Trial Protocol (Final)

Phase I/II investigator-initiated clinical trial of the human papillomavirus (HPV)-targeting immunotherapeutic agent IGMKK16E7 on patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN2-3)

Clinical Trial Protocol No.: IGMKK/16E7/P1-2
Phase of development: Phase I/II Clinical Trial
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List of abbreviations

Abbreviation	Official name, etc.
AGCs	Atypical glandular cells
ASC-H	Atypical squamous cell, cannot rule out high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
CIN	Cervical intraepithelial neoplasia
CR	Complete response
CTL	Cytotoxic T lymphocyte
CTCAE	Common Technology Criteria Adverse Event
EDC	Electronic Data Capture
FAS	Full Analysis Set
GALT	Gut-associated lymphatic tissue
GCP	Good Clinical Practice
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LSIL	Low-grade squamous intraepithelial lesion
MedDRA	Medical Dictionary for Regulatory Activities
NILM	Negative for intraepithelial lesion or malignancy
NE	Not evaluable
PD	Progressive disease
PPS	Per Protocol Set
PR	Partial response
SCC	Squamous cell carcinoma
SD	Stable disease
SIL	Squamous intraepithelial lesions

1. Outline of the clinical trial protocol

Title of the clinical trial:

Phase I/II investigator-initiated clinical trial of the human papillomavirus (HPV)-targeting immunotherapeutic agent IGMKK16E7 on patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN 2-3)

Purpose of the clinical trial:

IGMKK16E7 (study drug) will be orally administered to patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN2-3) to determine its safety and clinical dosage. Furthermore, this clinical trial will investigate the correlation between E7 protein expression in the precancerous cervical lesion and the effectiveness of IGMKK16E7.

Clinical trial design:

A placebo-controlled randomized double-blind comparative study (Phase I/II clinical trial) of the following four parallel dose groups: placebo, low-dose (0.5 g/administration/day), intermediate-dose (1.0 g/administration/day), and high-dose (1.5 g/administration/day).

Clinical trial implementation system:

Refer to attachments 1 and 2

Clinical trial period:

March 2019 to March 2023 (planned)

The start of the clinical trial shall be the time of enrollment of the first case. The end of the clinical trial shall be the final assessment of the last subject.

Target disease:

High-grade HSIL/CIN 2-3

Target number of subjects:

This clinical trial shall examine 164 cases (placebo, low-dose (0.5 g/administration/day), intermediate-dose (1.0 g/administration/day), and high-dose (1.5 g/administration/dose) groups; each administration group shall comprise 41 cases and each group shall have 10 cases with HSIL/CIN2 at the time of enrollment).

[Setting basis]

Based on the results of the GLBL-101c clinical study targeting HSIL/CIN3, the response rate for HSIL/CIN3 (expected value) in this clinical trial is assumed to be as follows: 10%, 20%, 30%, and 40% for the placebo, low-dose, intermediate-dose, and high-dose groups, respectively. Furthermore, the response rate for HSIL/CIN2 (expected value) is assumed to be the same as that for CIN3.

For CIN3 cases, the minimum number of subjects exceeding the detection power of 80% will be calculated using the Cochran-Armitage Test at 5% significance. The number of simulations shall be 5000. When the detection power was set at the ratio and the p-value of both sides is below 0.05 among the corresponding number of simulations, the number of cases per group was calculated to be 28. Based on the assumption that the dropout rate will be approximately 10%, the number of subjects per group will be 31 cases. Therefore, the target number of HSIL/CIN3 subjects in this clinical trial will be 31 cases per group. Furthermore, a clinical study targeting CIN3 cases included HSIL and moderate dysplasia (CIN2) revealed that the disease downgraded to low-grade squamous intraepithelial lesion (LSIL) or negative for squamous intraepithelial lesion or malignancy (NIML). Therefore, the target of this clinical trial was HSIL/CIN2-3. To explore the effectiveness of IGMKK16E7 against HSIL/CIN2, the number of HSIL/CIN2 subjects was set to 10 cases.

Therefore, the target number of subjects in this clinical trial was set to 41 cases for each of the four groups, totaling 164 cases.

Moreover, based on the mechanism of action of IGMKK16E7, E7 expression in the lesion site may be the effect prediction factor of the drug. Therefore, the examination of the correlation between E7 expression and IGMKK16E7 will be the secondary aim of this clinical trial. From this point of view, the examination can be performed with the selected number of subjects in this clinical trial.

Study drug:
IGMKK16E7 and placebo capsules

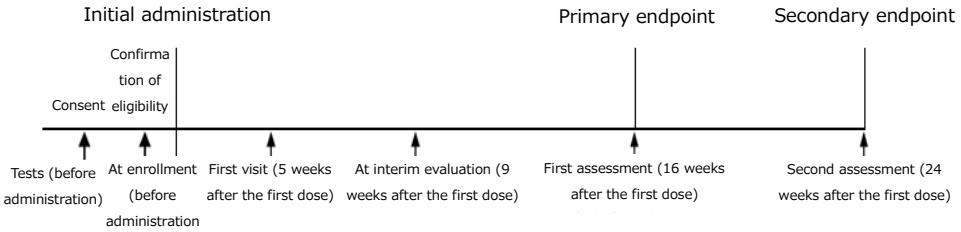
IGMKK16E7 is a representation of the E7 antigen (variant: ▲Rb) of HPV 16 on the lactic acid bacterial cell surface. The study drug induces an E7-specific immunity (T lymphocyte) on the mucosal surface against E7 by delivering an E7 antigen to the intestinal tract through oral administration. As the drug may induce the function of the E7-specific immunity (T lymphocyte), a synergetic cytotoxic effect against the cervical precancerous and tumor cells through natural killer (NK) cells, etc. is expected.

Clinical trial period and follow-up survey for each patient:

The clinical trial period will be 16 weeks from the first-dose Furthermore, after the diagnosis by the attending physician of the facility at week 16 post-first dose, the cases will be followed up until 24 weeks, except for cases determined to be CIN3 or invasive cancer.

Clinical trial title:

1. Clinical trial flow



2. Dosage and dose

Three sticks of the study drug will be administered once a day before breakfast. In principle, the consecutive administration of the study drug for 5 days is considered one cycle. The drug is administered for four cycles (Days 1–5, 8–12, 22–26, and 50–54). However, on day 1, the study drug will be administered in the hospital in between meals.

The permissible range for the administration days is as follows:

If the subjects forget to take the study drug before the meal on the day of the administration, they are allowed to take it before lunch or dinner on the same day. If the subjects forget to take the study drug at each cycle, they are allowed to take the drug as follows:

First cycle: If the subjects forget to take the study drug between days 2 and 5, they are allowed to take it until days 6 to 7.

Second cycle: If the subjects forget to take the study drug between days 8 and 12, they are allowed to take it until days 13 to 14.

Third cycle: If the subjects forget to take the study drug between days 22 and 26, they are allowed to take it until days 27 to 28.

Fourth cycle: If the subjects forget to take the study drug between days 50 and 54, they are allowed to take it until days 55 to 56.

3. Suspension or discontinuation of the clinical trial

The following measures will be taken for the safety of patients and ethical considerations.

(1) Five weeks after receiving the first administration, subjective symptoms (confirmation of health journal) and other findings will be confirmed. Additionally, clinical tests will be conducted, and guidance will be provided to the patient. Cases suspected of infiltrative cancer at the time of intermediate evaluation (9 weeks after the first administration) will undergo biopsy. If cervical cancer is detected, the participation of the corresponding patient in the clinical trial will be immediately terminated and surgical treatment will be conducted irrespective of the type diagnosed at enrollment.

(2) As the study drug has not been applied in a clinical setting, in the event of an unknown serious adverse event that may have been caused by the study drug (including events later found to have been caused by the study drug after the initial report), the clinical trial coordinator must submit a report to the safety review board to confirm the opinion of all boards on the continuation of the entire clinical trial, the continuation of the drug administration to the subject, the necessity to revise the clinical trial protocol, the necessity to revise the informed consent form, the enrollment of new patients, and other relevant matters. After confirming the opinion of all the boards, the clinical trial coordinator will determine the response to the clinical trial based on the occurrence

of the corresponding event and contact the investigators of all participating medical institutions (for details, please refer to the separately attached procedures). Furthermore, the subinvestigators shall check the health status of the subjects, etc. as needed, and confirm via phone call, considering the response policy contacted by a clinical trial coordinator and the background of the subject.

The safety review board will convene once 80 subjects have been enrolled to evaluate the safety of the study drug. Furthermore, if the clinical trial investigator deems it necessary, this board will convene regardless of the regulations required for the corresponding board to convene.

4. Interim analysis

No interim analysis will be performed in this clinical trial.

Eligibility criteria:

Selection criteria:

This clinical trial will target patients who meet all of the following criteria:

(1) Women with type 16 infection determined using HPV genotyping of cells collected from the cervix (not necessarily type 16 infection alone)
(2) Patients histologically diagnosed with HSIL/CIN2 or HSIL/CIN3
(3) Patients aged between 20 and 45 years at the time of obtaining informed consent
(4) Subjects who are outpatients at the time of obtaining informed consent
(5) Patients who have provided their voluntary written consent after receiving sufficient explanation about clinical trial participation

Exclusion criteria:

Patients who meet any of the following conditions will not be enrolled in this study:

(1) Patients with an aberrant immune function who require treatment or are receiving treatment for immunosuppression
(2) Patients who were cytologically confirmed to have squamous cell carcinoma (SCC)
(3) Patients planning to undergo laser vaporization
(4) Patients planning to undergo cervical conization
(5) Patients with serious acute diseases
(6) Patients with a history of hypersensitivity to foods containing lactic acid bacteria (yogurt, etc.), lactic acid bacterial preparations, or soybean lecithin (soybean products: tofu, etc.)
(7) Patients allergic to milk
(8) Patients who are pregnant or who may be pregnant
(9) Patients who are currently nursing
(10) Patients who received other study drugs or unapproved treatments within 4 weeks before the start of the study drug administration
(11) Patients who have been previously administered with GLBL-101c and IGMKK16E7
(12) Patients diagnosed with or suspected of having chronic or acute pancreatitis at the start of the study drug administration
(13) Other patients who are judged to be ineligible by the investigator/subinvestigator

Setting the endpoints:

[Primary outcomes]: (1) Safety and (2) efficacy in each treatment group (histopathological regression at 16 weeks after the first dose: All patients and according to CIN at enrollment)

a. Safety

Type of adverse event, incidence rate, severity, seriousness, the period from the start of drug administration to the date of symptom onset, and duration

b. Efficacy

Complete response (CR) rate and CR + partial response (PR) (CR+PR) rate for each group using the histopathological improvement indicators of CIN.

Complete response (CR): Regression to normal

Partial response (PR): Regression to CIN1

Stable disease (SD): No change from HSIL/CIN2 at enrollment to HSIL/CIN2, no change from HSIL/CIN3 at enrollment, or no change from HSIL/CIN3 to HSIL/CIN2

Progressive disease (PD): Progression from HSIL/CIN2 at enrollment to HSIL/CIN3, progression to cervical cancer irrespective of classification at enrollment

Not evaluable (NE): Unable to determine as CR, PR, SD, or PD

Cases whose participation was discontinued upon detection of cervical cancer during the interim assessment will be considered PD, and their data will be included in the 16-week tabulation.

[Setting basis]

This clinical trial aims to examine the safety and efficacy of IGMKK16E7 (determination of recommended dose). Furthermore, the recommended dose will be estimated using the regression rate, which is an indicator of the therapeutic effect of IGMKK16E7 on the lesion. When assessing the regression rate, the CR rate and CR+PR rate will be used irrespective of the initial HSIL/CIN assessment, considering the clinical significance of changes in HSIL/CIN assessment. Furthermore, in case of change from HSIL/CIN3 to HSIL/CIN2 (both are judged to be in the same category in the Bethesda classification), the evaluation in this trial will be set as SD.

