Placebo-controlled, double-blind, randomized phase III Study of comparing NK1 receptor antagonist/ palonosetron/ olanzapine/ dexamethasone on day 1 +/- dexamethasone on day 2-4 in high emetogenic chemotherapy
(SPARED trial)

Study Protocol

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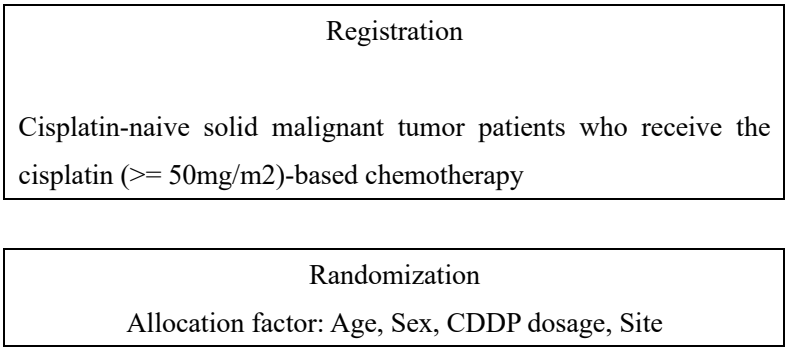
0. Outline

0.1 Schema



NK-1RA: NK-1 receptor antagonist, PALO: Palonosetron, OLZ: Olanzapine, DEX: Dexamethasone

0.2 Aims

To conduct a controlled trial of patients with malignant tumor receiving treatment by Highly Emetogenic Chemotherapy (HEC) including cisplatin (CDDP) randomly allocated to the day 1-4 group (group A) given NK-1 receptor antagonist (NK-1RA) + palonosetron (PALO) + olanzapine (OLZ) + dexamethasone (DEX), and the day 1 group (group B) given NK-1RA+PALO+OLZ+DEX, to examine non-inferiority of group B to group A.

Primary endpoint

- The rate of complete inhibition of vomiting in the delayed phase (within 24 - 120 hours after CDDP administration) (CR rate: Complete Response rate).

Secondary endpoint

- CR rate in the acute phase (within 24 hours of CDDP treatment commencement), and in the overall phase (within 120 hours of CDDP administration)
- The rate of complete inhibition of nausea and vomiting (CC rate: Complete Control rate) in the overall phase, acute phase, and delayed phase
- The total control rate (TC rate) of nausea and vomiting in the overall phase, acute phase, and delayed phase.
- No vomiting rate in the overall phase, acute phase, and delayed phase. (No vomiting）
- No nausea rate in the overall phase, acute phase, and delayed phase（No nausea）
- Time to treatment failure (TTF)
- Nausea severity during the overall phase
- Quality of Life （EORTC QLQ-C30）
- Adverse events

0.3 Subject

Patients with solid malignant tumor scheduled to receive HEC including CDDP ≧ 50mg/m2 as first-line treatment.

0.4 Treatment

Arm A: Control arm

With Fosaprepitant

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant i.v.	150 mg			
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethasone i.v.	9.9 mg	6.6 mg	13.2 mg	13.2 mg

With Aprepitant

	Day 1	Day 2	Day 3	Day 4
Aprepitant p.o.	125 mg	80 mg	80 mg	
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethasone i.v.	9.9 mg	6.6 mg	6.6 mg	6.6 mg

Arm B: Intervention arm

With Fosaprepitant

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant i.v.	150 mg			
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethasone i.v.	9.9 mg			
Placebo i.v.		Placebo	Placebo	Placebo

With Aprepitant

	Day 1	Day 2	Day 3	Day 4
Aprepitant p.o.	125 mg	80 mg	80 mg	
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethasone i.v.	9.9 mg			
Placebo i.v.		Placebo	Placebo	Placebo

0.5 Planned Enrollment and Research Period

Target enrollment　280（Arm A: 140, Arm B: 140）

Enrollment period June, 2018 to June, 2021

Duration required for analysis June, 2021 to June, 2022

0.6 Contact

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1. Aims

To conduct a controlled trial of patients receiving treatment by Highly Emetogenic Chemotherapy (HEC) including cisplatin (CDDP) (≧50mg/m2) randomly allocated to the day 1-4 group (group A) given standard antiemetic treatment of NK-1 receptor antagonist (NK-1RA) + palonosetron (PALO) + olanzapine (OLZ) + dexamethasone (DEX), compared to the day 1 group (group B) given NK-1RA+PALO+OLZ+DEX, to examine non-inferiority of group B to group A.

1.1 Primary endpoint

The rate of complete inhibition of vomiting in the delayed phase (within 24 - 120 hours after CDDP administration) (CR rate: Complete Response rate).

*[1]Vomiting includes retching

*[2]No vomiting / retching, no rescue use

1.2 Secondary endpoint

1） CR rate in the acute phase (within 24 hours of CDDP treatment commencement), and in the overall phase (within 120 hours of CDDP administration)

2） The rate of complete inhibition of nausea and vomiting (CC rate: Complete Control rate) in the overall phase, acute phase, and delayed phase

3） The total control rate (TC rate) of nausea and vomiting in the overall phase, acute phase, and delayed phase.

4） No vomiting rate in the overall phase, acute phase, and delayed phase. (No vomiting）

5） No nausea rate in the overall phase, acute phase, and delayed phase（No nausea）

6） Time to treatment failure (TTF)

7） Nausea severity during the overall phase Quality of Life （EORTC QLQ-C30）

8） Adverse event

2. Background and grounds for setting the trial plan

2.1 Subjects

The subject sample of the present trial will include patients with solid malignant tumor receiving receive treatment with HEC including CDDP ≧ 50mg/m^2.

2.1.1 Outline and mechanism of nausea and vomiting

Chemotherapy Induced Nausea and Vomiting (CINV) is one of the most frequent adverse reactions, and considerably reduces patient quality of life (QOL). In recent years, it has been reported that nausea has a greater impact on QOL than vomiting.[1)] Nausea and vomiting are induced by afferent stimulation sent from the chemoreceptor trigger zone (CTZ), the gastrointestinal tract, and the cerebral cortex to the vomiting center. [2)] In the CTZ, vomiting center, and gastrointestinal tract, there is a large amount of neurotransmitter receptors, and receptors found to be associated with nausea and vomiting include vitamin D2 receptors, 5-HT3 receptors, and neurokinin-1 (NK-1) receptors that bind to substance-P. It is thought that CINV is caused when these receptors are stimulated by chemotherapy.

2.1.2 CINV classification

CINV is classified according to the onset timing into 1) acute nausea and vomiting, 2) delayed nausea and vomiting, and 3) anticipatory nausea and vomiting. Acute nausea and vomiting occur within 24 hours of commencing chemotherapy. Delayed nausea and vomiting occur after 24 hours of commencing chemotherapy and continue for approximately one week. Anticipatory nausea and vomiting are brought about by psychological factors and appears prior to commencing chemotherapy.

2.1.3 Emetic risk classification of chemotherapy agents

The incidence of CINV is greatly affected by the emetic nature of the chemotherapy agent used, and while there have been classifications proposed to define the degree of CINV, none have been established. Internationally, guidelines on antiemesis therapy have been presented from the National Comprehensive Cancer Network (NCCN)[3)], Multinational Association of Supportive Care in Cancer (MASCC), the European Society for Medical Oncology (ESM)[4)], and the American Society of Clinical Oncology (ASCO)[5)], which have classified the incidence of nausea and vomiting into four categories in accordance with the rate (%) of nausea and vomiting onset within 24 hours of administration of each type of chemotherapy without prophylactic antiemetics.

In Japan, the Japan Society of Clinical Oncology (JSCO) has presented the ‘Clinical practice guidelines for antiemesis in oncology’, which notes the dosage of prophylactic antiemetics according to each risk classification along with the following risk classification as per the international guidelines[6)].

Table 1 Emetic risk classification of chemotherapeutic agents in antiemetic proper use guidelines

Highly emetogenic chemotherapy （HEC）	> 90% frequency of emesis	Anthracycline/cyclophosphamide combination Cisplatin,etc
Moderately emetogenic chemotherapy（MEC)	> 30 to 90% frequency of emesis	Carboplatin, Oxaliplatin, etc.
Low emetogenic chemotherapy（LEC）	> 10 to 30% frequency of emesis	Gemcitabine, Paclitaxel, etc.
Minimal emetogenic chemotherapy	emetic risk less than 10%	Trastuzumab, Vinorelbine, etc.

2.1.4 Risk factor

Factors associated with CINV include treatment-related factors and patient-related factors. In a retrospective survey in Japan by Tamura et al., female gender, a history of motion sickness, and morning sickness were identified as patient-related acute phase and delayed phase risk factors.[7] In recent years, an algorhithm has been developed to score the risk of CINV of grade 2 or above (CTCAE v4.3), in which age (≤ 60 years), pre-treatment anxiety, < 7 hours of sleep, a history of morning sickness, chemotherapy with CDDP or anthracyclines, experience of CINV prior to treatment, and the use of rescue treatment were considered risk factors. [8]

2.1.5 Rationale for selecting the target population

In the NCCN guidelines up to 2012, high-dose CDDP (≥70mg/m2) was considered to be a HEC. However, from 2013 onwards, CDDP was classified as HEC irrespective of the dose level. [3] It was also classified as HEC irrespective of the dose level in the 2017 ASCO guideline, [5] 2016 MASCC guideline, [4] and JSCO Clinical practice guidelines for antiemesis in oncology.

The CDDP dose level was ≥ 50mg/m2 in a clinical trial to reduce the number of days of DEX in HEC, [9] therefore we selected the same target population in the present study.

2.2 Standard treatment for subjets

The standard antiemetic treatment for CINV in CDDP is NK-1RA+PALO+OLZ（day1-4）+DEX（day1-4）.

2.2.1 CINV countermeasures

The aim of CINV countermeasures is not symptomatic but preventive. As antiemetic therapy for CDDP, high-dose metoclopramide therapy, and glucocorticoids (primarily DEX) were reported to have an antiemetic effect in the 1980. [10,11]

In the 1990s, 5-HT_3 receptor anatogonists (5-HT_3RA) became available, and were found to be effective for acute nausea and vomiting. [12,13] Excluding PALO, the existing 5-HT_3RA were equally effective for acute nausea and vomiting, [14-16] and are considered to have little effect on delayed nausea and vomiting. [17,18] The ASCO guideline published in 1999 recommended antiemetic treatment for CDDP with 5-HT3RA combined with glucocorticoids in the acute phase, and glucocorticoid combined with metoclopramide in the delayed phase. [19]

Entering the 2000s, NK-1RA was developed. Substance-P binds to NK-1 receptors widely distributed in the CTZ, and induces nausea and vomiting. In a clinical study examining the antiemetic effect of aprepitant (APR) for high dose CDDP (≥70mg/m^2), the APR＋5-HT3RA＋DEX group showed a significantly higher CR rate up to 120 hours after chemotherapy compared to the 5-HT3RA＋DEX group. [20-22] In recent years, it has been reported that OLZ, which is a Multi-Acting Receptor Targeted Antipsychotic (MARTA) developed as a therapeutic drug for schizophrenia, is effective for CINV.

