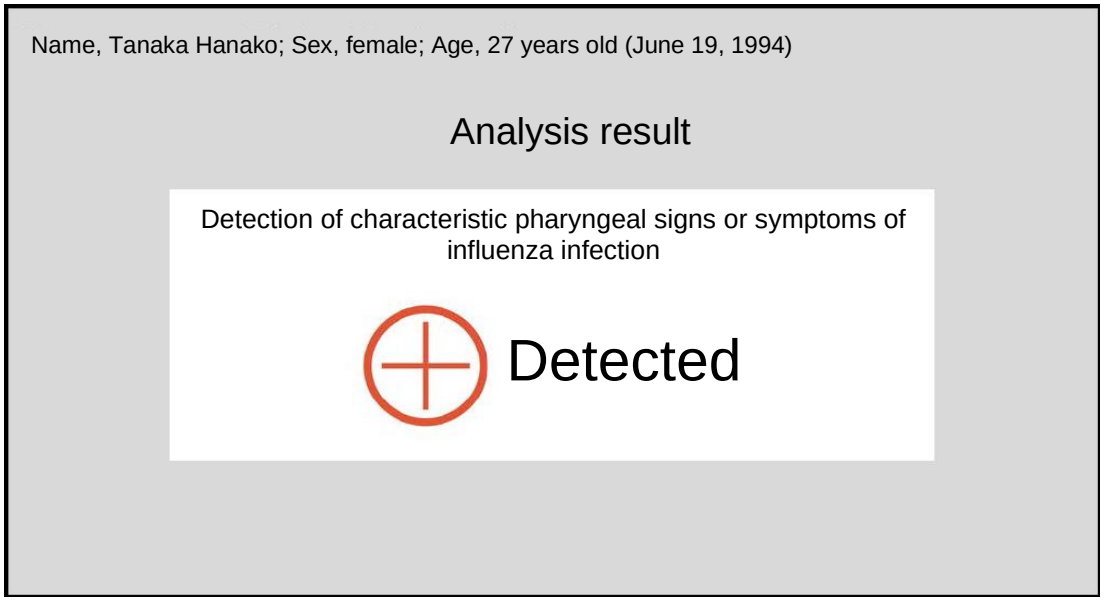


Figure 6. Example of analysis result display

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on nodoca declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Rapid and accurate diagnosis of influenza infection is essential in ensuring the proper use of anti-influenza drugs and preventing the spread of infection. In Japan, influenza infection is typically diagnosed by comprehensive assessment of clinical symptoms and test results using an immunochromatographic *in vitro* diagnostics (term name, influenza virus kit; "immunochromatography"). Immunochromatography is found to have a high specificity of ≥90%. Most patients who tested positive by immunochromatography are diagnosed with influenza infection. For patients to test positive by immunochromatography, however, a certain amount of antigen is needed, because the sensitivity of immunochromatography is known to be as low as 52.2% to 62.3%.[1,2,3] The low sensitivity of immunochromatography can be explained by a positive correlation between the time after onset and the amount of antigen. For this reason, in the current clinical practice, it is not uncommon to see patients who test negative by immunochromatography on the day of onset but become positive after a re-test on the following day. In particular, the sensitivity of immunochromatography tends to be low within 12 hours after onset. Only 30% of patients who are found to be positive in the end receive an anti-influenza drug within 12 hours after onset.[4]

Specimens are collected for immunochromatography by inserting a cotton swab for mucus collection into the nasopharynx. This may cause patients to sneeze or cough, putting healthcare professionals at risk of exposure to droplets containing the virus. In addition, inserting a cotton swab into the nose of patients is invasive, which may cause nose to bleed.

Recently, Miyamoto et al. reported that early diagnosis can be made within 12 hours after the development of fever, 1 hour at the shortest, based on the shape and other characteristics of lymph follicles in the posterior pharyngeal wall, which are unique to influenza infection. The sensitivity (98.8%) and specificity (100%) are superior to immunochromatography in the diagnosis of influenza infection.[5]

On the basis of the above, the applicant developed nodoca with the concept of aiding physicians to diagnose influenza infection in a more minimally invasive manner by analyzing pharyngeal images with artificial intelligence (AI) technology to detect characteristic signs of influenza infection.

1.A.(2) Use in foreign countries

As of February 2022, nodoca is not regulatory-approved in foreign countries.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications of the whole system of nodoca are designed to ensure its sensitivity, specificity, electrical safety and electromagnetic compatibility, mechanical safety, and software life cycle process.

The proposed performance and safety specifications of the camera are designed to ensure the maximum diameter of the insertion, viewing angle, viewing direction, illuminance, resolution, and conformity to the particular requirements for the basic safety and essential performance of endoscopic equipment (Japanese Industrial Standard [JIS] T 0601-2-18:2013).

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the data relating to the performance and safety specifications proposed by the applicant and concluded that there was no particular problem with the specifications. There was also no particular problem with the proposed sensitivity and specificity specifications of the whole system because those specifications are based on the acceptance criteria defined in the protocol of the clinical study and their thresholds are clinically significant as determined from publications.[1,2,3]

2.(2) Performance specifications

2.(2).A Summary of the data submitted

The applicant submitted the sensitivity and specificity results from the clinical study to support the performance of the whole system of nodoca. The applicant also submitted the data on the maximum diameter of the insertion, viewing angle, viewing direction, illuminance, and resolution of the camera to support the performance of the camera. All of the test results met the specifications, indicating that the performance of nodoca is assured.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data relating to the performance of nodoca and concluded that there was no particular problem.

2.(3) Safety specifications

2.(3).1) Electrical safety and electromagnetic compatibility

2.(3).1).A Summary of the data submitted

The applicant submitted data showing that nodoca meets the standard specifying general requirements for basic safety and essential performance of medical electrical equipment (JIS T 0601-1:2017), the standard specifying electromagnetic compatibility of medical electrical equipment (JIS T 0601-1-2:2018), and the standard specifying particular requirements for basic safety and essential performance of endoscopic equipment (JIS T 0601-2-18:2013), to support the electrical safety and electromagnetic

compatibility of the camera, camera stand, and console. All of the test results met the standards, indicating that the electrical safety and electromagnetic compatibility of nodoca are assured.

2.(3).1).B Outline of the review conducted by PMDA

PMDA reviewed the data relating to the electrical safety and electromagnetic compatibility of nodoca and concluded that there was no particular problem.