[Secondary endpoints]:

(1) Efficacy: The following will be tabulated for all cases and grouped by CIN at enrollment.

a. Histopathological regression rate (CR or CR+PR rates) at 24 weeks after the first dose

b. Presence of HPV E7-specific immune response at 16 weeks and 24 weeks after the first dose

c. Change in HPV 16 E7 molecule protein expression level: at 16 and 24 weeks after the first dose.

d. Improvement rate through cytological diagnosis at 16 weeks and 24 weeks after the first dose

Response: Regression to LSIL, ASC-US or NILM

SD: No change from HSIL

PD: Progression to SCC

NE: Change to atypical gland cells (AGCs) or atypical squamous cells cannot rule out HSIL (ASC-H)

e. Viral clearance: HPV16 negative at 16 weeks and 24 weeks after the first dose

f. The rates of "CR," PR," "SD," "PD," and "NE" in the pathological improvement indicator of CIN at weeks 16 and 24 after the first dose

g. Disease control rate: Rate of improvement to CIN2 or lower at 16 weeks and 24 weeks after the first dose

Discontinuation criteria for individual subjects:

The investigator/subinvestigator will discontinue the trial participation of the subject if any of the following criteria apply to the subject during the study period:

1. If the subject requests to withdraw consent
2. If the clinical trial is suspended due to the circumstances (relocation, change of physician or hospital transfer, busy schedule, unable to follow-up, etc.) of the subject
3. If it has been clarified that the subject is not eligible after the start of the clinical trial
4. If the investigator/subinvestigator deems it necessary to discontinue the trial participation of the subject in the event of an adverse event (including progression of complication or accident)
5. If the clinical trial cannot be continued due to the progression of symptoms of the primary disease
6. If the subject was identified to be pregnant
7. If there is a significant deviation from this protocol and it is determined that the subject is NE
8. If the investigator/subinvestigator judges that it is difficult to continue the clinical trial and that it is appropriate to discontinue the clinical trial

Contraindicated medications and therapies:

After obtaining informed consent, the following treatments are prohibited until 16 weeks at the end of the study period.

1. Other vaccinations (although influenza, rubella, measles, and SARS-CoV-2 (new coronavirus) vaccines can be used together)
2. Gamma globulin preparation
3. High dose of steroids
4. Cyclosporine preparations, etc.
5. Imiquimod etc. (topical agent)
6. Radiotherapy
7. Laser vaporization
8. Cervical conization
9. Other study drugs and therapies

However, in an emergency, if it is deemed necessary for the treatment of patients, it can be used in combination while carefully observing the condition of the patient.

Compatible therapies:

In principle, drugs other than those listed in "contraindicated drugs and therapies" stipulated in this protocol can be concomitantly used. Furthermore, the subject is advised not to change the medication that they are currently taking.

Table 1 Observation and investigation during the study (follow-up) period and test items

Observation/survey and test items during study period (follow-up)

Item	Eligibility confirmation period	Study period										Follow-up period		At discontinuation
	Initial visit	Administration start date Day 1	(Week 1) Day 2～7	(Week 2) Day 8～14	(Week 3) Day15～21	(Week 4) Day22～28	(Week 5) Day29～35	(Week 6-7) Day36～49	(Week 8) Day 50～56	(Week 9) Day 57～63	(Week 10-15) Day64～105	(Week 16) Day106～112	(Week 17-23) Day 113～161	(Week 24) Day 162～168	
Arrival	○	○					●			●		●		◎	●
Permitted scope of arrival							Day29～42			Day57～77		Day106～126[k]		Day162～182[k]	
Prescription of the clinical trial		●													
Administration of the study drug		←→	←→	←→		←→			←→						
Confirmation of drug status							●			●					
Consent	○														
Confirmation of selection/exclusion criteria	○[a]	○													
Case enrollment		○													
HPV genotype test (for eligibility confirmation)	○[b]														
HPV genotype test (Central test)		○[c]										●		◎	●
Histology (Central pathological judgment)	○[b]											●		◎[j]	●
Histology (Implementing medical institution judgment)										△					
Cytology	○[b]									●		●		◎	●
Colposcopy	○[b]									●		●		◎	●
Laboratory test		○[d, e]					●			●		●		◎	●
Pregnancy reaction (Serum hCG)		○[d, e]										●			●
HIV test	○[f]														
HPV16E7 protein expression level		○[c]										●		◎	●
E7 protein expression (cervical cells)		○[g]													
HPV E7 Atypical immune reaction		○										●		◎	●
Subjective symptoms[h]/objective findings		●	●	●	●	●	●	●	●	●	●	●		◎	●
Concomitant drugs/therapies	←											→			
Confirmation of medical history and complications	○														
Confirmation of adverse events[i]		←→										←→	←- - - - -	←- - - - -	

○: Item confirming the implementation or test results before the start of administration ●: Item implemented after the start of administration △: Item implemented in case of suspected infiltrative cancer ◎: Item implemented only on corresponding cases and judged cases in the follow-up survey at week 16 after administration

a: Implement test for selection/exclusion criteria confirmation after obtaining consent b: Confirm eligibility based on corresponding data in case there are data within 90 days before obtaining consent (data at another hospital, in-hospital data not required). Implement the test after obtaining consent in case there are no corresponding data.

c: Implement test using E7 protein expression specimen collected on the same day d: Confirm that there is no problem with the test results (no possibility of pregnancy) before prescription of the study drug. The administration of the study drug shall start within 10 days from the date when the corresponding laboratory test was conducted. e: Perform the laboratory test on the date of consent. If the start date of administration was within 10 days from the date when the corresponding test was conducted, there is no need to conduct a new test on the date of administration. f: Perform at initial visit or on the start date of administration. Confirm that the subject does not have human immunodeficiency virus (HIV) infection before prescribing the study drug. Start the administration of the study drug within 14 days from the date when the corresponding test was conducted. g: Perform human papilloma virus (HPV) genotyping on the same day using the collected specimen. h: The subject shall record the subjective symptoms in the health journal. i: Confirm the entries in the health journal during administration period. The follow-up period (from week 17) after the end of the study period shall only confirm adverse events that were clearly caused by the study drug. j: For subjects judged to be healthy at week 16 after the initial administration, perform the test only if cervical precancerous lesion area was confirmed in the colposcopy conducted on the same day (week 24). k: In case retest is necessary due to the condition of the specimen, retest is permitted within 14 days from the date when the initial test was performed.

Analysis set:

[Efficacy analysis set]

Full Analysis Set (FAS)

A set in which the following cases were excluded among the enrolled subjects:

(1) Examples of serious Good Clinical Practice (GCP) violations (breach of consent acquisition, breach of contract, and non-deliberation by the Institutional Review Board (IRB))
(2) Cases violating eligibility criteria and those who were unblinded using non-regular procedures
(3) Study drug-naïve cases
(4) Cases with no efficacy data

Per Protocol Set (PPS)

A set in which the following cases were excluded among the enrolled subjects:

(1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, and non-deliberation by the IRB)
(2) Serious protocol violations (eligibility criteria violations, serious regulatory violations related to compatible medications, serious treatment violations, assignment violations, and cases unblinded using non-regular procedures)
(3) Patients who do not meet the minimum values set in the clinical trial protocol
(4) Patients who took less than 80% of the study drug throughout the study period
(5) Cases with no efficacy data

[Safety analysis set]

A set in which the following cases were excluded from all enrolled cases:

(1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, and non-deliberation by the IRB)
(2) Study drug-naïve cases
(3) Cases in which all endpoints related to safety assessment after the start of the clinical trial cannot be used

Assignment of subjects to treatment groups:

Enrolled subjects will be randomized in a 1:1:1:1 ratio to each of the four dose groups. Randomization will be performed with the use of a Web-based system by minimization (dynamic balancing) and stratified according to center, CIN grading (CIN2 or 3) and HPV genotype (HPV16 single or HPV16 and other types).

The following three factors are used as assignment adjustment factors:

(1) Diagnosis (HSIL/CIN2 and HSIL/CIN3)
(2) HPV genotype (type 16 single infection, multiple infections, including type 16)
(3) Facilities (4 facilities)

Clinical trial design: (The first and second cases will be enrolled at a single facility at the Nihon University Itabashi Hospital)

(1) The interval between the recruitment of the first and second subjects will be determined after safety confirmation at the end of one cycle. Subjects are selected such that the assignment conditions for the first and second subjects are the same. (Ratio factor: HPV type 16 single infection and patients with HSIL/CIN3)
(2) Confirmation of the safety of the first subject: The safety of the subject will be confirmed at the end of the five-day administration of the first cycle of the first case.(Confirmation method: Subjects will be contacted via phone or email on days 5–7 (the final day of the acceptable range of administration) to confirm their health status.)
(3) Enrollment of the second subject and confirmation of health status: The health status of the subject will be confirmed after taking the drug for five days using the same method as that used for the first case.
(4) After confirming the health status of these two cases, the third and subsequent cases will be sequentially included.

2. Trial Implementation System

2.1. Name, title, and address of the investigators of the medical institution (for each participating institution)

See "Clinical trial implementation system (Attachment 1)"

2.2. Name, address, and scope of work of the clinical trial contractor

See "Clinical trial implementation system (Attachment 1)"

2.3. Name and location of the medical institution

See "List of Implementing Facilities (Attachment 2)"

3. Background, process, and rationale for the clinical trial plan

3.1. Treatment for cervical cancer

Cervical cancer is the second most common cancer among women worldwide after breast cancer. As the HPV gene is detected in ≥99% of cervical cancer cases, it is considered to be the etiological agent for cervical cancer. Approximately 15 high-risk HPV subtypes are associated with cervical cancer, and approximately half of cervical cancer cases test positive for HPV type 16. Approximately 10% of HPV-infected individuals progress to cervical intraepithelial neoplasia (CIN)[1]. CIN stages are divided into mild (CIN1), moderate (CIN2), and severe (CIN3) stages. As CIN progresses to the CIN2-3 stage, the expression of E6 or E7, a protein associated with carcinogenesis, gradually increases, contributing to the progression to cervical cancer (the peak age at which cervical cancer occurs is 35 years). Among the viral genes, E6 and E7 are always expressed in cancer cells, indicating that they are involved in carcinogenesis and the maintenance of cancer traits[2].

The precursor lesions of cervical SCC are commonly referred to as CIN. However, in The General Rules for Clinical and Pathological Management of Uterine Corpus Cancer Pathological Edition (Japan Society of Obstetrics and Gynecology The Japanese Society of Pathology Edition, July 2017[3]) (General Rules), the term squamous intraepithelial lesions used in the Bethesda classification, which is a guideline for cytological reporting, was adopted and used as the histological diagnosis name (Table 2). In this clinical trial, the histological diagnosis name based on the General Rules will be used.

Table 2 Classification of precursor lesion of cervical squamous cell carcinoma

Histological diagnosis name	Abbreviation	Pathological findings	CIN classification
Low-grade squamous intraepithelial lesion	LSIL	Mild dysplasia	CIN1
High-grade squamous intraepithelial lesion	HSIL	Moderate dysplasia	CIN2
		High-grade dysplasia	CIN3
		Intraepithelial carcinoma	CIN3

Currently, therapeutic drugs are not available for patients with CIN (previously infected) at the HPV persistent infection stage. Therefore, patients at this stage are recommended to undergo follow-up examinations with cytology and colposcopy once every 3 to 6 months. The rate of progression from CIN1 to CIN3 or higher is 12%–16% with an approximately 90% remission rate in women aged under 30 years. CIN2 has a progression rate of 22%–25% and is likely to regress in women aged under 30 years and pregnant women. However, high-risk HPV-positive patients, including those infected with type 16, have a high probability of progression to CIN3 within 5 years (40.5%). In particular, type 16-positive, type 18-positive, or type 33-positive patients are reported to be at a high risk of progression[4]. Therefore, surgical

treatment is selected at the CIN3 stage. Surgical procedures include cervical conization and laser vaporization. Cervical conization is associated with postoperative complications, such as dysmenorrhea due to cervical stenosis, infertility due to cervical mucus adenectomy, and miscarriage/premature birth due to cervical asthenia. Laser vaporization, which is associated with a high recurrence rate, does not allow a histopathological diagnosis[5].

3.2. History of IGMKK16E7 development

3.2.1. Therapeutic vaccine against HPV infection

Various groups have attempted research and development to meet the need for a therapeutic vaccine for HPV infection, and all the developed vaccines are injectable preparations. Although clinical trials of various therapeutic vaccines have been conducted overseas for more than 10 years, a clinically applicable vaccine with high efficacy is not available[6]. This is attributed to the insufficient induction of cytotoxic T cells (CTLs) on the cervical mucosa, which is the focal site, by these vaccines. The basic experimental system used in therapeutic vaccine development involves tumor-bearing mice obtained by subcutaneously inoculating HPV-induced E6/E7 immortalized cells. In this case, systemic immunity alone exerts an anti-tumor effect without the involvement of mucosal immunity. The ability of mucosal immunity to induce CTL has not been investigated. Additionally, the induction of mucosal immunity is considered essential for the therapeutic effect on CIN3 in the human cervical epithelium. Thus, intramuscular and subcutaneous vaccines currently under development may not be suitable.

3.2.2. Immunotherapeutic agent: IGMKK16E7

IGMKK16E7 (study drug) is an HPV 16-derived E7 protein (mutant: ▲Rb) expressed in lactic acid bacterial (*Lacticaseibacillus paracasei*) cells.