2.2.2 Evidence of OLZ

OLZ is a MARTA with an antagonistic action on dopamine receptors (D_1,D_2,D_4), serotonin ((5-hydroxytryptamine (5-HT)) receptors (5-HT_2A,5-HT_2,、 5-HT_3), α_1 adrenergic receptors, histamine receptors (H1), and multiple muscarine receptors, [23] In Japan, it is indicated to improve manic symptoms and depressive symptoms in schizophrenia and bipolar disorder (BD).

OLZ acts on several receptors, and in particular, the antagonistic action on D_2、5-HT_2C、5-HT_3 receptors might affect CINV, and several clinical trials have been performed to investigate this. In a non-blinded randomized trial comparing the antimetic effect of OLZ and APR, [24] the OLZ group (DEX + PALO + OLZ) was compared against the APR group (DEX + PALO + APR) among patients scheduled to received first-line HEC (CDDP ≥ combined with 70mg/m^2). As the primary endpoint, the CR rate of the overall period was 77 % (93/121 patients) in the OLZ group, and 73 % (88/120 patients) in the APR group, with no statistically significant difference observed. As the secondary endpoints, acute phase and delayed phase CR revealed no statistically significant difference; however, the rate of patients with nausea tended to be higher in the OLZ group in the delayed phase and overall period (delayed phase: OLZ group 69 %, APR group 38 %; overall period: OLZ group 69 %, APR group 38 %). Similarly, the randomized double-blinded trial by Navari et al. examined the added effect of OLZ (day1-4 10mg) to conventional three-drug combination therapy (NK1-RA＋5-HT3RA+DEX) for HEC (n=380). [25] As the primary endpoint, the proportion of patients who did not experience nausea was significantly higher in the OLZ group for the overall period, acute phase, and the delayed phase (table 2). In this trial, as the secondary endpoint, the CR rate was statistically significantly higher in the OLZ group for all periods; however, on day 2, ‘sedation’ scores were higher compared to those of the placebo group.

Table 2　Trial results confirming the antiemetic effect of OLZ on HEC [25]

		Placebo (%) n = 188	OLZ (%) n = 192	p value
No nausea	Total (0-120h)	21.9	37.3	0.002
	Acute (0-24h)	45.3	73.8	<0.001
	Delayed (24-120h)	25.4	42.4	0.001
CR	Total (0-120h)	40.6	63.6	<0.001
	Acute (0-24h)	64.6	85.7	<0.001
	Delayed (24-120h)	52.4	66.9	0.007

In Japan, a double-blinded randomize controlled trial has been conducted to compare standard antiemetic therapy (APR+PALO+DEX) with OLZ 10 mg or 5 mg added on days 1 – 4 for patients scheduled to receive HEC with no history of chemotherapy by CDDP (phase II trial). As the primary endpoint, the CR rate in the delayed phase was 77.6 % in the OLZ 10 mg group, and 85.7 % in the OLZ 5 mg group. The main adverse event was drowsiness, and the rate of grade 2 drowsiness or below was 53.3 % and 45.5 % in the 10 mg group and 5 mg group, respectively. Based on such reports in Japan and overseas, on June 9, 2017, the pre-evaluation in the public knowledge-based application of the Ministry of Health, Labour, and Welfare was completed, and the use of OLZ became available in routine clinical practice. The indications made public included 'gastrointestinal symptoms (nausea and vomiting) associated with anti-malignant tumor drugs (such as CDDP)', and as administration method and dose level it was reported that 'when combined with other anitemetics, usually, for adults, OLZ should be administered once per day at a dose of 5 mg. Furthermore, while the dose is increased as needed according to the patient's condition, it shall not exceed 10 mg per day'. [27] On December 25, 2017, the administration method and dose level were added to the indications in the same public knowledge-based application.

2.2.3 Standard antiemetic treatment in the present trial

For HEC, the second edition of the Clinical practice guidelines for antiemesis in oncology[6] recommends three-drug combination therapy with 5-HT3RA and NK-1RA on day 1, and then DEX administered from day 1 to 4 or 5. With regards to 5-HT3RA, a phase III trial comparing first generation (serotonin) and second generation (PALO) [28] found no superiority in the primary endpoint, i.e., CR rate for the overall period, at 59 % and 66 %, respectively (p=0.0539). However, as the secondary endpoint, CR rate of the delayed period was 59 % in the serotonin group and 67 % in the PALO group (p=0.0142), indicating good results, and therefore, the guidelines noted that 'for HEC, second generation 5-HT_3 receptor antagonists are preferable'.

The 2016 MASCC guidelines, [4] as per in Japan, recommends three-drug combination therapy with 5-HT3RA, DEX, and NK-1RA. On the other hand, as antiemetic treatment other than three-drug combination therapy, the NCCN guidelines (Version2.2017)[3] lists OLZ+PALO+DEX using OLZ instead of NK-1RA (DEX given on day 1 only), and four-drug combination therapy with additional OLZ to conventional three-drug combination therapy. Furthermore, in the ASCO guideline published in 2017,[5] for HEC other than AC (anthracycline and cyclophosphamide) combination therapy, it has been revised to recommend four-drug combination therapy with 5-HT3RA and KN-1RA given on day 1, and with DEX and OLZ given on days 1 – 4.

Based on the results of such recent phase III clinical trials of OLZ, four-drug combination therapy including OLZ has gained popularity for HEC. In the present trial, we decided to administer four-drug combination therapy including PALO and OLZ as the standard antiemetic therapy (table 3). Furthermore, the dose of OLZ was set at 5 mg based on the adminisatration method and dose level as per the aforementioned indications.

Table 3 Standard antiemetic therapy for HEC in this study

With Fosaprepitant

	Day 1	Day 2	Day 3	Day 4

Fosaprepitant i.v.	150 mg			
Palonosetron i.v.	0.75 mg			
Olanzapin p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethazone i.v.	9.9 mg	6.6 mg	13.2 mg	13.2 mg

With Aprepitant

	Day 1	Day 2	Day 3	Day 1
Aprepitant p.o.	125 mg	80 mg	80 mg	
Palonosetron i.v.	0.75 mg			
Olanzapin p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethazone i.v.	9.9 mg	6.6 mg	13.2 mg	13.2 mg

2.3 Rationale for setting the trial treatment

In this trial, the standard treatment of DEX administered on day 1 only will be used as the trial treatment: NK-1RA+PALO+DEX（day1）+OLZ（day1-4）.

2.3.1 Side effects of glucocorticoid used for CINV

The use of DEX, a typical glucocorticoid, the efficacy of which has been demonstrated is recommended in each guideline. [3-6] However, the mode of action of DEX is not understood as much as that of sebsequently developed 5-HT3RA and NK-1RA. While the concurrent use with other antiemetics is considered safe, medical care providers should pay due care to adverse reactions of glucocorticoids over several days. [29] In the study by J Vardy et al., adverse reactions to glucocorticoids used to prevent delayed emesis was examined in moderately emetogenic chemotherapy (MEC) including AC combination therapy. They reported that among 60 patients, moderate-to-severe adverse reactions included insomnia (45%), stomach discomfort (27%), agitation (27%), increased appetite (19%), body weight gain (16%), and acne (15%).[30] Furthermore, in the ESPRESSO-01 trial evaluating the effect of intermittent glucocorticoid therapy on bone metabolism in chemotherapy for pateints with gastrointestinal cancer, changes in bone mineral density (BMD) and bone metabolism markers of the lumbar spine were examined in 74 patients after 16 weeks of commencing treatment. [31] As a result, BMD of the lumbar spine after 16 weeks decreased in 74.3 % of patients, and the mean change in BMD was -1.89 %, which therefore suggested a relationship between BMD and intermittent glucocorticoid therapy. In a pilot study examining glucocorticoid-induced diabetes mellitus in patients receiving HEC and MEC for gastric cancer (n＝77), [32] multivariate analysis revealed a significant relationship between the incidence of glucocorticoid-induced diabetes mellitus and the cumulative dose of DEX (p=0.049). Furthermore, upon performing an ACTH-loading study of 350 patients who received at least three courses of DEX in which DEX was used for 3 days or more per course as antiemetic for HEC and MEC, it was reported that within six months, 16 % of patients developed secondary adrenal hypofunction. [33]

2.3.2. Steroid-sparing

In recent years, out of concern for adverse reactions to glucocorticoids, attempts have been underway to study Steroid-sparing antiemetic therapy, whereby glucocorticoids are omitted after day 2. In a phase III double-blinded, randomized controlled trial conducted by Aapro et al. (n=300) of breast cancer patients receiving AC combination therapy, when combined with PALO, a reduced dose of DEX alone (day 1 group) was compared against conventional DEX on days 1 – 3 (day 1 – 3 group). This trial revealed that the CR rates for the day 1 group and day 1- 3 group were equivalent (53.6%,53.7%), demonstrating non-inferiority of the day 1 group to the day 1 – 3 group. Furthermore, the adverse reaction of insomnia occurred at a significantly lower rate in the day 1 group (2.6%、8.7%, p=0.023). [34] In the phase III randomized controlled trial of Celio et al., the day 1 group (n=163) was compared with the day 1 – 3 group (n=161) when combined with PALO in patients receiving MEC including AC combination therapy. As a result, the CR rate was 67.5 % in the day 1 group and 71.1 % in the day 1 – 3 group, demonstrating non-inferiority. [35] In Japan, a multicenter, randomized, double-blinded controlled trial (DEX-1) has been conducted to examine the non-inferiority of the NK-1RA+PALO+DEX day1 group to the NK-1RA+PALO+DEX day1-3 group in patients receiving HEC with CDDP (≥50mg/m^2) and AC combination therapy, which has been previously examined. [9] The results are presented in table 4.

Table 4 CR rate of each period of subgroup analysis by chemotherapy in DEX-1 trial. [9]

		Day 1-3 n=196	Day 1 n=200	risk difference 95%CI	p value
CR (%)	Total (0-120h)	46.9	44	-2.9% [-12.6%, 6.8%]	0.007
	Acute (0-24h)	63.3	64.5	1.2% [-8.1%, 10.6%]	≦0.001
	Delayed (24-120h)	56.6	51.5	-5.1% [-14.8%, 4.6%]	0.023

<AC regimen>

		day1-3 n=151	day1 n=155	risk difference 95%CI	p value
CR(%)	Total (0-120h)	41.4	40	-1.1% [-12.0%, 9.8%]	0.006
	Acute (0-24h)	53.6	55.5	1.8% [-9.2%, 12.9%]	0.001
	Delayed (24-120h)	53	49.7	-3.3% [-14.4%, 7.8%]	0.019

<CDDP regimen>

		day1-3 n=45	day1 n=45	risk difference 95%CI	p value
CR (%)	Total (0-120h)	66.7	57.8	-8.9% [-28.7%, 10.9%]	0.273
	Acute (0-24h)	95.6	95.6	0% [-11.9%, 11.9%]	0.007
	Delayed (24-120h)	68.9	57.8	-11.1% [-30.8%, 8.6%]	0.349

In the DEX-1 trial, non-inferiority was demonstrated for the primary endpoint, i.e. the CR rate for the overall period.

However, in the subgroup analysis, the CR rate for the overall period showed non-inferiority for AC combination therapy, whereas non-inferiority was not found for CDDP for the overall or delayed period, and in particular, the CR rate was lower in the dex 1 group for the delayed period.
Based on the results above, For AC combination therapy even in HEC, a consensus has been obtained that glucocorticoids can be omitted from day 2 onwards, and the 2017 ASCO guideline was revised to recommend the administration of glucocorticoids for AC combination therapy on day 1 only. On the other hand, steroid-sparing for CDDP remains controversial.

