PAlliative medicine Steroid intervention Quality Of Life trial team (PASQol)

Multicenter Randomized, Placebo-controlled, Double-blind Clinical Trial Assessing the Effects of Corticosteroid Administration on Fatigue and QOL in Advanced Cancer Patients

Protocol

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Trial period: June 2014 to June 2019

Table of Contents

Flow of Reporting/Responding to Serious Adverse Events

Independent Enrollment Audit Committee Bylaw

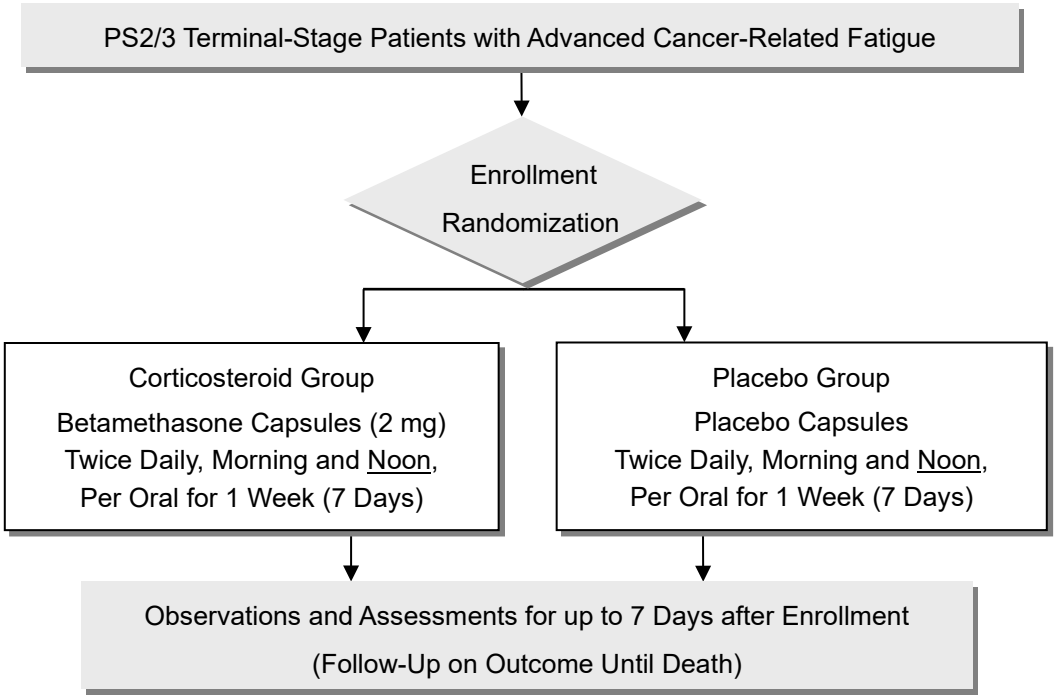
Independent Enrollment Audit Committee Inquiry Form

Manual on Obtaining Informed Consent

0 SUMMARY

0.1 Study Design

Multicenter randomized, placebo-controlled, double-blind, parallel group study



0.2 Objectives

The objective is to evaluate the effectiveness of oral corticosteroid administration (2 mg betamethasone, twice daily, total of 4 mg a day) in alleviating fatigue in PS2/3 terminal-stage patients with advanced cancer-related fatigue. Secondary objectives are to evaluate the quality of life (QOL) improvement by corticosteroid administration and to assess safety by obtaining information on the severity and frequency of adverse events. An additional objective is to exploratorily assess the relationship between fatigue and blood test values.

0.3 Study Hypothesis

When the study treatment (1 week of corticosteroid or placebo administration) is given to PS2/3 terminal-stage patients with advanced cancer-related fatigue, the alleviation of fatigue, as indicated by the FA (fatigue) score in EORTC QLQ-C15-PAL, in the corticosteroid group is superior to that in the placebo group.

0.4 Endpoints

0.4.1 Primary endpoint

The FA (fatigue) score in EORTC QLQ-C15-PAL

0.4.2 Secondary endpoints

(1) Efficacy endpoints

1) Non-FA QOL scores in EORTC QLQ-C15-PAL

2) Numeric rating scale (NRS)

3) Survival time

(2) Safety endpoint

Adverse events

0.4.3 Exploratory endpoint

Blood tests (C-reactive protein [CRP], white blood cell count, hemoglobin, platelet count, blood glucose level)

0.5 Study Population

The study population in this trial will be PS2/3 terminal-stage patients with advanced cancer-related fatigue. Eligible subjects may be outpatients, inpatients, or someone receiving treatment at home.

0.6 Target Sample Size and Trial Period

(1) Target sample size: 210 patients (corticosteroid group, 105; placebo group, 105)

(2) Planned trial period: June 17, 2014 (after ethics committee approval) to June 16, 2019

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List of Abbreviations and Definition of Terms

Abbreviation	Expanded Term	Explanation
CRC	Clinical Research Coordinator	Clinical research coordinator
CRF	case report form	Case report form In this study, it mainly refers to a paper-based patient questionnaire
CRP	C-reactive protein	C-reactive protein, an indicator used to measure inflammatory responses and destruction of body tissue
EAPC	European Association for Palliative Care	European Association for Palliative Care
ECOG PS	Eastern Cooperative Oncology Group Performance Status	A scale by the Eastern Cooperative Oncology Group (ECOG) used to assess the patient's general condition
EDC	Electronic Data Capture	Electronic Data Capture In this study, it mainly refers to information input on a computer
EORTC QLQ-C15-PAL	European Organisation for Research and Treatment of Cancer quality of life questionnaire core 15 palliative	Palliative patients' quality of life questionnaire compiled by the European Organisation for Research and Treatment of Cancer
FA PF AP QL	fatigue physical functioning appetite loss overall quality of life	QOL fatigue subscale QOL physical functioning subscale QOL appetite-loss subscale QOL overall-quality-of-life subscale
FAS	Full analysis set	Full analysis set
IC	Informed consent	Informed consent
ID	Identification	A unique number that identifies an individual
IRB	Institutional review board	Institutional review board
JCOG	Japan Clinical Oncology Group	Japan Clinical Oncology Group
JMDC	Japan Medical Data Center	Japan Medical Data Center
MID	Minimally Important Difference	Minimal difference that is still clinically significant
NCCN	National Comprehensive Cancer Network	A U.S. cancer network
NRS	numeric rating scale	A method for measuring intensity on an 11-point scale from 0 to 10
PPS	Per protocol set	A population of participants deemed to be protocol compliant without protocol violations
QOL	Quality of Life	Quality of life
UMIN-CTR	University Hospital Medical Information Network Clinical Trials Registry	University Hospital Medical Information Network Clinical Trials Registry
WHO	World Health Organization	World Health Organization