Lactic acid bacteria, which are associated with high safety and food applications, were selected as the study drug carriers (vectors) of the E7 antigen to the intestinal mucosa. Based on the mechanism through which immunity induced by the intestinal mucosa is homed to the uterus, [7] IGMKK16E7 is an immunotherapeutic agent that directs lymphocytes involved in gut-associated lymphoid tissue to the local cervical mucosa.

Additionally, this study drug induces E7-specific immunity (T lymphocytes) against E7 on the mucosal surface by delivering the E7 antigen to the intestinal tract after oral administration as enteric-coated soft granule capsules. As this drug induces the function of the E7-specific immunity (T lymphocyte), a synergetic cytotoxic effect on the cervical precancerous and tumor cells through NK cells, etc. is expected.

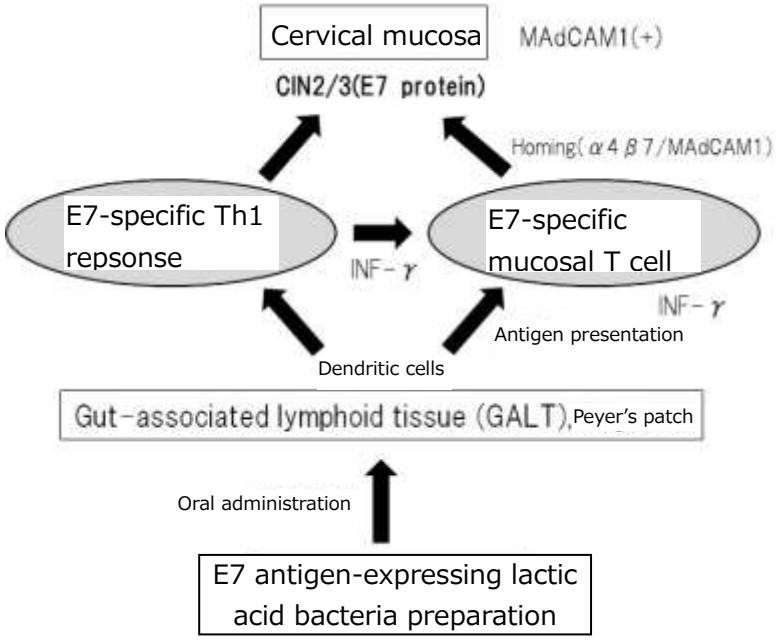


Figure 1 Mechanism of action of recombinant E7 antigen-expressing lactic acid bacteria (attenuated)

3.3. Summary of non-clinical evaluation data

3.3.1. IGMKK16E7 non-clinical trials

3.3.1.1. Safety pharmacology

In a five-day repeated oral administration test of the study drug in mice, no deaths or aberrations were not observed under general conditions even at a dose approximately 66 times the planned clinical dose. Therefore, the study drug did not affect major physiological functions (central nervous system, cardiovascular system, and respiratory system functions).

3.3.1.2. Pharmacokinetic study

Pharmacokinetic studies have not been performed.

3.3.1.3. Non-clinical studies conducted on the study drug

To evaluate the CTL induction ability in the intestinal mucosa via IFN-γ production, female C57BL/6 mice were administered with IGMKK16E7 and excipients in physiological saline at the blending ratio at the time of formulation. IGMKK16E7 and physiological saline with excipients added at the formulation ratio were orally administered to female C57BL/6 mice once a day for 5 days a week in weeks 1, 2, 4, and 8 of the study (1 mg/head/dose of the test substance, which was adjusted by adding excipients at the blending ratio at the time of formulation, to 1 mg of the drug substance of the investigational drug GMP lot). Next, intestinal epithelial intercellular lymphocytes (IELs) were collected, and the number of E7 antigen-specific IFN-γ-producing cells in the IEL was counted using the ELISPOT method.

The study drug GMP lot IGMKK16E7 induced cell-mediated immunity compared to the negative subjects.

3.4. Summary of results of investigator-initiated clinical studies

This agent has not yet been applied in clinical settings. Two investigator-initiated clinical studies of E7-expressing lactic acid bacterial preparations (first generation GLBL-101c/CIN2, CIN3) are currently ongoing.

3.4.1. Clinical studies targeting patients with CIN3

A phase I/IIa clinical study of the oral administration of GLBL-101c in patients with CIN3 (CIN3 clinical study) was conducted[8]. In a CIN3 clinical study, GLBL-101c capsules (250 mg/cap) were administered once daily for 5 consecutive days at weeks 1, 2, 4, and 8. The dose was escalated to 1 (1 case), 2 (3 cases), 4 (3 cases), and 6 capsules (3 cases) (step 1). The administration of 4 capsules, which maximized the ability to induce anti-E7 cellular immunity to cervical mucosal lymphocytes, was determined to be the clinically recommended dose, and 7 additional cases were added (Step 2).

Of the 17 cases treated with GLBL-101c in the CIN3 clinical study, the only adverse event for which a causal relationship to GLBL-101c could not be ruled out was mild abdominal pain (non-serious: administration of the 4 capsules, 1 event per subject), and the adverse event resolved on day 4 of onset. Safety was confirmed for the administration of up to 6 capsules, which is the maximum dose set in the CIN3 clinical study.

Of the 10 cases to whom 4 capsules were administered, CIN3 was downgraded to CIN2 in 7 cases (70%) at week 9 after the first administration.

A CIN3 clinical study confirmed the correlation between the pharmacological and clinical effects of administering the 4 capsules to patients with CIN3.

Cytological examination revealed that HSIL downgraded to LSIL or NILM in 3 out of 10 cases (30%) at week 24 after administration of the 4 capsules, as well as in 4 out of 10 cases (40%) after 48 weeks.

Table 3 shows the study outline of this CIN3 clinical study.

Table 3 CIN3 clinical study summary

Item	Details
Title of study	GLBL-101c exploratory phase I/IIa clinical study on CIN3 patients
Target disease	High-grade cervical intraepithelial neoplasia (CIN3)
Purpose of the study	The aim of this study was to confirm the induction of cellular anti-E7 immunity of cervical mucosal lymphocytes through oral administration of GLBL-101c capsule and explore the safety and efficacy of GLBL-101c on the target diseases CIN3.
Design	Single-center, open-label, single-arm
	*Step 1: Examine safety through dose escalation and determine the clinically recommended dose
	*Step 2: Examine the efficacy using the clinically recommended dose
Dosage/dose	GLBL-101c capsule shall be consecutively administered for five days at weeks 1, 2, 4, and 8 (days 1–5, 8–12, 22–26, and 50–54). The GLBL-101c capsule dose shall be four doses of 1, 2, 4, and 6 capsules/time/day
Age/sex	20–49 years, female
Selection criteria	1) Female with HPV16 infection
	2) Observable area of entire lesion through colposcopy
	3) Patients judged to require cervical conization and patients who want to receive the procedure
	4) Patients aged 20–50 years at the time of obtaining consent
	5) Outpatient
	6) Patients who can provide consent with sufficient understanding after receiving adequate explanation about their participation in this study
Exclusion criteria	1) Patients who have diseases causing evident immune function aberrations and patients receiving contraindicated drugs (therapies) expected to suppress the immune system
	2) Class 5 patients based on cytological analysis
	3) Patients who wish to undergo laser vaporization
	4) Patients suffering from serious acute diseases
	5) Patients who have a medical history of hypersensitivity to lactic acid bacteria-containing food (yogurt, etc.) and lactic acid bacteria preparation
	6) Patients who are allergic to milk
	7) Women who are pregnant or are possibly pregnant
	8) Women with nursing children
	9) Patients who have received other study drug or investigational drugs within 3 months before the start of administration of this study drug
	10) Patients who have taken GLBL-101c
	11) Patients judged to be ineligible by the investigator or subinvestigator
Number of cases	17 cases

3.4.2. Clinical study in patients with CIN2

After the CIN3 clinical study, a placebo-controlled, randomized, double-blind study in patients with CIN2 (exploratory late phase II clinical study: hereafter referred to as CIN2 clinical study) has been conducted using the dose recommended in the CIN3 clinical study (GLBL-101c 250 mg/cap, 4 capsules once daily), and the results are currently being reviewed. Table 4 shows a summary of the CIN2 clinical study.

Table 4 CIN2 Clinical Study Trial Summary

Item	Details
Title of study	GLBL-101c exploratory phase II clinical study on patients with CIN2
Target disease	Moderate cervical intraepithelial neoplasia (CIN2)
Purpose of the study	The aim of this study was to explore the superiority of GLBL-101c capsule against a placebo based on the primary outcome, which is the pathological response on the cervical lesion.
Design	Single-center, randomized, double-blinded (placebo-controlled)
Dosage/dose	GLBL-101c capsule shall be consecutively administered for five days at weeks 1, 2, 4, and 8 (days 1–5, 8–12, 22–26, and 50–54). The daily dose of GLBL-101c capsule and placebo shall be four capsules/time/day.
Age/sex	20–49 years, female
Selection criteria	1) Female with HPV16 infection
	2) Observable area of entire lesion through colposcopy
	3) Patients judged to require observation upon histological diagnosis with CIN2
	4) Patients aged 20–50 years at the time of obtaining consent
	5) Outpatient
	6) Patients who can provide consent with sufficient understanding after receiving adequate explanation about their participation in this study
Exclusion criteria	1) Patients who have diseases causing evident immune function aberrations and patients receiving contraindicated drugs (therapies) expected to suppress the immune system
	2) Class 5 patients determined based on cytology
	3) Patients who wish to undergo laser vaporization
	4) Patients suffering from serious acute diseases
	5) Patients who have a medical history of hypersensitivity to lactic acid bacteria-containing food (yogurt, etc.) and lactic acid bacteria preparation
	6) Patients who are allergic to milk
	7) Women who are pregnant or are possibly pregnant
	8) Women with nursing children
	9) Patients who have received other study drug or investigational drugs within 3 months before the start of administration of this study drug
	10) Patients who have taken GLBL-101c
	11) Patients judged to be ineligible by the investigator or subinvestigator
Number of cases	40 cases (20 cases in the GLBL-101c group and 20 cases in the placebo group)

3.4.3. Clinical Trial in South Korea targeting patients with CIN3

BioLeaders Co. Ltd. (South Korea), who provided GLBL-101, has the right to develop a cancer

immunotherapeutic agent for precancerous lesions of cervical cancer by expressing E7 protein (variant: ▲Rb) derived from HPV type 16 in lactic acid bacterial cells (*Lacticaseibacillus paracasei*) in South Korea. The company is independently conducting clinical development in its country (product name: MucoMax, code name: BLS-ILB-E710c). In a multicenter phase I/IIa clinical trial in South Korea, 3, 2, 4, and 6 capsules of BLS-ILB-E710c were administered to 19 patients with CIN consecutively for 5 days at weeks 1, 2, 4, and 8 (days 1–5, 8–12, 22–26, and 50–54). After the Phase I/IIa clinical trial, BioLeaders Co. Ltd. is currently conducting a multicenter, placebo-controlled, randomized, double-blind study with 126 patients with CIN 2 and CIN 3 (HSIL patients) in South Korea (Phase II clinical trial).

3.5. Validity of the implementation of this clinical trial

Medical treatment is not available for patients with HSIL/CIN2 harboring HPV infection, and follow-up is continued on an outpatient basis once every 3–4 months. Surgical procedures, such as cervical conization and laser vaporization have been performed in patients with HSIL/CIN3.

Cervical conization is associated with complications, such as postoperative dysmenorrhea due to cervical stenosis, infertility due to cervical mucoadenectomy, and postoperative disorders, including miscarriage and premature birth, due to cervical incompetence.

Laser vaporization is associated with problems concerning postoperative histopathological diagnosis and postoperative recurrence. Patients with HSIL/CIN2 are in constant fear of their condition progressing to HSIL/CIN3 or cervical cancer during follow-up. Additionally, patients with HSIL/CIN3 have problems after surgical treatment. Furthermore, patients with HSIL/CIN2-3 are treated via surgical measures overseas.

Based on the implementation of this trial, we believe that avoiding surgical measures and preventing progression to cervical cancer by developing a medical treatment method for patients with HSIL/CIN2 who must be followed up until they are indicated for surgical measures and patients with HSIL/CIN3 who are indicated for surgical measures are of medical significance.

This treatment concept is a global unmet medical need for patients with HSIL/CIN2-3 harboring cervical precancerous lesions. We believe that the significance of the development of this drug is extremely high.

Although this drug has not been administered to patients before this clinical trial, the efficacy and safety of GLBL-101c, a similar drug, have been investigated in clinical studies, and its safety has been confirmed in animal experiments. Therefore, we considered it possible to examine the safety and efficacy of this drug in subjects by proceeding with clinical trials and evaluating clinical safety. Furthermore, as this drug may induce a stronger immune response than GLBL-101c, it is considered appropriate to conduct a placebo-controlled dose-finding study based on the doses studied in clinical studies of GLBL-101c.

