Phase I/II investigator-initiated clinical trial of Human Papillomavirus (HPV)-targeting immunotherapeutic agent IGMKK16E7 on patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN 2-3) (Trial protocol No.: IGMKK/16E7/P1-2)

Statistical analysis plan

Ver. 2.1

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1. Introduction

1.1 Role of statistical analysis plan

This document is the statistical analysis plan of "Phase I/II investigator-initiated clinical trial of Human Papillomavirus (HPV)-targeting immunotherapeutic agent IGMKK16E7 on patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN 2-3) (Trial Protocol No.: IGMKK/16E7/P1-2)". This plan was created before the registration of the first subject and finalized before data fixation. If changes or additions need to be made after Ver. 1 has been finalized, a revised version will be created after the change history and reasons are clarified.

1.2 Changes from trial protocol

This analysis plan (Ver. 2) is a revision of Ver. 1 (May 27, 2019). In Ver. 2, the following revisions have been made in accordance with the revisions from V8.0 (dated January 10, 2020) to V13.0 (dated March 9, 2022) of the trial protocol.

- The analysis target of evaluating the improvement in cytology of HSIL/CIN 2-3 lesions, which is a secondary endpoint, was changed.
- Analysis methods for the following three secondary endpoints were added: 1) change in HPV 16 E7 molecule protein expression level (relative quantification value) and 2) disease control rate.

Furthermore, the HPV 16 E7 molecule protein expression level (absolute quantification value) before the start of administration and the HPV E7-specific immune response before the start of administration were added as stratification factors for the stratification analysis. Additionally, the following were added as exploratory analyses.

1) Investigation of the distribution of E7 protein expression level (absolute quantification value) before first administration.
2) Investigation of the relationship between the E7 protein expression level (absolute quantification value) before first administration and the improvement effect of the trial drug.
3) Investigation of the relationship between changes in the E7 protein expression level (relative quantification value) after administration and pathological judgment.
4) Investigation of the relationship between the presence or absence of HPV E7-specific immune response before first administration and the improvement effect of the trial drug.
5) Investigation of the relationship between the presence or absence of HPV E7-specific immune response after administration and pathological judgment.
6) Investigation of the relationship between the HPV E7-specific immune response SFC value after administration and pathological judgment.
7) Investigation of the relationship between the log-transformed HPV E7-specific immune response SFC value after administration and pathological judgment.

Moreover, we found that the analysis plan (Ver. 2) did not accurately reflect the changes in the

revision items of the clinical trial protocol; therefore, the following items were revised in this analysis plan (Ver. 2.1).

- When the protocol was revised to Ver. 2, the permitted range for subject visits was changed; however, this change was not reflected in the analysis plan. Therefore, the range of data adoption for the evaluation periods (Section 6.4.4) was changed to reflect the permitted range of visits in the protocol.
- When the protocol was revised to Ver. 5 of this protocol, we clarified the regulations regarding histology at week 24 for cases judged to be normal at week 16. Separately, we stipulated that follow-ups up to 24 weeks would be conducted according to the diagnosis by the attending physician at the facility 16 weeks after the first dose, except for cases judged to be CIN3 requiring treatment or invasive cancer. However, this content was not reflected in this analysis plan. Therefore, the above items were added to the primary endpoint (Section 4.1.1), and the handling of missing values (Section 6.5) was revised to reflect this content.

2. Purpose of trial

The aim of this clinical trial was to orally administer IGMKK16E7 (the trial drug) to patients with high-grade cervical intraepithelial neoplasia (HSIL/CIN 2-3) to confirm the safety of the trial drug and determine the clinical recommended dose.

3. Trial method

3.1 Trial design

The trial was 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).

- Dosage and dose: The subject will take three sticks of trial drug once daily before breakfast. Consecutive administration for five days constitutes one course, with a total of four courses administered from the first administration (Day 1 to Day 5), Day 8 to Day 12, Day 22 to Day 26, and Day 50 to Day 54. However, the dose on Day 1 will be administered between meals in the hospital.
- Trial period: 16 weeks. Primary evaluation at 16 weeks after first dose.
- Follow-up period: eight weeks. Pathological evaluation (biopsy) was performed 16 weeks after the first dose to avoid missing patients who had progressed to invasive cancer; if the lesion was CIN3 or lower, the patients were again evaluated pathologically 24 weeks after the first dose. If a patient was diagnosed clinically as CIN3 or more at week 16, she received standard therapy.

3.2 Randomization

Registered subjects will be randomized in a 1:1:1:1 ratio for each of the four dose groups. The following three factors are used as allocation adjustment factors.

1. Diagnosis (HSIL/CIN2, HSIL/CIN3)
2. HPV genotype (HPV16 only, HPV16+other types)
3. Facilities (four facilities)

3.3 Target sample size

The sample includes 164 cases, with 41 cases each for the placebo group, low-dose group (0.5 g/administration/day), intermediate-dose group (1.0 g/administration/day), and high-dose group (1.5 g/administration/dose). Each group will have 10 cases with HSIL/CIN2 at the time of registration. See Section 5.2 of the trial protocol for the setting basis.

3.4 Interim analysis and data monitoring

No interim analysis is planned in this trial.

3.5 Trial schedule

Table 1 shows the trial schedule.

4. Endpoints

4.1 Efficacy endpoints

1.1.1 *Primary endpoint*

The primary endpoint is the histopathological regression rate at 16 weeks after the first dose, that is, the pathological improvement indicator based on the histology* of cervical intraepithelial neoplasia and changes from before administration of the trial drug are judged according to the following stages.

- Complete response (CR): Regression to normal.
- Partial response (PR): Regression to LSIL/CIN 1.
- Stable disease (SD): No change from HSIL/CIN 2 at registration, no change from HSIL/CIN 3 at registration, or no change from HSIL/CIN 3 to HSIL/CIN 2.
- Progressive disease (PD): Progression from HSIL/CIN2 at registration to HSIL/CIN3, or change to cervical cancer regardless of classification at registration.
- Not evaluable (NE): Unable to determine as CR, PR, SD, or PD.

Cases whose participation was discontinued upon detection of cervical cancer during interim evaluation (nine weeks after the first administration) will be considered as PD and included in the 16-week tabulation.

The primary objective of this trial is to investigate the dose-response of each regression rate in each dose group and determine the clinically recommended dose.

* Histology: Histopathological tests of the cervix will be conducted before administration of the trial drug, at 16 weeks after first dose (or at discontinuation), and at 24 weeks after first dose (applicable

cases only). The implementation of histopathological tests at 24 weeks after the first dose (applicable cases only) of cases that were judged to be normal at 16 weeks after the first dose is also stipulated in cases where a precancerous cervical lesion area is confirmed by colposcopy tests at 24 weeks after the first dose.