1 Background

Cancer has been the leading cause of death in Japan since 1981 and accounted for 29.5% of all deaths in 2010. The number of deaths from cancer has been on a rising trend[1]. Given the large number of deaths from cancer at present, even if no complete cure is available, medical interventions are needed to alleviate as much as possible the discomfort of terminally ill patients[2]. In Japan, the Cancer Control Act went into effect in April 2007, and the Basic Plan to Promote Cancer Control Programs drawn up in the following year clearly focused on addressing three issues, including palliative care[3][4]. The Basic Plan to Promote Cancer Control Programs was revised in April 2012 to further promote such programs, and the revised basic plan still continues to list the promotion of palliative care as one of the key issues that should be addressed[5].

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life (QOL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and meticulous assessment and treatment of pain and other physical, psychosocial, and spiritual issues[6]. There is also a report indicating that early palliative care aimed at improving QOL resulted in prolonging survival[7]. Since the goal of palliative care is to improve patients' QOL, assessing QOL allows the outcome of palliative care to be obtained.

Fatigue, along with the perception of pain and dyspnea, is one of the discomforts affecting the QOL of terminal cancer patients. Fatigue is the most frequent physical condition in terminal cancer patients and is reportedly experienced by 66% to 100% of patients[8-11]. Fatigue in cancer patients mainly includes the fatigue associated with the cancer treatment and that stemming from the cancer itself. The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue as “a subjective perception of physical, mental, and cognitive weariness and/or exhaustion, relative to daily activities, that is related to cancer with persistent pain and cancer treatment and hinders normal functioning”[12]. The Research Steering Committee of the European Association for Palliative Care (EAPC) defines fatigue in terminally ill patients as “a subjective perception of weariness, weakness, and lack of energy"[13]. While both definitions consider fatigue as a "subjective perception," there has been no consensus on a unified definition.

Corticosteroids are often used in palliative care in Japan to treat fatigue in terminal cancer patients[14][15]. However, there have been no high evidence-level studies focusing on the relationship between corticosteroid administration and fatigue[16]. Methylphenidate, one of the therapeutic modalities for treating cancer-related fatigue, has been reported to be slightly more effective than placebo, but not enough for it to be recommended as treatment for fatigue[17-19]. The effectiveness of thalidomide, another therapeutic modality, in treating fatigue has been controversial, but most of the reports involve patients undergoing chemotherapy rather than terminal-stage patients[20]. Given this situation, at the 2012 American Society of Clinical Oncology (ASCO) conference, the MD Anderson Cancer Center in the United States stated that corticosteroid therapy intervention for patients with

advanced cancer is effective in alleviating fatigue and reported in July 2013 that a randomized controlled trial comparing a corticosteroid (Decadron® 8 mg/day) group and a placebo group[21)22)] showed the efficacy of corticosteroid in alleviating fatigue in patients with advanced cancer. However, Decadron® 8 mg/day is a very high dose compared with the clinical doses commonly used in Japan for palliative care, thus raising a concern about the potential of overdose in Japanese due to their smaller body size[23)].

At present, there is no established standard treatment with respect to corticosteroid administration to alleviate fatigue in terminal-stage patients. Corticosteroids have been administered to terminal cancer patients based on the experience of palliative care clinicians with the aim of improving a patient's general condition, even though there is no evidence of their effectiveness[14)]. However, there are no reports on how fatigue is treated in most terminal cancer patients in Japan who die without palliative care. Accumulating evidence, which can be passed on to clinical practice, showing the benefits of corticosteroids as a treatment for fatigue in terminal-stage patients will contribute to the establishment of a standard treatment. We believe the establishment of a standard treatment for fatigue in the terminal stage of cancer will also allow many cancer patients, who currently die without treatment from a palliative care specialist, to receive treatment for fatigue. Clinical research in Japan is needed on corticosteroid doses that can be used to treat fatigue in terminal cancer patients.

[The number of cancer patients in Japan who die without treatment from a palliative care specialist]

There are sporadic regional or institutional reports but no nationwide reports on the number of cancer patients who received treatment from a palliative care specialist before their death. The applicant performed an estimation using the insurance claim database of a health insurance union (Japan Medical Data Center [JMDC])[24)] with about one million enrollments. Approximately 15% of the patients who died of lung, stomach, colorectal, pancreatic, breast, or prostate cancer between 2005 and June 2012 received treatment from a palliative care specialist before their death either as an inpatient in a palliative care ward or through a palliative care team. The efficacy evaluation of corticosteroid administration for treating fatigue in this study is expected to lead to the identification of an effective treatment regimen to alleviate fatigue for the nearly 85% of cancer patients who are not expected to receive any treatment from a palliative care specialist before their death.

2 Objectives

The primary objective is to evaluate the effectiveness of oral corticosteroid administration (2 mg betamethasone, twice daily, total of 4 mg a day) in alleviating fatigue in PS2/3 terminal-stage patients with advanced cancer-related fatigue. Secondary objectives are to evaluate the quality of life (QOL) improvement by corticosteroid administration and to assess safety by obtaining information on the severity and frequency of adverse events.

2.1 Target Disease Name

In this study, the target disease is broadly defined cancer, including leukemia, malignant lymphoma, carcinoma, and sarcoma of epithelial, hematopoietic, or non-epithelial origin.

2.2 Study Hypothesis

When the study treatment (1 week of corticosteroid or placebo administration) is given to PS2/3 terminal-stage patients with advanced cancer-related fatigue, the alleviation of fatigue, as indicated by the FA (fatigue) score in EORTC QLQ-C15-PAL, in the corticosteroid group is superior to that in the placebo group.

3 Study Population

The study population in this trial will be PS2/3 terminal-stage patients with advanced cancer-related fatigue. Eligible subjects may be outpatients, inpatients, or someone receiving treatment at home who meet all of the following inclusion criteria and none of the exclusion criteria. Unless otherwise specified, determinations will be made based on the medical data obtained on the eligibility confirmation date or those obtained within 2 weeks before eligibility confirmation.