2.(3).2) Mechanical safety

2.(3).2).A Summary of the data submitted

The mechanical safety of nodoca was also assessed based on the submitted data showing the conformity of nodoca to the standard specifying general requirements for basic safety and essential performance of medical electrical equipment (JIS T 0601-1:2017). The mechanical safety of nodoca was shown to be assured.

2.(3).2).B Outline of the review conducted by PMDA

PMDA reviewed the data relating to the mechanical safety of nodoca and concluded that there was no particular problem.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that nodoca meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of nodoca to the Essential Principles as shown below.

(a) PMDA's view on the conformity of nodoca to Article 1, which defines preconditions, etc. for designing medical devices (particularly conditions for users, such as technical knowledge, experience, education, and training for intended user):
As described later in Section "7.B Outline of the review conducted by PMDA," nodoca can be operated using a similar procedure as that of pharyngoscopy, and physicians who are capable of diagnosing influenza infection will be able to use nodoca without special training. Thus, PMDA concluded that nodoca conforms to Article 1.

(b) PMDA's view on the conformity of nodoca to Article 3, which defines the performance and function of medical devices, and Article 6, which defines the efficacy of medical devices:
As described later in Section "6.B.(1) Efficacy and safety of nodoca," the results of the additional study met the performance targets, demonstrating the efficacy and safety of nodoca in patients with

influenza-like symptoms. Thus, PMDA concluded that nodoca conforms to Article 3 and Article 6.

(c) PMDA's view on the conformity of nodoca to Article 9, which defines the environment in which medical devices are intended to be used in combination with other medical devices:
As described later in Section "6.B.(1) Efficacy and safety of nodoca," all adverse events related to nodoca were mild in severity. Thus, PMDA concluded that nodoca conforms to Article 9.

(d) PMDA's view on the conformity of nodoca to Article 10, which defines requirements for measuring functions:
As described earlier in Section "2.(2).B Outline of the review conducted by PMDA," the sufficient sensitivity and specificity of nodoca and the sufficient performance of the camera to be used as an aid to the diagnosis of influenza infection have been shown. Thus, PMDA concluded that nodoca conforms to Article 10.

(e) PMDA's view on the conformity of nodoca to Article 12, which defines requirements for development life cycle of medical devices that incorporate software:
As described earlier in Section "2.(1).B Outline of the review conducted by PMDA" and Section "2.(2).B Outline of the review conducted by PMDA," the proper software life cycle process and operation of nodoca have been assessed, showing justification. Thus, PMDA concluded that nodoca conforms to Article 12.

(f) PMDA's view on the conformity of nodoca to Article 13, which defines requirements for active medical devices, Article 14, which defines requirements to protect against mechanical risks of medical devices, and Article 15, which defines requirements for medical devices that supply energy:
As described earlier in Section "2.(2).B Outline of the review conducted by PMDA" and described later in Section "4.B Outline of the review conducted by PMDA," nodoca has demonstrated appropriateness for the requirements on active medical devices, the requirements to protect against mechanical risks of medical devices, and the requirements for medical devices that supply energy to patients. Thus, PMDA concluded that nodoca conforms to Article 13, Article 14, and Article 15.

(g) PMDA's view on the conformity of nodoca to Article 17, which defines general requirements for information provision to users through information on precautions, etc.:
As described later in Section "6.B.(2) Clinical positioning of testing with nodoca," it is essential for users to use nodoca after they fully understand the clinical positioning and intended use of nodoca in order to maintain its risk-benefit balance. To this end, the clinical positioning of nodoca should be clarified in the Intended Use. In addition, sufficient information should be provided through information on precautions, etc.

PMDA comprehensively reviewed the conformity of nodoca to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for nodoca in accordance with JIS T 14971:2012 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the submitted data on risk management, taking into consideration the earlier discussions in Section "2.(3).1).B Outline of the review conducted by PMDA," Section "2.(3).2).B Outline of the review conducted by PMDA," and Section "3.B Outline of the review conducted by PMDA." PMDA concluded that there was no particular problem with the risk management.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the manufacturing process and manufacturing site of nodoca. The applicant also submitted data on the inspection during manufacturing process of nodoca to support the validity of their quality control.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process of nodoca and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted data from a clinical study conducted in 708 patients at 11 study sites using the previous generation model of nodoca (hereinafter referred to as "investigational device") in Japan. As described later, the investigational device failed to meet a protocol-defined performance target in the clinical study. For this reason, the applicant modified the software program, including [redacted], and added a monitor to the camera base in order to develop nodoca. In addition to the results of the clinical study, the applicant submitted data from an additional study to verify the performance of nodoca, using patient data collected in the clinical study after excluding ineligible data that could not be analyzed ("additional study").

6.A.(1) Clinical study (Study period, January [redacted], 20[redacted] to March [redacted], 20[redacted])

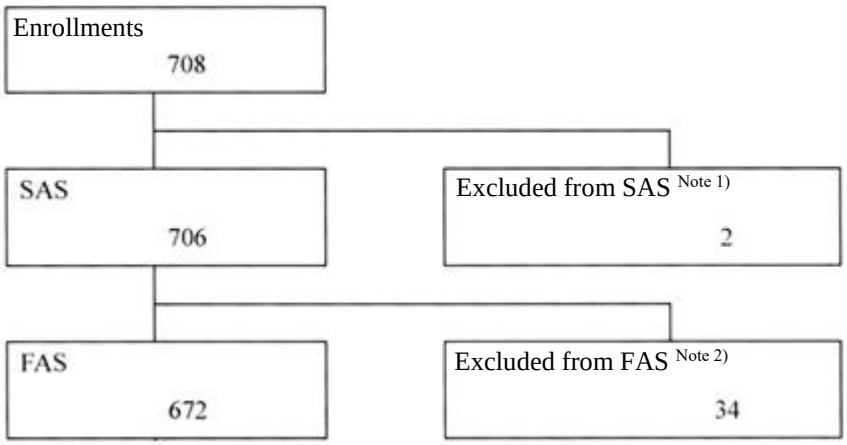
6.A.(1).1) Study design

Table 5 shows a summary of the clinical study. The clinical study is an open-label, multicenter study in patients with influenza-like symptoms in Japan. The study was conducted to compare the results of 3 types of tests (investigational device, immunochromatography, and PCR) in patients with influenza-like symptoms. A total of 708 patients were enrolled in the study. The safety was evaluated in 706 patients (safety analysis set [SAS]) after excluding 2 from 708 enrolled patients. The efficacy was analyzed using data from 672 patients (199 for PCR positive, 473 for PCR negative) (full analysis set [FAS]) after excluding 36 from the enrolled patients. Figure 7 shows the disposition of patients and the reasons for study withdrawal.