2.3.3 Setting the trial treatment
In antiemetic treatment for CINV in HEC excluding AC combination therapy, the administration of DEX for 4 days is considered standard. On the other hand, in a trial comparing OLZ and NK-1RA for HEC, [24] the OLZ group showed good results for delayed nausea despite receiving DEX on day 1 only. Furthermore, based on recent studies of OLZ, [25,26] the use of OLZ is expected to be effective for delayed phase CINV. Therefore, with the concurrent use of OLZ in conventional three-drug combination therapy for HEC including CDDP (≧50mg/m^2), we can expect to omit glucocorticoids from day 2 onwards, and thus we set the standard treatment group receiving DEX on day 1 only as the trial treatment group.

2.3.4 Expected treatment after completion of protocol treatment
There is no stipulated antiemetic treatment after the protocol treatment. The present trial examines the period from 24 to 120 hours after CDDP administration, and antiemetic treatment after 120 hours will not affect the trial results.

2.4 Trial design
The present trial is a multicenter, randomized, double-blinded controlled trial to evaluate the non-inferiority of the NK-1RA+PALO+OLZ+DEX day1 group to the NK-1RA+PALO+OLZ+DEX day 1-4 group to prevent CINV in patients with solid malignant tumor receiving HEC including CDDP (≧50mg/m2).

2.4.1 Rationale for setting the endpoints
In the present trial, the CR rate for the delayed phase was set as the primary entpoint. The CR rate is a highly reliable measurement item, and has thus been used as the primary endpoint in past trials. [20-22) 24) 26) 28) 33-36)] In a subgroup analysis of the DEX-1 trial, the CR rate did not show non-inferiority in the overall period and delayed phase. [26)] In particular, the CR rate of the delayed phase has been used as the primary endpoint, [26)] thus we decided to use the delayed phase CR rate as the primary endpoint in the present trial as the period in which DEX was omitted was during the delayed phase.

2.4.2 Clinical hypothesis and rationale for setting the target number of enrolments
The main hypothesis of the present study was that ‘the delayed phase CR rate of group B, i.e. the trial treatment group, is not inferior to that of group A, i.e. the standard treatment group’. When investigating this hypothesis, even with DEX administered on day 1 only, sufficient antiemetic effect can be obtained in the delayed phase, which is

expected to reduce adverse events caused by glycocorticoids in patients.
In previous studies with OLZ added to conventional antiemetic treatment for CDDP, [24,26,36] the delayed phase CR rate ranged from 75 to 85 %, and therefore in the present trial, we postulated that the delayed phase CR rate would be 75 %. Upon calculating the necessary subject sized for a one-sided α of 0.025, statistical power of 80 %, and non-inferiority margin of 15 %, a total of 262 patients will be needed, with 131 patients per group. Considering that some patients will be ineligible or unable to enrol, the target subject sample size was set at 280 patients.

2.4.3 Expected number of enrolments
We expect to enroll 140 patients per year, to complete enrolments over a two-year period. Upon conducting a questionnaire survey in advance of the expected number of patient enrolments of the eight participating institutions, the total per year was 160 patients, and therefore, we believe that it will be possible to accumulate the target subject sample over two years.

2.4.5 Allocation adjustment factors and rationale for setting them
As allocation adjustment factors, the following have been added in addition to the institution.
1) Sex and age （≥ 60 years vs. < 60 years）
In the Clinical practice guidelines for antiemesis in oncology [6] patient-related factors of nausea and vomiting include age, sex, and habitual alcohol consumption. In a Japanese factual survey of CINV in HEC and MEC, sex (women) and age (young) were identified as factors associated with acute phase nausea and vomiting, whereas sex (women) was extracted as a factor associated with delayed phase nausea and vomiting. [7] Various age cut-offs have been reported; however, in the DEX-1 trial conducted previously, age ≥ 60 years vs. < 60 years was the cut-off age, [9] and in a predictive tool to identify patients at high risk of CINV analyzed based on the data of 1198 individuals overseas, the cut-off age was 60 years, [8] and therefore we set the cut-off age based on such data.

2) CDDP dose levels （≥ 70mg/m^2 vs. <70mg/m^2）
In the various current guidelines, CDDP is considered HEC irrespective of the dose level; however, in the past, CDDP ≥ 70mg/m^2 was considered HEC. In the DEX-1 trial[9] conducted earlier, allocation adjustment factors were set in the same manner.

2.5 Summary of anticipated advantages and disadvantages associated with trial participation

2.5.1 Anticipated advantages
The antiemetic used in the present trial is a drug widely used in routine clinical practice that is covered by health insurance. Furthermore, all medical costs including drug costs during the trial will be covered by the patient or paid at the expense of the patient, and therefore, compared to routine medical practice, patients are at no advantage medically and financially by participating in the present trial. When allocated to group B, it is possible that less adverse events due to the glucocorticoid will be experienced than in group A because the glucocorticoid will be omitted on days 2 – 4. However, as to whether or not adverse events due to glucocorticoids will appear will be

determined based on the results of the present trial, and therefore it is unclear whether or not it will truly be an advantage.

2.5.2 Anticipated risks and disadvantages

The standard antiemetic treatment administered to group A will be the drug administered as normal medical practice covered by health insurance, and compared to routine clinical practice, there is no reason for particular risks and disadvantages to arise. In group B, it is possible that the absence of DEX administration on days 2 – 4 will exacerbate delayed phase CINV.

The Data Center and the Efficacy and Safety Evaluation Committee will monitor to determine whether or not adverse events are within the anticipated range, thoroughly examine and audit when serious adverse events occur, and adopt the system to implement the necessary countermeasures.

2.6 Significance of the present trial

While DEX has long since been used in antiemetic treatment, the associated mode of action has not been elucidated, and at present, antiemetic drugs with various modes of action have been developed, and the use of which is questioned. From the perspective of steroid-sparing, the guideline was revised to omit administration from day 2 onwards in AC therapy; [4,5] however, it has yet to be shown for CDDP. In the present study, when steroid-sparing was shown with the additional effect of OLZ, we believe that it provided the opportunity to re-examine the guidelines on antiemetic treatment in Japan and overseas. On the other hand, when non-inferiority is not shown based on the results of the present trial, it will not be recommended to omit DEX from day 2 onwards in routine medical care.

2.7 Accompanying research

It is not planned at the time of protocol development.

3. Patient selection criteria

Patients who satisfy all of the items in section '3.1 eligibility criteria' below at the time of acquiring consent, and who do not fall under any of the items in section '3.2 exclusion criteria' will be considered eligible patients.

3.1 Eligibility criteria

1) Patients with malignant tumor, excluding hematological malignancies, receiving first-line treatment with CDDP ≥ 50mg/m^2.
   (previous use of moderately or less emetogenic cancer chemotherapy is permitted)
2) Patients aged 20 – 75 years at the time of providing consent
3) Patients with nausea and vomiting of grade 0 according to CTCAE v.4.0. in the 24 hours prior to enrolment.
4) Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 – 1
5) Patients with the following functions maintained less than 2 weeks prior to enrolment:
   ALT (alanine aminotransferase) ＜100 IU/L
   AST (aspartate aminotransferase) ＜100 IU/L
   T-Bil ＜2.0 mg/dL
   sCr ＜1.5 mg/dL
6) Patients with expected prognosis of three months or more
7) Patients who provide written consent at their own free will after fully understanding a thorough explanation about participation in the present trial

3.2 Exclusion criteria

1) Patients receiving systemic glucocorticoid therapy (oral or intravenous)
2) Patients using the following antiemetics (table 5) other than the trial drug at least one day before the registration date
3) Patients scheduled to receive moderately emetogenic chemotherapy within approximately 6 days, excluding the starting date of chemotherapy (drugs that are low emetogenic or minimal are permitted on all days)

① Examples of regimens that are not excluded:

・CDDP/CPT-11【High／moderate】
(cisplatin (CDDP) 60mg/m^2 day1, irinotecan 60mg/m^2 day1、8、15)
・CDDP/5-FU【High／mild】
(cisplatin (CDDP) 80mg/m^2 day1, 5-FU 800mg/m^2 day1-day5)

② Examples of regimens that are excluded:

・CDDP/EPI【high／moderate】
(cisplatin (CDDP)75mg/m^2 day1, epirubicin 50mg/m^2 day2)
・CDDP/EPI/IFM【high／moderate／moderate】

（cisplatin (CDDP) 50mg/m^2 day1, epirubicin 60mg/m^2 day1, ifosfamide (IFM) 1500mg/m^2 day1-day5）

4） Patients who cannot be hospitalized until after 120 hours have passed since CDDP administration (day 6)

5） Patients receiving radiation therapy to abdomen or pelvis within 6 days prior to enrollment until 6 days after CDDP administration. . Furthermore, localized radiotherapy to bones (lumbar spine) for bone metastasis is not excluded. Moreover, chemoradiation above the diaphragm, chest and neck will not be excluded.

6） Patients with symptomatic brain metastasis

7） Patients with diabetes mellitus receiving treatment with insulin and/ or oral hypoglycemic agents, and patients with HbA1c (NGSP) > 6.5 % (> 6.1 % in the event of JDS) less than 28 days prior to enrolment.

8） Patients with convulsive disorder requiring treatment with anticonvulsants

9） Patients who are incapable of taking oral agents

10） Patients with mental illness or psychiatric symptoms that impede activities of daily life, and for whom participation in the trial is deemed difficult

11） Patients with a medical history of allergy to the drug used in the present trial or similar compounds.

12） Women who are pregnant, breastfeeding, or might be pregnant, and patients who do not wish to use contraception

13） Other, patients judged unsuitable as subjects for the present trial by the attending physician.

Table 5

Classification	Drugs
NK-1RA	Aprepitant, Fosaprepitan
5-HT3RA	Granisetron, Ondansetron, Azasetron, Tropisetron, Ramosetron, Indisetron, Palonosetron
Glucocorticoids	All
Anti-dopamin	Metoclopramide, Domperidone
Phenothiazine	Prochlorperazine, Perphenazine
Antihistamines	Chlorpheniramine maleate, diphenhydramine, dimenhydrinate, hydroxyzine, promethazine
Benzodiazepine (Including thienodiazepines)	All
Others	Haloperidol, Droperidol, Scopolamine

* Combinations of benzodiazepines (including etizolam, crotiazepam, etc.) are prohibited

However, administration is permitted for the following sleep medications aimed at improving insomnia.

1 Ultra short-acting (Triazolam, Zopiclone, Zolpidem)

2 Short-acting (Brotizolam, Lormetazepam, Rilmazaphon)

4. Enrolment and allocation

4.1 Enrolment system

Enrolments will be performed via the Internet using the Electric Data Capture (EDC) system, Viedoc. In the event of Internet enrolments, the researcher will need an individual account and password for this system. If unknown, the study secretariat should be contacted. Furthermore, the study secretariat is responsible for queries regarding patient enrolment and the enrolment system. Viedoc is the EDC system used for clinical trials in Japan also, and is a system with which all relevant regulation can be observed in North America, Europe and Japan, including Part 11 of Title 21 Code of Federal Regulations (21 CFR Part 11), Computerized Systems used in Clinical Investigations (CSUCI), ICH GCP, the Health Insurance Portability and Accountability Act (HIPPPA), and Annex 11 for good manufacturing practice (GMP) of medicinal products by the European Medicines Agency (EMA) (PuL and EU Annex 11).