3.1 Inclusion Criteria

(1) A diagnosis of stage 4 cancer, for which surgery aimed at complete recovery is impossible, and a decision has been made to prioritize palliative care over cancer treatment with the aim of maintaining/improving QOL

(2) A determination by two medical staff members that the cancer is in the terminal stage
The two medical staff members must have a good understanding of the patient's symptoms and include at least one physician.

(3) Aged 20 to 89 years at the time of informed consent

(4) Someone whose responses at the time of examination to any of the two questions below in EORTC QLQ-C15-PAL on the fatigue (FA) subscale is “quite a bit” or “very much,” from among the following response options: “not at all,” “a little,” “quite a bit,” and “very much”

1) Have you felt weak?
2) Were you tired?

(5) An ECOG PS score of 2 or 3 at the time of examination

Japanese translation of the ECOG Performance Status (PS) scale[25)]

Score	Definition
0	Able to carry out activities without any problems. Able to carry on daily living just as before the disease without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

(6) Able to take the investigational product (capsules) orally

(7) Approval from the independent enrollment audit committee to carry out informed consent

(8) A patient who has given written informed consent personally to participate in this study

(9) A patient whose family has given written informed consent for the patient to participate in this study

[Rationales]

(1) and (2) The criteria were established to identify suitable study participants.

(2) The definition of the term “end stage” varies and refers to a time period anywhere within 6 months of expected death, depending on the corresponding period specified by the respective treatment. In this study, the term “end-stage” refers to the last 1 to 2 months before the expected death of a subject to be treated, during which time fatigue is reported to occur frequently[26) 27)].

(3) The criterion was established in consideration of the legal age at which individuals can give valid consent.

(4) through (6) The criteria were established to identify subjects eligible to participate in this study.

(7) The criterion was established in consideration of the study subjects’ circumstance of having an end-stage disease.

(8) The criterion was established for ethical considerations.

(9) The criterion was established in consideration of the study subjects’ circumstance of having an end-stage disease.

3.2 Exclusion Criteria

(1) Use of a corticosteroid by injection or orally within 1 week before enrollment
(2) Use of a synthetic corpus luteum preparation within 4 weeks before enrollment
(3) Undergoing surgery within 4 weeks before enrollment
(4) Undergoing radiation therapy (excluding symptom-alleviating radiation therapies) at the time of enrollment
(5) Chemotherapy within 4 weeks before enrollment or within the regimen period
(6) A history of diabetes that was treated with drugs (excluding diabetes that is well controlled or not expected to exacerbate with betamethasone administration)
(7) An apparent comorbidity with infection
(8) A comorbidity with peptic ulcer that was treated with drugs
(9) Presence of a mental illness related to cognitive function (including delirium)
(10) Someone for whom any of the contraindications listed on the package insert of Betamethasone Tablets applies
(11) Any other patients whom the attending physician deems inappropriate for inclusion as a subject in this study

[Rationales]

(1) and (2) The criteria were established in consideration of a potential impact on the evaluation of the study treatment.

(3) through (8) The criteria were established in consideration of the participants’ safety.

(9) and (10) The criteria were established to identify subjects eligible to participate in this study.

(11) The criterion was established to exclude patients whom the attending physician deems inappropriate for inclusion as a subject in this study for reasons that could not be anticipated at the planning stage.

4 Protocol

4.1 Study Design

A multicenter, placebo-controlled, double-blind (attending physicians and patients), randomized, parallel-group comparative study.

The present trial is a clinical trial that compares alleviation of fatigue (systemic conditions), an approved indication of betamethasone, between betamethasone- and placebo-treated groups of performance status 2 or 3 (PS2/3) terminal-stage patients with advanced cancer-related fatigue. The study treatment period for individual participants begins on the day (Day 1) after the enrollment-baseline date (Day 0) and ends at study treatment discontinuation or completion (Day 7). During the trial period, the randomly allocated study treatment (with steroid or placebo) will be administered to all participants under blinded conditions. Furthermore, in the present trial, an outcome survey on death of individual participants after the end of their study treatment will be conducted.

[Rationales for the choice of study design]

(1) The multicenter design of the present trial was chosen to 1) increase the likelihood of obtaining generalized findings by recruiting diverse study sites, given the impacts from factors intrinsic to a particular study site, and 2) ensure a sufficient number of enrolled patients.

(2) The placebo-controlled design was chosen for the following reasons. 1) The study intends to provide patients appropriate palliative care regardless of whether intervention with a steroid is given and to determine the efficacy of the steroid's effect. Thus, to accurately assess the steroid's effect, placebo is needed as a comparator. The appropriate palliative care mentioned above refers to alleviation (or spiritual care in some facilities) of various distressing physical symptoms (e.g., treatment for dyspnea, in the case of lung cancer, or for nausea, vomiting, and constipation/diarrhea, in the case of gastrointestinal cancer) related to certain types of incipient cancer; pain, insomnia, and other physical symptoms associated with many end-stage cancers; and psychological and social issues. 2) Given that a placebo has the potential to provide a certain effect (placebo effect) in terms of alleviating fatigue, a subjective symptom, it is necessary to assess whether treatment with a steroid in the intervention group provides an added effect over and above the placebo effect. 3) We had the following discussion with collaborating physicians involved in palliative care about whether it is ethical to use a placebo control fatigue in PS2/3 terminal-stage patients with advanced cancer-related fatigue. Based on empirical knowledge derived from clinical practice, unlike pain therapy and other treatments that must be rendered promptly, no standard therapeutic intervention has yet been established to improve the quality of life (QOL) of fatigued patients, and the time to commence such a therapy may vary by about a week in normal clinical practice. Unlike therapies to treat pain, nausea, and dyspnea, which must be rendered promptly based on a specified procedure to determine when to commence treatment in clinical practice, a delay of about a week in giving the placebo group treatment with a steroid for fatigue in the present trial is not considered a material deviation from current clinical practice.

Nevertheless, for reference purposes, a placebo-controlled, double-blind clinical trial has been conducted in Japan to confirm the effect of a drug in pain therapy[28]. As for fatigue therapy, an interim report of a clinical trial on a steroid (Decadron®, 8 mg/day) conducted in advanced cancer patients by the MD Anderson Cancer Center in the U.S. was presented at the annual meeting of the American Society of Clinical Oncology (ASCO) held in June 2012. The report indicated that a steroid has efficacy in the treatment of fatigue associated with cancer[21], and detailed results from the study were published on July 29, 2013[22]. While the duration of placebo treatment was two weeks in the U.S. study, a duration of one week was selected for the present trial based on the clinical practice experience described above.