Table 5. Summary of the clinical study

Study objective	To evaluate the usefulness of the investigational device in patients with influenza-like symptoms
Study design	Open-label, multicenter study
Number of enrollments	708
Number of study sites	11 (Japan)
Study population	Inclusion criteria Patients had to meet the following major inclusion criteria to participate in the clinical study: 1. Patients or their authorized representative providing written voluntary informed consent to participate in the clinical study 2. Patients aged ≥6 years at the time of consent 3. Patients who meet at least 2 of Conditions 1) to 4) shown below, except for patients in whom Condition 1), 2), or 3) is chronic (symptoms persisting for >48 hours at the time of consent) 1) Pyrexia of ≥37.0°C, including when measured at home 2) General symptom such as arthralgia, myalgia, headache, general malaise, or inappetence 3) Respiratory symptom accompanied by cough, pharyngodynia, or nasal discharge/nasal congestion 4) Suspected influenza infection in the investigator's opinion based on close contact with patients with influenza infection, etc. Exclusion criteria Patients who met any of the following major exclusion criteria were not allowed to participate in the clinical study: 1. Patients with a mobile tooth 2. Patients who have a severe lesion in the oral cavity with which the investigational device comes into contact 3. Patients who are not a candidate for the use of the investigational device because of severe queasy in the investigator's opinion 4. Patients who have difficulty in opening the mouth for photographing with the investigational device 5. Patients with disturbed consciousness or respiratory disorder (respiratory failure) 6. Patients who plan to participate in other clinical studies or research, excluding post-marketing surveillance, between the day of consent and the end of the study period 7. Patients who are unable to comply with the protocol or receive follow-up for a psychological, family, social, or geographic reason 8. Children clearly not having enough understanding of this clinical study 9. Otherwise, patients who are ineligible for this study in the investigator's opinion
Primary endpoint	The sensitivity and specificity of the investigational device in diagnosing influenza infection compared with PCR, which is the gold standard for influenza diagnosis Target threshold: Sensitivity ≥[redacted]% (lower limit of 95% CI) Specificity ≥[redacted]% (lower limit of 95% CI)
Secondary endpoints	1. Non-inferiority of the investigational device to widely-used immunochromatography in sensitivity for diagnosing influenza infection Target threshold: False negative rate <[redacted]% (upper limit of 95% CI) Positive rate >[redacted]% (lower limit of 95% CI) 2. Superiority of the investigational device in sensitivity for diagnosing influenza infection to immunochromatography, which is known to be less sensitive during early phase of infection 3. Usefulness of pharyngeal images in AI-supported diagnosis of influenza infection 4. Pain and lacrimation associated with the investigational device compared with immunochromatography 5. Incidence of vomiturition or vomiting caused by the use of investigational device 6. Sensitivity and specificity of the AI program installed in the investigational device for diagnosing influenza infection 7. How the investigational device feels to the investigator or subject compared with immunochromatography 8. Sensitivity and specificity of the AI program for diagnosing influenza infection when images were re-selected only in subjects whose images previously used by the investigator were poor

The sample size was determined as follows: [redacted] subjects were needed to have positive PCR results when the threshold of the lower limit of the 95% confidence interval of sensitivity, the primary endpoint, exceeds [redacted]%, with a percent expectation with investigational device of [redacted]% and a power of [redacted]%. On the other hand, [redacted] subjects were needed to have negative PCR results when the threshold of the lower limit of the 95% confidence interval of specificity exceeds [redacted]%, with a percent expectation with investigational device of [redacted]%, and a power of [redacted]%. Allowing some dropouts and considering the secondary endpoints, the target sample size of 700 was determined.



Note 1)	Reason for exclusion: Incomplete informed consent form (n = 2)		
Note 2)	Reason for exclusion	1	No image selected for AI diagnosis (n = 18)
		2	Reflection of black dots (n = 4)
		3	Photographing more than the specified number of times (n = 2), no image selected after photographing (n = 2), blurry image (n = 2)
		4	Others (n = 6)

Figure 7. Disposition of subjects and the reasons for study withdrawal

6.A.(1).2) Patient characteristics

Table 6 shows the characteristics of patients enrolled in the clinical study.

Table 6. Patient characteristics

Parameter	Category	
Total number of subjects		706
Sex (n)	Male (%)	341 (48.3%)
	Female (%)	365 (51.7%)
Age (years)	Number of subjects	706
	Mean (standard deviation)	33.8 (17.6)
	Median (minimum, maximum)	33.0 (6, 88)
Time from onset (hour)	Number of subjects	706
	Mean (standard deviation)	27.8 (31.1)
	Median (minimum, maximum)	23.0 (1, 697)
Body temperature at visit (°C)	Number of subjects	706
	Mean (standard deviation)	37.48 (0.85)
	Median (minimum, maximum)	37.30 (35.1, 40.2)
Peak body temperature after onset (°C)	Number of subjects	706
	Mean (standard deviation)	38.22 (0.80)
	Median (minimum, maximum)	38.20 (36.2, 40.7)
Prior flu vaccination	Yes (%) No (%)	300 (42.5%) 406 (57.5%)
Contact with a patient with fever or influenza infection	Yes (housemate) (%) Yes (school or workplace) (%) Yes (others) (%)	96 (13.6%) 120 (17.0%) 11 (1.6%)
	No (%)	485 (68.7%)
PCR	Positive (type A) (%) Positive (type B) (%) Negative (%)	150 (21.2%) 58 (8.2%) 497 (70.4%)
	Not tested (%)	1 (0.1%)

6.A.(1).3) Study results

6.A.(1).3).a) Primary endpoint

The primary efficacy endpoint of the study was the "sensitivity and specificity of the investigational device in diagnosing influenza infection compared with PCR." The protocol-defined performance targets were sensitivity of [redacted]% (lower limit of 95% CI) and specificity of [redacted]% (lower limit of 95% CI).

In FAS, the investigational device provided a sensitivity of [redacted]% (lower limit of 95% CI, [redacted]%) and a specificity of [redacted]% (lower limit of 95% CI, [redacted]%) (Table 7). The study results verified the hypothesis about specificity, but not sensitivity.

Table 7. Sensitivity and specificity of the investigational device compared with PCR (standard of truth)

Parameter	Point estimate	CI*	*P*-value**
Sensitivity	[redacted]	[redacted]	[redacted]
Specificity	[redacted]	[redacted]	[redacted]

* Accurate CI using mid-*P*-value. For sensitivity and specificity, one-sided 95% CI (lower confidence limit).