Due to its mechanism of action, this drug is expected to be highly effective in patients who express E7 protein. Although some studies have examined E7 protein expression in patients with HSIL/CIN2 and HSIL/CIN3, the measurement system has not been standardized. Therefore, in this clinical trial, E7 protein expression was not used as a factor for patient selection. Additionally, a secondary objective was set to explore the effects of this drug on E7 protein expression in the collected specimens. The results of this clinical trial are expected to establish an E7 protein expression measurement system as a companion diagnostic agent in the future.

3.6. Summary of known and potential risks and benefits to the subject

3.6.1. Risks

① Anticipated side effects/adverse events

As the study drug will be used in humans for the first time in this study, no information on known hazards has been collected. However, "side effects and adverse events" in investigator-initiated clinical studies of E7-expressing lactic acid bacterial preparation (GLBL-101c, first generation) conducted so far are shown below.

Phase I/IIa study in patients with CIN3 (17 cases)

Table 5 Phase I/IIa study in patients with CIN3: List of side effects

Side effect	No. of people	Incidence (%)	No. of cases
Abdominal pain	1	5.90	1

Table 6 Phase I/IIa study in patients with CIN3

Adverse events	No. of people	Incidence (%)	No. of cases
Nausea	1	5.90	1
Cold	3	17.60	3
Suspected cervical spondylosis	1	5.90	2
Menstrual pain	1	5.90	1
Menstrual pain	1	5.90	1
Aggravation of cystitis	1	5.90	1
Stomach pain	2	11.80	4
Indigestion	1	5.90	1
Palpitation	1	5.90	1
Lower back pain	2	11.80	3
Constipation	1	5.90	2
Headache	1	5.90	1
Abdominal pain	1	5.90	1
Increased leucorrhea	1	5.90	1
Sty	1	5.90	1

Phase IIb study in patients with CIN2 (40 cases)

Table 7 Phase IIb study in patients with CIN2: List of side effects

Adverse events	GLBL101c group (N=20)			Placebo group (N=20)		
	No. of people	Incidence (%)	No. of cases	No. of people	Incidence (%)	No. of cases
Abdominal pain	0	0.00	0	1	5.00	1

Table 8 Phase IIb study in patients with CIN2: List of adverse events

Adverse events	GLBL101c group (N = 20)			Placebo group (N = 20)		
	No. of people	Incidence (%)	No. of cases	No. of people	Incidence (%)	No. of cases
Constipation	0	0.00	0	0	0.00	0
Abdominal pain	2	10.00	2	3	15.00	3
Nausea	1	5.00	1	0	0.00	0
Palpitation	0	0.00	0	0	0.00	0
Headache	4	20.00	6	1	5.00	1
Numbness	0	0.00	0	1	5.00	1
Itching	1	5.00	1	0	0.00	0
Rash	2	10.00	2	0	0.00	0
Others	7	35.00	13	6	30.00	12

3.6.2. Benefits

Oral administration of the study drug will induce an E7-specific immune response in the intestinal mucosa. E7-specific immunity (T lymphocytes) induced by the study drug is expected to kill tumor cells in cervical precancerous lesions and exert a synergistic effect with NK cells. Based on this, patients with HSIL/CIN2 are expected to benefit from the inhibition of the progression to HSIL/CIN3 or cervical cancer and downgrade to LSIL/CIN1 or healthy status. Furthermore, patients with HSIL/CIN3 are also expected to benefit from the inhibition of the progression to cervical cancer and downgrade to HSIL/CIN2, LSIL/CIN1, or healthy status.

4. The aim of the trial

IGMKK16E7 (study drug) will be orally administered to patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN2-3) to confirm the safety of the study drug and determine the clinically recommended dose. Furthermore, this clinical trial will investigate the correlation between E7 protein expression in the precancerous lesion and the efficacy of IGMKK16E7.

5. Trial method

5.1. Target disease

High-grade HSIL/CIN 2-3

5.2. Target number of subjects

This clinical trial shall examine 164 cases (placebo, low-dose (0.5 g/administration/day), intermediate-dose (1.0 g/administration/day), and high-dose (1.5 g/administration/dose) groups; each administration group shall comprise 41 cases and each group shall have 10 cases with HSIL/CIN2 at the time of enrollment).

[Administration group]

Placebo group
Low-dose group (0.5 g/dose/day)
Intermediate-dose group (1.0 g/dose/day)
High-dose group (1.5 g/dose/day)
[Setting basis]

Based on the results of GLBL-101c clinical study targeting HSIL/CIN3, the response rate for HSIL/CIN3 (expected value) in this clinical trial is assumed as follows: 10%, 20%, 30%, and 40% for the placebo, low-dose, intermediate-dose, and high-dose groups, respectively. Furthermore, the response rate for HSIL/CIN2 (expected value) is assumed to be the same as that for CIN3[5-6].

For CIN3 cases, the minimum number of subjects exceeding the detection power of 80% was calculated using the Cochran-Armitage Test at 5% significance. The number of simulations shall be 5000. When the detection power was set at the ratio and the p-value of both sides was below 0.05 among the corresponding number of simulations, the number of cases per group was calculated to be 28. Assuming that the dropout rate will be approximately 10%, the number of subjects per group would be 31 cases. Therefore, the target number of HSIL/CIN3 subjects in this clinical trial would be 31 cases per group.

Furthermore, a clinical study targeting CIN3 cases included HSIL and CIN2 and reported the cases downgraded to LSIL or NIML cases. Therefore, the target of this clinical trial was HSIL/CIN2-3. To explore the effectiveness of this drug against HSIL/CIN2, the number of HSIL/CIN2 subjects was set to 10 cases.

Therefore, the target number of subjects in this clinical trial was set to 41 cases for each of the four groups, totaling 164 cases.

Furthermore, the detection power of multiple-dose relationships as shown below will be confirmed when the number of cases in each group is 37 (4 dropouts).

	Response rate			
	Placebo	Low-dose group	Intermediate-dose group	High-dose group
① Linear dose-response relationship	10%	20%	30%	40%
② Plateau in the low-dose group	10%	30%	30%	30%
③ Plateau in the intermediate-dose group	10%	20%	30%	30%
④ Effect in the low-dose group only	10%	30%	10%	10%
⑤ Effect in the intermediate-dose group only	10%	10%	30%	10%
⑥ Effect in the high-dose group only	10%	10%	10%	30%

The contrasts corresponding to the above dose-response relationships include ① [-1.5, −0.5, 0.5, 1.5], ② [−3, 1, 1, 1], ③ [−2, 0, 1, 1], ④ [−1, 3, −1, −1], ⑤ [−1, −1, 3, −1], and ⑥ [−1, −1, −1, 3]. Under the two-sided significance level of 5%, the detection power to make each contrast significant is shown in the table below. All dose relationships have > 70% power when paired contrasts are used (diagonal contrasts correspond to true dose-response relationships).

	①	②	③	④	⑤	⑥
① Linear dose-response relationship	90.3	75.1	87.1	14.0	15.5	68.5
② Plateau in the low-dose group	50.6	75.7	68.9	13.5	15.2	17.0
③ Plateau in the intermediate-dose group	65.2	58.8	70.3	7.6	26.1	26.5
④ Effect in the low-dose group only	8.6	17.0	2.6	80.3	15.4	13.5

⑤ Effect in the intermediate-dose group only	8.9	14.4	28.8	16.7	83.7	14.7
⑥ Effect in the high-dose group only	65.3	16.0	30.4	17.6	16.0	82.3

*Numbers in the top row correspond to the corresponding contrasts.

Tests are performed using the six established contrasts without adjusting for multiplicity. The contrast that gives the smallest p-value is judged to have a dose-response relationship between the placebo and the study drug.

Moreover, based on the mechanism of action of this drug, E7 expression in the lesion site may be the effect prediction factor of the drug. Therefore, the exploration of the correlation between the corresponding E7 expression and this drug would be the secondary purpose of this clinical trial. From this point of view, the examination can be performed with the enrolled number of subjects in this clinical trial.

5.3. Trial design

A placebo-controlled randomized double-blind comparative study (Phase I/II clinical trial) of four dose parallel groups: placebo, low-dose (0.5 g/administration/day), intermediate-dose (1.0 g/administration/day), and high-dose (1.5 g/administration/day) groups.

Additionally, the inclusion of the first and second cases and the inclusion of the third and subsequent cases will be as follows (Register the first and second cases at the independent facility of Nihon University Itabashi Hospital).

(1) The interval between the recruitment of the first and second subjects will be after confirming the safety at the end of one cycle.

Subjects are selected so that the assignment conditions for the first and second subjects are identical.

(Ratio factor: HPV type 16 single infection and HSIL/CIN3 cases)

(2) Confirmation of safety of the first subject

The safety of the subject will be confirmed at the end of the five-day administration of the first cycle of the first case.

(Confirmation method: Subjects will be contacted via phone or email on days 5–7 (the final day of the acceptable range of administration) to confirm their health status.)

(3) Enrollment of the second subject and confirmation of health status

The health status of the subject will be confirmed after they take the drug for five days using the same method as that used for the first case.

(4) After confirming the health status of these two cases, the third and subsequent cases will be sequentially included.

[Setting basis]

In clinical studies of GLBL-101c capsules, which are similar drugs, 1.0 g/dose/day is the recommended clinical dose because it maximizes the ability to induce anti-E7 cell-mediated immunity to cervical mucosal lymphocytes. However, the immune response of this drug is expected to be stronger than that of GLBL-101c capsules. Hence, a dose-finding study with an intermediate dose of 1.0 g/dose/day along with low and high doses was considered to be appropriate. Additionally, considering the spontaneous regression of lesions in CIN2, this design was selected because a placebo-controlled comparative study would elucidate the effect of this drug.

① In a five-day continuous administration toxicity test of this drug to mice in clinical practice (five-day continuous administration of 33 times the clinical dose), the bodyweight, aberrations in general conditions, and death were not observed in mice, suggesting that it is highly safe. Using this as reference information, a clinical study at the University of Tokyo Hospital where a similar drug (GLBL-101c) was administered revealed that there were no aberrant health conditions (confirmed from health journals) in CIN3 and CIN2 subjects after taking GLBL-101c for 5 days.

② Based on the results of GLP studies and clinical studies of similar drugs, the safety of this drug can be ensured by confirming the health status after continuous administration for five days (1 course).

5.4. Selection criteria

This clinical trial will target patients who meet all of the following criteria:

(1) Women with type 16 infection determined using HPV genotyping of cells collected from the cervix (not necessarily type 16 infection alone)
(2) Patients histologically diagnosed with HSIL/CIN2 or HSIL/CIN3
(3) Patients aged between 20 and 45 years at the time of obtaining informed consent
(4) Subjects who are outpatients at the time of obtaining informed consent
(5) Patients who have given their voluntary written consent after receiving sufficient explanation about clinical trial participation

[Setting basis]
(1) and (2) were selected as appropriate subjects for efficacy evaluation.
(3) and (4) were selected as appropriate and easily implemented targets for the evaluation of this study.
(5) It was established based on the belief that it is essential for the patient to fully understand the content of the clinical trial and voluntarily consent to participate in the clinical trial.

5.5. Exclusion criteria

Patients who meet any of the following conditions will not be enrolled in this clinical trial:
(1) Patients with an aberrant immune function who require treatment or who are receiving treatment for immunosuppression
(2) Patients confirmed to have SCC through cytological diagnosis
(3) Patients planning to undergo laser vaporization
(4) Patients planning to undergo cervical conization
(5) Patients with serious acute diseases
(6) Patients with a history of hypersensitivity to foods containing lactic acid bacteria (yogurt, etc.), lactic acid bacteria preparations, or soybean lecithin (soybean products: tofu, etc.)
(7) Patients allergic to milk
(8) Patients who are pregnant or who may be pregnant*
(9) Patients who are currently nursing
(10) Patients who received other study drugs or unapproved treatments within 4 weeks before the start of study drug administration
(11) Patients who have been administered GLBL-101c and the study drug
(12) Patients diagnosed or suspected of having chronic or acute pancreatitis at the start of study drug administration
(13) Other patients who are judged to be ineligible as subjects by the investigator/subinvestigator

[Setting basis]
Criterion (1) was set because it may affect the efficacy and safety evaluation of this investigational drug.
Criterion (2) was set because the possibility of invasive cancer cannot be ruled out.
Criterion (3) was set because laser vaporization could not provide an index for evaluating efficacy (histopathological examination).
Criteria (4) to (8), (10), and (12) were established to ensure the safety of subjects.
Criterion (9) was set to ensure the safety of the study drug on nursing infants has not yet been confirmed. Even if breastfeeding is stopped, the patient may be required to resume breastfeeding for specific reasons (including temporary breastfeeding). Hence, these patients have been excluded.
Criterion (11) was set because it may have an immune booster effect.