Enrolment System:	Viedoc 4
URL	https://v4jp.viedoc.net/
Web registration	Always available

Contact	Hiroko Minatogawa St. Marianna University school of Medicine Hospital Department of Pharmacy 2-16-1 Sugao Miyamae-ku Kawasaki-city, Kanagawa,216-8511 TEL: +81-44-977-8111 (main) FAX: +81-44-977-5752 E-mail：hiroko.shinoda@marianna-u.ac.jp

4.2 Enrolment procedure

After logging onto the EDC website, click on ‘add new card’, and commence patient enrolment. Next, after registering the necessary information, the screen displaying the electronic case report form (eCRF) will appear. At this point in time, an institution number for the present trial will be issued together with a patient ID for the trial combined with the number issued by the institution indicating the enrolment order. Upon issue of this ID, enrolment will be completed.

4.3 Important matters regarding enrolment

- Enrolment is performed by accessing the URL given in section 4.1 ‘patient enrolment’
- Except when a patient withdraws consent, including refusal for data to be used in the study, once a patient is enrolled, the enrolment will not be cancelled (deleted from the database). In the event of duplicate enrolment, the first enrolment (enrolment number) will be used in all instances.

- When consent is withdrawn and the use of data is refused, the data will not be deleted from the database; however, the data will be deleted when outputted from the EDC.
- When erroneous enrolment or duplicate enrolment is discovered, the Data Center must be contacted without delay.
- After enrolment, a correspondence table will be created, in which the patient ID and ID for the trial will be input within the medical institution promptly.

4.4 Random allocation and allocation adjustment factors

Eligible patients were randomly allocated by the Data Center to either group A or group B treatment group. Adjustment factors to avoid a major bias from arising when randomly allocating patients included 1) age (60 years (< 60 years/ ≥ 60 years), 2) sex, 3) CDDP dose level (≥70mg/m2/ < 70mg/m2), and 4) institution. For random allocation, the minimization method will be used. Researchers at participating institutions were not informed of the detailed allocation procedure.

5. Blinding

5.1 Blinding method

To ensure that the present trial is performed blindly, the blinded staff who carries out the role of the coordinator will not be informed of the allocation information. Therefore, the name and role of the necessary staff is as follows.

（1) Person in charge of allocation information

Non-blinded staff who have access to allocation information

This individual will perform allocation procedures on the EDC system, receive allocation information, and will be established in advance such as from among pharmacists, clinical trial management staff or assistants. Their profession does not need to be a pharmacist.

（2） Pharmacist in charge of drug preparations

Non-blinded staff who has access to allocation information.

This individual prepares and dispenses drugs in accordance with the allocation information and is established in advanced from among pharmacists.

The pharmacist in charge of drug preparations will prepare the drugs in a manner so as to make it impossible to identify the trial drug and placebo based on outside appearance. In the event of the placebo, the infusion solution will only have the rubber plug unsealed and not have drug mixed into the solution.

（3） Blinded staff

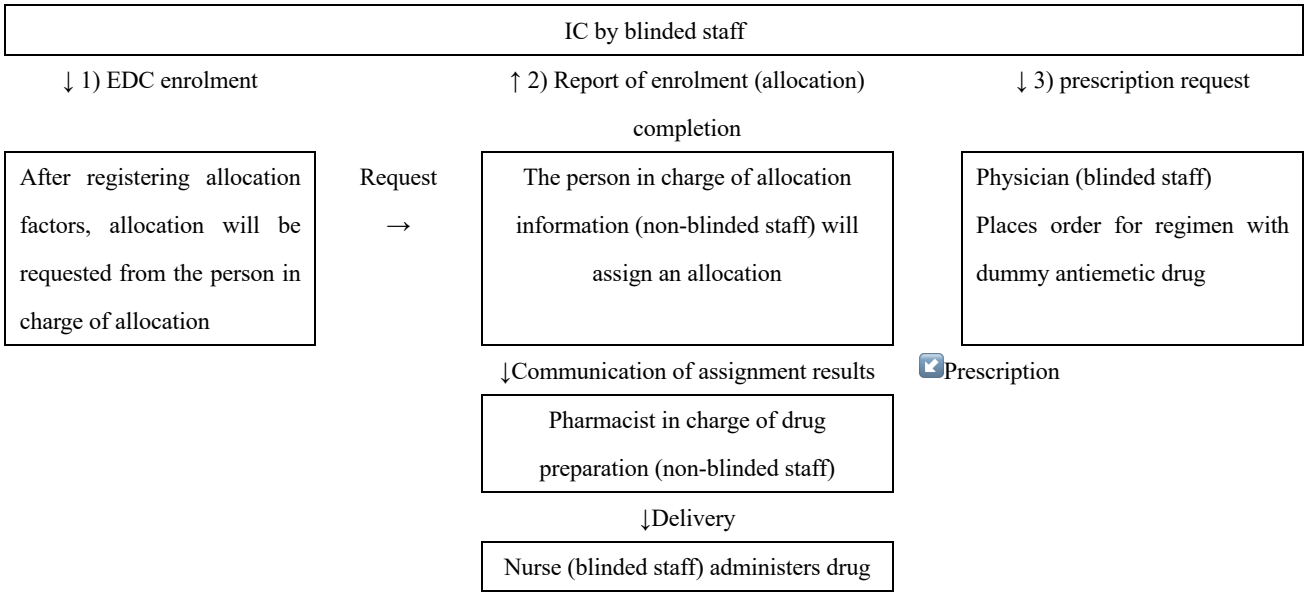
Blinded staff do not have access to allocation information

In the present trial, blinded staff carry out the role of the clinical trial coordinator such as obtaining informed

consent and sending enrolment eligibility confirmation form. They will establish the implementation system within the hospital, and exchange information with the study secretariat and data center, in an effort to make the present trial proceed smoothly. If possible, a pharmacist is preferable.
If a physician serves this role, it is preferable that blinded staff other than a physician conducted evaluations.

After blinded staff register allocation adjustment factors in the EDC system, they will communicate the request for allocation to the person in charge of allocation information. At the same time, they will request the physician to place a regimen order with a dummy antiemetic. The person in charge of allocation information will access the EDC system, and after confirming that the allocation adjustment factors are registered, they will place the allocation on the EDC system. The allocation results will be communicated to the pharmacist in charge of drug preparation, who will prepare the drug.

5.2 Schema of the blinding procedure



5.3 Key open in an emergency

As a rule, no data will be disclosed until fixed. However, during the trial period, when it is considered necessary to know the details of the trial drug to ensure subject safety, such as due to serious adverse events, the study representative and study secretariat will make an inquiry to and discuss with the efficacy and safety evaluation committee about the need for disclosure. When disclosure is deemed necessary as a result of the consultation, the details will be communicated to the study secretariat, and the details of the trial drug will be disclosed.

6. Treatment plan and criteria for treatment changes

6.1 Protocol treatment

The protocol treatment will commence within 8 days of enrolment (including the day of enrolment). For whatever reason, when the treatment commences on day 9 or later, the reason shall be noted on the treatment commencement progress record. When it is deemed that the treatment cannot be commenced, the details shall be noted on the 'discontinuation form' as 'discontinuation of protocol treatment'. After enrolment, when laboratory test values deteriorate, and the eligibility criteria is no longer satisfied prior to commencing treatment, commencement or discontinuation of the protocol treatment will be determined at the discretion of the attending physician.

6.2 Regimen

The dose level of CDDP will be ≥ 50mg/m^2.

1） With regards to combination therapy, moderately emetogenic drugs are not permitted within approximately 6 days, excluding the starting day of chemotherapy (drugs that are mildly emetogenic or less are permitted on all days)

Examples of regimens that are not excluded:

・CDDP/CPT-11【High／moderate】

（cisplatin (CDDP) 60mg/m^2　day 1, irinotecan 60mg/m^2　day 1, 8, 15）

・CDDP/5-FU【High／mild】

（cisplatin (CDDP)　80mg/m^2　day 1, 5-FU 800mg/m^2　day 1 – day 5）

Examples of regimens that are excluded:

・CDDP/EPI【high／moderate】

（cisplatin (CDDP) 75mg/m^2　day1, epirubicin 50mg/m^2　day 2）

・CDDP/EPI/IFM【high／moderate／moderate】

（cisplatin (CDDP) 50mg/m^2　day 1, epirubicin 60mg/m^2　day 1, ifosfamide (IFO) 1500mg/m^2 day 1 - day 5）

2） Other

Regimens used in combination with the clinical trial drug are permitted. However, if in trials conducted by another party, if there are exclusion criteria stipulated that overlaps with the other clinical trial it will be deemed appropriate for each institution.

6.3 Details of Protocol treatment

The following antiemetic treatment will be given for four days from commencing CDDP therapy. When using fosaprepitant, the dose level will be increased on days 3 and 4 due to interaction with DEX up to day 2.

Group A: Control Arm

With Fosaprepitant

	Day 1	Day 2	Day 3	day4

Fosaprepitant i.v.	150 mg			
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethazone i.v.	9.9 mg	6.6 mg	13.2 mg	13.2 mg

With Aprepitant

	Day 1	Day 2	Day 3	day4
Aprepitant p.o.	125 mg	80 mg	80 mg	
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethazone i.v.	9.9 mg	6.6 mg	13.2 mg	13.2 mg

Group B: Intervention Arm

With Fosaprepitant

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant i.v.	150 mg			
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethazone i.v.	9.9 mg	6.6 mg	13.2 mg	13.2 mg
Placebo i.v.		Placebo	Placebo	Placebo

With Aprepitant

	Day 1	Day 2	Day 3	Day 4
Fosaprepitant i.v.	125 mg	80 mg	80 mg	
Palonosetron i.v.	0.75 mg			
Olanzapine p.o.	5 mg	5 mg	5 mg	5 mg
Dexamethazone i.v.	9.9 mg			
Placebo i.v.		Placebo	Placebo	Placebo

- Fosaprepitant: Administered at least 60 min prior to CDDP administration
- Aprepitant: on day1, administer before at least 60 min prior to CDDP administration, and on days 2 – 3, administer by noon
- Palonosetron: Administer prior to CDDP administration
- Olanzapine: Administer orally, once a day after dinner
- Dexamethazone (day 1): Administer prior to CDDP administration
- Dexamethazone / Placebo (day 2 – 4): Administer by noon
- Generic drug: Usage of generic drugs is not restricted.

6.4 Regulations regarding concomitant drugs (treatments)

6.4.1 Antiemetic treatment (rescue)

When nausea and vomiting developed as a result of chemotherapy, appropriate treatment will be administered as deemed necessary by the physician or if the subject requests antiemetic treatment. Listed below is the choice of antiemetic drugs when administered therapeutically for nausea and vomiting occurring after administration of chemotherapy.

1) The antiemetic drugs used in the protocol treatment cannot be used, and other than APR, and PALO, NK-1RA and 5-HT_3RA cannot be used.
2) Regular prescriptions of additional antiemetics are not permitted.