** One-sided *P*-value determined by accurate binominal test using mid-*P*-value

6.A.(1).3).b) Secondary endpoints

The key results are shown below.

i) "Non-inferiority of the investigational device to immunochromatography in sensitivity for diagnosing influenza infection"

To assess the non-inferiority of the investigational device to immunochromatography in sensitivity, the analysis results with the investigational device and those with immunochromatography were compared in 157 subjects who tested positive by both PCR and immunochromatography in FAS. The false negative rate and the positive concordance rate were determined. As shown in Table 8, the percentage of subjects who were found to be negative with the investigational device (false negative rate) was [redacted]% (upper limit of 95% CI, [redacted]%). The positive concordance rate was [redacted]% (lower limit of 95% CI, [redacted]%). Neither of the results met their respective protocol-defined thresholds, i.e., the false negative rate, the upper limit of 95% confidence interval of [redacted]%; and the positive concordance rate, the lower limit of 95% confidence interval of [redacted]%. The study failed to verify the hypothesis.

Table 8. Evaluation of the investigational device in subjects with positive PCR and immunochromatography results

Investigational device	Number of patients	Percentage (CI*)	*P*-value**
Negative	[redacted]	[redacted]% ([redacted])	>0.999
Positive	[redacted]	[redacted]% ([redacted])	>0.999

* Accurate one-sided 95% CI using mid-*P*-value. Upper confidence limit for the false negative rate (upper column) and the lower confidence limit for the positive concordance rate (lower column).

** One-sided *P*-value determined by accurate binominal test using mid-*P*-value

ii) "Superiority of the investigational device in sensitivity for diagnosing influenza infection to immunochromatography, which is known to be less sensitive during early phase of infection"

The sensitivity of the investigational device was compared to that of immunochromatography in subjects with a positive PCR result by time after onset (every 6 hours) based on the information on the medical questionnaire. As shown in Table 9, a comparison of the sensitivity between immunochromatography and the investigational device in 199 subjects with a positive PCR result in FAS by category of time after onset revealed no significant difference between these tests by the time after onset, showing no superiority of the investigational device to immunochromatography in sensitivity.

Table 9. Comparison of sensitivity between tests in subjects with a positive PCR result by category of time after onset (every 6 hours)

Time after onset	Test	Total number of subjects	Number of subjects with a positive result	Positive rate (CI*)	*P*-value**
0-6 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
6-12 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
12-18 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
18-24 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
24-30 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
30-36 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
36-42 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
42-48 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	
≥48 h	Immunochromatography	[redacted]	[redacted]	[redacted]% ([redacted])	[redacted]
	Investigational device	[redacted]	[redacted]	[redacted]% ([redacted])	

* Accurate two-sided 90% CI using mid-*P*-value.
** Accurate χ^2 test using mid-*P*-value.

iii) Pain and lacrimation associated with the investigational device compared with immunochromatography

Pain and lacrimation during specimen collection were assessed using a numerical rating scale (NRS) in 672 subjects in FAS for each testing method. As shown in Table 10, the mean NRS score was 5.1 for immunochromatography and 0.8 for the investigational device, indicating that the investigational device is associated with milder pain than immunochromatography.

Table 10. Pain associated with the investigational device compared with immunochromatography

Parameter	Immunochromatography	Investigational device	Difference*	*P*-value**
NRS	5.1	0.8	4.3	<0.001

* Immunochromatography - Investigational device
** Paired one-sided t-test (upper)

A total of 373 subjects (55.5%) experienced lacrimation associated with immunochromatography and no lacrimation associated with the investigational device, while 3 subjects (0.4%) experienced no lacrimation associated with immunochromatography and lacrimation associated with the investigational device, indicating a significantly higher incidence of lacrimation associated with immunochromatography (Table 11).

Table 11. Comparison of the incidence of lacrimation between immunochromatography and the investigational device

Immunochromatography	Investigational device		Total	*P*-value*
	Lacrimation	No lacrimation		
Lacrimation	46 (6.8%)	373 (55.5%)	419 (62.4%)	<0.001
No lacrimation	3 (0.4%)	250 (37.2%)	253 (37.6%)	
Total	49 (7.3%)	623 (92.7%)	672	

* McNemar testing

iv) "Incidence of vomiturition (including vomiting reflex) and vomiting caused by the use of investigational device"

The camera, a component of the investigational device, needs to be inserted into the pharynx to take pharyngeal images. The incidence of vomiturition or vomiting was investigated in FAS. Vomiturition was observed in 9 subjects (incidence, 1.3%). No subject experienced vomiting (Table 12).

Table 12. Incidence of vomiturition or vomiting

Parameter	Number of subjects with event	Incidence (CI*)
Vomiturition	9	1.3% (0.7, 2.2)
Vomiting	0	0.0% (-)

* Accurate two-sided 90% CI using mid-*P*-value.

6.A.(1).3).c) Adverse events

The safety of the investigational device was evaluated in 706 of 708 enrolled subjects (SAS). Adverse events were observed in 12 subjects (12 events; incidence, 1.7%) (Table 13). All of the adverse events reported in the study were retching (vomiturition or vomiting reflex). All cases were mild in severity (Table 14).

Table 13. List of adverse events

Parameter	Total number of subjects	Number of subjects with event	Number of events	Incidence (%)	Two-sided 95% CI*
Adverse events	706	12	12	1.7	0.9, 3.0

* Accurate two-sided 95% CI by Clopper-Pearson method

Table 14. Number of adverse events by event and severity

System organ class	Preferred term	Grade			
		Mild	Moderate	Severe	Total
Gastrointestinal disorders	Retching	12 (1.7%)	0 (0.0%)	0 (0.0%)	12 (1.7%)

Medical Dictionary for Regulatory Activities (MedDRA)/J version 22.1.

6.A.(1).3).d) Malfunctions

In SAS, 16 units of the investigational device were used, and 12 malfunctions were reported. The most frequently reported malfunction was reflection of black dots in images, which was reported in 4 subjects (0.6%) (Table 15). None of the malfunctions resulted in trial-related injury in any subject.