Table 1　Observation / survey and test items during the trial (follow-up) period

試験（追跡）期間中の観察・調査及び検査項目

項目	適格性確認期間		試験期間										追跡期間		
	初回来院	服用開始日 Day 1	（第1週） Day 2～7	（第2週） Day 8～14	（第3週） Day15～21	（第4週） Day22～28	（第5週） Day29～35	（第6～7週） Day36～49	（第8週） Day 50～56	（第9週） Day 57～63	（第10～15） Day64～105	（第16週） Day106～112	（第17～23週） Day 113～161	（第24週） Day 162～168	中止時
来院	○	○					●			●		●		◎	●
来院の許容幅							Day29～42			Day57～77		Day106～126[h]		Day162～182[h]	
治験薬の処方		●													
治験薬の服用		←→	←→	←→		←→			←→						
服薬状況の確認							●			●					
同意取得	○														
選択・除外基準の確認	○[a]	○													
症例登録		○													
HPVジェノタイプ検査（適格性確認用）	○[b]														
HPVジェノタイプ検査（中央検査）		○[c]										●		◎	●
細胞診（中央病理判定）	○[b]											●		◎[j]	●
細胞診（実施医療機関判定）										△					
細胞診	○[b]									●		●		◎	●
コルポスコピー検査	○[b]									●		●		◎	●
臨床検査		○[d, e]					●			●		●		◎	●
妊娠反応（血清hCG）		○[d, e]										●			●
HIV検査	○[f]														
HPV16/E7 タンパク質発現量		○[c]										●		◎	●
E7タンパク質発現（子宮頸部擦過細胞）		○[g]													
HPV E7特異的免疫応答		○										●		◎	●
自覚症状[h]・他覚所見		●	●	●	●	●	●	●	●	●	●	●		◎	●
併用薬・併用療法	←											→			
既往歴、合併症の確認	○														
有害事象の確認[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　△：感染症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：同意取得後に、選択・除外基準確認のための検査を実施する　b：同意取得前90日以内のデータ（他院データ、院内データ不問）がある場合、当該データにて適格性を確認する。該当するデータがない場合には同意取得後に検査を実施する。

c：同日に採取するE7タンパク質発現用の検体を用いて検査を実施する。　d：治験薬の処方前に問題が無い検査結果である（妊娠している可能性が無い）ことを確認する。治験薬の投与（服用）は、当該臨床検査の実施日から10日以内に開始する。

e：同意取得日に臨床検査が実施されており、服用開始日が当該検査の実施日から10日以内の場合、服用開始日に新たに検査を実施する必要はない。

f：初回来院時又は服用開始日に実施する。治験薬の処方前にHIVに感染していないことを確認する。治験薬の投与（服用）は、当該検査の実施日から14日以内に開始する。　g：本検体を用いて、同日のHPVジェノタイプ検査も実施する。

h：被験者は、健康日誌に自覚症状を記録する。　i：投与期間中は健康日誌の記載内容を確認する。試験期間終了後の追跡期間（第17週以降）は本治験薬に起因することが明らかな有害事象のみを確認する。

j：初回投与後16週時に正常と判定された被験者については、同日（第24週時）のコルポスコピー検査にて子宮頸部前がん病変領域が確認された場合にのみ実施する。

k：検体の状態に伴う再検査が必要な場合には、初回の検査実施日を起点として更に14日以内の再検査を許容する。

Item	Eligibility confirmation period		Trial period										Follow-up period		
	Initial visit	Administration start day Day 1	(Week 1)	(Week 2)	(Week 3)	(Week 4)	(Week 5)	(Week 6–7)	(Week 8)	(Week 9)	(Week 10–15)	(Week 16)	(Week 17–23)	(Week 24)	At discontinuation
Visit															
Permitted range of visit															
Prescription of trial drug															
Administration of trial drug															
Confirmation of drug administration status															
Consent acquisition															

Confirmation of selection / exclusion criteria															
Case registration															
HPV genotype test (for eligibility confirmation)															
HPV genotype test (central test)															
Histology (central pathological judgment)															
Histology (implementing medical facility judgment)															
Histology															

Colposcopy															
Laboratory test															
Pregnancy reaction (serum hCG)															
HIV test															
HPV16E7 protein expression level															
E7 protein expression (cervical cells)															
HPVE7-specific immune response															
Subjective symptoms[h] / objective findings															

Concomitant drugs / therapies															
Confirmation of medical history and complications															
Confirmation of adverse events[i]															

○: Item that is implemented before the start of administration or confirms the test results; ●: Item that is implemented after the start of administration; △: Item that is implemented in case of suspected invasive cancer; ◎: Item that is implemented only on cases judged to be applicable in the follow-up survey at 16 weeks after administration

a: Implement test for selection/exclusion criteria confirmation after consent

b: Confirm eligibility based on applicable data in case there is data within 90 days prior to consent (data at another hospital, in-hospital data not required). Implement the test after consent in case there is no applicable data.

c: Implement test using E7 protein expression specimen collected on the same day

d: Confirm no problem with the test results (no possibility of pregnancy) before prescription of the trial drug. Administration of the trial drug shall start within 10 days from the day when the applicable laboratory test was conducted.

e: If the laboratory test was conducted on the date of consent and the administration start date was within 10 days from the date when the applicable test was conducted, there is no need to conduct a new test on the administration start date.

f: Perform at initial visit or on the administration start date. Confirm that the subject does not have HIV prior to prescribing the trial drug. Start administration of the trial drug within 14 days from the date when the applicable test was conducted.

g: Perform HPV genotyping on the same day using the collected specimen.

h: Subject shall record subjective symptoms in a health journal.

i: Confirm entries in the health journal during the administration period. The follow-up period (from week 17) shall only confirm adverse events that were clearly caused by the trial drug.

j: For subjects judged to be normal at week 16, perform only if a precancerous cervical disease was confirmed by colposcopy conducted on the same day (week 24).

k: In case retest is necessary because of the condition of the specimen, retest is permitted within 14 days from the date when the initial test was performed.

4.1.2 Secondary endpoints

1) Regression rate at 24 weeks after the first dose

2) HPV E7-specific immune response: before trial drug administration, 16 and 24 weeks after the first dose.

The presence or absence of HPV E7-specific immune response at 16 weeks after the first dose and at 24 weeks after the first dose will be used as an endpoint. Separately, the presence or absence of HPV E7-specific immune response prior to the first dose will be used as a stratification factor for stratified analysis.

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

HPV 16 E7 molecule protein expression level will involve measurements of the expression level (copy/ng) by relative quantification before first administration of the trial drug, and at 16 and 24 weeks after the first dose. The expression level by absolute quantification will also be measured only before the first administration of the trial drug. The magnitude and rate of change of the expression level (relative quantification value) from before first administration to 16 and 24 weeks after the first dose will be the endpoint. Separately, the expression level (absolute quantitative value) before the first dose is used as a stratification factor for stratification analysis. For this stratification factor, two categories of "below median" and "above median" and three categories of "below first tertile," "above first tertile, below second tertile," and "above second tertile" will be used.

4) Improvement in cytology* of HSIL/CIN 2-3 lesions: at 16 and at 24 weeks after the first dose. Changes in lesions in cytology are judged by any of the following in subjects diagnosed with HSIL at the time of registration.

PR: Change to LSIL, ASC-US, or NILM

SD: No change from HSIL

PD: Change to SCC

NE: Change to AGC or ASC-H

* Cytology: Cytological tests of the cervix will be conducted before trial drug administration, nine weeks after the first dose, 16 and 24 weeks after the first dose.