*Definition of a woman of childbearing potential:
① Women are undergoing sterilization or female genital mutilation, or ② menopausal women who do not meet either

For amenorrhea (including those who have not had menstruation within at least 1 year after menopause) due to treatment with antineoplastic agents, a pregnancy test is performed if the possibility of pregnancy cannot be completely ruled out.

5.6. Blinding method and assignment of subjects to treatment groups

5.6.1. Blinding method

Blinding is performed by assigning indistinguishable study drugs using a predetermined randomization method by the drug allocation manager.

The drug allocation manager will separately prepare and store an emergency key to ensure the safety of this trial. The method of opening the emergency key is specified in a separate procedure manual. The investigational product allocation manager will confirm the unidentifiable appearance/characteristics, packaging form, labeling, etc. before and after the start of the clinical trial.

5.6.2. Assignment of subjects to treatment Groups

Enrolled subjects are randomly assigned to each of the four administration groups in a 1:1:1:1 ratio via minimization.

The following three factors are used as assignment adjustment factors.

(1) Diagnosis (CIN2 and CIN3)
(2) HPV genotype (type 16 single infection and multiple infections, including type 16)
(3) Facilities (4 facilities)

5.7. Clinical trial schedule

5.7.1. Observation period

(1) Study period: 16 weeks
(2) Follow-up period: Furthermore, based on the diagnosis of the attending physician of the facility at week 16 after the administration, the cases will be tracked until 24 weeks, except for cases determined to require treatment for CIN3 or invasive cancer.

[Setting basis]

At week 40 after the first dose administration at the clinically recommended dose (1.0 g/4 capsules group) of the clinical study of GLBL-101c for CIN3, a response rate of 30% was confirmed in the pathological improvement index determined using the same criteria as those established in this trial. In this study, the observation period was set on the assumption that similar effects would be obtained 16 weeks after the initial administration. In addition, an additional 8-week follow-up observation was set to confirm the delayed improvement after 16 weeks and the maintenance of the improvement, cases with HSIL/CIN2 and CIN1, which did not require surgery at 16 weeks, and all CIN lesions that disappeared.

5.8. Study drug

5.8.1. Name of the investigational drug, etc.

(1) Name: IGMKK16E7 and placebo capsules

Dosage form: Granular soft capsule formulation with a diameter of approximately 2.5 mm packaged in a stick

Ingredients and content

[IGMKK16E7 Stick]

Active ingredient: *Lacticaseibacillus paracasei* (attenuated cells) expressing HPV16 mutated E7 full-length antigen (mutant: ▲in Rb-binding domain) on the surface

Content: 500 μg in seamless capsule preparation 3.12 g

Additives: Hydrogenated oil, gelatin, polyethylene glycol, soybean lecithin, pectin, and caramel coloring

[Placebo stick]

Content: Sugar powder

Additives: Hydrogenated oil, gelatin, polyethylene glycol, soybean lecithin, pectin, and caramel coloring

Placebo seamless capsules that cannot be distinguished by appearance, weight, taste, or smell are packaged in sticks and formulations that cannot be distinguished by appearance or weight

(2) Dosage and dose

The subject will take three sticks of the study drug once daily before breakfast with 150 mL (about 1 glass) of water. Consecutive administration for 5 days constitutes 1 course. In total, 4 courses (days 1–5, days 8–12, days 22–26, and days 50–54) will be administered. However, the drug will be administered between meals on day 1 in the hospital in the presence of the investigator/subinvestigator, and the patient will be observed for approximately 30 min (to confirm the lack of no acute symptoms, such as vomiting).

The permissible range for the administrations days is as follows:

If the subjects forget to take the study drug before the meal on the day of the administration, they are allowed to take it before lunch or dinner on the same day. If the subjects forget to take the study drug at

each cycle, they are allowed to take the drug as follows:

First cycle: If the patients forget to take the study drug between days 2 and 5, they are allowed to take it between days 6 and 7.

Second cycle: If the patients forget to take the study drug between days 8 and 12, they are allowed to take it between days 13 and 14.

Third cycle: If the patients forget to take the study drug between days 22 and 26, they are allowed to take it between days 27 and 28.

Fourth cycle: If the patients forget to take the study drug between days 50 and 54, they are allowed to take it between days 55 and 56.

(3) Packaging

One packet: Stick packaging (Approximately 120 mm x approximately 24 mm/piece, packaging material: PET/PE/AL/PE)

Three OP/CP packages for 1 day and 20 days-worth in 1 box.

(4) Label

The label shall indicate the following items.

The fact that it is for clinical use, the drug number, the identification code (IGMKK16E7), the manufacturing number, the storage method (protect from light and store at < 8°C to avoid freezing), the name of the coordinating investigator, and the address. The expiry date shall be specified in the separately defined protocol for the management of the study drug.

(5) Storage method

Protect from light, avoid freezing, and store at ≤ 8°C

(6) Investigational drug sponsor

GLOVACC Co. Ltd.

Address: 3-1-13 Unit E 4F Urban Shibakoen Building Shibakoen, Minato City, Tokyo 105-0011

Telephone number: 03-6450-1811 (Reception)

5.8.2. Storage, management, and return of study drug

(1) Study drug manager shall store and manage the study drug according to the “Procedure for study drug management” provided by the investigator. A study drug management table shall be created for the entry/exit at the medical institution, the usage status for each subject, and the return.

(2) After the completion of each subject's medication, the study drug manager confirms the consistency of each subject's prescription quantity, dosage quantity, quantity discarded (or lost) by the subject (if applicable), quantity of unconsumed study drug collected, etc. After entering these records in the investigational drug management table, the study drug that has not been taken, empty boxes, etc. will be discarded at the medical institution. When discarding, the disposal procedure of each medical institution shall be followed.

5.8.3. Key code opening procedure

Procedures for opening the key code in an emergency are specified in a separate procedure manual.

The randomization table shall be kept securely by the study drug allocator until the key is opened, and the randomization table shall be opened after the case report forms and data have been fixed.

5.9. Observation/investigation and inspection items of the test

Table 9 shows the observation/survey and inspection items of the test.

Table 9 Observation/survey and inspection items during the test (follow-up) period

Item	Eligibility confirmation period															
	Initial visit	Administration start date Day 1	(Week 1) Day 2～7	(Week 2) Day 8～14	(Week 3) Day15～21	(Week 4) Day22～28	(Week 5) Day29～35	(Week 6-7) Day36～49	(Week 8) Day 50～56	(Week 9) Day 57～63	(Week 10-15) Day64～105	(Week 16) Day106～112	(Week 17-23) Day 113～161	(Week 24) Day 162～168	At discontinuation
Arrival	○	○					●			●		●		◎	●
Permitted scope of arrival							Day29～42			Day57～77		Day106～126[k]		Day162～182[k]	
Prescription of the clinical trial		●													
Administration of the study drug		←	→	→		→			←						
Confirmation of drug status							●			●					
Consent	○														
Confirmation of selection/exclusion criteria	○[a]	○													
Case enrollment		○													
HPV genotype test (for eligibility confirmation)	○[b]														
HPV genotype test (Central test)		○[c]										●		◎	●
Histology (Central pathological judgment)	○[b]											●		◎[j]	●
Histology (Implementing medical institution judgment)										△					
Cytology	○[b]									●		●		◎	●
Colposcopy	○[b]									●		●		◎	●
Laboratory test		○[d, e]					●			●		●		◎	●
Pregnancy reaction (Serum hCG)		○[d, e]										●			●
HIV test	○[f]														
HPV16E7 protein expression level		○[c]										●		◎	●
E7 protein expression (cervical cells)		○[g]													
HPV E7 Atypical immune reaction		○										●		◎	●
Subjective symptoms[h]/objective findings		●	●	●	●	●	●	●	●	●	●	●		◎	●
Concomitant drugs/therapies	←											→			
Confirmation of medical history and complications	○														
Confirmation of adverse events[i]		←	→	→	→	→	→	→	→	→	→	→	- - - →	- - - →	

○：服用開始前に実施又は検査結果を確認する項目　●：服用開始後に実施する項目　△：浸潤癌の疑いがある場合に実施する項目　◎：投与後16週で追跡調査の該当症例と判断された症例のみ実施する項目

a ○: Item confirming the implementation or test results before the start of administration ●: Item implemented after the start of administration △: Item implemented in case of suspected infiltrative cancer ◎: Item implemented only on corresponding cases and judged cases in the follow-up survey at week 16 after administration
c a: Implement test for selection/exclusion criteria confirmation after obtaining consent b: Confirm eligibility based on corresponding data in case there are data within 90 days before obtaining consent (data at another hospital, in-hospital data not required). Implement the test after obtaining consent in case there
e are no corresponding data.
f ·c: Implement test using E7 protein expression specimen collected on the same day d: Confirm that there is no problem with the test results (no possibility of pregnancy) before prescription of the study drug. The administration of the study drug shall start within 10 days from the date when the corresponding
h laboratory test was conducted. e: Perform the laboratory test on the date of consent. If the start date of administration was within 10 days from the date when the corresponding test was conducted, there is no need to conduct a new test on the date of administration. f: Perform at initial visit or on the start date of
j : administration. Confirm that the subject does not have human immunodeficiency virus (HIV) infection before prescribing the study drug. Start the administration of the study drug within 14 days from the date when the corresponding test was conducted. g: Perform HPV genotyping on the same day using the
k collected specimen. h: The subject shall record the subjective symptoms in the health journal. i: Confirm the entries in the health journal during administration period. The follow-up period (from week 17) after the end of the study period shall only confirm adverse events that were clearly caused by the study drug. j: For subjects judged to be healthy at week 16 after the initial administration, perform the test only if cervical precancerous lesion area was confirmed in the colposcopy conducted on the same day (week 24). k: In case retest is necessary due to the condition of the specimen, retest is permitted within 14 days from the date when the initial test was performed.

5.9.1. Consent acquisition

The investigator (subinvestigator) will obtain the patient's consent according to "15.3.1. Obtaining written consent." Before obtaining consent, the investigator/subinvestigator shall sufficiently explain the need to use effective contraception (specifically, condoms, intrauterine devices, and oral contraceptives) for the duration of the study (four months). Consent will be obtained after sufficiently explaining the aim of the study and ensuring that the subject understands the aim. Additionally, if the subjects have a male partner, they will be advised on the need for contraception (specifically, a barrier contraceptive method like a condom), and the partner's full understanding will be obtained.)

Definition of a woman of childbearing potential:

(1) Women who have undergone sterilization or female genital mutilation, or (2) menopausal women who do not satisfy either

For amenorrhea (including those who have not had menstruation within at least 1 year after menopause) due to treatment with antineoplastic agents, a pregnancy test is performed for subjects in whom the possibility of pregnancy cannot be completely ruled out.

5.9.2. Enrollment of subjects

In case of candidate patients, the investigator/subinvestigator or clinical trial collaborator will explain the clinical trial, obtain written consent for voluntary participation in this clinical trial, and enroll the subjects according to the following procedure.

5.9.2.1. Subject background factor survey

The investigator/subinvestigator will investigate the following items after obtaining written consent from the subject.

1) Subject identification code
2) Date of consent acquisition
3) Date of birth
4) Height and weight
5) Treatment category
6) Name of diagnosis
7) Time of diagnosis
8) Other medical history/complications and concomitant medications

5.9.2.2. Confirmation of selection and exclusion criteria

The investigator/subinvestigator will confirm that all subjects meet the inclusion criteria stipulated in this study and do not meet the exclusion criteria.

5.9.2.3. Subject registration (issuance of drug number)

The investigator/subinvestigator or clinical trial collaborator shall use the electronic case report form (EDC) to register the subject (issuance of the drug number) according to the separately defined “eCRF input manual.”

Furthermore, information will be collected according to the separately defined "eCRF input manual" for subjects who did not meet the eligibility criteria after obtaining informed consent.

5.9.2.4. Creation of subject registration list

The investigator/subinvestigator will create a "subject registration list" that records the patient's medical record number, consent acquisition date, eligibility confirmation date, subject identification number, etc. of subjects who have provided the written consent.

5.9.3. Observation/inspection items during the study (follow-up) period

5.9.3.1. HPV genotype test

After obtaining the written informed consent, the investigator/subinvestigator will perform HPV genotype testing to confirm eligibility. Additionally, if test data for a case referred by a previous doctor, etc. are available, they can be used at the time of eligibility confirmation. Furthermore, before the first dose administration and at weeks 16 (or at the time of discontinuation) and 24 (applicable cases only), only specimens for genotype testing will be collected. Specimen collection, storage, and transportation shall be conducted according to the separately determined procedures. The genotype test will be conducted according to a separately defined procedure.