Table 15. List of malfunctions

Malfunction	Frequency	
	Number of subjects (incidence)	Number of malfunctions
Power loss due to accidental disconnection of AC adapter	2 (0.3%)	2
Freeze after reading QR code	1 (0.1%)	1
Failure to capture images to USB/image loss	1 (0.1%)	1
Image not saved appropriately	1 (0.1%)	1
Blurry image	3 (0.4%)	3
Reflection of black dots in image	4 (0.6%)	4

6.A.(2) Additional study (Study period, [redacted], 20[redacted] to [redacted], 20[redacted])

6.A.(2).1) Reason for conducting the additional study

On the basis of the results of the clinical study, the applicant modified the investigational device as shown in Table 16. The proposed product (nodoca) is the modified version of the investigational device. This additional study was conducted in order to confirm the performance of the modified investigational device.

Table 16. Details of modification

Modification	Description
1 Change in program	• Introduction of [redacted] Introduction of a detecting method that [redacted]) Improvement of [redacted] Automation of [redacted] and standardization of [redacted]) • Improvement in preprocessing Learning of images [redacted]) and other changes
2 Change in CPU and GPU	Improvement in processing speed
3 Change in camera	• Addition of a monitor to the camera base to improve the convenience of users • Change to internal power drive

6.A.(2).2) Study design

The additional study was conducted in 659 subjects (196 with positive PCR result, 463 with negative PCR result) after excluding 13 subjects from FAS of the clinical study with ineligible data that could not be analyzed with nodoca because of the system modifications. Table 17 shows a summary of the additional study. The primary endpoint of the additional study was the same as that of the clinical study. However, some of the secondary safety endpoints of the clinical study were not evaluated in the additional study because the modifications are unlikely to alter the safety profile of nodoca as shown in Table 16.

Table 17. Summary of the additional study

Study objective	To evaluate the usefulness of nodoca in patients with influenza-like symptoms
Study methodology	Patient data collected in the clinical study will be analyzed with nodoca using the same method as that in the clinical study.
Number of subjects analyzed	659
Primary endpoint	The sensitivity and specificity of nodoca in diagnosing influenza infection compared with PCR, which is the gold standard for influenza diagnosis Target threshold: Sensitivity ≥[redacted]% (lower limit of 95% CI) Specificity ≥[redacted]% (lower limit of 95% CI)
Secondary endpoints	1. Non-inferiority of nodoca to widely-used immunochromatography in sensitivity for diagnosing influenza infection Target threshold: False negative rate ≥[redacted]% (lower limit of 95% CI) Positive rate ≥[redacted]% (lower limit of 95% CI) 2. Superiority of nodoca in sensitivity for diagnosing influenza infection to immunochromatography, which is known to be less sensitive during early phase of infection

6.A.(2).3) Study results

6.A.(2).3).a) Primary endpoint

As shown in Table 18, results of the primary efficacy endpoint in the additional study were 76.0% (lower limit of 95% CI, 70.7%) for sensitivity and 88.1% (lower limit of 95% CI, 85.5%) for specificity. The hypothesis was verified because nodoca met the protocol-defined performance targets of the sensitivity of [redacted]% (lower limit of 95% CI) and the specificity of [redacted]% (lower limit of 95% CI).

Table 18. Sensitivity and specificity of nodoca compared with PCR (standard of truth)

Parameter	Point estimate	CI*	*P*-value**
Sensitivity	76.0	70.7, 100.0	[redacted]
Specificity	88.1	85.5, 100.0	[redacted]

* Accurate CI using mid-*P*-value. For sensitivity and specificity, one-sided 95% CI (lower confidence limit).
** One-sided *P*-value determined by accurate binominal test using mid-*P*-value

6.A.(2).3).b) Secondary endpoints

i) "Non-inferiority of nodoca to immunochromatography in sensitivity for diagnosing influenza infection"

To assess the non-inferiority of nodoca to immunochromatography in sensitivity, the analysis results with nodoca and those with immunochromatography were compared in 154 subjects after excluding 3 subjects with ineligible data that could not be analyzed with nodoca because of the system modifications from 157 subjects who were found to be positive by both PCR and immunochromatography in FAS. The false negative rate and the positive concordance rate were evaluated. As shown in Table 19, the percentage of subjects who were found to be negative by nodoca (false negative rate) was 21.4% (upper limit of 95% CI, 27.3%). The positive concordance rate was 78.6% (lower limit of 95% CI, 72.7%). Neither of the results met their respective protocol-defined thresholds, i.e., the false negative rate, the upper limit of 95% confidence interval of [redacted]%; and the positive concordance rate, the lower limit of 95% confidence interval of [redacted]%. The study failed to verify the hypothesis.

Table 19. Evaluation of nodoca in subjects with positive PCR and immunochromatography results

nodoca	Number of patients	Percentage (CI*)	*P*-value**
Negative	33	21.4% (0.0, 27.3)	>0.999
Positive	121	78.6% (72.7, 100.0)	>0.999

* Accurate one-sided 95% CI using mid-*P*-value. Upper confidence limit for the false negative rate (upper column) and the lower confidence limit for the sensitivity (lower column).
** One-sided *P*-value determined by accurate binominal test using mid-*P*-value

ii) "Comparison of sensitivity between tests in subjects with a positive PCR result by category of time after onset (every 6 hours)"

The sensitivity of nodoca and immunochromatography was compared in subjects with a positive PCR result by time after onset (every 6 hours) as determined from the information on the medical questionnaire. As shown in Table 20, the comparison of sensitivity between immunochromatography and nodoca in 199 subjects with a positive PCR test in FAS by category of time after onset revealed no significant difference, showing no superiority of nodoca to immunochromatography in sensitivity.

Table 20. Comparison of sensitivity between tests in subjects with a positive PCR result by category of time after onset (every 6 hours)

Time after onset (h)	Test	Total number of subjects	Number of subjects with a positive result	Positive rate (CI*)	*P*-value**
0-6	Immunochromatography	5	3	60.0% (23.4, 89.4)	0.762
	nodoca	5	3	60.0% (23.4, 89.4)	
6-12	Immunochromatography	12	8	66.7% (42.2, 85.7)	0.177
	nodoca	12	11	91.7% (70.1, 99.2)	
12-18	Immunochromatography	33	20	60.6% (46.1, 73.8)	0.705
	nodoca	32	21	65.6% (50.9, 78.3)	
18-24	Immunochromatography	55	41	74.5% (64.0, 83.2)	0.829
	nodoca	55	42	76.4% (65.9, 84.8)	
24-30	Immunochromatography	43	39	90.7% (81.2, 96.2)	0.105
	nodoca	42	33	78.6% (66.7, 87.6)	
30-36	Immunochromatography	11	10	90.9% (67.8, 99.1)	0.738
	nodoca	11	10	90.9% (67.8, 99.1)	
36-42	Immunochromatography	18	17	94.4% (79.1, 99.4)	0.353
	nodoca	18	15	83.3% (64.9, 94.2)	
42-48	Immunochromatography	19	17	89.5% (73.0, 97.4)	0.161
	nodoca	18	13	72.2% (52.6, 86.9)	
≥48	Immunochromatography	3	2	66.7% (18.9, 96.7)	0.550
	nodoca	3	1	33.3% (3.3, 81.1)	

* Accurate two-sided 90% CI using mid-*P*-value.
** Accurate χ^2 test using mid-*P*-value.