5) Percentages of “CR,” “PR,” “SD,” and “PD” in the pathological improvement indicators of cervical intraepithelial neoplasia lesions: at 16 and 24 weeks after the first dose.

6) Presence or absence of changes in the HPV16: at 16 and 24 weeks after the first dose. HPV genotype test: conducted before trial drug administration, 16 and 24 weeks after the first dose (applicable cases only) to measure the HPV genotype.

7) The one with better results at both 16 weeks and 24 weeks after the first dose is considered the best response determination.

8) Disease control rate: percentage of subjects with histology of CIN3 at registration improving to CIN2 or lower at 16 and 24 weeks after the first dose.

4.1.3 Exploratory endpoints

1) Investigate distribution of the E7 protein expression level (absolute quantification value) before first administration.

2) Investigate the relationship between the E7 protein expression level (absolute quantification value) before first administration and the improvement effect of the trial drug.

3) Investigate the relationship between changes in the E7 protein expression level (relative quantification value) after administration and pathological judgment.

4) Investigate the relationship between the presence or absence of HPV E7-specific immune response before first administration and the improvement effect of the trial drug.

5) Investigate the relationship between the presence or absence of an HPV E7-specific immune response after administration and pathological judgment.

6) Investigation of the relationship between the HPV E7-specific immune response SFC value after administration and histopathological regression. [For the HPV E7-specific immune response, data on continuous values of the E7-specific immune response (SFC/10^6 cells) are obtained. Hence this item will be referred to as the HPV E7-specific immune response SFC value].

7) Investigate the relationship between the log-transformed HPV E7-specific immune response SFC value after administration and histopathological regression.

4.2 Safety endpoints

1) Incidence of adverse events and side effects

This refers to any unfavorable event occurring between the use (administration) and the end of use (administration) of this trial drug, regardless of whether or not it is related to the trial drug. During the follow-up period, information will be collected only for events for which a causal relationship cannot be rejected.

2) Laboratory test values

Hematology tests, blood biochemistry tests, and urinalysis.

5. Analysis set

5.1 Full analysis set (FAS)

The FAS was a set in which the following cases were excluded from all registered cases:

1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, non-deliberation by the IRB).

2) Cases violating eligibility criteria, cases unblinded by non-regular procedures.

3) Trial drug-naive cases.

4) Cases with no efficacy data.

5.2 Per protocol set (PPS)

The PPS was a set in which the following cases were excluded from all registered cases:

1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, non-deliberation by the IRB).

2) Serious protocol violations (eligibility criteria violations, serious regulatory violations related to compatible medications, serious treatment violations, assignment violations, unblinded cases due to non-regular procedures).

3) Patients who do not meet the minimum values set in the clinical trial protocol (e.g., if the percentage of drugs taken before meals (regardless of morning, afternoon, or evening) is less than 50%).

4) Patients who took less than 80% of the trial drug throughout the trial period.

5) Cases with no efficacy data.

5.3 Safety analysis set

The safety analysis set was a set in which the following cases were excluded from all registered cases:

1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, non-deliberation by the IRB).

2) Trial drug-naive cases.

3) Cases in which all endpoints related to safety evaluation after the start of the trial cannot be used.

6. Statistical analysis policy

6.1 Significance level and confidence level

Unless otherwise specified, tests are two-sided tests with a significance level of 0.05, and the confidence interval is a two-sided confidence interval with a confidence coefficient of 95%.

6.2 Multiplicity adjustment

Given that this trial is a phase I/II trial, multiplicity was not considered in either pairwise comparisons or dose-response evaluations using the maximum contrast method of the response rate, which is the primary efficacy endpoint, between each dose group and the placebo group. Additionally, multiplicity of tests will not be considered when tests are repeated for secondary endpoints.

6.3 Summary statistics

In this statistical analysis plan, unless otherwise specified, the quantitative summary statistics are set as the number of subjects, mean, standard deviation, minimum, median, and maximum; and the qualitative summary statistics are the number of subjects in each category and their percentages (%).

6.4 Handling of time-series data

6.4.1 Calculation of number of days

In this statistical analysis plan, the calculation of the number of days is standardized by the following calculation method:

administration start day onwards = target day – administration start day (day 1)+1

before administration start day = target day – administration start day

Therefore, the administration start day is day 1, the day after the start of administration is day 2, and the day before the start of administration is day −1.

6.4.2 Baseline

The baseline for evaluation of the time-series data is the value observed at the most recent time point prior to the first administration of the trial drug.

6.4.3 Discontinuation of trial

In this document, the terms “discontinue” and “at discontinuation” are used to mean “discontinuation of the trial” and “at the time of discontinuation of the trial,” respectively. The “discontinuation of trial drug administration” will be written exactly as described.

6.4.4 Range of data adoption for evaluation periods

Table 2 shows the trial protocol-stipulated evaluation periods and the corresponding time intervals of the efficacy endpoints of histology, cytology, presence or absence of an HPV E7-specific immune response, and HPV genotype changes, as well as the safety endpoints of laboratory tests. In practice, the tests may be conducted at a time point outside the defined time interval. Therefore, the range of data adoption is defined in the rightmost column of Table 2, and the following two points are set as the policy for setting the range of data adoption in such cases:

1) For the four visits at weeks 5, 9, 16, and 24, for which laboratory test measurements are planned, there should be no overlap in the two ranges of data adoption that correspond to two adjacent visits, and no gaps in time.

2) For weeks 5, 9, and 16, the upper limit of the range of data adoption should be one week after the last day of the permissible range of visits (e.g., for week 5, the range should be until day 49, which is one week after day 42, i.e., the last day of that week).

The data obtained within the range of data adoption should be adopted as the data of the corresponding visit. For example, if histology was conducted within the range of day 85–day 133, then the results will be adopted as data at the end of the trial (16 weeks after first administration).

Table 2. Trial protocol-stipulated evaluation period and range of data adoption

Evaluation period	Time interval (according to clinical trial	Test item				Range of data adoption
		Histology	Cytology	HPV*	Laboratory test	

	protocol)					
First visit		○	○			~ Day1
Administration start day	Day 1			○	○	~ Day1
Week 1	Day 2–7					
Week 2	Day 8–14					
Week 3	Day 15–21					
Week 4	Day 22–28					
Week 5	Day 29–42**				●	~ Day 2–49
Week 6–7	Day 36–49					
Week 8	Day 50–56					
Week 9	Day 57–77**		●		●	~ Day 50–84
Week 10–15	Day 64–105					
Week 16	Day 106–126**	●	●	●	●	~ Day 85–133
Week 17–23	Day 113–161					
Week 24	Day 162–182**	◎	◎	◎	◎	~ Day 134
At discontinuation		●	●	●	●	

* HPV: HPVE7-specific immune response, HPV genotype

** : Permissible range of visit

○ : Implemented before start of administration; ● : Implemented after start of administration; ◎ : Implemented only for cases subject to follow-up survey

If the test was conducted multiple times within the range of data adoption, including the test at the time of discontinuation of the trial, the date closest to the middle day of the protocol-specified time interval is adopted (e.g., for week 16, this is day 116, which is the middle day of the time interval of day 106–126). If there are two test dates that are the same number of days apart before and after the middle day of the stipulated time interval, the data of the latter test date is adopted. Data of laboratory tests conducted at discontinuation of the trial will also be tabulated separately as data for the evaluation period of “at time of discontinuation.” However, it should be noted that the acceptance or rejection of data at the time of discontinuation of the trial also depends on the reason for discontinuation (see Section 6.6).