Table 6 List of drugs that can be used for antiemetic treatment

Classification	Drugs	The day before registration	Until the 6th day after the test start	
			(as required)	(scheduled)
NK-1RA	Aprepitant, Fosaprepitant	×	×	×
5-HT_3RA	Granisetron, Ondansetron, Azasetron, Tropisetron, Ramosetron, Indisetron, Palonosetron	×	×	×
Glucocorticoids	All	×	×	×
Multi-acting receptor targeted antipsychotic (MARTA)	All (except OLZ as protocol treatment)	×	×	×
Anti-dopamin	Metoclopramide, Domperidone	×	○	×
Phenothiazine	Prochlorperazine	×	○	×
Antihistamines	Chlorpheniramine maleate,	×	○	×
Benzodiazepine	Alprazolam, Lorazepam	×	○	×
Others	Haloperidol	×	○	×

○ : permitted

× : not permitted

6.4.2 Forbidden concomitant drugs

1) Among concomitant chemotherapy drugs, moderately emetogenic drugs are not permitted for approximately 6 days before and after, excluding the day of commencing chemotherapy
2) Antiemetic drugs from the day prior to enrolment (refer to section 4.2. exclusion criteria)
3) The use of the following drugs is forbidden until after 120 hours have elapsed since the time of commencing CDDP therapy
    - Benzodiazepines other than alprazolam, and lorazepam used as antiemetic treatment
      However, the administration of the following sleeping pills to improve insomnia is permitted.
      Ultrashort-acting hypnotics (triazolam, zoplicone, and zolpidem tartrate)

Short-acting hypnotics (brotizolam, lormetazepam, and rilmazafone hydrochloride hydrate)

- Selective serotonin (5-hydroxytryptamine (5-HT)) reuptake inhibitors (SSRI), and serotonin (5-HT) and noradrenalin reuptake inhibitors (SNRI)
- Serotonin (5-HT)- dopamine antagonists（SDA）, and Multi-Acting Receptor Targeted Antipsychotics（MARTA）
  However, OLZ is excluded from the protocol treatment
- CYP3A4 substrates, inhibitors, and inducers (the following drugs that might have a drug-drug interaction with APR)
  CYP3A substrates, and inhibitors: pimozide, clarithromycin, ketoconazole, and itraconazole
  CYP3A4 inducers: barbiturates (primidone, and phenobarbital), rifampicin, phenytoin, and carbamazepine
- CYP1A2 inhibitors (the following drugs that may have a drug-drug interaction with OLZ)
  fluvoxamine, and ciprofloxacin
  When prophylactic quinolone antibacterials are commenced to prevent bacterial infection during the protocol treatment, substitution with levofloxacin, which does not have an inhibitory effect on CYP1A2, should be investigated.
- Chlorpromazine

4） Use drugs listed in Table 6 (List of drugs that can be used for antiemetic purposes) for purposes other than antiemetic.
(e.g., metoclopramide use during hiccup, haloperidol use during restlessness)

6.4.3 Forbidden concomitant therapy

Abdominal (below the diaphragm) and pelvic radiotherapy is forbidden from 6 days before enrolment to 6 days after commencing CDDP.

6.5 Criteria for the discontinuation and completion of the protocol

6.5.1 Definition of completion of the protocol treatment

Completion of the protocol treatment is defined when administration of the trial drug is completed on day 4 after CDDP administration.

6.5.2 Criteria for protocol treatment discontinuation

In the event of the following, the trial will be discontinued. When discontinued, the underlying reason will be made clear and noted on a case report form.

1） When it is judged that additional dexamethasone is needed.
During the protocol treatment, other than the trial drug, the use of dexamethasone is not permitted; however, when additional dexamethasone is deemed necessary for treatment, the protocol treatment will be

discontinued, and administration of dexamethasone will be permitted.

2） When the protocol treatment cannot be continued due to adverse events.

3） When a patient requests to discontinue the protocol treatment for a reason in which a relationship with an adverse event cannot be ruled out.

4） When a patient requests to discontinue the protocol treatment for a reason in which a relationship with adverse events can be ruled out (including patient refusal after enrolment, and prior to commencing the protocol treatment).

5） Exacerbation of the underlying disease or death after enrolment (including when the protocol treatment cannot be administered due to exacerbation of nausea and vomiting after enrolment and prior to treatment)

6） Other, when a violation to the protocol is found, or when the treatment is changed such as for a change in pathological diagnosis after enrolment)

The day of protocol discontinuation will be defined as the day when the attending physician judges a subject to be ineligible in the event that ineligibility is found after enrolment, and as the day when the attending physician decides to discontinue the protocol treatment for other instances.

6.5.3 After treatment (antiemetic treatment)

There is no stipulated after treatment with antiemetics after 120 hours (day 6) have passed since commencing CDDP therapy. The efficacy evaluation period is at 120 hours after CDDP administration, and subsequent treatment with antiemetics will have no effect on the results.

7. Anticipated adverse reactions

For information regarding anticipated adverse drug reactions to each individual drug, refer to the latest ‘package insert data of prescription drugs at http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html on the homepage of the Pharmaceuticals and Medical Devices Agency.

7.1 Anticipated adverse reactions

7.1.1 Adverse reactions of each treatment group

1） Anticipated adverse reactions to the standard treatment group (group A)

The adverse events of the OLZ 5 mg group observed in the double-blinded randomized controlled trial (phase II trial of OLZ 10 mg or 5 mg given in addition to APR + PALO + DEX for CDDP>50mg/m^2 are presented below.

Table 7 Adverse Events in the OLZ 5 mg group

N=77 （%）	Grade 1	Grade 2	Grade 3
Somnolence	34 （44.2）	1 （1.3）	0 （0）
Constipation	10 （13.0）	4 （5.2）	1 （1.3）
ALT rise	8 （10.4）	0 （0）	0 （0）

Hiccups	3 （3.9）	0 （0）	0 （0）
Hyponatremia	3 （3.9）	0 （0）	1 （1.3）
Dry mouth	1 （1.3）	0 （0）	0 （0）
Hyperglycemia	4 （5.2）	0 （0）	0 （0）
Hypochloremia	1 （1.3）	0 （0）	0 （0）
Discomfort	1 （1.3）	0 （0）	0 （0）
Fatigue	2 （2.6）	0 （0）	0 （0）

2） Anticipated adverse reactions to the trial treatment group (group B)

It is thought that no adverse reactions will appear as a result of additional drugs because in the trial treatment group DEX is omitted on days 2 – 4.

7.2 Assessment of adverse event/adverse reactions

Adverse events/ adverse reactions will be evaluated using the ‘NCI-Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0), Japanese Clinical Oncology Group edition’ (CTCAE v4.0-JCOG), and the patient reported outcomes (PRO)-CTCAE™ (version1.0).

7.2.1 Grading of adverse events

When grading adverse events, the event will be defined according to the grade closest to each respective definition of grade 0 – 4. In the event of treatment-related death, the causative adverse event is defined as ‘grade 5’ in the original NCI-CTCAE; however, in the present trial it will be defined as ‘grade 4’ and not ‘grade 5’ on the record of the present trial. For inquiries into the causal relationship between death and the adverse event observed in treatment-related death, the adverse event will be reported, a treatment completion report will be prepared, the adverse event will be described in the field for ‘condition at the time of death’ in the follow-up survey, and an expedited report will be made. (In post-hoc investigations including that of the expedited report, the decision will be made as to whether or not to describe the adverse event as grade 5.)

With regards to adverse events stipulated in section ‘8.2.1 observations and evaluation items performed during the protocol treatment period’, the grade will be input into an eCRF. For all other adverse events, only those of grade 3 or above will be input into an eCRF. The present trial is a study to evaluate short-term antiemetic (DEX) treatment, and thus there is no plan to evaluate hematotoxicity.

8. Evaluation items, clinical laboratory tests, and evaluation schedule

8.1 Instruments used and evaluation items

8.1.1 PRO-CTCAE™ (version1.0)

As a standard evaluation commonly used in various countries, evaluations of antitumor effects, and safety evaluations such as the NCI-CTCAE ver4.0 are widely used in clinical trials of cancer, and have come to be considered objective evaluations by medical professionals.

However, since the 1990s, in the development of medical care and new drugs, a patient-centered approach or patient participation-type medical care has gained a great deal of popularity primarily in Western countries, and in recent years, the importance of subjective evaluation by the patient themselves (Patient-Reported Outcome ; PRO) has been acknowledged. In the Guidance for Industry Patient-Reported Outcome Measure to measure PRO created in 2009 by the Food and Drug Administration (FDA), a regulatory agency in the USA, PRO is defined as 'reporting of a patient's health status obtained directly from the patient, without interpretation of the patient's response by a clinician or anyone else'.

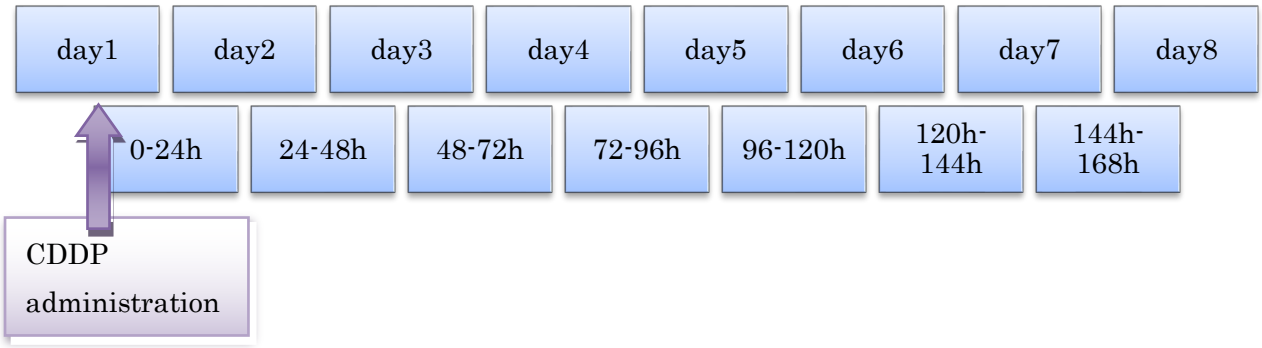
Adverse events in anticancer drug treatment include adverse events that are easily evaluated in some kind of objective manner such as by test values, and dermal toxicity; however, there are also adverse events that are difficult to evaluate objectively such as fatigue and loss of appetite. It has been found that such adverse events are difficult to convey to medical professionals and can be under-evaluated. [37] Therefore, at the National Cancer Institute (NCI) of America, the PRO approach is indicated in the evaluation of adverse events in clinical trials of cancer, and in the aim of creating an evaluation system to perform grading with greater accuracy and precision, the PRO-CTCAE™ (version1.0) was developed[38]. Thereafter, the validity of the tool was examined in multiple languages, and on February 2017, the Japanese version was made public on the NCI home page. The linguistic validity and psychometric properties of the Japanese version has been examined. [39,40] The PRO-CTCAE consists of 124 questions covering 80 adverse events which can be partially used according to the aims of each study, and a 7-day recall period is recommended (the period of having patients reflect on their symptoms). In the present trial, the endpoints are evaluated in a short period of 120 hours after commencing treatment, and DEX therapy in the day 1 group is compared against the day 1 – 4 group, and therefore, we believe that a recall period of 24 hours is appropriate. With regards to 24-hour recall, Basch et al. noted that it is feasible under specific conditions. [41]

8.1.2 Quality of life questionnaire（EORTC QLQ-C30　version 3）

The EORTC QLQ-C30, developed by Aaronson et al., [42] is a questionnaire of the QOL of cancer patients, and the reliability and validity of the Japanese version of the QLQ-C30 has been demonstrated. [43] The questionnaire consists of 30 items covering five functions (physical, role, cognitive, emotional, and social), nine physical symptoms/ items (fatigue, nausea, vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties), and global health/QOL status. Patients evaluate their symptoms according to a four-point scale, including 'never', 'sometimes', 'often', and 'very often'. Higher scores for function and global QOL indicate better status, whereas higher scores for physical symptoms indicate poorer status.