6.B Outline of the review conducted by PMDA

6.B.(1) Efficacy and safety of nodoca

Taking account of comments from the Expert Discussion, PMDA focused on the following points in the review.

6.B.(1).1) Study design

The clinical usefulness of a new diagnostic device is generally verified in a controlled study that demonstrates the non-inferiority of the device to other "gold standard" tests by calculating endpoints such as concordance rate, sensitivity, and specificity when the tests or final diagnosis are the standard of truth (SOT). For example, nodoca would be expected to be evaluated in a study that is designed to verify the non-inferiority of nodoca to immunochromatography by directly comparing sensitivity, specificity, etc. when PCR is the SOT. However, neither a clinical study nor an additional study was conducted as a controlled study. The studies involved only a single arm to assess whether the investigational device or nodoca met the predefined performance targets. PMDA asked the applicant to explain the reason for not conducting a controlled study and the rationale for the entire study design, including the performance targets.

The applicant's explanation:
The primary endpoint of the clinical study and the additional study was the sensitivity and specificity of the investigational device or nodoca when PCR was the SOT. On the basis of the results of the prior exploratory study and publications on the performance of immunochromatography in clinical practice,[1,2,3] sensitivity of [redacted]% and specificity of [redacted]% were selected as the protocol-defined performance targets. In the clinical study, specimens for PCR, in addition to immunochromatography, are needed to be collected, and specimens were assumed to be carefully collected. Therefore, the clinical study was

not designed to directly compare with immunochromatography, considering possible differences between the results of immunochromatography in the clinical study and real-world data. However, a comparison with immunochromatography was selected as a secondary endpoint. The clinical study was designed to enable comprehensive evaluation based on the primary and secondary endpoints.

PMDA's view:
There is no particular problem with using PCR as the gold standard because it is commonly used in evaluation of the performance of *in vitro* diagnostics. The applicant referred to appropriate basic research and publications to determine the performance targets. This approach was supported in the Expert Discussion. There is no particular problem with the predefined performance targets.

6.B.(1).2) Modifications of the investigational device

In relation to modifications during the development of nodoca, PMDA asked the applicant to provide a justification for the claim that no intentional modification was made to nodoca in its development to improve its performance based on the results of the clinical study.

The applicant's explanation:
The results of the clinical study were to be in the condition of [redacted] product [redacted]. In the management of the clinical study data, a development process was used to ensure that [redacted].

PMDA accepted the applicant's explanation, considering that the applicant was under no circumstances to make intentional modifications to nodoca to improve its performance based on the results of the clinical study.

6.B.(1).3) Evaluating the efficacy of nodoca based on the results of the additional study

In relation to additional study data being handled as the main evaluation data, PMDA asked the applicant to provide a justification for the claim that modifications made to nodoca were not optimized only on the basis of the clinical study results.

The applicant's explanation:
Other than the patient data from the clinical study, the results of a study using patient data collected in the clinical research (jRCTs032190120) ("results of the study using the clinical research data") are presented (Table 21). The study using the clinical research data was conducted using data of [redacted] subjects with positive PCR and [redacted] subjects with negative PCR [redacted] of the patient data collected in the clinical research (jRCTs032190120). As a result, the sensitivity was [redacted]% with the specificity of [redacted]%. The performance results in the additional study (sensitivity 76.0%, specificity 88.1%) were comparable to those in the study using the clinical research data (sensitivity [redacted]%, specificity [redacted]%), indicating that modifications made to nodoca were not optimized only on the basis of the clinical study results.

Table 21. Results of the study using patient data collected in the clinical research (jRCTs032190120)

		PCR		
		Positive	Negative	Total
nodoca	Positive	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]

Sensitivity [redacted]% ([redacted]), specificity [redacted]% ([redacted])

PMDA's view:
PMDA accepted the applicant's justification, considering that modifications made to nodoca were not optimized only based on the clinical study results because the performance results were comparable between the clinical study and the study using the clinical research data. Taking account of comments raised in the Expert Discussion, it is reasonable to evaluate the efficacy of nodoca in the additional study.

Although the additional study failed to meet the secondary endpoint of "non-inferiority of nodoca to immunochromatography in sensitivity," nodoca met the performance targets of "sensitivity and specificity of the investigational device in diagnosing influenza infection compared with PCR" selected as the primary efficacy endpoint, showing the efficacy of nodoca to a certain extent.

6.B.(1).4) Performance in differentiating infectious diseases

PMDA asked the applicant to explain infectious diseases with lymph follicles in the posterior pharyngeal wall, other than influenza virus infection, and the performance of nodoca in differentiating these infectious diseases.

The applicant's explanation:
Lymph follicles appear in the posterior pharyngeal wall after infection with viruses, such as coronavirus, RS virus, hemolytic streptococcus, adenovirus, and enterovirus. Since the clinical study and the additional study enrolled patients with clinical symptoms of suspected influenza infection, patients with other infectious diseases with lymph follicles may also have been included in these studies. Nevertheless, sensitivity and specificity met the performance target in these studies, suggesting the good performance of the investigational device or nodoca in differentiating infectious diseases. In addition, nodoca analyzes information entered on the medical questionnaire to detect characteristic findings of influenza infection and assess based on those findings and other information. There is no problem in differentiating performance.

PMDA's view:
The applicant's explanation is understandable as an explanation based on the results of the clinical study and the specifications of nodoca. Since it is not common to take photographs of the pharynx in clinical practice, there is not enough pharyngeal image data available from patients with other infectious diseases. Currently, therefore, the performance of nodoca in differentiating viruses cannot be fully evaluated. Knowing that there is only limited data available, PMDA asked the applicant whether the performance of nodoca in differentiating influenza infection from other infectious diseases could be evaluated based on the results obtained from the clinical study.

The applicant's explanation:
Specimens collected from 659 subjects in the clinical study were subjected to PCR tests for coronavirus,[i] etc. A total of 113 of 659 subjects were positive for coronavirus. The negative concordance rate between nodoca and immunochromatography was 88% (95 of 108) of subjects (Table 22).