6.5 Handling of missing values

As a general rule, missing data will not be supplemented. However, as described in Section 4.4.1, the implementation of histopathological tests at 24 weeks after the first dose (applicable cases only) for cases judged to be normal at 16 weeks after the first dose is also stipulated in cases where CIN lesion is confirmed by colposcopy. Based on these points, handling will be as follows: (1) In the cases judged to be “normal” at 16 weeks after the first dose, the data of “at week 24” will be handled as normal. (2) In the cases judged to be “CIN3” at 16 weeks after the first dose, the data of “at week 24” will be handled as CIN3. (3) In the cases with missing histopathological tests at 16 weeks after the first dose will be handled as missing data.

6.6 Handling of data at discontinuation

The handling of data obtained at discontinuation when discontinuing the trial for individual subjects is shown in Table 3, in accordance with the reason for discontinuation.

Table 3. Handling of data at discontinuation

Reason for discontinuation	Handling of data obtained at discontinuation	
	Efficacy	Safety
Cervical cancer detected at interim evaluation (nine weeks after first administration)	Adoption Histology at end of trial (16 weeks after first administration) is handled as PD	
Request for withdrawal of consent from subject	Adoption However, non-adoption if use of data is refused	
Suspension of trial because of subject circumstances (address relocation, change in physician / hospital transfer, busy schedule, unable to follow-up, etc.)	Adoption	
Revealed after start of trial as not eligible	Exclusion from FAS and PPS	Adoption
Judgment of discontinuation by investigator / sub-investigator because of occurrence of adverse event	Adoption	
Difficult to continue treatment because of worsening symptoms of primary disease	Adoption	
Revealed to be pregnant after start of trial	Adoption	
Judged not evaluable because of significant deviation from this trial protocol	Adoption in FAS, exclusion from PPS	Adoption

Judged difficult to continue treatment by investigator / sub-investigator for other reasons	Adoption

6.7 Handling of safety data

6.7.1 Adverse events / side effects

Adverse events and side effects that occur after the first administration of the trial drug are targeted.

- Number of incident cases: if multiple adverse events (side effects listed in Table in the Appendix) that correspond to the same PT code (or SOC code) occur in the same subject, they will be counted as a single case.
- Incidence proportion: calculated as the number of incident cases / number of observed cases.
- Number of occurrences: if multiple adverse events (side effects listed in Table in the Appendix) that correspond to the same PT code (or SOC code) occur in the same subject, they will be counted as a single occurrence.

6.7.2 Laboratory test values

See Appendix 1 for laboratory test items conducted in this trial.

7. Analysis method

See Appendix 2 for the list of forms created in this analysis, and Appendix 3 for the software and dictionaries used.

7.1 Case composition

7.1.1 Breakdown of subjects

Analysis target: Registered / allocated cases

Analysis content: Calculate the following for each group, where the denominator of the percentage is the number of registered / allocated cases:

・Number of cases who were administered the trial drug, number of cases who were not administered the trial drug, and their percentages

・Number of cases who completed four courses of administration; number of cases who did not complete four courses of administration; number of cases who completed one, two, or three courses of administration; and their percentages

・Number of cases who completed observation during the trial period (16 weeks) and the percentage

・Number of cases who completed observation during the follow-up period (eight weeks) and the percentage

・Number of cases who discontinued the trial during the trial period or follow-up

period and the percentage

・Number of cases by reason for discontinuation. See Table 2 for classification of the reasons for discontinuation

7.1.2 Deviation from trial protocol

Analysis target: Registered / allocated cases

Analysis content: Calculate the following for each group, where the denominator of the percentage is the number of registered / allocated cases:

・Number of cases with the presence or absence of deviation and the percentage.

・Number of cases according to each reason for deviation.

The reasons for deviation are classified as follows:

1) Deviation relating to selection / exclusion criteria
2) Deviation relating to trial drug discontinuation criteria
3) Deviation relating to trial drug administration method
4) Deviation relating to concomitant drug / therapy
5) Other deviation

Remarks: If multiple reasons for deviation apply to the same subject, each reason for deviation is counted

7.1.3 Analysis set

Target population: Registered / allocated cases

Analysis content: Calculate the number of cases of adoption / non-adoption and the percentage for the FAS, PPS, and safety analysis set, respectively. The denominator of the percentage is the number of registered / allocated cases. Also calculate the number of cases for each reason for non-adoption. The reasons for non-adoption are classified as follows:

・Reasons for non-adoption to FAS

1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, non-deliberation by the IRB)
2) Cases violating eligibility criteria, cases unblinded by non-regular procedures
3) Trial drug-naive cases
4) Cases with no efficacy data

・Reasons for non-adoption to PPS

1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, non-deliberation by the IRB)
2) Serious protocol violations (eligibility criteria violations, serious regulatory

violations related to compatible medications, serious treatment violations, assignment violations, unblinded cases due to non-regular procedures)

3) Patients who do not meet the minimum values set in the clinical trial protocol (e.g., the percentage of drugs taken before meals (regardless of morning, afternoon, or evening) is less than 50%)

4) Patients who took less than 80% of the trial drug throughout the trial period

5) Cases with no efficacy data

・Reasons for non-adoption to safety analysis set

1) Examples of serious GCP violations (breach of consent acquisition, breach of contract, non-deliberation by the IRB)

2) Trial drug-naive cases

3) Cases in which all endpoints related to safety evaluation after the start of the trial cannot be used

Remarks: If there are multiple reasons for non-adoption in the same subject, each reason for non-adoption is counted

7.2 Demographic and other baseline characteristics

7.2.1. Subject background

Target population: FAS

Items: Age (at time of consent acquisition), height, weight, clinical classification, diagnosis, HPV genotype, HPV 16 E7 molecule protein expression level (absolute quantification value) before start of administration, and HPV E7-specific immune response before start of administration (total = eight items).

Categories: Clinical classification: inpatient, outpatient
Diagnosis: HSIL/CIN2, HSIL/CIN3
HPV genotype: positive for HPV16 only, HPV16+other types
HPV16 E7 molecule protein expression level (absolute quantification value) before start of administration
HPV E7-specific immune response before start of administration, 16 and 24 weeks after the first dose

Analysis content: Tabulation is conducted for each group according to the data type of each item, and the uniformity of the distribution is confirmed. The significance level of the test was not specified, and only the p-value of the test is shown.

Item	Data type	Analysis content
Age, height, weight, HPV16 E7 molecule	Continuous	Summary statistics, Kruskal–Wallis test

protein expression level (absolute quantification value) before start of administration		
Clinical classification, diagnosis, HPV genotype, HPV16 E7 molecule protein expression level (absolute quantification value, two categories) before start of administration	Binary	Number of cases, percentage, chi-squared test
HPV16 E7 molecule protein expression level (absolute quantification value, three categories) before start of administration	Three categories	Number of cases, percentage, Kruskal–Wallis test

Definition: "Unknown" and "missing"

When there are either "unknown" or "missing" variables in the target variables, they are not distinguished and both handled as "unknown." The "unknown" classification is displayed only when there are applicable subjects. It should be included in the denominator of the percentage calculation and excluded from the test.