5.9.3.2. E7 protein expression and HPV 16 E7 protein expression level

The investigator/subinvestigator will collect samples for evaluating E7 protein expression after obtaining written informed consent and before the first dose administration. Furthermore, the HPV 16 E7

protein expression levels will be measured using the test specimens collected before the first dose and at weeks 16 (or at the time of discontinuation) and 24 (applicable cases only). Moreover, specimen collection, storage, and transportation shall be conducted according to the separately determined procedures. The E7 and HPV 16 E7 protein expression levels will be examined according to the separately defined procedure.

5.9.3.3. Human immunodeficiency virus (HIV) test

The investigator/subinvestigator shall perform an HIV test during the period between obtaining written informed consent and the first dose administration. The study drug should be started within 14 days from the day of the examination after obtaining written informed consent.

5.9.3.4. Histology (Pathological improvement indicator)

During the confirmation of eligibility (the pathological sample data can be used for cases referred from a previous doctor), the investigator/subinvestigator shall conduct a histopathological test of the cervix at weeks 16 (or at discontinuation) and 24 after the first dose. At week 9 after the first administration (if invasive cancer is suspected), judgment will be made at the medical facility. The histopathological test at week 24 after the first dose for cases judged to be normal at week 16 after the first dose shall be conducted if cervical precancerous lesion area is confirmed according to Colposcopy examination will be performed at week 24.

Furthermore, at the time of enrollment and weeks 16 and 24 after the first dose, judgments will be made after consultation with multiple pathologists based on a separately defined procedure (Central Pathological Review: CPR).

5.9.3.5. Colposcopy examination

To assess the area of the cervical lesion, the investigator/subinvestigator shall conduct a colposcopy test during the confirmation of eligibility (at week 9 after initial administration) and at weeks 16 and 24 after the first dose (applicable cases only).

5.9.3.6. Laboratory tests

The investigator/subinvestigator shall conduct the following laboratory tests during the period between obtaining written informed consent and initial administration and at weeks 5, 9, 16 (or at discontinuation), and 24 after the first dose. The study drug should be started within 10 days from the day of the examination after obtaining written informed consent. The laboratory tests necessary for this clinical trial shall be performed at the clinical trial medical institution.

Hematological test: White blood cell count, red blood cell count, hemoglobin level, hematocrit level, platelet count, and whole blood cell fraction

Blood biochemistry: Total protein, albumin, lactate dehydrogenase, aspartate aminotransferase, alanine transaminase, γ-GTP, alkaline phosphatase, total bilirubin, direct bilirubin, total cholesterol, neutral fat, blood urea nitrogen, creatinine, sodium, potassium, chlorine, uric acid, and creatine phosphokinase

Urinalysis: Urine qualitative (urine sugar, urinary protein, urobilinogen, occult blood, and pH)

5.9.3.7. Pregnancy reaction (serum hCG measurement)

As the safety of administration of this study drug during pregnancy has not been established, an examination will be conducted at the study site at week 16 after the first dose (or at the time of discontinuation) during the period between obtaining written informed consent and the first dose.

*Definition of a woman of childbearing potential:

(1) Women who have undergone sterilization or female genital mutilation, or (2) menopausal women who do not satisfy either

For amenorrhea (including those who have not had menstruation within at least 1 year after menopause) caused due to treatment with antineoplastic agents, a pregnancy test is performed for subjects in whom the possibility of pregnancy cannot be completely ruled out.

5.9.3.8. Subjective symptoms and objective findings

For the subjective symptoms and objective findings, the investigator/subinvestigator shall conduct confirmation, interview, and consultation based on the health journal on the start date of the study drug administration and at weeks 5, 9, 16 (or at discontinuation), and 24 after the first dose. If an adverse event is observed, the investigator/subinvestigator shall take appropriate measures and investigate and evaluate the event according to “6.2.1 Adverse events”.

5.9.3.9. Compliance status

The investigator/subinvestigator will confirm whether the subject was taking the drug correctly based on the health journal at the time of examination at week 5 after the first administration. If the drug was not taken correctly, the subject shall be given instructions on the correct method for drug consumption.

5.9.3.10. Cytology

The investigator/subinvestigator shall conduct a cytology test of the cervical cells during the confirmation of eligibility (at 9 weeks after initial administration) and at weeks 16 (or at discontinuation)

and 24 after the first dose.

5.9.3.11. HPV E7-specific immune response

To confirm the effect on the immune system at a cellular level, the investigator/subinvestigator shall collect blood samples during a period between obtaining written informed consent and initial administration and at weeks 16 (or at discontinuation) and 24 after the first dose. Separation, storage, and transport of peripheral blood mononuclear cells from the collected blood will be performed, following the separately defined procedures. Evaluation of HPV E7-specific immune response shall be performed according to a separately defined procedure.

5.9.3.12. Concomitant drugs and therapies

The investigator/subinvestigator shall investigate all drugs and therapies used from the time of obtaining written informed consent until the end of the study period or the time of discontinuation. For drugs (including OTC), the presence or absence of drugs used, drug name, single dose, unit, number of times per day, route of administration, start/end date of administration, and purpose of use shall be confirmed. For concomitant therapy, the presence/absence of therapy, name of therapy, start/end date, and purpose of implementation shall be confirmed.

5.10. Concomitant therapies and contraindicated drugs and therapies

5.10.1. Concomitant therapies

In principle, the use of concomitant drugs not mentioned in “contraindicated drugs and therapies” stipulated in this protocol is permitted. Furthermore, the subject is advised not to change the medication that they are currently taking.

[Setting basis]

Currently, treatments are not available for the target disease of this study. Drugs other than contraindicated drugs and therapies may affect efficacy and safety.

5.10.2. Contraindicated drugs and therapies

After obtaining informed consent, the following treatments are prohibited until the end of the study period.

(1) Inoculation of other vaccines
(However, influenza, rubella, measles, and SARS-CoV-2 (new coronavirus) vaccines can be used together.)
(2) Gamma globulin preparation
(3) High dose of steroids
(4) Cyclosporine preparations, etc.
(5) Imiquimod etc. (topical agent)
(6) Radiotherapy
(7) Laser vaporization
(8) Cervical conization
(9) Other study drugs and therapies

[Setting basis]

It was set because it may affect efficacy and safety.

6. Outcomes

6.1. Efficacy

6.1.1. Primary outcome

Primary endpoint: (1) safety and (2) histopathological regression at week 16 after the first dose.

(1) Safety: Type of adverse event, incidence rate, severity, seriousness, the period from the start of drug administration to the date of symptom onset, and duration
(2) Efficacy: The histopathological regression rate (CR rate and CR+PR rate) in each treatment group shall be calculated using the histopathological improvement indicator of CIN lesions before the administration of the study drug and at the end of the study (week 16 after the first dose).
CR: Regression to normal
PR: Regression to CIN1
SD: No change from HSIL/CIN2 at enrollment to HSIL/CIN2, no change from HSIL/CIN3 at

enrollment, or change from HSIL/CIN3 to HSIL/CIN2 at enrollment

PD: Progression from HSIL/CIN2 at enrollment to HSIL/CIN3 or cervical cancer irrespective of classification at enrollment

NE: Unable to determine as CR, PR, SD, or PD

If there is cervical cancer at the time of the interim evaluation (week 9 after the first administration), the study will be discontinued according to "8.1 Criteria for the discontinuation of the clinical trial for individual subjects based on the interim assessment".

[Setting basis]

The efficacy of each study drug administration group will be evaluated from the downgrade rate (response rate) from HSIL to LSIL or healthy, and dose-response will be examined to determine the clinically recommended dose of the study drug.

6.1.2. Secondary outcomes

(1) Efficacy: The histopathological regression rate (CR rate and CR+PR rate) at 24 weeks after the first dose. Histopathological improvement at 24 weeks after the first dose will be evaluated according to "6.1.1 Primary outcome."
(2) Immunological responses: The magnitude of HPV16 E7-specific Th1 immune response calculated using ELISpot assay using HPV16 E7 overlapping peptides as a stimulant.
(3) Change in HPV 16 E7 molecule protein expression level: at 16 and 24 weeks after the first dose.
(4) Improvement in cytological features:
Response: Regression to LSIL, ASC-US, or NILM
Stable disease: No change from HSIL
Progression: Progression to SCC
Unevaluable: Change to AGC or ASC-H
Subjects diagnosed with HSIL at enrollment shall be evaluated.
(5) Viral clearance: HPV16 negative at weeks 16 and 24 after the first dose
(6) The rates of "CR," PR," "SD," "PD," and "NE" in the pathological improvement indicator of CIN at weeks 16 and 24 after the first dose
(7) Disease control rate: Percentage of improvement to CIN2 or less at week 16 and 24 after the first dose in subjects with histology of CIN3 at enrollment

[Setting basis]

Criterion (1) was set to compare the change in pathological improvement (response rate) in the study drug group over time with that in the placebo group.
Criterion (2) was set to evaluate the ability of the study drug to induce immunity.
Criterion (3) was set to evaluate the change of E7 expression levels at the cervix
Criterion (4) was set to evaluate changes in lesions using cytology.
Criterion (5) was set to compare the rate of viral clearance of HPV16 after drug administration.
Criterion (6) was set up to comparatively confirm the therapeutic effects of the study drug and placebo and to detect the exacerbation prevention effect.
Criterion (7) was set to examine the improvement of tissue diagnosis from CIN3 to CIN2 or less as it has a clinical significance of avoiding surgery.

6.2. Safety

The type, incidence, severity, severity, date of onset, duration, etc. of adverse events shall be evaluated until 24 weeks after the first dose and recorded according to the following procedure.

6.2.1. Adverse events

An adverse event is any unfavorable event occurring during the study period after the use (administration) of the study drug irrespective of its relation to the study drug. During the follow-up period, only adverse events with a clear causal relationship to the study drug will be followed up.

[What are considered adverse events]

1. Aggravation beyond the natural course of the disease that was present before the administration of the study drug
2. Increased frequency or severity of symptoms or diseases that existed before the

administration of the investigational drug beyond the range of the natural course
3. Events that may have existed before the administration of the study drug but were discovered or diagnosed after the study drug administration
4. Unfavorable events that occurred due to invasive tests performed for this clinical trial, changes in treatment, etc.

[What is not considered adverse events]
1. Medical or surgical procedures, such as surgery, endoscopy, tooth extraction, etc. (However, the original symptoms requiring these procedures are treated as adverse events.)
2. Signs or symptoms that persisted before the start of the study and did not exacerbate
3. When no adverse medical events have occurred (planned hospitalization for cosmetic surgery, hospitalization for convenience reasons, etc.)
4. Events that do not aggravate disease or disease-related signs or symptoms (including physiological phenomena such as menstruation) that are the subject of this study do not worsen as expected from the patient's condition

6.2.2. Serious adverse events

Serious adverse events are events that fall under the following categories. In the event of a serious adverse event, the response shall be carried out according to "6.2.2.4. Response to serious adverse events."

1) Death
2) May lead to death
3) Requires hospitalization or clinic admission or extended hospital stay for treatment
4) Disability (development of dysfunction that interferes with daily life)
5) May lead to disability
6) Serious based on above
7) Congenital diseases or aberrations that could be inherited by future generations

6.2.2.1. Evaluation items

(1) Subjective symptoms and objective findings

For all unfavorable subjective symptoms and objective findings that have come to knowledge, the investigator/subinvestigator shall fill out the following information on the EDC as needed: name of the adverse event, date of onset, severity (Grade), severity, outcome, date of disappearance, relationship to study drug, presence/absence of concomitant medication/therapy, discontinuation of study drug use, and comments. Signs, symptoms, and diagnoses with a clear correlation with the study drug are recorded on the EDC as a single diagnosis.

(2) Laboratory test results

For laboratory test results, any aggravation at ≥Grade 3 based on the Common Technology Criteria Adverse Event (CTCAE) Grade 3 shall be regarded as an adverse event. The investigator/subinvestigator shall fill out the following information on the EDC after administration: name of the adverse event, date of onset, severity (Grade), severity, outcome, date of disappearance, relationship to study drug, presence/absence of concomitant medication/therapy, discontinuation of study drug use, and comments. However, aberrant laboratory test results should not be listed as adverse events but should be recorded as diseases as much as possible.

6.2.2.2. Assessment method and criteria

(1) Name of adverse event

Adverse event names are collected according to MedDRA (version 22.0). If the diagnosis cannot be specified, individual symptoms/signs will be recorded.

(2) Date of onset

The date when the adverse event was first observed shall be recorded. In case of aggravated symptoms or diseases that existed before the use of the study drug, the date of exacerbation shall be the date of onset.