Table 22. Specificity test (coronavirus)

	Immunochromatography	nodoca
Positive	5	17
Negative	108	95
Total	113	113

Negative concordance rate, 95 of 108 subjects (88%)

PMDA's view:
The results presented in the additional explanation show some specificity of nodoca in differentiating influenza virus from some subtype of coronavirus. However, the protocol of the clinical study was not designed to evaluate the performance of the investigational device in differentiating influenza virus from coronavirus. The performance in differentiating influenza virus from variants of novel coronavirus (SARS-CoV-2) was not fully investigated either. The above results alone do not suffice to conclude that the performance of nodoca in differentiating influenza virus from coronavirus has been fully evaluated. In addition, no sufficient finding on the performance of nodoca in differentiating influenza infection from other infectious diseases presenting lymph follicles, other than coronavirus, has been presented. PMDA instructed the applicant to add the following precautions to the Intended Use or Precautions Concerning Indications in information on precautions, etc.: "Abnormal lymph follicles may also appear in other infectious diseases. Currently, there is no finding that nodoca sufficiently differentiates influenza infection from such infectious diseases"; and "Other tests should be performed as necessary when the possibility of other infectious disease cannot be ruled out." The applicant accepted it.

6.B.(1).5) Safety

Since evaluation in the additional study was based on patient data from the clinical study, no adverse event- or safety-related secondary endpoint was newly investigated.

PMDA's view:
The only difference between nodoca and the investigational device is the monitor at the camera base and the housing of nodoca is almost the same as that of the investigational device. These differences will not affect the directions for use. The investigational device and nodoca have no different features that may affect safety. It is possible to evaluate the safety of nodoca based on the results of the clinical study using the investigational device. As shown in the results of the clinical study using the investigational device (Table 14), the investigational device was associated with a low incidence of retching (vomiturition or vomiting reflex) and significantly lower scores for pain and lacrimation during specimen collection than immunochromatography. There is no particular concern about the safety of nodoca.

[i] HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1

6.B.(2) Clinical positioning of testing with nodoca

PMDA asked the applicant to explain the clinical positioning of nodoca based on the results of the additional study, etc. of nodoca.

The applicant's explanation:
Because the sensitivity of immunochromatography is low soon after the onset of symptoms, anti-influenza drugs are not administered in a timely manner. This is a challenge in clinical practice. In addition, immunochromatography involves insertion of a cotton swab into the pharynx or nasal cavity at the time of specimen collection, causing pain in patients. There is a need for nodoca, which causes less pain. The additional study showed the efficacy of nodoca, without any safety concern. The clinical positioning of testing with nodoca should be "a substitute for immunochromatography."

PMDA's view on the clinical positioning of nodoca:
Currently, influenza infection is diagnosed according to the "Influenza Diagnostic Manual[6]" issued by the National Institute of Infectious Diseases. As recommended by the diagnostic criteria in this manual, the season should be taken into consideration in diagnosing influenza infection, and influenza infection can be diagnosed based only on symptoms if it is obvious from the symptoms. If symptoms are not conclusive for influenza infection, immunochromatography is used at the physician's discretion. nodoca does not directly observe influenza virus. nodoca and immunochromatography use a different mechanism to detect influenza virus. In addition, the additional study failed to show the "non-inferiority of nodoca to immunochromatography in sensitivity," a secondary endpoint. For these reasons, the clinical positioning of nodoca should not be "a substitute for immunochromatography" proposed by the applicant. nodoca indicates analysis results such as "characteristic pharyngeal signs or symptoms of influenza infection detected in patients." The clinical positioning of nodoca should be "An aid to the diagnosis of influenza infection by providing reference information for physicians to observe clinical findings." PMDA instructed the applicant to change the Intended Use as shown below to ensure that healthcare professionals in clinical practice understand that the analysis result with nodoca is not synonymous with the result of immunochromatography. The applicant agreed. A diagnosis of influenza infection should be made by physicians based on a comprehensive assessment of not only the analysis result with nodoca but also clinical symptoms and other factors. A caution statement should be included in the information on precautions, etc. accordingly.

Intended Use
nodoca photographs the patient's pharynx and collectively analyzes findings of the pharynx, such as the lymph tissue (including the tonsil and lymph follicles) on the pharyngeal images and patient's medical information to detect characteristic signs and symptoms of influenza infection. nodoca is used as an aid to the diagnosis of influenza infection. nodoca is not intended to make a definite diagnosis based on analysis results alone.

PMDA instructed the applicant to change the analysis result screen of nodoca in association with the above change in the Intended Use so that healthcare professionals clearly see that symptoms or signs of influenza infection are being detected. The applicant agreed.

According to the principle that nodoca detects lymph follicles that are characteristic of influenza infection, its sensitivity is expected to decrease with time as lymph follicles heal over time. On the other hand, the sensitivity of immunochromatography is low during the early phase of the influenza infection because the amount of antigen produced is low. The sensitivity increases over time as the amount of antigen increases with time. Figure 8 is a graph, showing the data in Table 20 with time after onset (every 12 hours) on the horizontal axis and sensitivity on the vertical axis. Although the sample size was limited, the graph shows a tendency to support the above characteristics of these tests.