7.2.2. Concomitant drugs and therapies

Target population: FAS

Analysis content: Calculate the number of cases and percentages for each concomitant drug and concomitant therapy used from the first dose of the trial drug to the end of the trial for each group.

Definition: ・Exclude from the tabulated subjects those whose start day is after Day 112 (16 weeks after the first dose) or whose end day is before Day 1.

・In tabulations of concomitant drugs and concomitant therapies (both generic names), cases where multiple drugs / therapies that correspond to the same generic name are used will be tabulated as a single drug / therapy.

7.2.3 Therapy compliance status

Analysis FAS

target:

Analysis content: Calculate the number of cases and percentages of the following items for each group.

・Completed number of courses: four courses, three courses, two courses, one course, zero courses.

・Drug compliance rate: “less than 80%;” “80% or more.” Separately calculate summary statistics for each group as continuous values.

・Presence or absence of discontinuation of trial drug use.

Definition: Drug compliance rate (%)＝100×[total number of sticks taken/(20*3)]

7.2.4 Trial drug exposure status

Analysis target: Safety analysis set

Analysis content: Conduct the same analysis as in Section 7.2.5.

7.3 Efficacy analysis

7.3.1. Analysis of primary endpoint

The primary efficacy endpoint is the regression rate at 16 weeks after the first dose.

7.3.1.1. Primary analysis

Target population: FAS

Analysis content: 1) Estimation of the regression rate for each group

Calculate the regression rate and its 95% confidence interval (Clopper–Pearson method) for each group. Conduct the same analysis by stratification by the following five factors:

・Diagnosis: “HSIL/CIN2;” “HSIL/CIN3”

・HPV genotype: “HPV16 only” “HPV16+other types”

・Facilities: four facilities

・HPV16 E7 molecule protein expression level before start of administration.

・HPV E7-specific immune response (spot-forming cell: SFC/10^6 cells)

2) Pairwise comparison between each dose group and placebo group

Pairwise comparisons of low-dose group vs. placebo group, intermediate-dose group vs. placebo group, and high-dose group vs. placebo group are conducted by Fisher’s exact test.

3) Evaluation of the dose-response relationship by the maximum contrast method. The following six contrasts are set for the dose-response relationships of the placebo group, low-dose group, intermediate-dose group, and high-dose

group: (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]. The p-value for each contrast is calculated, and the dose-response relationship with the lowest p-value is identified. Specifically, the contrasting components of (1)-(6) are investigated using a logistic model in which the presence or absence of a response is set as the response variable and the dose group is the explanatory variable.

Definition:	・The judgment categories for the histopathological regression indicators of cervical intraepithelial neoplasia, which is the basis of response judgment, are set as “CR,” “PR,” “SD,” “PD,” and “No judgment.” Here, “No judgment” includes the following: “not judgeable” for reasons such as the histological test specimen being too small or diagnosis being difficult because of specimen preparation; missing judgment result because a test was not conducted. ・Regression rate (%)＝100×(number of response cases / number of FAS cases). ・Multiplicity adjustments are not conducted for 2) and 3).

7.3.1.2. Secondary analysis

Target population: PPS

Analysis content: Same as primary analysis. However, stratification analysis using the stratification factors is not conducted.

7.3.2. Analysis of secondary endpoints

Target population: FAS, PPS

Analysis content: 1) Regression rate at 24 weeks after the first dose

The same analysis as the primary and secondary analyses of the primary endpoint is conducted.

2) HPV E7-specific immune response is calculated for FAS and PPS for each group at 16 and 24 weeks after the first dose:

The 95% confidence interval is also calculated using the Clopper–Pearson method. Furthermore, the same analysis is conducted by stratification according to the stratification factors for FAS.

3) Change in HPV16 E7 molecule protein expression level (relative quantification value)

For FAS and PPS, summary statistics are calculated by group for the HPV16 E7 molecule protein expression level before the first administration, at 16 and 24

weeks after the first dose, as well as for the magnitude and rate of change at 16 and 24 weeks after the first dose. Furthermore, comparisons of the magnitude and rate of change between each dose group and the placebo group are conducted using the Wilcoxon rank sum test. The same analysis is conducted for FAS by stratification using the stratification factors. Additionally, for FAS and PPS, a spaghetti plot of HPV16 E7 molecule protein level is created for each group, from the first administration of the trial drug in each subject to weeks 16 and 24.

4) Effect of HSIL/CIN 2-3 lesions on cytology

For FAS and PPS, for subjects diagnosed with HSIL at registration, the percentages of “PR,” “SD,” “PD,” and “No judgment” are calculated for each group at weeks 16 and 24. The denominator of the percentage (%) of each judgment is the number of cases in the analysis set. Furthermore, for the FAS, the same tabulation is conducted by stratification using stratification factors.

5) Percentages of “CR,” “PR,” “SD,” and “PD” in the histopathological evaluation indicators of cervical intraepithelial neoplasia

For FAS and PPS, the percentages of “CR,” “PR,” “SD,” and “PD,” and “No judgment” are calculated for each group at weeks 16 and 24. The denominator of the percentage (%) of each judgment is the number of cases in the analysis set. Furthermore, for the CR rate, Fisher’s exact test is used for pairwise comparisons between each dose group and the placebo group. Additionally, the dose-response relationship is investigated with the same contrasts as in Section 7.3.1.1). For FAS, the same tabulation is conducted by stratification using the stratification factors.

6) Evaluation of changes in the HPV genotype

For FAS and PPS, the percentages of the number of cases for judgment categories (“negative,” “positive, but not including type 16,” “HPV16 only,” “HPV16+other types,” and “no judgment”) are calculated for each group at weeks 16 and 24, with the number of cases for each judgment of “HPV16 only” and “HPV16+other types” before trial drug administration. Separately, the number and percentage of cases is calculated for the category of “clearance of HPV16” by merging “negative” and “positive, but not including HPV16.” Furthermore, for FAS, the same tabulation is conducted by stratification using the stratification factors.

7) Disease control rate

For FAS and PPS, the percentage of subjects with histology of CIN3 at

registration improving to CIN2 or lower at weeks 16 and 24 is calculated for each group, and their 95% confidence intervals (Clopper–Pearson method) are calculated. Additionally, Fisher's exact test is used for pairwise comparisons between each dose group and the placebo group. Furthermore, for FAS, the same tabulation is conducted by stratification using the stratification factors.

Definition: ・For subjects diagnosed with HSIL at registration, the judgment categories for the effect of HSIL/CIN 2-3 in cytology are set as "PR," "SD," "PD," and "no judgment." Here, "no judgment" includes "NE" and missing judgment results because of tests not being conducted, etc.

・The judgment categories for pathological improvement indicators of cervical intraepithelial neoplasia are set as "CR," "PR," "SD," "PD," and "no judgment." Here, "no judgment" includes "NE" and missing judgment results because of tests not being conducted, etc.