(3) Severity

The severity of adverse events (Grade) shall be determined according to CTCAE (version V5.0).

(4) Date of outcome or disappearance

Adverse events occurring up to 16 weeks after the first administration should be followed up until recovery, in principle, and the date of recovery shall be recorded. However, for irreversible or permanent events, adverse events will be followed up until no change is observed based on medical judgment. Judgment shall be made according to the following six stages, and the date on which the outcome was confirmed (recovery date in case of recovery, death date in case of death) shall be recorded. If the follow-

up is discontinued for reasons other than "recovery," the reason shall be recorded in the source document.

1) Recovery: Adverse events resolved or returned to pretreatment status.
2) Remission: The severity of the adverse event has receded compared to that at the time of onset.
3) Unrecovered: The adverse event has not receded or recovered.
4) With sequelae: Adverse events left sequelae.
5) Death
6) Unclear

(5) Discontinuation of study drug use

If the adverse event was the direct cause of discontinuation of the study drug, it must be recorded.

(6) Association with study drug

The investigator/subinvestigator shall consider concomitant drugs/therapy, complications, subject background, etc., and make a judgment in the following two stages. If an association is determined, the reason for this judgment shall be entered in the EDC.

Furthermore, 1) means that it is a side effect.

1) Yes
2) No

≪ Definition of causal relationship classification≫

Yes: When a causal relationship with the use of the study drug cannot be denied.

See the criteria below.

1. Rechallenge positive (recurrence due to rechallenge)
2. Established and clear causality
3. Cogent time to onset
4. De-challenge positive (disappeared after administration was discontinued)
5. No confounding risk factors
6. Consistent with exposure dose and duration
7. Supported by an accurate anamnesis
8. Obvious and easily assessed in the case
9. Less likely due to concomitant treatments
10. No other reason to explain
11. Other judgments by the investigator/subinvestigator

None: It is clear that the adverse event was caused or aggravated by exacerbation of the underlying disease or other factors (comorbidities, other drugs/treatments, adverse events), and when a causal relationship with the use of the study drug is denied.

6.2.2.3. Response in the event of an adverse event

The investigator/subinvestigator will take appropriate measures when an adverse event occurs, pay attention to ensuring the safety of the subject, and strive to investigate the cause. If an adverse event for which a causal relationship to the study drug cannot be denied even after the completion of the study drug, a follow-up survey will be conducted until symptoms resolve, test values normalize, or return to pre-use status. However, for irreversible or permanent events, it shall be conducted until no change is observed based on medical judgment.

6.2.2.4. Responses when serious adverse events occur

Serious adverse events will be managed as follows. Furthermore, if the subject becomes pregnant, the same measures will be taken.

(1) The investigator/subinvestigator will take appropriate measures/treatments in the event of serious adverse events. The investigator shall create “Serious Adverse Event Report (Drug Clinical Trials: (Physician) Form 12)” within 24 h after learning of the occurrence of the event irrespective of whether there is a causal relationship. The person in charge of handling safety information (clinical trial coordinating office: CMIC Co. Ltd., see Attachment 1 of the protocol) will be contacted via email (when contacting, the coordinating investigator, investigators of all clinical trial medical institutions, investigational drug providers, CMIC Co. Ltd. monitoring department, and CMIC Co. Ltd. pharmacovigilance staff shall be copied in the email), and the information will be promptly shared among those involved in this clinical trial. Furthermore, the contents will be reported to the director of the medical institution in (medical) form 12 or the format specified by the medical institution as soon as possible.

(2) The investigator will consult with investigators at other medical institutions as necessary and

summarize their opinions as investigators.
(3) If determined that a report to the Minister of Health, Labor and Welfare is necessary in (2) above, the coordinating investigator will report to the regulatory authority within the prescribed period.
(4) When a serious adverse event is reported to the Minister of Health, Labor and Welfare, the investigator will report the contents of this report to the head of the medical institution as soon as possible.
(5) If additional information about the event becomes available, the investigator will make additional reports as soon as possible to the head of the site and the investigators and study drug providers of other sites. Such additional information shall be handled following the above procedures.

6.2.2.5. Provision of safety information

If new important information related to the safety of this clinical trial is obtained, the investigator shall promptly report in writing to the director of the clinical trial site and necessary measures shall be taken.

This information shall also be reported to the study drug provider and the coordinating investigator (clinical trial coordinating office).

7. Statistical analysis

Details of the statistical analysis shall be described in the analysis plan. An analysis plan shall be created before the first subject registration and finalized before data fixation. Unless otherwise specified, the significance level is 5% on both sides.

7.1. Analysis set

7.1.1. Population for efficacy analysis

FAS (full analysis set)

A set in which the following cases were excluded from all enrolled cases
(1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, and non-deliberation by the IRB)
(2) Cases violating eligibility criteria and cases unblinded by non-regular procedures
(3) Study drug-naïve cases
(4) Cases with no efficacy data

PPS (per-protocol set)

A set in which the following cases were excluded from all enrolled cases:
(1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, and non-deliberation by the IRB)
(2) Serious protocol violations (eligibility criteria violations, serious regulatory violations related to compatible medications, serious treatment violations, assignment violations, and unblinded cases due to non-regular procedures)
(3) Patients who do not meet the minimum values set in the clinical trial protocol
(4) Patients who took less than 80% of the study drug throughout the study period
(5) Cases with no efficacy data

7.1.2. Safety analysis set

A set in which the following cases were excluded from all enrolled cases:
(1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, and non-deliberation by the IRB)
(2) Study drug-naïve cases
(3) Cases in which all endpoints related to safety evaluation after the start of the trial cannot be used

7.2. Demographic statistics and other standard values

Summary statistics of subject demographic factors shall be calculated for each of the FAS and safety analyses, and the homogeneity of subject demographics shall be examined.

7.3. Analysis method of efficacy

7.3.1. Primary outcome

FAS is used to calculate the histopathological regression rate of HSIL/CIN2-3 lesions 16 weeks after

the first dose and its 95% confidence interval for each dose group. Furthermore, aggregation shall be performed by stratification through the allocation factor. Moreover, six contrasts [① [−1.5, −0.5, 0.5, 1.5] ② [−3, 1, 1, 1] ③ [−2, 0, 1, 1] ④ [−1, 3, −1, −1] ⑤ [−1, −1, 3, −1] ⑥ [−1, −1, −1, 3] were set for dose-response relationship of the placebo, low-dose, intermediate-dose, and high-dose groups. The p-value for each contrast shall be calculated, and the dose-response relationship with the lowest p-value shall be identified. Furthermore, no multiplicity adjustment shall be made. In addition, Fisher's exact test will be used to compare the response rate between each dose group and the placebo group.

A similar analysis as above shall be performed for the PPS.

7.3.2. Secondary outcomes

7.3.2.1. Histopathological improvement (regression rate) of HSIL/CIN 2-3 lesions at 24 weeks after the first dose

Based on FAS and PPS, the histopathological regression rate and its 95% confidence interval at follow-up shall be calculated for each dose group. Furthermore, FAS shall be aggregated by stratification through the allocation factor.

Moreover, a comparison of each dose group and placebo group will be performed using Fisher's test.

7.3.2.2. Presence or absence of HPV E7-specific immune response in HSIL/CIN 2-3 lesions at 16 and 24 weeks after the first dose.

Regarding the magnitude of HPV16 E7-specific Th1 immune response, the spot-forming cell (SFC) in stratification by allocation factors shall be examined in all FAS and PPS cases and FAS. In particular, the percentage of the “presence” of HPV E7-specific immune reactions and its 95% confidence interval at each measurement time point shall be calculated. Moreover, a comparison of each dose group and placebo group will be performed using Fisher's test.

7.3.2.3 Change in HPV 16 E7 molecule protein expression level: at 16 and 24 weeks after the first dose.

Summary statistics of change and rate of change in the protein expression level of HPV 16 E7 molecule for up to 16 and 24 weeks of initial administration shall be calculated for all cases in FAS and PPS and FAS stratified by allocation factors. Additionally, intergroup comparisons between each dose group and the placebo group were performed using the Wilcoxon rank sum test.

7.3.2.4 Effect on cytological features of HSIL/CIN 2-3 lesions at 16 and 24 weeks after the first dose

To evaluate the effect on cytological features, the percentage of "response," "stable disease," "progression" and "unevaluable" shall be tabulated by stratification according to the allocation factors for all FAS and PPS cases and FAS at each observation period.

7.2.3.5 Viral clearance of HPV16 at 16 and 24 weeks after the first dose.

Presence or absence of changes in HPV16 shall be aggregated by stratification according to allocation factors for all FAS and PPS cases and FAS.

7.2.3.6 The proportion of "CR," "PR," "SD," "PD," and "NE," which are pathological improvement indicators of CIN, at 16 and 24 weeks after the first dose.

The proportion of "CR," “PR,” “SD,” and “NE” shall be tabulated by stratification according to the allocation factors for all FAS and PPS cases and FAS at each observation period.

7.2.3.7 Disease control rate: Percentage of improvement to CIN2 or less at 16 and 24 weeks after the first dose in subjects with histology of CIN3 at enrollment

Among subjects who were histologically diagnosed with CIN3 at the time of enrollment, the proportion of subjects who improved to ≤CIN2 is expressed as the disease control rate. All FAS and PPS cases, as well as FAS, shall be stratified according to the allocation factors and the following analyses will be performed. The disease control rate and its 95% confidence interval shall be calculated for each dose group at the following two timepoints. Moreover, a comparison of each dose group and placebo group will be performed using Fisher's test.

7.3 Safety analysis method

Using the safety analysis set, the following tabulations will be performed for each dose group.

7.3.3 Adverse events

For adverse events, severity, seriousness, treatment, outcome, and relationship to study drug shall be tabulated, and the incidence rate shall be calculated. All adverse events up to week 16 of the first administration shall also be tabulated irrespective of their relationship to the study drug. From week 17 after the first administration, only adverse events with a clear causal relationship with the study drug shall

be followed up.

7.3.4 Laboratory test results

Summary statistics (mean, standard deviation, minimum, maximum, and median values) of laboratory test values and their changes from the pretreatment period shall be calculated for each test period.

7.4 Examination of recommended clinical dose

After the completion of administration, observation, and investigation of all cases, as well as after data fixation and unlocking, the clinically recommended dose of the study drug shall be determined based on the safety and pathological improvement (response rate) of HSIL/CIN 2-3 lesions.

7.5 Examination of E7 protein expression

E7 protein expression shall be examined in enrolled cases. The expression rate shall be tabulated according to the diagnosis of HSIL/CIN2 and HSIL/CIN3 at the time of enrollment. Additionally, the correlation between the expression of E7 protein and the therapeutic effect of the study drug in all patients and based on disease type (HSIL/CIN2 and HSIL/CIN3) at the time of enrollment will be examined.

7.6 Analytical treatment of subjects and data

Details of the criteria for subject analysis shall be provided in the analysis plan. Subsequent changes in subject handling standards shall be documented. The treatment of individual subjects shall be determined according to this standard before data fixation. Furthermore, the coordinating investigator shall decide how to handle unspecified issues before the data are fixed.

7.7 Significance level and confidence coefficient

The significance level and confidence coefficient for each analysis item will be defined in the analysis plan.

7.8 Interim analysis

No interim analysis shall be performed in this study.

8 Discontinuation of the clinical trial

8.1 Criteria for the discontinuation of the clinical trial for individual subjects based on the interim assessment

Cases suspected of having invasive cancer at the time of the interim assessment of this trial (week 9 after the first administration) shall undergo histological examination. If cervical cancer is detected irrespective of enrollment classification, the participation of the corresponding patient in this clinical trial shall be discontinued and will undergo surgical treatment.

8.2 Other criteria for the discontinuation of the clinical trial for individual subjects

If any of the following applies to a subject during the study period, the investigator/subinvestigator shall treat the corresponding subject as a discontinued case and conduct examination, observation, and evaluation at the time of discontinuation while continuing the necessary treatments. Furthermore, the date of discontinuation (the date when the investigator/subinvestigator decided to discontinue), the date of discontinuation of study drug administration, the reason for discontinuation, and the treatment/progress shall be recorded in the EDC. If treatment is discontinued due to an adverse event, a follow-up survey shall be conducted until the adverse event resolves in principle. However, for irreversible or permanent events, a follow-up study shall be conducted until no change is observed based on medical judgment. If tracking is not possible, the reason shall be recorded on the EDC.

If the subject does not come to the hospital, the investigator/subinvestigator shall conduct a follow-up survey of the subject via mail, telephone, etc. and follow-up as much as possible on the progress of symptoms, the presence or absence of adverse events, etc.