(3) The double-blind design was chosen with consideration given to the following: 1) influence from the attending physician; for instance, consideration of the degree of mutual trust built between physicians and patients; 2) an assumption that influence from the attending physician tends to be greater in PS2/3 terminal-stage patients with advanced cancer-related fatigue, the subjects of the present trial; and 3) minimization of influence on participants' subjective assessment, as the primary endpoint is the fatigue subscale in QOL assessment (a subjective assessment by participants) to be recorded by the participants.

(4) The choice of a randomized comparative study was to minimize the influence from all biases due to known and unknown factors when making a comparative analysis of the primary endpoint.

(5) A study treatment period of 7 days was chosen in consideration of participants who are outpatients receiving home care.

(6) The choice of betamethasone tablets among oral steroids was made for the following reasons. 1) A preliminary survey of collaborating hospitals and facilities that will be participating in this study showed that except for two facilities that use Decadron®, all have been using betamethasone tablets. 2) Its small dosage form makes handling easy when preparing a capsular formulation of the study drug.

(7) The package insert for betamethasone, the study drug in the present trial, provides the following dosage and administration: "Usually, for adults, administer orally 0.5 to 8 mg as betamethasone per day, divided into 1 to 4 doses." Dosages appropriate for end-stage cancer patients have yet to be determined[29]. Given that the lowest maximum dose of betamethasone was 4 mg according to a preliminary survey of collaborating hospitals and facilities that will be participating in this study, a dosage of 4 mg/day was selected for the study drug.

4.2 Target Sample Size and Trial Period

(1) Target sample size: 210 patients (corticosteroid group, 105; placebo group, 105)

(2) Trial period, planned: June 17, 2014 (after ethics committee approval) to June 16, 2019

[Rationale for the choice of sample size]

Our earlier study in palliative care patients showed that the change in the fatigue (FA) scale on the

Quality of Life Questionnaire - Core 15 Palliative (QLQ-C15-PAL) was −15.3 in the group of patients whose answer was “better” and 0.0 in those whose answer was either “no change” or “worse.” Assuming an intergroup difference of −15.5 for the detected change, the standard deviation for the change was 30.2, thus giving an effective size of 0.51. To detect an intergroup difference of 0.5 SD at a two-sided significance level of 5% and a statistical power of ≥90%, 168 patients in two groups (84 patients per group) are needed. Assuming a patient dropout rate of 20% during the trial, 210 patients in two groups (105 patients per group) are to be enrolled.

The assumption of a patient dropout rate of 20% during the trial is based on the following factors, which are unique to terminal-stage patients.

1) The QOL questionnaire is a survey form self-administered by patients. As cancer symptoms progress, some patients may not be able to self-administer the questionnaire a week after study commencement.
2) As the survey respondents are terminal-stage cancer patients, some of them may die.
3) Pain therapy and cancer progression may lower cognitive level.
4) Some of the patients may switch to home care during the end-stage of their lives.
5) Some of the end-stage patients may transfer to a hospital facility near their home for the remaining part of their lives.

[Rationale for the choice of trial period]

Given the target sample size of 210 patients and the number of study sites (24), an enrollment period of three years was chosen, as such a duration is needed to ensure the target sample size is reached. Although each participant is to receive the study treatment for one week, the subsequent outcome survey is expected to last for at least three to seven weeks. Meanwhile, with no reliable way of predicting expected survival durations available at present and a report that QOL improvements can extend patient survival[7], it is necessary to anticipate a survival period longer than that predicted at enrollment. Thus, a follow-up survey period of up to four months after enrollment (after 16 weeks) of the last patient was chosen, with the trial to end at the same time.

4.3 Screening of Candidate Subjects

(1) The investigator (attending physician) selects candidate patients based on information available in routine medical practice.
(2) The investigator, upon determining that a patient is potentially eligible to participate in this study (3.1 and 3.2), shall record on the Patient Screening Form (Appendix) an arbitrary symbol or number that is linkable within the study site. No patient screening forms linkable within the site will be submitted anywhere outside of the facility.
(3) The investigator shall communicate the information of a potentially eligible candidate on the IC Inquiry Forma (Appendix) to the independent enrollment supervisory board (16.6) by email

(audit@hi.med.kyoto-u.ac.jp).

(4) For candidates who are not enrolled, record on the Patient Screening Form “did not meet the inclusion criteria,” “declined to participate,” or “other reason.”

[Rationale for the choice of Patient Screening Form]

The Patient Screening Form was selected because it provides the information necessary to identify “did not meet the inclusion criteria,” “declined to participate,” or “other reason” in the process of preparing a flowchart for screening patients to be included in the analysis[30].

[Rationale for the choice of IC Inquiry Form]

Inquiries to the independent enrollment supervisory board require information that aids the verification of eligibility and the assessment of the justification for obtaining’ informed consent. Thus, the form gives the investigator the discretion to freely record information. Furthermore, with regard to the exclusion criterion, “presence of a mental illness related to cognitive function (including delirium),” the investigator is to inquire about “the patient’s overall condition (e.g., disease recognition, decision-making ability, relationship with the medical care team, and interest in the clinical trial).”

4.4 Informed Consent

(1) Inform patients after confirming approval has been granted by the independent enrollment supervisory board to administer informed consent.
(2) Inform patients as instructed in the Manual for Obtaining Informed Consent (Appendix), with the patient’s right to decide whether to participate or not fully respected
(3) When presenting information to a patient, pay due attention to the patient’s physical condition.
(4) The investigator (attending physician) shall use the Written Information (Appendix) to provide an explanation about the present trial to patients who are candidates for inclusion in the study and use the Informed Consent Form (Appendix) to obtain voluntary consent directly from the patient.
(5) Meanwhile, the investigator shall also obtain the signature of a family member of the patient to signify that the family has also consented to the patient’s inclusion in the trial.
(6) In cases where no consent could be obtained from a patient and his or her family member, the investigator shall indicate this on the Patient Screening Form.