・The judgment categories for HPV genotype are set as "negative," "positive, but not including HPV16," "HPV16 only," "HPV16+other types," and "no judgment." Here, "no judgment" includes missing judgment results because of tests not being conducted, etc.

・If either of the two time points is "NE" or the judgment result is missing, the judgment result at the other time point is set as the best effect. When a judgment result is not obtained at either of the two time points, the best effect is set as "no judgment."

7.3.3. Exploratory analysis

1）Investigation of the distribution of the E7 protein expression level (absolute quantification value) before first administration

Target population: FAS

Analysis content: Calculate summary statistics (number of cases, mean, standard deviation, minimum, median, maximum, first quartile, third quartile) of the E7 protein expression level (absolute quantification value) and display them in a box plot for each diagnosis (CIN2, CIN3) and the overall diagnosis.

2) Investigation of the relationship between the E7 protein expression level (absolute quantification value) before first administration and the improvement effect of IGMKK16E7

Target population: FAS

Analysis Explore whether the E7 protein expression level (absolute quantification value)

content: before the first dose can be a predictor of the therapeutic effect of IGMKK16E7. Here, a predictor of the therapeutic effect is a factor for which a higher therapeutic effect of IGMKK16E7 can be expected according to its value. The regression rate at weeks 16, which is the primary endpoint, is used as the therapeutic effect. The specific analysis procedure is described below.

1. Cases when the E7 protein expression level before first administration are divided into two categories (see definition section):

1-1) The following analysis is conducted for each of the three cases related to the presence or absence of IGMKK16E7 administration (see definition section).

1-2) Set a value, C, for all possible classifications of E7 protein expression level before first administration. For each C, the number of cases and the response rate are calculated for the presence or absence of IGMKK16E7 administration for each of the categories “less than C” and “C or greater.” However, when the number of cases for either “administration present” or “administration absent” is less than two, the analysis using the applicable classification value C will not be conducted.

1-3) For each C, conduct a logistic regression analysis where the presence or absence of response is set as the response variable; and the presence or absence of IGMKK16E7 administration, E7 protein expression level before first administration, and interaction between the presence or absence of IGMKK16E7 administration and E7 protein expression level before first administration (henceforth, referred to as “interaction”) are set as the explanatory variables. Then, record the p-value of the interaction. Additionally, create a plot of the p-value of the interaction for each case.

1-4) Referencing the p-value plot of the above-mentioned interaction, output the analysis result under each of the classification values among all the possible classification C values where the p-value of the interaction is at a minimum (or 2–3 that are close to the minimum). Specifically, output the estimated value of the regression coefficient of the logistic regression as well as the odds ratio of the IGMKK16E7 response with respect to that of the placebo for each category of “less than C” and “C or greater” of the E7 protein expression level before the first administration. Additionally, create a plot of the estimated value of the response rates for each of the IGMKK16E7 and placebo for each category of “less than C” and “C or greater” of the E7 protein expression level before the first administration, and their two-sided 95% confidence interval. Use the Clopper–Pearson method to calculate the 95% confidence interval.

2. Cases where the E7 protein expression level before first administration is classified into three categories:

2-1) Conduct the following analyses in each of the three cases related to the presence or absence of IGMKK16E7 administration.

2-2) Set all possible classification value pairs C1 and C2 (>C1) of the E7 protein expression level before first administration. For each pair of C1 and C2, calculate the number of cases and the response rate of the presence or absence of IGMKK16E7 administration for each category of “less than C1,” “C1 or greater and less than C2,” and “C2 or greater.” However, when the number of cases for either “administration present” or “administration absent” is less than two, the analysis using the applicable classification value pair C1 and C2 will not be conducted.

2-3) For each pair C1 and C2, conduct a logistic regression analysis where the presence or absence of a response is set as the response variable; and the presence or absence of IGMKK16E7 administration, E7 protein expression level before first administration, and interaction between the presence or absence of IGMKK16E7 administration and E7 protein expression level before first administration (henceforth, referred to as “interaction”) are set as the explanatory variables. At that time, the E7 protein expression level before first administration is treated as a continuous explanatory variable with three levels of ordinal category values. For each case, record the p-value of the interaction. Additionally, create a plot of the p-value of the interaction for each case.

2-4) Referencing the p-value plot of the above-mentioned interaction, output the analysis result under each of the classification value pairs among all the possible classification value pairs C1 and C2, where the p-value of the interaction is at a minimum (or 2–3 that are close to the minimum). Specifically, plot the estimated value of the regression coefficient of the logistic regression as well as the estimated value of the response rate for each category of “less than C1,” “C1 or greater and less than C2,” and “C2 or greater,” of the E7 protein expression level before the first administration. Calculate and plot their two-sided 95% confidence intervals using the Clopper–Pearson method.

Definition: Response variable: set as the presence or absence of response at week 16. This is the primary endpoint of this trial.

Explanatory variables: E7 protein expression level before first administration and presence or absence of IGMKK16E7 administration (total = two variables); multiple cases are investigated for each.

・E7 protein expression level before first administration. The following two cases are investigated:

Case	Category
Two categories	“Less than C,” “C or higher”
Three categories	“Less than C1,” “C1 or higher and less than C2,” “C2 or higher”

C (or C1 and C2) is the scaled classification value of the E7 protein expression level. Order statistics of the E7 protein expression level are used to set all possible values of the classification value C (or C1 and C2) in a sequential manner. At that time, classification values in either of the two categories of “less than C” or “C or higher” (or three categories of “less than C1,” “C1 or higher and less than C2,” or “C2 or higher”), where the number of cases for either category of “administration present” or “administration absence” of the IGMKK16E7 administration below is less than two, are excluded from the investigation.

・Presence or absence of IGMKK16E7 administration. The following three cases are investigated.

Case	IGMKK16E7 administration		Content
	Administration present	Administration absent	
1	High-dose group + intermediate-dose group + low-dose group	Placebo group	IGMKK16E7 vs. placebo
2	High-dose group + intermediate-dose group	Placebo group	High and intermediate dose of IGMKK16E7 vs. placebo
3	High-dose group	Placebo group	High dose of IGMKK16E7 vs. placebo

3）Investigation of the relationship between changes in the E7 protein expression level (relative quantification value) after administration and pathological judgment

Target population:	FAS
Analysis content:	For each of the three IGMKK16E7 dose groups of the IGMKK16E7 administration group (high-dose group + intermediate-dose group + low-dose group) and the placebo group, summary statistics are calculated for the magnitude and rate of change in the E7 protein expression level (relative quantification value) after administration for each category of the pathological judgment results after administration. ・Categories of pathological judgment results: “CR,” “PR,” “SD,” “PD,” “NE,” “response (CR or PR),” and “non-response (SD or PD)” ・Evaluation time points: 16 and 24 weeks after the first dose

4）Investigation of the relationship between the presence or absence of an HPV E7-specific immune response before first administration and the improvement effect of IGMKK16E7

Target population:	FAS
Analysis content:	Conduct a logistic regression analysis where the presence or absence of a response is set as the response variable; the presence or absence of IGMKK16E7 administration, presence or absence of an HPV E7-specific immune response before first administration, and the interaction between the presence or absence of IGMKK16E7 administration and the presence or absence of an HPV E7-specific immune response before first administration are the explanatory variables. Based on this result, output the estimated value of the regression coefficient of the logistic regression as well as the odds ratio of the IGMKK response with respect to that of the placebo for each category of “no response” and “response” of the HPV E7-specific immune response before first administration. Furthermore, create a plot of the estimated value of the response rates for each of the IGMKK and placebo for each category of “no response” and “response” of the HPV E7-specific immune response before the first administration. Calculate and plot their two-sided 95% confidence interval using the Clopper–Pearson method.
Definition:	Response variable: set as the presence or absence of a response at 16 weeks

after the first dose. Explanatory variables: presence or absence of an HPV E7-specific immune response and presence or absence of IGMKK16E7 administration (total = two variables). The same three cases are investigated as in point 2) mentioned above for the presence or absence of IGMKK16E7 administration.