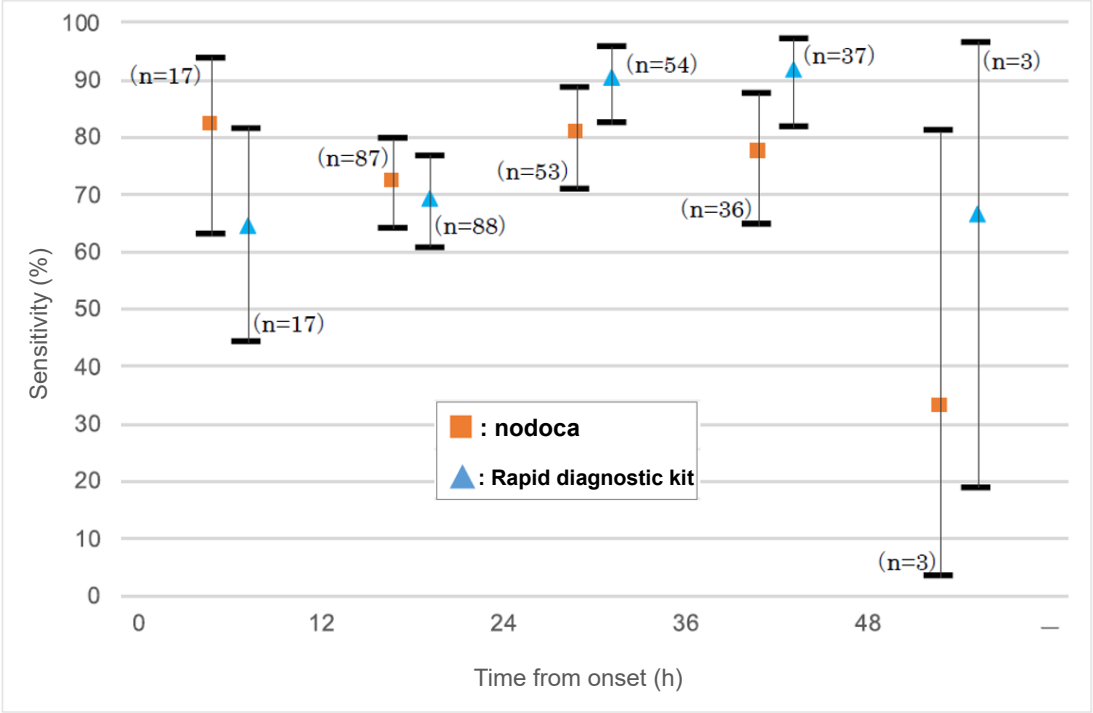


Figure 8. Sensitivity of nodoca and immunochromatography every 12 hours after onset

To ensure that the characteristics of nodoca are accurately communicated to users, PMDA instructed the applicant to include Figure 8 and a caution statement in the information on precautions, etc. so that users are aware of a possible change with time in the sensitivity of nodoca after the onset of influenza infection. The applicant agreed.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant submitted no data regarding a plan for post-marketing surveillance, etc. for the following reasons.

nodoca can be easily operated using a similar procedure as that of pharyngoscopy. The results of the clinical study revealed neither a particular safety concern nor a risk of potential unknown adverse events. No use-results survey of nodoca is required in a post-marketing setting.

7.B Outline of the review conducted by PMDA

PMDA's view:

As described in Section "2.(3) Safety" and Section "6 Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare," there is no particular safety concern with nodoca that should be newly investigated in a post-marketing setting. The clinical study was conducted in an environment close to actual clinical practice involving patients who were expected to undergo testing with nodoca in clinical practice. Since the additional study was conducted using data from these patients, the efficacy of nodoca in the intended patient population was evaluated in the additional study.

For these reasons as well as taking account of comments raised in the Expert Discussion, PMDA concluded that nodoca did not need to be designated as a medical device subject to a use-results survey.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

The medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Law No. 145 of 1960). On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

A system called "nodoca" collectively analyzes information on medical questionnaires entered by users and information on pharyngeal image captured by a camera to detect characteristic signs and symptoms of influenza infection in the diagnosis of patients with suspected influenza infection. The main issues in the reviews of nodoca were (1) the efficacy and safety of nodoca, and (2) the clinical positioning of nodoca. PMDA's view based on the comments from the Expert Discussion is described in the following sections.

(1) Efficacy and safety of nodoca

The efficacy and safety of nodoca were evaluated based on the followings: (1) results of the clinical study using the investigational device, (2) results of the additional study conducted using the patient data collected in the clinical study after excluding ineligible data that could not be analyzed, and the same endpoints as those used in the clinical study.

The primary endpoint of each study was the "sensitivity and specificity of the investigational device or nodoca in diagnosing influenza infection compared with PCR." The lower limit of the 95% confidence interval in the clinical study was [redacted]% for sensitivity and [redacted]% for specificity. The lower limit of the 95% confidence interval of specificity met the protocol-defined performance target of [redacted]%, while that of sensitivity did not meet the predefined threshold of [redacted]%. On the basis of these results, the applicant modified the investigational device and conducted an additional study using patient data collected in the previous clinical study after excluding ineligible data that could not be analyzed. The lower limit of the 95% confidence interval in the additional study was 70.7% for sensitivity and 85.5% for specificity,

meeting the protocol-defined respective performance targets. The applicant determined that nodoca demonstrated the efficacy.

The safety of nodoca was evaluated based on adverse events and malfunctions reported in the clinical study because the only difference between nodoca and the investigational device is the monitor at the camera base and the housing of nodoca is almost the same as that of the investigational device; these differences do not affect the directions for use, and the investigational device and nodoca have no different features that may affect safety. In the clinical study, retching (vomiturition or vomiting reflex) was reported in 12 (1.7%) of patients as an adverse event. All of the cases resolved soon, and no noteworthy adverse event was reported. The safety risk for the efficacy of nodoca is clinically acceptable.

On the basis of the above, PMDA has concluded that there is no particular problem in approving nodoca as one of the options to help physicians make a diagnosis of influenza infection.

(2) Clinical positioning of testing with nodoca

The applicant developed nodoca with the concept of aiding physicians to diagnose influenza infection in a more minimally invasive manner by analyzing pharyngeal images with AI technology to detect characteristic signs of influenza infection. The clinical positioning of nodoca proposed by the applicant was "a substitute for immunochromatography."

Because nodoca does not directly examine influenza virus, nodoca is a different product from immunochromatography. In addition, the additional study failed to show the "non-inferiority of nodoca to immunochromatography in sensitivity," a secondary endpoint. Rather, the analyzed information of nodoca indicates "characteristic pharyngeal signs or symptoms of influenza infection detected in patients." The clinical positioning of nodoca, therefore, should be "an aid to the diagnosis of influenza infection by providing reference information for physicians to observe clinical findings," but not as "a substitute for immunochromatography."

According to the principle that nodoca detects lymph follicles that are characteristic of influenza infection, users must fully understand the characteristics of nodoca prior to its use. A caution statement should be included in the information on precautions, etc. to ensure that physicians make a diagnosis of influenza infection based on comprehensive assessment of not only the analysis result with nodoca but also clinical symptoms and other factors.

As a result of the above review, PMDA concluded that nodoca may be approved after modifying the intended use or indication as shown below.

Intended Use

nodoca photographs the patient's pharynx and collectively analyzes findings of the pharynx, such as the lymph tissue (including the tonsil and lymph follicles) on the pharyngeal images and patient's medical information to detect characteristic signs and symptoms of influenza infection. nodoca is used as an aid to the diagnosis of influenza infection. nodoca is not intended to make a definite diagnosis based on analysis results alone.

The product is not classified as a biological product or a specified biological product. The product is not designated as a medical device subject to a use-results survey.

PMDA has concluded that this application should be deliberated at the Subcommittee on Software as a Medical Device.

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