4.5 Eligibility Verification

(1) The investigator (attending physician) shall verify the eligibility of participants who gave consent to participate in the study.
(2) Assess eligibility based on clinical data available on the day of eligibility verification or clinical data obtained within 2 weeks before the eligibility verification.
(3) In cases where a patient is deemed ineligible, indicate this on the Patient Screening Form.
(4) In cases where a patient is potentially eligible (3.1 and 3.2), the investigator shall communicate

this to the independent enrollment supervisory board by email promptly once the patient becomes a candidate for informed consent. (4.3 (3)).

4.6 Enrollment

(1) To enroll a participant, the investigator (attending physician) shall fill out a hard copy of the enrollment form with the required information, which is to be verified by two individuals: the investigator (attending physician) and another clinician.

(2) The investigator shall enter the eligibility criteria-related information in the data center-provided enrollment form (electronic data capture [EDC]) on a computer and inform the secretariat through its mailing list (PASQol@umin.ac.jp).

(3) In the present trial, for outpatients, carry out the procedures from informed consent to enrollment on the same day and commence treatment with the study drug on the following day (Day 1).

4.6.1 Enrollment Procedure

The investigator (attending physician) shall enter on the Enrollment Form, the date of enrollment, the name of the study site and a predetermined symbol for the study site, a serial number (participant enrollment number) assigned within the study site, participant's information (date of birth or age, sex, date on which the independent enrollment supervisory board gave approval, date of informed consent, date of treatment commencement, name of the primary cancer diagnosed, date of diagnosis, and Eastern Cooperative Oncology Group Performance Status [ECOG PS]), and the result of eligibility verification (a check list of inclusion and exclusion criteria).

(1) The investigator (attending physician) shall ask a clinician other than an investigator (attending physician) to verify the information provided on the Enrollment Form.

(2) The investigator, after the information on the Enrollment Form has been verified, shall verify the allocation number without changing the study drug's serial number that has been distributed in advance to the study site and enter the number on the Enrollment Form.

(3) The investigator (attending physician) shall ask a clinician other than another investigator (attending physician) to verify the allocation number of the study drug concerned. The individual who verifies the information shall sign and date the verification section of the Enrollment Form.

(4) The investigator (attending physician) shall enter the allocation number on the Patient Screening Form (Appendix), which is used as a reference table for anonymized numbers within the study site.

(5) The investigator (attending physician) shall retain the Enrollment Form and the Patient Screening Form, which is used as a reference table for anonymized numbers.

4.6.2 Participant Enrollment Numbers

A participant enrollment number (XX-YY) comprises the following parts.

XX: the study site number

YY: a serial number assigned within a study site to a participant enrolled in the present trial

4.6.3 Random Drug Allocation

(1) Randomly allocate drugs according to the allocation schedule prepared by the allocation manager (16.9 and 16.10 below).

(2) Allocate drug numbers so that the ratio of corticosteroid group to placebo group is 1:1.

(3) Allocation is to be carried out by the variable block randomization method at the pharmacy department of the study drug manager.

(4) The allocation manager shall supervise the variable block allocation and verify the drug allocation according to the operating procedure for allocation (16.9 and 16.10 below).

[Rationale for the choice of variable block allocation]

The present trial is to be conducted in both outpatients receiving home care and inpatients. The wait time during office visits should be minimized as much as possible for PS2/3 terminal-stage patients with advanced cancer-related fatigue. Thus, we chose block allocation, which allows the study drug to be prepared in advance. Given the need to blind the study drug in block allocation, variable block allocation was selected.

4.7 Blinding

4.7.1 Allocation Concealment

The present trial is a placebo-controlled, double-blind, comparative study.

The allocation is carried out by the variable block randomization method based on a written specification for creating allocation schedules prepared by the allocation manager, who keeps the allocation schedule confidential to conceal the allocation.

4.7.2 Ensuring Blindness

(1) Confirming indistinguishability between the investigational product and placebo

Before blinding the study drug, the allocation manager shall check the study drug to be allocated to confirm that the investigational product and placebo are indistinguishable.

(2) Generating and retaining allocation numbers

The allocation manager shall generate allocation numbers based on the written specification for creating allocation schedules and retain the numbers under seal until the declaration of data lock by the principal investigator (10.4 below) after the completion of data check following the completion of the trial in all patients (10.2 below).

(3) Review of blindness

The allocation manager, after the declaration of data lock, shall review the blindness of the study drugs that have been stored in random order as opposed to the enrollment numbers and verify whether the study drugs were allocated based on the allocation schedule (16.9 and 16.10 below).

4.8 Emergency Code Breaking

In the event a participant develops a serious adverse event during the study treatment period that is

life-threatening or requires emergency treatment and the information on whether betamethasone was administered is deemed necessary to make a treatment decision for the participant, the investigator (attending physician) shall follow the following procedures to have the participant's allocation number disclosed.

4.8.1 Procedures for Emergency Disclosure of Allocation Numbers

(1) In the event the conditions described above for disclosure of allocation numbers are deemed met, the investigator (attending physician) shall take actions according to one of the two procedures below.

(2) Procedure 1: The investigator (attending physician) shall unseal the envelope marked "Procedure for Emergency Code Breaking of Allocation Numbers" that has been prepared in advance by the head of the independent data monitoring board and sealed and distributed by the secretariat, and follow the instructions provided therein.

(3) Procedure 2: The investigator (attending physician) shall contact the secretariat by phone and follow the procedures as instructed.

(4) When contacted by the investigator (attending physician) per Procedure 2, if the secretariat alone is unable to take actions in response, he/she shall promptly contact the allocation manager to confirm the study drug group and contact the investigator (attending physician) by phone or email.

4.9 Baseline Survey and Study Treatment Commencement

The investigator (attending physician) shall present information to the patient, obtain informed consent, and carry out baseline observations and assessments immediately after completing the patient's enrollment. After contacting the secretariat by email, commence the study treatment on the morning of the next day (Day 1) after the baseline survey (Day 0).

In the event the study treatment cannot be commenced as a participant is found to be ineligible after his/her enrollment or cannot participate for some other reason, discontinue the study for the participant, record the reason for doing so on the case report form (CRF), and contact the secretariat promptly by email or phone.

4.10 Study Treatment

4.10.1 Definition of Study Treatment

The study treatment is defined as the randomly allocated treatment as described for the two groups below.

(1) Steroid group

Administer orally a steroid (2 mg of betamethasone tablets 0.5 mg "SAWAI" twice daily in the

morning and noon) for one week (until Day 7).

(2) Placebo group

Administer orally placebo capsules (twice daily in the morning and noon) for one week (until Day 7).