5）Investigation of the relationship between the presence or absence of an HPV E7-specific immune response after administration and pathological judgment

Target population: FAS

Analysis content: For each of the three IGMKK16E7 dose groups of the IGMKK16E7 administration group (high-dose group + intermediate-dose group + low-dose group) and the placebo group, a contingency table is created between the pathological judgment result after administration and the presence or absence of an HPV E7-specific immune response.

・Categories of pathological judgment results: “CR,” “PR,” “SD,” “PD,” “NE,” “response (CR or PR),” and “non-response (SD or PD)”

・Evaluation time points: 16 and 24 weeks after the first dose

6）Investigation of the relationship between the HPV E7-specific immune response SFC value after administration and pathological judgment

Target population: FAS

Analysis content: For each of the three IGMKK16E7 dose groups of the IGMKK16E7 administration group (high-dose group + intermediate-dose group + low-dose group) and the placebo group, summary statistics are calculated for the HPV E7-specific immune response SFC value after administration for each category of the pathological judgment results after administration.

・Categories of pathological judgment results: “CR,” “PR,” “SD,” “PD,” “NE,” “response (CR or PR),” and “non-response (SD or PD)”

・Evaluation time points: 16 and 24 weeks after the first dose

7）Investigation of the relationship between the log-transformed HPV E7-specific immune response SFC value after administration and pathological judgment

Target population: FAS

Analysis content: For each of the three IGMKK16E7 dose groups of the IGMKK16E7 administration group (high-dose group + intermediate-dose group + low-dose group) and the placebo group, summary statistics (number of cases, mean, standard deviation, minimum, median, maximum, first quartile, third quartile) are calculated for the magnitude of change of the log-transformed SFC value (geometric mean value ratio) and log-transformed SFC value after administration for each category of the pathological judgment result after administration. Note that the value 0.0 is read as 0.001 in log-transformation.

・Categories of pathological judgment results: CR," "PR," "SD," "PD," and "NE"

・Evaluation time points: 16 and 24 weeks after the first dose

・In addition to the above, the best change in log-transformed SFC value (bigger value between 16 and 24 weeks after first administration)

Additionally, all the above-mentioned results are displayed in a box plot.

7.4 Safety analysis

7.4.1. Adverse events / side effects

Item name	Definition
Adverse event	This refers to any unfavorable event occurring between the use (administration) and the end of use (administration) of this trial drug, regardless of whether or not it is related to the trial drug. During the follow-up period, information will be collected only for events for which a causal relationship cannot be rejected.
Side effect	The relationship between an adverse event and the trial drug is judged as "relationship cannot be denied" or "no relationship with the trial drug." Adverse events that fall under the former category of "relationship cannot be denied" are treated as a side effect.

7.4.1.1. Occurrence of adverse events and side effects

Target population: Safety analysis set

Analysis content: ・For both the adverse events and side effects in each group, calculate the number of incident cases, number of occurrences, percentage of the number of cases (%), and their two-sided 95% confidence intervals for all events that

occurred, serious events, severe events (NCI-CTCAE Grade 3 or higher), and events that led to discontinuation of the trial drug. The denominator of the percentage (%) of the number of cases is the number of cases in the target population, and the Clopper–Pearson method is used to calculate the two-sided 95% confidence interval.

7.4.1.2. Adverse event severity, outcomes, treatment presence or absence

Target population: Safety analysis set

Analysis content: ・For both the adverse events and side effects in each group, calculate the number of cases and its percentage (%) corresponding to each category of the severity (NCI-CTCAE grade), outcome, and presence or absence of treatment. The denominator of the percentage (%) is the number of cases in the target population.

Definition: ・The NCI-CTCAE Grade covers five grades from 1 to 5.

・Outcomes are judged in the six categories of “recovery,” “remission,” “unrecovered,” “with sequelae,” “death,” and “unknown.”

・Treatment for adverse events was judged in the three categories of concomitant drug use, concomitant therapy use, and no treatment; and “treatment present” was set when there was either concomitant drug use or concomitant therapy use.

・If multiple adverse events occurred in the same case, the severity was counted for the highest grade event, and the outcome was determined based on severity as follows, with the most severe event counted: “death” > “with sequelae” > “unrecovered” > “unknown” > “remission” > “recovery.” Furthermore, for the presence or absence of treatment, cases where treatment was conducted for any event were counted as treatment “present.”

7.4.1.3. Occurrence of adverse events and side effects for each symptom

Target population: Safety analysis set

Analysis content: ・Calculate the number of incident cases and incidence rate of adverse events (or side effects) for each group according to symptom (SOC, PT).

Definition: ・If there are multiple events with the same SOC (PT when tabulating according to PT) in the same case, this is counted as one case.

7.4.1.4. Seriousness-based occurrence of adverse events and side effects for each symptom

Target population: Safety analysis set

Analysis content: ・Calculate the number of incident cases and incidence rate of adverse events (or side effects) for each group according to symptom (SOC, PT) and seriousness.

Definition: ・Seriousness: non-serious; serious

・If there are multiple events with the same SOC (PT when tabulating according to PT) in the same case, the event with the highest seriousness is used and counted as one case.

7.4.1.5. Severity grade-based occurrence of adverse events and side effects

Target population: Safety analysis set

Analysis content: ・Calculate the number of incident cases and incidence rate of adverse events (or side effects) for each group according to symptom (SOC, PT) and grade.

Definition: ・Grade: Grade 1; Grade 2; Grade 3-5 (according to CTCAE v4.0)

・If there are multiple events with the same SOC (PT when tabulating according to PT) in the same case, the event with the highest grade is used and counted as one case.

7.4.1.6. Occurrence of adverse events and side effects leading to discontinuation of the trial drug

Analysis content: ・Calculate the number of incident cases and incidence rate of the adverse events (or side effects) that led to discontinuation of trial drug administration among any of the four groups for each group according to symptom (SOC, PT).

Definition: ・Adverse events leading to discontinuation of trial drug administration: adverse events where the response to “Discontinuation of Study Treatment” in the eCRF was “Yes”

・If there are multiple events with the same SOC (PT when tabulating according to PT) in the same case, this is counted as one case.