8.2 Definition of the trial follow-up period

The follow-up period is defined as the period from enrolment up to day 8 or the day of discontinuation. To evaluate efficacy, patients will be hospitalized for at least 120 hours (day 6) after CDDP administration. Thereafter, patients will be discharged, and the evaluation on day 8 at home is permitted.



8.3 Evaluation before commencing treatment

8.3.1 Matters performed by the attending physician or pharmacist in charge of the clinical trial

The attending physician or pharmacist in charge of the clinical trial will conduct observations, tests, and evaluations for the following items, and based on the results, they will confirm eligibility of the patient in the trial and complete the enrolment procedures on an eCRF. When tests performed in routine medical practice are available, they can be used as data for the present trial with prior consent. The trial drug will be administered within eight days from the day of enrolment. Furthermore, ePRO, which is an input form for patients, will be activated.

1） Demogprahics

・Cancer type

（lung / esophagus / gastric / head and neck / ovarian / cervical / uterine / bladder / upper urinary tract/ other）

・sex, birth of date, age at date of registration, height / weight (body surface area: DuBois）

・Chemotherapy regimen

（CDDP+VP-16 / CDDP+CPT-11 / CDDP+PEM / CDDP+VNR / CDDP+GEM / CDDP+DOC / FP / XP / SP / DCF / FP+Cmab / AP / CDDP+PTX / CDDP monotherapy / other）

・Concomitant use of radiation (yes / no)

・Dosage of CDDP （mg/m^2）

・Type of NK-1RA (aprepitant / fosaprepitant)

2） ECOG PS（0 / 1）

3） Laboratory test

Within 14 days from registration date

WBC, Plate, Hb, T-Bil, AST, ALT, Alb, Cr, BUN, Na, CK

Within 28 days from registration date

HbA1c

8.3.2　Questionnaire to patients

The patient enters the following items into ePRO after registration and before the start of CDDP administration.

1）　Risk factor

・Drinking habit

Are you drinking more than 5 times a week? (Yes / No)

・Motion sickness

Do you think you are susceptible to motion sickness? (Yes / No)

・Morning Sickness

Do you have experience with morning sickness? (Yes / No) *

* Patients without pregnancy experience (including men) are excluded

2）　PRO-CTCAE™（version1.0）

nausea, vomiting, discouraged, Sad or unhappy feelings, anxious, insomnia, decreased appetite, constipation, diarrhea, hot flashes, hicupps, fatigue, taste changes, dry mouth, mouth/throat sores, headahe, bloating, (somnolence, dysosmia)

3）　EORTC QLQ-C30 version 3

8.4　Evalutation during trial period

8.4.1　Outcome reported by physicians or pahrmacists

The attending physician or pharmacists inputs the CDDP administration start time into the eCRF after the initiation of the CDDP administration. In addition, for the following items, observation is performed every 24 hours after the start of CDDP until 120 hours, and the result is input to eCRF.

・Antiemetics use as rescue　(date and time, frequency, drug used) (day 2-6)

Metoclopramide / domperidone / prochlorperazine / alprazolam / lorazepam / chlorpheniramine / haloperidol / other

8.4.2　Patient reported outcome

Of the following items, 1), 2), and 3) are input to ePRO every 24 hours until 120 hours after the start of CDDP. 4) Fill in the questionnaire (paper and pen) on day 8.

1）　Nausea: Numerical Rating Scale: NRS (day2 to 6)

2）　Vomiting, retching: presence or absence, count (day2 to 6)

3）　PRO-CTCAE™ (version1.0) (day2-6)

nausea, vomiting, discouraged, Sad or unhappy feelings, anxious, insomnia, decreased appetite, constipation, diarrhea, hot flashes, hicupps, fatigue, taste changes, dry mouth, mouth/throat sores, headahe, bloating, (somnolence, dysosmia)

4）　EORTC QLQ-C30 version 3 (day8)

8.5　Evalutation after trial period

8.5.1 Outcome reported by physicians or pahrmacists

The attending physician or the researcher evaluatesthe worst value up to 120 hours after the start of CDDP (day 6) for the following items, and inputs the result into the eCRF.

1） CTCAE v4.0-JCOG

nausea, vomiting, depression, anxiety, insomnia, anorexia, constipation, diarrhea, hot flashes, hicupps, somnolence, fatigue, dysgeusia, dry mouth, mucositis oral, headache, bloating, olfactory nerve disorder, and others which is Grade 3 or higher adverse events (excluding blood toxicity)

8.6 At the time that protocol treatment is discontinued

The attending physician or pharmacists inputs the protocol treatment discontinuation date, the reason for discontinuation (refer to 6.5.2 Protocol discontinuation criteria) in the eCRF.

8.7 Schedule

Assessment items	Observation period										
	Pre-treatment		Protocol treatment								
	Pre-Registration	Registration	Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
			Pre-CDDP administration	Post-CDDP administration							
Informed consent / Eligibility criteria	●										
Registration/ allocation		●									
CDDP administration time				●							
Fosaprepitant / APR administration			●								
			●		●	●					
PALO administaration			●								
OLZ administaration				●	●	●	●				
DEX administaration			●								
DEX or placebo administaration					●	●	●				
Demographics	●*										
ECOG PS	●*										
Laboratory test: WBC, Plate, Hb	●★										
Lab: T-Bil、AST、ALT、Alb、Cr、BUN、Na、K	●★										
Lab: HbA1C	●☆										
Anti-emetics resucue use					●	●	●	●	●		
CTCAE v4.0-JCOG			◄	———	———	———	———	———	▲		
Date of discontinuation											
Reason for discontinuation											
Risk factor			○※								
QOL			○※								○
Nausea (NRS)			○※		○	○	○	○	○		
Presense of nausea and vomiting			○※		○	○	○	○	○		
PRO-CTCAE			○※		○	○	○	○	○		

●: Investigator, ▲: Investigator, most worst value until 120 hr (day 6) after CDDP administration start

◄►: Assessment period by investigator, ○: ePRO

*: Within 8 days before registration, ★: Within 14 days before registration, ☆: Within 28 days before registration

※: Perform after registration and before starting CDDP administration

9. Data collection

9.1 Electronic Case Report Form :eCRF

9.1.1 Type and deadline of eCRF

In this study, data are collected at EDC. The eCRF to register and the input deadline are as follows.

Form	Contents	Input	Deadline
Patient registration	Date of IC, etc.	Investigator	At the time of registration
Eligibility	Eligibility criteria	Investigator	Within 8 days after registration
Demographics	Demographics, regimen, etc.	Investigator	Within 8 days after registration
Laboratory	Laboratory test	Investigator	Within 8 days after registration
Allocation	Allocation form	Investigator	Within 8 days after registration
Start time of CDDP administration	Start time of CDDP administration (Triger of ePRO)	Investigator	Within 8 days after registration
Anti-emetic resucue	Presence of anti-emetic rescue use	Investigator	Within 14 days after the completion of protocol treatment
Adverse Event (ClinRO)	CTCAE	Investigator	Within 14 days after the completion of protocol treatment
Anti-emetic resucue use	Content of anti-emetic rescue use	Investigator	Within 14 days after the completion of protocol treatment
Adverse event (PRO)	PRO-CTCAE	Patient	Within each regulation day
Habits and medical history	Risk factor	Patient	Before CDDP administration stard
Nausea and vomiting	Nausea and vomiting	Patient	Within each regulation day
Quality of life（QOL）	EORTC QLQ-C30	Patient	Day8
Discontinuation	Reason for discontinuation	Investigator	Any time
Other adverse events	CTCAE	Investigator	Within 14 days after the completion of protocol treatment

9.1.2 Types of CRF and submission

For the quality of life (EORTC QLQ-C30) Day 8 (patient input), ask the patient to write in a paper. Allow delay up to Day 11. After collection by investigator, submit to the data center by direct collection or mail.

9.1.3 Storage of eCRF data

During the trial period, data is stored in EDC. After fixing the data following the end of the trial, the data is output from EDC, and is deleted from EDC. The data is stored at the research office for more than 10 years (semi-permanently) in the state of electronic media. If it is to be destroyed, it shall be conducted with the consent of the principal investigator and the research office.

9.1.4 Revision of eCRF

If defects such as missing items required for CRF are found after the start of the study, in the following cases, the CRF can be modified upon agreement between the principal investigator and the research office. 1. If the range of collected data specified in “8. Evaluation items” is not exceeded. 2. If it is determined that the CRF correction will not increase the medical and financial burden of registered patients. Modification of CRF that does not require revision of the protocol text is not considered protocol revision. Whether the CRF's corrections are reported to the head of the medical institution or submitted for revision is in accordance with the regulations of the sites.

10. Reporting of adverse events

Reporting of adverse events will be performed in accordance with this chapter based on the adverse event reporting guideline of the Japan Cancer Trial Network (JCTN).

10.1 Adverse events requiring expedited reporting

1） Death

2） Grade 4 adverse events

3） Unexpected adverse events of grades 1, 2, and 3, adverse events that require hospitalization or prolongation※ of the hospital stay of 24 hours or more for treatment.

※ ‘Hospitalization or prolongation of the hospital stay’ only indicates hospitalization/hospital stay prolongation of 24 hours or more that is medically required for treatment of an adverse event, the following instances do not require reporting.

・Hospitalization/ hospital stay prolongation performed for follow-up observation despite disappearance or remission of the adverse event

・Hospitalization/ hospital stay prolongation to alleviate patient burden, such as in the event of consultations from a remote distance.

・Other, hospitalization/ hospital stay prolongation that is not medically necessary

4） Other adverse events that are judged to be a medically significant condition

※ However, when any of the following apply, expedited reporting will not be necessary.

a) Among adverse events that occur 31 days or more after the final day of the protocol treatment (including death), those for which a causal relationship with the treatment can be ruled out.

b) Myelodysplastic syndromes (MDS), and secondary cancer onset

10.2 Mandatory reporting and report deadlines

When adverse events that correspond to ‘adverse events requiring expedited reporting’ are observed, the principal investigator at each institution will report to the study secretariat in accordance with the following procedure.

1) Death or grade 4 adverse events

① Preliminary report

The attending physician who detects the onset of an adverse event will report to the principal investigator of

the institution without delay. Upon receiving the report, the principal investigator will use the prescribed form to report the information perceived regarding the adverse event within 72 hours of being informed of the occurrence of the adverse event.

② Second report

The principal investigator of the institution will create a report with additional detailed information of the adverse event to the prescribed form within 7 days of being informed of the occurrence of the adverse event, and if needed, they will attach copies such as of test data, images and biopsy result.

2) Adverse events < grade 3, and other adverse events that are judged to be medically significant conditions

The attending physician who detects the onset of an adverse event will report to the principal investigator of the institution without delay. Upon receiving the report, the principal investigator will use the prescribed form to note the detailed information of the adverse event within 10 days of being informed of the occurrence of the adverse event, and if needed, they will attach copies such as of test data, images and biopsy results to the report.

3) Additional reports

When new information is obtained after preparing the abovementioned reports, the principal investigator of the institution will add the information to the prescribed form, and report at any time as needed.