(1) If the subject requests to withdraw consent

(2) If the clinical trial is suspended due to the circumstances (relocation, change of physician or hospital transfer, busy schedule, unable to follow-up, etc.) of the subject

(3) If it has been clarified that the subject is not eligible after the start of clinical trial

(4) If the investigator/subinvestigator deems it necessary to discontinue the trial participation of the

subject in the event of an adverse event (including progression of complication or accident)
(5) If the clinical trial cannot be continued due to the progression of symptoms of the primary disease
(6) If the subject is discovered to be pregnant
(7) If there is a significant deviation from this protocol and it is determined that the subject is NE
(8) If the investigator/subinvestigator determines that it is difficult to continue the trial

8.3 Discontinuation of the clinical trial protocol

8.3.1 Discontinuation and suspension of the entire clinical trial plan

As there is no clinical application experience of this investigational drug, a safety evaluation committee comprising third-party experts shall be established in this clinical trial. In the following cases, the coordinating investigator confirms with the safety evaluation committee whether or not to continue this clinical trial, decides on the response for this clinical trial, and informs the investigator of each medical institution (details are according to a separate procedure manual).

① When 80 subjects are enrolled

② If a serious adverse event for which a causal relationship to the study drug cannot be ruled out occurs

If an unknown serious adverse event occurs for which a causal relationship to the study drug cannot be ruled out (including events that have been changed to have a causal relationship since the initial report), the coordinating investigator shall promptly report to the safety evaluation committee and confirm the opinion of each committee member on whether or not to continue the entire clinical trial, whether or not study drug administration can be continued in the study subjects, the need for protocol revisions, the need to revise the informed consent document, whether new subjects can be enrolled, and other necessary matters. After confirming the opinions of each committee member, the coordinating investigator shall determine the response for this clinical trial based on the occurrence of the relevant event and contact the investigator of each medical institution. Furthermore, the subinvestigators shall check the health status of the subjects, etc. as needed, and confirm via phone call, considering the response policy contacted by a clinical trial coordinator and the background of the subject.

The investigator shall promptly report in writing to all investigators (subinvestigators), the head of the site, and the IRB.

(1) Efficacy and safety information that could have a significant impact on the continuation of the clinical trial is clear
(2) If other reasons that make it difficult to continue the clinical trial occur

8.3.2 Discontinuation and suspension of clinical trials at some medical institutions

If any of the following apply, the clinical trial at the relevant medical institution will be discontinued or suspended. If any subject is still in the clinical trial, the investigator/subinvestigator shall promptly inform the subject of the discontinuation of the trial and take necessary measures, such as changing to other appropriate treatments.

(1) When the investigator, subinvestigator, medical institution, etc. are found to be in serious or persistent non-compliance with the GCP or protocol via monitoring or auditing by the investigator or a person entrusted according to a separately determined procedure
(2) When the investigator determines that it is difficult to continue the clinical trial at the medical institution and obtains approval from the IRB

9 Deviations/changes from protocol

(1) If changes to the protocol are unavoidable after the start of the trial, the investigator may revise the protocol.
(2) Investigators/subinvestigators shall not implement changes to the revised protocol before approval by the IRB at the trial site.
(3) The investigator shall document all protocol deviations. To avoid imminent danger to the subject of deviant behavior, the investigator shall prepare a record explaining the reasons for non-compliance with the protocol for other unavoidable medical reasons and immediately submit it to the director of the medical institution, and maintain a copy of it. The submitted information shall be promptly reported to the IRB via the head of the medical institution.
(4) The investigator shall notify the head of the site and the IRB through the head of the site of any changes to the trial that would materially affect the conduct of the trial or increase the risk to subjects and

promptly submit a report.

10 Monitoring procedure

(1) A person designated by the coordinating investigator monitors the study to ensure that the study is being conducted appropriately and that the reliability of the data is sufficiently maintained. The method of monitoring, timing of implementation, etc. shall be according to the separately determined monitoring plan.
(2) Investigators, subinvestigators, study drug managers, and sites shall cooperate with monitoring by a person designated by the coordinating investigator.

11 Direct browsing of source materials, etc.

The head of the clinical trial site and the investigator or subinvestigator shall accept and cooperate with monitoring and audits of personnel designated by the coordinating investigator and investigations by the IRB and regulatory authorities. In this case, all clinical trial-related records, including source documents, shall be made available for direct inspection upon request by monitors, auditors, IRB, or regulatory authorities.

Furthermore, all clinical trial-related records include the documents to be stored, such as records related to clinical trial requests/contracts, original data related to the implementation of clinical trials, health journals, records of the study drug, records of the subject's consent, and records of the IRB. These records shall be the source material.

[Items for which EDC data can be used as source material]

Among the data entered into the EDC, the items listed below that are directly entered into the EDC by the investigator/subinvestigator shall be permitted to use the EDC data as the source material. Furthermore, if these items are described in the clinical trial-related records, the clinical trial-related records containing these descriptions shall be the source documents.

(1) Physician comments in EDC
(2) Reason for judging the relationship between the adverse event and the study drug as "related"

12 Case report form and notes on preparation

12.1 Case report form

The case report form for this clinical trial shall be the "IGMKK16E7 phase I/II clinical trial electronic case report form."

12.2 Preparation and submission of EDC

(1) The investigator/subinvestigator prepares the EDC according to the provisions of the protocol and the "EDC operation manual" and "eCRF input manual" prepared by the coordinating investigator. Furthermore, at the time of preparation, the clinical trial collaborator may transcribe the EDC description from the original document.
(2) The investigator shall check, verify, and sign the contents of the EDC prepared by the subinvestigator.
(3) The data in the EDC must be consistent with the source material. If there are any discrepancies, the investigator will create and keep a record explaining the reasons.

12.3 Correction of the EDC

(1) Corrections to the content of the EDC shall be made by the investigator or subinvestigator according to the "EDC Operation Manual" and "eCRF Input Manual." The clinical trial collaborator can make corrections to the parts transcribed by the clinical trial collaborator.
(2) The investigator will check the EDC corrections made by the subinvestigator and the clinical trial collaborator and confirm that there are no discrepancies.

12.4 Precautions when creating and modifying EDC

(1) Passwords and IDs must be strictly managed so that they cannot be seen by others.

(2) Training shall be conducted in advance on how to operate the EDC. Personnel who do not complete the training shall not be allowed to operate the EDC.

13 Clinical trial quality control and quality assurance

13.1 Quality control

The investigator shall perform quality control of the clinical trial by entrusting the clinical trial work according to the procedure document specified separately.

13.2 Quality assurance

The investigator will ensure the quality of each development work by performing the above-mentioned quality control.

To evaluate whether clinical trial systems and clinical trials are conducted according to the Pharmaceuticals and Medical Devices Law, their enforcement regulations, GCP, clinical trial protocols, standard operating procedures, and procedures established by medical institutions, an auditor who is independent of departments involved in drug development systematically investigates and confirms the work and documents related to clinical trials.

14 Saving the records

(1) The head of the medical institution shall retain the required documents at the medical institution until 1) or 2) (whichever is later) mentioned below. When storing records, a person in charge of storage shall be appointed.
 1) The date on which the study drug provider receives manufacturing and marketing approval for the drug related to the test drug (if development is discontinued, the date on which 3 years have passed since the date of notification of development discontinuation)
 2) The day on which 3 years since the trial was discontinued or completed

(2) The investigator shall retain the required documents to be retained until 1) or 2), whichever is later.
 1) The date on which the study drug provider receives manufacturing and marketing approval for the drug related to the test drug (if development is discontinued, the date on which 3 years have passed since the date of notification of development discontinuation)
 2) The day on which 3 years since the trial was discontinued or completed

(3) The investigator shall notify the head of the medical institution when it is no longer necessary to maintain the essential documents.

15 Research ethics

15.1 Laws and standards to be observed

The clinical trial shall be conducted according to this clinical trial protocol, Pharmaceutical and Medical Device Act (previously the Pharmaceutical Affairs Act; criteria prescribed in Article 14, Paragraph 3 and Article 80-2), Ministerial Ordinance on Standards for Conducting Clinical Trials of Pharmaceuticals (MHLW Ordinance No. 28, March 27, 1997; Last revision: MHLW Ordinance No. 9, January 22, 2016) and ethical principles based on the Declaration of Helsinki (revised on October 19, 2013).

15.2 IRB in the participating medical institution

Before the implementation of this clinical trial, the IRB of the medical institution shall approve the contents of the clinical trial protocol, case report form, informed consent form for the subjects, eligibility of the investigator/subinvestigator, and appropriateness of conducting clinical trial.

The same shall apply when revising the clinical trial protocol and informed consent document for subjects.

Furthermore, if the duration of the clinical trial exceeds 1 year, we will continue to review whether the clinical trial is being conducted appropriately at least once a year. In addition, if necessary, the implementation status of clinical trials will be investigated.

15.3 Consent of subjects

15.3.1 Obtaining written consent

Before the start of this trial, the investigator (subinvestigator) shall explain the contents of the informed consent document approved by the IRB to the subject before case registration. Voluntary written consent shall be obtained from subjects for participation in clinical trials. When obtaining informed consent, subjects shall be given the opportunity to ask questions and sufficient time to decide whether or not to participate in the study. Additionally, sufficient answers are given to the questions of the subjects.

Subjects shall sign a dated consent form to certify their consent to participate in this study. The investigator or subinvestigator shall also sign the dated consent form and hand over a copy of the consent form and the informed consent form to the subject.

If the clinical trial collaborator shall provide a supplementary explanation, the clinical trial collaborator shall also sign the dated informed consent form.

If the subject is being treated by another physician, the investigator (subinvestigator), with the consent of the subject, shall notify the physician that the subject will participate in the study.

<Items to be explained to the subject>

(1) The trial involves research
(2) The aim of the trial
(3) Clinical trial methods (experimental aspects of clinical trials, subject selection criteria, etc.)
(4) The planned participation period of the subject in the trial
(5) The expected number of participants in the clinical trial
(6) Anticipated health benefits and hazards
(7) Presence or absence of other treatment methods for the subject and expected significant risks and benefits of these treatment methods
(8) The compensation and treatment that subjects may receive in the event of clinical trial-related health hazards
(9) Participation in the trial is at the discretion of the subject. The subject may refuse or withdraw the participation in the trial at any time. The refusal or withdrawal will not cause the subject to be treated unfavorably or lose due benefits if they opt out of the clinical trial.
(10) The subjects or their representative will be promptly informed upon obtaining information that may affect the intent of the subjects or their representatives regarding their continued participation in the trial.
(11) The conditions or reasons for discontinuing participation in a clinical trial
(12) Monitors, auditors, IRB, and regulatory authorities should be able to access source documents. The confidentiality of subjects should be preserved in such cases. The subject must sign and seal the consent form to allow access to medical records
(13) The confidentiality of subjects should be preserved even when trial results are published
(14) The details of the expenses, if any, borne by the subject
(15) The details of monetary compensation, if any, to the subject (calculation of the payment, etc.)
(16) Name, title, and contact information of investigator/subinvestigator
(17) The information desk of the implementing medical institution that should be contacted if the subject wishes to obtain further information regarding the trial and the rights of subjects or the contact information in the event of a health hazard related to the trial.
(18) The matters to be observed by the subject
(19) Type of IRB that investigates and deliberates on the appropriateness of the relevant clinical trial
(20) Matters to be investigated and deliberated by each IRB
(21) Other matters related to the IRB

15.3.2 Revision of informed consent document

If information is obtained that may affect the decision of the subject to continue participating in the study, the investigator/subinvestigator shall promptly provide the relevant information to the study subjects, confirm their intention to continue participating in the study, and record this in a document (medical record).

If the investigator deems it necessary, the explanatory document will be revised and approved by the IRB.

After the revision of the explanatory document has been approved by the IRB, the investigator/subinvestigator shall explain the contents of the document to the study subjects. The voluntary written consent of the subjects shall be collected for their continued participation in the clinical

trial.

15.4 Subject privacy protection

When creating EDCs and handling subject data, etc., due consideration must be given to the confidentiality of subjects. Subjects shall be identified using subject identification codes. Monitors and auditors appointed by the coordinating investigator, the IRB, and regulatory authorities shall protect the privacy of subjects when directly viewing medical records (source materials).

16 Monetary payment and insurance

16.1 Monetary payment

As this is an investigator-initiated clinical trial, the expenses related to the subject during the clinical trial period, except for the study drug, are covered by the non-insurance combined medical expense system. Hence, no monetary compensation shall be paid to the subjects.

16.2 Health damage compensation and insurance

Compensation for the health damage of subjects is stipulated in the "Procedure for Subject's Health Damage Compensation."

If a subject suffers health damage during this clinical trial, the investigator/subinvestigator shall compensate, unless the damage is caused by reasons attributable to the subject. The investigator/subinvestigator shall secure the liability via insurance.

17 References

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