7.4.2. Laboratory test values

7.4.2.1. Tabulation of laboratory test values

Target population: Safety analysis set

Analysis content: ・Calculate summary statistics of test items of quantitative values for each group and each evaluation period. For the test items of qualitative values, calculate the number of test cases for each group and the evaluation period, as well as the number of cases and percentages (%) of each test result category.

Definition: ・See Appendix 1 for the test items.

・The evaluation periods were before the start of drug administration, week 5, week 9, week 16, week 24, and at the time of discontinuation of the trial.

・See Section 6.4.4 “Range of data adoption for the evaluation periods” and Section 6.6 “Handling of data at discontinuation” regarding the handling of clinical test value data at the time of discontinuation of the trial.

7.4.2.2. Diagram of changes in laboratory test values

Target population: Safety analysis set

Analysis content: ・Create a spaghetti plot of each test item for each group, from the first administration of the trial drug in each subject to the end of the trial (or discontinuation).

8. References

None

Appendix

Appendix 1 Laboratory test items

Classification	Item name	Unit	Displayed digits	Remarks
Hematology test	RBC (red blood cell count)	[×10^6/μL]	0.01	
	Hgb (hemoglobin amount)	[g/dL]	0.1	
	Hct (hematocrit value)	[%]	0.1	
	Plt (platelet count)	[×10^3/μL]	1	
	WBC (white blood cell count)	[×10^3/μL]	0.1	
	Neut (neutrophils)	[%]	0.1	
	Lymp (lymphocytes)	[%]	0.1	
	Mono (monocytes)	[%]	0.1	
	Eos (eosinophils)	[%]	0.1	
	Baso (basophils)	[%]	0.1	
Blood biochemistry test	TP (total protein)	[g/dL]	0.1	
	Alb (albumin)	[g/dL]	0.1	
	LDH	[U/L]	1	
	GOT (AST)	[U/L]	1	
	GPT (ALT)	[U/L]	1	
	γ-GTP	[U/L]	1	
	ALP	[U/L]	1	
	TB (total bilirubin)	[mg/dL]	0.1	
	DB (direct bilirubin)	[mg/dL]	0.1	
	TC (total cholesterol)	[mg/dL]	1	
	TG (triglyceride)	[mg/dL]	1	
	BUN (blood urea nitrogen)	[mg/dL]	1	
	Cr (creatinine)	[mg/dL]	0.1	
	Na (sodium)	[mmol/L]	1	1mEq/L=1mmol/L
	K (potassium)	[mmol/L]	0.1	1mEq/L=1mmol/L
	Cl (chlorine)	[mmol/L]	1	1mEq/L=1mmol/L
	UA (uric acid)	[mg/dL]	0.1	
	CK (creatine phosphokinase)	[U/L]	1	
Urinalysis	Glucose	—	—	Qualitative
	Protein	—	—	Qualitative
	Urobilinogen	—	—	Qualitative
	Occult blood	—	—	Qualitative
	pH	—	0.1	

Appendix 2 List of forms created

The forms to be created are listed below. Refer to the separate chart plan for details.

Tables

- Breakdown of subjects
- Screening dropout
- Deviation from trial protocol
- Analysis set
- Subject background
- Concomitant drugs
- Concomitant therapy
- Treatment compliance status
- Analysis of response rate in histology
- Analysis of CR rate in histology
- HPV E7-specific immune response
- Changes in HPV16 E7 molecule protein expression level (relative quantification value)
- Effect of HSIL/CIN 2-3 lesions on cytology
- Effect of cervical intraepithelial neoplasia on pathological improvement indicators
- Changes in HPV genotype
- Disease control rate
- Summary statistics of distribution of HPV16 E7 molecule protein expression level (absolute quantification value) before start of administration
- Relationship between E7 protein expression level (absolute quantification value, two categories) before start of administration and response rate in histology for each treatment group
- Logistic regression analysis result: E7 protein expression level (absolute quantification value) before start of administration (two categories)
- Relationship between E7 protein expression level (absolute quantification value, three categories) before start of administration and response rate in histology for each treatment group
- Logistic regression analysis result: E7 protein expression level (absolute quantification value) before start of administration (three categories)
- Logistic regression analysis result: HPV E7-specific immune response before start of administration used as an explanatory variable
- Relationship between E7 protein expression level (relative quantification value) after administration and pathological judgment
- Relationship between HPV E7-specific immune response SFC value after administration and pathological judgment
- Relationship between log-transformed HPV E7-specific immune response SFC value after administration and pathological judgment
- Trial drug exposure status
- Occurrences of adverse events and side effects
- Adverse event and side effect severity, outcome, and treatment presence or absence
- Occurrence of adverse events for each symptom
- Occurrence of side effects for each symptom
- Seriousness-based occurrence of adverse events for each symptom
- Seriousness-based occurrence of side effects for each symptom
- Severity grade-based occurrence of adverse events for each symptom
- Severity grade-based occurrence of side effects for each symptom

- Occurrence of adverse events leading to discontinuation of trial drug
- Occurrence of side effects leading to discontinuation of trial drug
- Changes in laboratory test values (quantitative)
- Changes in laboratory test values (qualitative)

Figures

- Flow diagram of breakdown of subjects
- Diagram (spaghetti plot) of changes in HPV16 E7 molecule protein expression level (relative quantification value)
- Box plot of HPV16 E7 molecule protein expression level (absolute quantification value) before start of administration
- P-value of interaction between E7 protein expression level (absolute quantification value, two categories) before administration and treatment group
- Plot of improvement rate by E7 protein expression level (absolute quantification value, two categories) before administration and by treatment group
- P-value of interaction between E7 protein expression level (absolute quantification value, three categories) before administration and treatment group
- Plot of improvement rate by E7 protein expression level (absolute quantification value, three categories) before administration and by treatment group
- Box plot of log-transformed HPV E7-specific immune response SFC value after administration
- Diagram (spaghetti plot) of changes in laboratory test values

Lists

- List of discontinued cases
- List of cases deviating from clinical trial protocol
- List of cases excluded from the efficacy analysis
- List of demographic data
- List of drug compliance status
- List of individual efficacy response data
- List of adverse events
- List of side effects
- List of serious side effects
- List of adverse events that led to discontinuation of the trial drug
- List of laboratory test values (hematology tests)
- List of laboratory test values (biochemistry tests)
- List of laboratory test values (urinalysis)

Appendix 3 Software and dictionaries used

Statistical analysis and tabulation software

	Software and version
OS	Microsoft Windows Server 2016 [or later version]
Statistical analysis software	SAS Ver.9.4 or later version
Tabulation software	Microsoft Excel 2016 or later version

Dictionaries used

Item	Dictionary name and version	Remarks
Adverse event name (adverse event) and degree	ICH Medical Dictionary for Regulatory Activities (MedDRA) v22.0 Common Terminology Criteria for Adverse Events (CTCAE) v5.0	・SOC is used for organ classification and PT is used for symptom names. ・When displaying SOC, display according to internationally agreed order. ・When displaying PT, place in PT code order.
Drug name (concomitant drug)	WHODrug Global 2019MAR B3 format	Classify broadly by ATC Level 1, then tabulate by ATC Level 2 based on this (in alphabetical order of code, ascending order of numerical value).