Table 10 Summary of expedited reporting, duty and reporting time frames for adverse events

	Grade 1/2/3				Grade 4	Death	
	Expected		unexpected		Expected / unexpected		Other medically important conditions
	No admission	admission	No admission	admission			
causal relationship	No reporting required	No reporting required	No reporting required	First time: within 10 days Addition: Any time	Primary report: within 72 hours Secondary report: within 7 days Additional report: Any time		First time: within 10 days Addition: Any time
No causal relationship	No reporting required	No reporting required	No reporting required	<Within 30 days of treatment or last protocol treatment day> First time: within 10 days Addition: Any time	<During treatment or last protocol treatment date Within 30 days of> Primary report: within 72 hours Secondary report: within 7 days Additional report: Any time		<Within 30 days of treatment or last protocol treatment day> First time: within 10 days Addition: Any time

※All matters that require reporting must also be reported to the directors of all study institutions. Furthermore, among matters that require reporting, all unexpected events, and those for which a causal relationship with the protocol treatment cannot be ruled out must be reported to the Minister of Health, Labour, and Welfare by the director of the study institution where the adverse event occurred.

4） Report form

When ‘adverse events with mandatory reporting’ occur, the adverse event report form can be obtained from the JCTN home page for common guidelines of adverse event reporting (http://jctn.jp/guideline_03.html), and the report should be sent to the study secretariat by FAX or e-mail.

10.3 Duties of the principal investigator and study secretariat

10.3.1 Emergency response decisions

Upon receiving reports from each institution, the study secretariat will report to and consult with the principal investigator to determine the level of urgency, importance, and impact of the report content, and adopt measures as needed, such as temporary discontinuation of enrolments, and emergency contact of necessary information to participating institutions. Furthermore, they will examine the need to discontinue the trial, and to revise the protocol.

10.3.2 Reporting to the Data and Safety Monitoring. Committee / DSMC

The study secretariat will report the opinion of the principal investigator/ study secretariat regarding the adverse event reported by expedited reporting, and the countermeasures adopted to the efficacy and safety evaluation committee, and request the committee to evaluate the adverse event, as well as the validity of the countermeasures adopted.

11. Outcome assessment and definition of endpoints

11.1 Outcome assessment

1） Vomiting (vomiting and retching)

Subjects will record the presence or absence of vomiting (including retching), and frequency thereof per 24-hour period up to 120 hours from the point in time of commencing CDDP therapy.

Instances of vomiting will include the discharge of gastric juice, and stomach contents such as food out of the mouth via the esophagus, and vomiting movement even if there is no discharge of the stomach contents (retching).

2） Nausea

Subjects will evaluate and record the degree of nausea per 24-hour period up to 120 hours from the point in time of commencing CDDP therapy according to an 11-point numerical rating scale, in which the absence of nausea is defined as ‘0’, and the worst conceivable nausea as ‘10’. Furthermore, the subject will record their judgements made based on their own subjectivity to the best of their ability.

3） Additional antiemetic treatment

Additional antiemetic treatment will be administered appropriately when nausea and vomiting occurs after CDDP administration, and the attending physician judges it necessary, or when the subject requests treatment. The drugs used will be done in accordance with the drugs noted in section 7.4.1 antiemetic treatment.

4） Complete Response : CR

Absence of vomiting and/or retching, and no additional antiemetic treatment administered

5） Complete Control : CC

Absence of vomiting and/or retching, with no additional antiemetic treatment administered, and nausea is absent or mild※

※ Nausea absent（NRS 0）, mild（< NRS 2）

6） Total Control : TC(total cholesterol)

Absence of vomiting and/or retching, with no additional antiemetic treatment administered, and nausea is absent ※※

※※Nausea absent（NRS 0）

7） Time to Treatment Failure : TTF

The time until the initial onset of vomiting (including retching), or additional antiemetic treatment is administered, whichever is earliest.

	Vomiting (including retching)	Nausea	Rescue use of antiemetics
Complete Response: CR	None	(does not matter)	None
Complete Control: CC	None	None or mild (under NRS 2)	None
Total Control: TC	None	None	None
No vomiting	None	(does not matter)	(does not matter)
No nausea	(does not matter)	None	(does not matter)

11.2 Definition of endpoints

1） Complete Response Rate

Acute CR: The rate of complete inhibition of vomiting within 24 hours of commencing CDDP therapy

Delayed CR: The rate of complete inhibition of vomiting within 24 – 120 hours of commencing CDDP therapy

Overall CR: The rate of complete inhibition of vomiting within 120 hours of commencing CDDP therapy

2） Complete Control Rate

Acute CC: The rate of complete inhibition of nausea and vomiting within 24 hours of commencing CDDP therapy

Delayed CC: The rate of complete inhibition of nausea and vomiting within 24 – 120 hours of commencing CDDP therapy

Overall CC: The rate of complete inhibition of nausea and vomiting within 120 hours of commencing CDDP therapy

3） Total Control Rate

Acute TC: The rate of total control of nausea and vomiting within 24 hours of commencing CDDP therapy

Delayed TC: The rate of total control of nausea and vomiting within 24 – 120 hours of commencing CDDP therapy

Overall TC: The rate of total control of nausea and vomiting within 120 hours of commencing CDDP therapy

4） No vomiting

Acute No vomiting: The rate of no vomiting within 24 hours of commencing CDDP therapy

Delayed No vomiting: The rate of no vomiting within 24 – 120 hours of commencing CDDP therapy

Overall No vomiting: The rate of no vomiting within 120 hours of commencing CDDP therapy

5） No nausea

Acute No nausea: The rate of no nausea (NRS 0) within 24 hours of commencing CDDP therap

Delayed No nausea: The rate of no nausea (NRS 0) within 24 – 120 hours of commencing CDDP therapy

Overall No nausea: The rate of no nausea (NRS 0) within 120 hours of commencing CDDP therapy

6） Time to Treatment Failure: TTF

The time until the initial onset of vomiting (including retching), or additional antiemetic treatment is administered, whichever is earliest. If neither event occurs, the cut-off time will be at 120 hours.

7） Nausea severity during the overall phase

The transition in the nausea level (NRS) every 24 hours until 120 hours after commencing CDDP therapy.

8） The incidence of adverse events

The incidence of the worst grade will be calculated per group during the protocol treatment according to the CTCAE v4.0 for each adverse event with all treatment as the denominator. Furthermore, for the PRO-CTCAE, in addition to observed values, items that exacerbated from baseline will be reported.

9） Incidence of serious adverse events

The incidence of serious adverse events will be calculated by the number of patients who exhibit one or more of any of the following serious adverse events as the numerator, and the safety analysis set as the denominator.

1） Early death

All deaths during the protocol treatment period, or within 30 days of the day of the final protocol treatment. (Death irrespective of the causal relationship with the treatment)

2） Treatment-related death

Deaths in which a causal relationship with the treatment cannot be ruled out, even when 31 days have elapsed from the final day of the protocol treatment.

12. Statistical considerations

12.1 Analysis set

The analysis set used in the present trial is defined as follows. When the handling of a patient cannot be determined by the criteria listed below, the statistical analysis manager, principal investigator, and study secretariat will discuss such patient prior to data fixation while blinded.

Definition of the analysis set for the present trial

Analysis set	Definition
All enrolments	All enrolled patients
Efficacy analysis set	The population from 'all enrolments' excluding patients who meet the following criteria ・ Patients who are found to be clearly ineligible at the time of enrolment. ・ Patients who do not receive the HEC specified in this protocol. ・ Patients who did not receive any protocol treatment.
Safety analysis set	All patients who received at least some of the protocol treatment.

12.2 Primary analysis

In each group adjusted by allocation factors, the CR rate, inter-group difference in point estimation, and 95 % confidence interval (CI) will be calculated. Furthermore, the null hypothesis, i.e. that the CR rate of group A -15 % and group B are comparable, will be tested by the Cochran-Mantel-Haenzsel test. When the lower limit of the 95 % CI exceeds -0.15, non-inferiority of group B to group A will be considered to have been verified. A two-tailed test p value of 2.5 % will be considered statistically significant.

12.3 Secondary analysis

For the CR rate of the acute phase and overall period, CC rate and TC rate of the overall period, acute phase, and delayed phase, and for the rate of no vomiting and no nausea, the CR rate of the delayed phase for each group, inter-group difference in point estimation, and 95 % CI will be calculated. Furthermore, an inter-group comparison will be performed using a chi-square test. With regards to the TTF, the estimated median, and 95 % CI will be calculated for each group using the Kaplan-Meier method, and an inter-group comparison will be performed using a log rank test. A two-tailed test p value of 5 % will be considered statistically significant.

12.4 Safety analysis

For adverse events, the grade distribution of each event will be recorded for each group, and an inter-group comparison will be performed using a Mantel test. A two-tailed test p value of 5 % will be considered statistically significant

12.5 Analysis of the PRO-CTCAE and QLQ-C30

For the PRO-CTCAE, the grade distribution of each symptom will be recorded for each group, and an inter-group

comparison will be performed using a Mantel test. For the QLQ-C30, the distribution of scores for the global QOL, each domain, and each item will be recorded for each group, and an inter-group comparison will be performed using a t-test. A two-tailed test p value of 5 % will be considered statistically significant.

12.6 Grounds for setting the planned number of enrolments

Based on section '2.4.2. Clinical hypothesis and grounds for setting the target number of enrolments', we hypothesized that the delayed phase CR rate would be 75 % in group A, and 75 % in group B also, and upon calculating the necessary subject size for a one-sided α of 0.025, statistical power of 80 %, and non-inferiority margin of 15 %, a total of 262 patients will be needed, with 131 patients per group. Considering that some patients will be ineligible or unable to enrol, the target subject sample size was set at 280 patients.

12.7 Interim analysis

Interim analysis is not planned.

13. Ethical Issues

13.1 Protection of clinical trial subjects

All investigators involved in the current research will conduct this study in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and "Ethical principles for medical research involving human subjects" (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare Notification No. 3 of 2014, partial revision on December 22, 2015 and February 28, 2017 http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka / 0000069410.pdf). In addition, investigator adhere to this study protocol as long as they do not compromise patient safety and human rights.

13.2 Informed consent

Before enrolling a patient, the physician gives the patient an explanatory document approved by the medical institution, and verbally explains the following contents. "Medical institution approval" means that the director of the medical institution obtains an approved document issued to the applicant's researcher based on the results reviewed by the Institutional Review Board (IRB).

Contents of explanation

1) Name of disease, explanation about chemotherapy
2) This study is a clinical trial
3) Design and rationale
4) Contents of protocol treatment
5) Expected effects of protocol treatment
6) Predicted adverse events, complications, sequelae and coping methods

Explanation of the severity and frequency of predicted adverse events, including complications, sequelae, and treatment-related deaths, and a description of how to handle them when they occur.

7) Post-treatment after protocol treatment should be properly performed

8) Cost sharing and compensation

The cost of treatment is covered by the insurance system. Compensation for health problems is the same as for general medical care.

9) Alternative treatment

Explanation of treatments that can be taken if patients do not participate in this study.

10) Expected benefits and potential disadvantages

Explanation of the potential benefits and disadvantages of taking part in this study.