4.10.2 Administration of Study Treatment

(1) The investigator (attending physician) shall administer the study treatment prepared as allocated starting from the day following enrollment (Day 1).

(2) Dispense the study drug without changing the order of packaging.

(3) The study drug is provided to outpatient participants by the investigator (attending physician) and to inpatient participants by the investigator (attending physician) or a clinician instructed by the investigator (attending physician).

4.10.3 Study Drugs

(1) In the present trial, patients in the control group will be treated with placebo. Thus, prepare capsules by filling JP-conforming capsules with betamethasone drug product and lactose, and prepare placebo in a similar manner by filling the capsules with lactose alone.

(2) An opinion issued on January 7, 2013 by officials of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare on the preparation of the study drug for the present trial indicated that this protocol does not violate the Pharmaceutical Affairs Law[31)32)].

(3) A study drug manager appointed by the allocation manager shall prepare and label the study drug according to the allocation schedule generated by the allocation manager in a formulation room that meets class 10,000 clean room standards.

(4) The packaging form of the study drug is as follows. Dispense a total of 14 doses (for 7 days), with each dose wrapped in a piece of powder wrapping paper and labeled with the allocation number on the exterior. Place the required number of packets for one participant into an aluminum zipper bag containing a desiccant to remove moisture. Place security tape over the opening of the zipper bag to allow identification of any bags that have been opened.

4.10.4 Investigational Product (steroid)

Capsules containing a 2-mg betamethasone tablet, a synthetic adrenocortical hormone, per capsule

Nonproprietary name: Betamethasone

Chemical name: 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione

See the package insert of Betamethasone Tablets (Appendix) for details. Always obtain the latest version of the package insert to verify information.

4.10.5 Control Drug (placebo)

Capsules containing lactose that are superficially indistinguishable from the investigational product

4.10.6 Method of Study Drug Administration

(1) Administer orally one capsule twice daily, morning and noon.
(2) There shall be no dose increase or reduction during study treatment.
(3) In the event the treatment is interrupted (dose interruption) after study commencement, continue to carry out the study and perform assessments as specified. The term “interruption” in the present trial means an interruption (dose interruption) of the study treatment for some unspecified reason followed by treatment resumption.
(4) In the event the administration of the study drug is discontinued after study commencement, perform assessments promptly after discontinuation of the study treatment. The term “study treatment discontinuation” in this study means discontinuation of the study treatment followed by no resumption of the study treatment.
(5) Survey the drug compliance status by asking the participants to mark a verification check box on the dosing diary (Appendix) each time the participant takes a dose during the study treatment period.
(6) Instruct the participants to always drink water before taking a capsule.
(7) In cases where there is leftover study drug after the study treatment, check the dosing diary and collect any leftover study drug.

4.10.7 Study Drug Management

(1) The study drug manager shall create a standard operating procedure to ensure quality control is maintained in the conduct of the study and establish a standard operating procedure for study drug management.
(2) Document distribution, storage, control, and collection of the study drug each time the study drug is transferred or delivered/received.
(3) The study drugs shall be managed as directed in the standard operating procedure to ensure quality control is maintained in the conduct of the study.

4.11 Concomitant Therapies

4.11.1 Administration and Documentation of Concomitant Therapies

(1) During the study period, follow the provisions provided below under “Prohibited Concomitant Therapies.”
(2) Treat adverse events appropriately, at the discretion of the investigator (attending physician) at the study site where the event occurred.
(3) Survey and document any concomitant therapies administered between eligibility verification and study treatment completion or discontinuation.

4.11.2 Prohibited Concomitant Therapies

During the study period, the administration for the first time of any of the medications or therapies described below is prohibited. In cases where a prohibited concomitant therapy cannot be discontinued

or must continue, withdraw the participant concerned from the study.

(1) Oral or injectable adrenocortical hormone preparations other than the therapeutic agent used in the study
(2) Oral administration of a synthetic corpus luteum hormone preparation
(3) Surgery
(4) Radiation therapy (except radiation therapy to alleviate symptoms)
(5) Chemotherapy

[Rationales]

(1), (2) Such hormone preparations can affect efficacy evaluations

(3) Postoperative healing of surgical wounds is affected

(4), (5) Decreased white blood cell count affects susceptibility to infections

4.12 Study Treatment Discontinuation

4.12.1 Study Treatment Discontinuation and Study Discontinuation

The investigator (attending physician) shall promptly discontinue the study treatment in a participant if any of the following apply after his/her enrollment and discontinue the study in the participant.

(1) When the investigator (attending physician) concludes that a participant is unable to continue the study treatment due to the occurrence of an adverse event
(2) When a participant must receive a prohibited concomitant therapy
(3) When a participant expresses the wish to discontinue the study treatment or to discontinue or withdraw consent for study participation
(4) When a participant is found to be ineligible after his/her enrollment
(5) When the independent enrollment supervisory board requests a discontinuation
(6) When a participant stops making office visits after relocation or transferring to another hospital
(7) When a blood test other than those scheduled during the trial period is required
(8) When a participant is deemed by the investigator (attending physician) as unable to continue the study due to a reason other than those described in items (1) through (7) above

4.12.2 Data Related to Study Treatment Discontinuation

Perform observations, tests, and assessments required at discontinuation as soon as possible. If 3 days' worth of data before study treatment discontinuation are available, such data may be used as the data at study treatment discontinuation.

Record the reason for discontinuing study treatment on the CRF.

4.13 Completion of Study

4.13.1 Study Completion and Assessments

The investigator (attending physician), after performing the study treatment in a patient for one week

starting from the day of commencement, shall conclude the study treatment and complete the study in the participant.

On the day of study completion (Day 7), perform the observations, tests, and assessments required at study completion.

4.13.2 Outcome Survey after Study Completion

After study completion, conduct an outcome survey on deaths of participants.

4.14 Completion of Study in All Participants

After the study is completed in all participants, the principal investigator shall declare a data lock according to the procedures below and then perform unblinding.

(1) After completion of the trial in all participants, the data center shall send a notice of data-check completion to the principal investigator.
(2) The principal investigator, after verifying the notice of completion, shall sign and date the data lock declaration (under 10.4 below).
(3) The allocation manager, after verifying the data lock declaration issued by the principal investigator, shall disclose the allocation numbers.
(4) There is no potential for data obtained in the present trial to be used for other purposes.