11) About direct browsing of medical history

Explanation of acceptance of audits such as "medical staff of other medical institutions obtain permission of head of medical institution and directly view medical history etc. for quality control"

12) Rejection of consent and withdrawal of consent

Be free to refuse prior to participation in the trial, and be free to withdraw after consent once, so that you will not receive undue medical disadvantages

17) Right to question

Explanation of being free to question about trial and treatment. Provision of the contact information of the research representative of the medical institution and the principal investigator (or the research office) , in addition to the contact information of the physician in charge, in documents.

13) Human rights protection

Maximum effort should be made to keep name and personal information confidential

14) Conflicts of interest

15) Secondary use of data

Possibility of secondary use of data (meta analysis etc.) without linking to personal identification information

16) Method of disclosing information about research

17) Right to ask question

Not only the contact information of the physician in charge but also the contact information of the research director of the medical institution and the principal investigator of the study (or the research office), and an explanation that you can freely ask questions about the examination and treatment.

13.3 Consent

A patient should be given an explanation by using the informed consent form and sufficient time to understand the contents of this study that may be involved before he/she is asked to participate. If the patient agrees to participate in the study, he/she will sign the informed consent form. The person in charge is to confirm that the name of the explainer and the date of explanation as well as the name of the patient and the date of consent in informed consent form. Two copies of the written consent will be made, one handed to the patient himself, and one kept by the facility coordinator. Originals should be stored in a medical record or in a storage place specified by the medical institution.

13.4 Reseponse to inquiries and consultations after consent

In principle, if a patient or his / her family members have consulted after the registration, the investigator at the patient's medical institution (investigator at the research site, facility coordinator, physician in charge) will respond. If investigator do not know how to respond, investigator will respond in consultation with the research office, principal investigator, data center, etc. according to the content of the consultation.

13.5 Protection of personal information and patient identification

Patient identification is only possible on the correspondence table, where the patient ID on medical records are given along with the patient registration number given by the data center after registration. Information that leads to patient identification is managed by the personal information manager of each facility and never passed to a third party. Data exchange protects the privacy as much as possible, regardless of paper or electronic media.

Storage of data

The retention period of data on this study will be 5 years from the date of submission of the final analysis report, or 3 years from the publication date of any paper related to this study, whichever is later. It is recommended to keep for as long as possible after the deadline. When discarding the information related to this study after the storage period has passed, anonymize and discard.

Secondary use of data

The data obtained in this study may be secondarily used (meta-analysis etc.) without linking to personal identification information under the responsibility of the principal investigator.

13.6 Complianse with the research protocol

All investigator participating in this study should adhere to this protocol as long as they do not compromise patient safety and human rights.

13.7 Approbal by ethical review board

Approval at the start of the trial

Researchers must obtain approval from the head of each medical institution to conduct the study using this protocol and the patient's explanattory document to begin enrollment in this study. The explanatory document for patients can be modified for each medical institution without departing from the requirements for clinical trials and can be used after obtaining approval from the medical institution. However, regarding the protocol, content changes by medical institutions are not permitted. Researchers should use a common protocol for all facilities. If it is necessary to change the contents, amendment or revision should be performed as a common protocol used in all facilities. The facility coordinator should consult with the research office if there is a request for any modification of the protocol from a medical institution.

Annual update of approval of each medical institution

The necessity of annual renewal of the approval for this protocol and patient explanatory documents in each medical institution follows the regulations of each medical institution.

13.8 Change of protocol content

13.8.1 Classification of protocol content change

When changing protocol contents, "protocol revision application" must be submitted to the Data Safety Monitoring Committee for approval prior to implementation of the changes. All applications from researchers are "Revision applications". Addition of supplementary explanations that do not correspond to changes in the protocol content is distinguished as memorandum. The definition and handling are as follows.

1） Amendment

Partial modifications to the protocol that may increase the risk for patients participating or that are related to the primary endpoint require review and approval by the Data and Safety Monitoring Committee and each Institutional Ethics Review Board.

2） Revision

Protocol modifications that do not have the potential to increase the risk for patients participating and that are not related to the primary endpoint require the approval of the Data and Safety Monitoring Committee. The review approval of the ethics review board of each facility follows the rules of each facility.

3） Memorandum

The supplementary description of the protocol distributed by the Principal Investigator / Laboratory is defined as a memorandum. This is not to change the content of the protocol, but to reduce variations in text interpretation or to draw special attention. The format does not matter.

13.8.2 Approval by ethical review committee at the time of amendment / revision of the protocol

If the protocol or the explanatory documents is revised with the approval of the Data and Safety Monitoring Committee during the study, researchers must obtain approval from the Ethics Review Board for the revised protocol and explanatory documents. If the content change is not amendment but revision, it is necessary to follow the rules of each facility to require the approval of the Ethics Review Board.

13.9 Conflict of Interest: COI

About COI of person involved in this study in medical practice in participating facilities such as facility researcher and facility coordinator, follow the regulations of medical facilities of participating facilities.

13.10 Compensation

With regard to the health hazards caused by participating in this clinical trial, appropriate medical treatment depending on the condition is provided as insurance medical care. At that time, the patient shall bear the burden of

the medical fee. In addition, financial compensation such as money for offering and various benefits will not be provided.

13.11Information disclosure of this study

The outline, progress and main results of this study will be published at UMIN-CTR (www.umin.ac.jp/ctr/).

14. Monitoring and audit

14.1 Scheduled monitoring

In principle, scheduled monitoring is performed once a year to confirm that the study is conducted safely and in accordance with the protocol and whether the data is correctly collected. Monitoring is central monitoring based on the eCRF data collected at the data center. facility visit monitoring conducted including facility reference visits at facility visits will not be conducted in principle. In principle, we will not conduct on-site monitoring that involves matching with original documents at facility visits.

Central monitoring will be conducted referring to the JCTN-monitoring guidelines and the contents will be summarized in the monitoring report.

Monitoring reports prepared by the data center will be submitted to the research office / principal investigator r for consideration. The purpose of monitoring is to provide feedback on issues to enhance the science and ethics of the this trial, and is not intended to identify issues of this trial or facility. The research office, principal investigator, and facility research representive share information with the researchers at each site with the issues pointed out in the report and strive to improve them.

14.2 Admissible range of adverse events

Researchers should report to the Date and Safety Monitoring Committee every time treatment related death occurs and ask for their decision to suspend registration or to discontinue the entire study.

14.3 Items of monitoring

1） Achievement of accumulation
2） Eligibility: ineligible cases / cases in which there is a possibility of ineligibility
3） Protocol During treatment / treatment termination, discontinuation / termination reason
4） Backgrounds / Demographics
5） Serious adverse events
6） Adverse Reaction / Adverse Event
7） Protocol deviation
8） Other issues related to trial progress and safety

14.4 Protocol deviation, vilolation

If the drug administration, clinical examination, efficacy / safety assessment, etc. were not performed according to

the provisions of the protocol, it is considered as a protocol deviation.

1） Violation

Deviation from the protocol that is clinically inappropriate and in principle falls into the following items is defined as "violation".

A) Affects the assessment of study endpoints

B) Physician and/or site is/are cause

C) Intentional or systematic

D) The degree of risk or deviation is significant

2） Deviation

A deviation that does not fall within the scope of a violation or tolerance

3） Acceptable deviation

A deviation from the protocol is acceptable.

14.5 Consent withdrawal

Withdrawing consent means withdrawal of consent to study participation, and it is distinguished from refusal of protocol treatment continuation (the following 1). If withdrawal of consent is stated, clarify either of the following 2 or 3 and promptly contact the data center.

In the case of "2. Withdrawal of consent", the data center cancels the request for follow-up according to the following protocol. In case 3, the patient's data is deleted from the database when it is confirmed that all consent has been withdrawn. The procedures for discontinuing the patient's follow-up request and deleting patient data will be separately determined in the procedure manual, and the completion of each work will be reported to the principan investigator and research office.

1. Patient refusal: refusal to continue protocol treatment (follow up continues).

2. Withdrawal of consent: Withdraw from consent to study participation and make all treatment and follow-up in accordance with the following protocol impossible. Research use of data prior to consent withdrawal is permitted.

3. Withdrawal of all consents: Withdraw from consent to study participation and disallow the use of all data from the time of study participation, including information at the time of registration.

14.6 Audit

Conduct audits as necessary *. When conducting, audits follow CTN audit guidelines.

* If the Data and Safety Monitoring Committee determines that it is necessary (for example, when a problem occurs such that the quality of the clinical trial is not ensured), then establish an audit committee composed of the members appointed by the Data and Safety Monitoring Committee, and conduct and evaluate audits.

15. Organization

15.1 Principal investigator

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15.5 Protocol steering committee

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Naoki Izawa, Department of Medical Oncology, St. Marianna University school of Medicine Hospital
Hiroko Minatogawa, Department of Pharmacy, St. Marianna University school of Medicine Hospital

15.6 Protocol Review Comittee・Data and Safety Monitoring Committee

Chair: Toshimi Takano, Department of Medical Oncology, Toranomon Hospital
Sadatomo Zenda, Department of Radiation Oncology, National Cancer Center Hospital East
Toshinori Hayashi, Department of Pharmaceutical and Health Care Management, Faculty of Pharmaceutical Sciences, Fukuoka University

15.7 Site

Changes in content due to the addition of participating facilities and changes in the facility researcher will be made at the time of the protocol revision and amendment application, and no change is made at any other time.
When sites are added, the addition of sites will be made known in memorandum first.

Site	Coordinator (Pharmacist)	Manager (Physician)
St. Marianna University School of Medicine Hospital	Ayako Yokomizo	Naoki Izawa
Kawasaki Municipal Tama Hospital	Ayako Tsuboya	Takashi Ogura
Yokohama City Seibu HOspital	Hajime Morita	Naoya Hida
Showa University Northern Yokohama Hospital	Daisuke Ichikura	Hiroo Ishida
Yokohama Rosai Hospital	Tomoko Tateishi	Hitoshi Arioka
Nippon Medical School Musashi Kosugi Hospital	Akiko Konomatsu	Noriyuki Katsumata
Aichi Cancer Center Hospital	Kazuhiro Shimomura	Kazunori Honda
Gifu University Hospital	Hirotoshi Iihara	Yasushi Ohno
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16. Publication of results

The main results will be published in English journal.

The presentation of the purpose of the research introduction, the distribution of patient background after registration, and the presentation of safety data, excluding the analysis results of the endpoints, can be made with the approval of the principal investigator.

In principle, the author of the article disclosing the main results (the first disclosing the results of the primary endpoint) will be headed by the research office and the Corresponding Author will be the principal investigator. Then, one of the facility manager or facility coordinator of the site with the largest number of case registrations, and the member of protocol steering comittiee. From then on, according to the restrictions imposed by the authors instrucsion, the facility manager or facility coordinator with the second or higher number of case registrations will be selected as a coauthor, and the final author will be the principal investigator. The principal investigator decides the authors of papers other than the main published article (papers on secondary endpoints, papers on secondary analysis, etc.). All coauthors review the content of the draft paper prior to submission, and only those who agree on the content of the presentation will be coauthors. If there is no agreement on the content, the principal investigator is able to exclude the researcher who can not agree on the content from a co-author.

The members of the protocol steering committee have the right to be in charge of the main speaker of the conference presentation, and the person in charge is decided by the principal investigator and research office. At the time of presentation, the research office is responsible for the preparation and content of the presentation, and in principle, the research office will contact the data center. Presenters other than the research office can not receive the results directly from the data center without the consent of the research office.

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