Observations, Tests, Assessments

4.15 Information Subject to Reporting Requirement during Study/Observation Period and Reporting Schedule

Item \ Time	At Eligibility Verification	Enrollment Allocation	Baseline	During Study Treatment						Study Treatment Discontinuation or Completion (Day 7)	Outcome Survey
Day	0	0	0	1	2	3	4	5	6		
Inclusion/exclusion criteria verification	○										
Approval from the independent enrollment supervisory board	○										
Consent acquisition		○									
Patient characteristics: sex, date of birth or age, name of the diagnosed primary cancer		○									
Allocation (study drug) number		○									
Body height and weight[j]			○								
Study drug compliance				○	○	○	○	○	○	○	
Administration of concomitant therapies			○	○	○	○	○	○	○	○	
ECOG PS			○							○	
QOL assessment			○							○	
NRS			○							○	
Blood tests: CRP, white blood cell count, hemoglobin, platelet count, blood glucose test date			○[a)]							○[b)]	
Occurrence of adverse event				→	→	→	→	→	→	→	
If discontinued: date of and reason for discontinuation										○	
Outcome survey: date of death or verification of final outcome, reason for ending trial											○

a) Data obtained within the two weeks immediately prior to Day 0 may be referenced.

b) Data obtained within one week from Day 7 may be referenced.

Information Subject to Reporting Requirement at Enrollment on Day 0 (baseline)

Have at least two individuals check all categories of information in the following enrollment report and promptly enter the information in the EDC according to the operating procedure for EDC inputs prepared by the data center.

(1) Participant enrollment number
(2) Name of study site
(3) Name of investigator
(4) Date of enrollment
(5) Date on which the independent enrollment supervisory board issued an approval to administer IC
(6) Sex
(7) Date of birth or age
(8) Name of the diagnosed primary cancer
(9) Date of primary cancer diagnosis
(10) Inclusion criteria verification
(11) In cases where the exclusion criteria verification resulted in the patient as “otherwise deemed by the attending physician as inappropriate for inclusion in the present trial,” document the basis for such a determination.
(12) Verification of the status of informed consent (IC) acquisition
(13) Date of IC acquisition
(14) Allocation (drug) number
(15) Name of the individual who reports the double-check
(16) Date of the double-check

4.16 Information on Survey Period

(1) In the present trial, out of consideration for participants receiving outpatient palliative care while undergoing home care, conduct the eligibility verification, enrollment, allocation, and baseline survey on the same day (Day 0).
(2) On the day following enrollment and the baseline survey is defined as Day 1 of the study treatment, which continues until Day 7.
(3) Out of consideration for participants receiving outpatient palliative care while undergoing home care, the study treatment is to conclude on Day 7.
    1) If the next visit of an outpatient participant is postponed due to a holiday/weekend, give the participant an envelope containing a QOL questionnaire and an NRS form on Day 0 and ask the participant to fill out the forms on Day 7, place the forms in the envelope, and bring them to the next outpatient visit.
    2) If the next visit of an outpatient participant is postponed due to a holiday/weekend, the investigator (attending physician) is to conduct the ECOG PS survey on the outpatient

visit that is closest to Day 7.

(4) Conduct an outcome survey on death of participants after discontinuation or completion of the study treatment.

4.17 Information on Data to be Reported

4.17.1 Baseline and Day-0 Data to be Reported

(1) Enrollment number
(2) Name of study site
(3) Name of investigator
(4) Date of report
(5) Date of assessment
(6) Body height and weight
(7) The ECOG PS assessment is to be performed by the investigator (attending physician).
(8) Concomitant therapies are defined as the therapies administered on Day 0.
(9) Assess QOL using the Japanese version of EORTC QLQ-C15-PAL by requesting participants to fill out the form.
(10) EORTC QLQ-C15-PAL was developed for cancer patients receiving palliative care, and published results of a validation of its Japanese version by the principal investigator of the present trial, among others, are available[33)34)]. Registration with EORTC will take place before use.
Upon collecting a QOL questionnaire that has been filled out by a participant, check for any missing information immediately.
(11) Ask participants to rate their fatigue on a numeric rating scale (NRS) of 0 to 10.
(12) The NRS has been included as a fatigue screening tool in the U.S. National Comprehensive Cancer Network (NCCN) Fatigue Practice Guidelines 2013[12)] and used in earlier studies on fatigue.
The “NRS score by NCCN for rating severity of fatigue” is shown below.

NRS Score	Severity of Fatigue
0	No fatigue
1 to 3	Mild fatigue
4 to 6	Moderate fatigue
7 to 10	Severe fatigue
10	The most severe fatigue imaginable

(13) Do not collect blood samples for a blood test for the sole purpose of collecting data for the present trial.
(14) Report data from a blood test performed as part of the usual medical care within the two weeks immediately prior to Day 0, along with the date of the test.
(15) The blood test shall include parameters subject to substantial variations as a result of the study

drug treatment, including C-reactive protein (CRP), white blood cell count, hemoglobin, platelet count, and blood glucose.

4.17.2 Information to be Reported during Trial Period (Days 1 to 7)

(1) Ask participants receiving outpatient care to record study drug compliance by making entries in a drug compliance diary (Appendix). Participants who are inpatients may make entries in the drug compliance diary personally or have a clinician (physician, nurse, or pharmacist) do so on their behalf.

(2) With regard to the administration of concomitant therapies, the investigator (attending physician) is to record any drugs prescribed other than the study drug.

(3) With regard to occurrence of adverse events, see “5. Adverse Events Assessment and Reporting.”

(4) An interruption of study treatment is defined as a temporary discontinuation (dose interruption) after one or more doses of the study drug followed by resumption of study drug use. The specific period of and the reason for the interruption of study drug treatment shall be provided.

4.17.3 Information to be Reported at Discontinuation of Study Treatment

(1) Discontinuation of study treatment is defined as no resumption of the study drug on or before Day 7 after one or more doses of the study drug.

(2) Upon discontinuing the study treatment, conduct the observations and tests required at discontinuation as soon as possible.

(3) Ask patients to fill out the QOL questionnaire and NRS form.

(4) If 3 days’ worth of data before study treatment discontinuation are available, use such data as the data at study treatment discontinuation.

4.17.4 Information to be Reported at Completion of Study Treatment (Day 7)

(1) With regard to the administration of concomitant treatments, the investigator (attending physician) is to record any drugs prescribed other than the study drug.

(2) The investigator (attending physician) shall perform the ECOG PS assessment.

(3) Ask participants to assess QOL by filling out the Japanese version of the EORTC QLQ-C15-PAL. Upon collecting a QOL questionnaire that has been filled out by a participant, check for any missing information immediately.

(4) Ask participants to rate the severity of their fatigue on a scale from 0 to 10 on the NRS form for assessing the level of fatigue.

(5) Perform a blood test, in principle, on Day 7 (acceptable range Days 8 to 14). However, depending on the patient’s condition, it is acceptable to report data from a test conducted within one week from Day 7 on a day that is nearest to Day 7. The reported data are to include the date of the blood test, CRP, white blood cell count, hemoglobin, platelet count, and blood glucose.

(6) For occurrence of adverse events, see “5. Adverse Events Assessment and Reporting.”

(7) Participants shall record study drug compliance in the drug compliance diary (Appendix) and

submit the diary to the investigator (attending physician) on Day 7. The investigator (attending physician) shall check the drug compliance diary and transcribe the information into the CRF.

4.17.5 Information to be Reported from the Outcome Survey

(1) Date of confirmation of death outcome or the final outcome

(2) Outcome

(3) Cause of death

5 Adverse Events Assessment and Reporting

5.1 Definition of Adverse Event

In the present trial, all adverse events occurring during the study treatment are subject to evaluation. An adverse event for which a causal relationship to the study treatment cannot be ruled out is defined as an adverse drug reaction (ADR) to the study treatment. Of the ADRs occurring in the steroid group, those described in the package insert of Betamethasone Tablets (Appendix) are defined as known ADRs, and those not described in the package insert or those described but inconsistent in nature or severity are defined as unknown ADRs (unexpected ADRs)[35].

5.2 Adverse Events Assessment

In the present trial, adverse events are assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, Japanese Clinical Oncology Group (CTCAE v4.0-JCOG)[36].

5.3 Information Investigated

5.3.1 In the event the investigator (attending physician) confirms the occurrence of an adverse event, he/she shall investigate the following.

(1) Name of event (in principle, the name of the diagnosis)
(2) Date of occurrence
(3) Seriousness
(4) Grade (1, mild; 2, moderate; 3, severe or medically significant but not immediately life-threatening; 4, life-threatening; 5, death related to adverse event)
(5) Disposition of study treatment (continued, interrupted, discontinued)
(6) Action (action taken [if any action is taken, explain], no action taken)
(7) Outcome (resolved, resolving, unchanged, worsened, death, unknown [if the investigation ends with the outcome remaining unchanged, worsened, or unknown, provide a reason])
(8) Date of outcome confirmation
(9) Causal relationship to the study treatment (related, not related [basis for determining presence/absence of a causal relationship])

5.3.2 Definition of Seriousness

A serious adverse event is defined as any untoward medical occurrence associated with the use of the study drug that

(1) results in death
(2) is life-threatening
(3) requires inpatient hospitalization or causes prolongation of existing hospitalization
(4) results in persistent or significant disability or incapacity
(5) is a congenital anomaly, or
(6) other event or reaction deemed a medically significant condition

5.3.3 Grade

Determine the grade of an adverse event according to the following criteria based on the most severe condition during the time period the adverse event was observed.

Grade	Condition	Intervention
1	Mild; asymptomatic or presence of a mild symptom(s)	Clinical finding or laboratory test finding only; no treatment required
2	Moderate; requiring minimal/localized/noninvasive treatment	Limitation in age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening	Requiring inpatient hospitalization or prolongation of existing hospitalization; disability/incapacity; limitation in activities of daily living
4	Life-threatening	Requiring emergency treatment
5	Death related to adverse event	

5.3.4 Outcome

Outcomes are classified into any one of the following six categories: resolved, resolving, unchanged, worsened, death, and unknown.

The day of outcome confirmation, in cases where the adverse event resolved, was resolving, or resulted in death, is considered the day on which the outcome was actually confirmed. In cases where the follow-up ended with the outcome of unresolved or unknown, the day of the last confirmation of outcome by the investigator (attending physician) is considered the day of outcome confirmation, and the reason for ending the follow-up or why the outcome was unknown shall be described in the space for comments.

5.3.5 Causal Relationship to Study Treatment

The investigator at each study site shall determine whether an event is causally related to the study treatment based on the following criteria and describe the basis for such a determination in the space for comments.

(1) Not causally related: in cases where no temporal relationship exists between the occurrence of an adverse event and the study treatment or where the occurrence of the event can be explained by a medically appropriate reason other than the study treatment

(2) Causally related: in cases where the above does not apply

5.4 Adverse Events Reporting

In the present trial, upon occurrence of a serious adverse event during the study treatment period, the treatment approach for the participant concerned shall be reviewed, and, if obtaining the study drug

information is deemed necessary, communications shall be appropriately carried out according to the procedure established at each study site.

5.4.1 Serious Adverse Events Reporting

(1) Upon occurrence of a serious adverse event, the investigator shall promptly notify the director, the institutional review board, and the secretariat of the hospital facility according to the Kyoto University Graduate School of Medicine and Faculty of Medicine and Kyoto University Hospital Medical Ethics Committee Operating Procedure 11 (Reporting of Serious Adverse Events/Safety Information in Medical Research Involving Human Subjects) (Appendix).

(2) Complete a “Serious Adverse Event Reporting Form” on the data center’s electronic data capture (EDC) system within 72 hours.

(3) The secretariat, upon receiving a notification that a serious adverse event has occurred, shall notify the independent data monitoring board.

(4) In cases where the serious adverse event is unexpected and associated with invasive medical intervention/research, the principal investigator shall publicly disclose information on the course of the event under the name of the hospital director and report to the Ministry of Health, Labour and Welfare periodically as the information becomes available using the form specified in the notification by the Research and Development Division of the Health Policy Bureau according to the Institutional Review Board Operating Procedure 11 for Kyoto University Graduate School of Medicine and Faculty of Medicine/Kyoto University Hospital (Reporting of Serious Adverse Events/Safety Information in Medical Research in Humans) (Appendix).

(5) The principal investigator shall report, as appropriate, occurrences of any adverse drug reactions, infections, or problems due to the use of a pharmaceutical or medical device that has been approved for marketing in accordance with the “Pharmaceuticals and Medical Devices Safety Information Reporting System” provided in Paragraph 2 of Article 77-4-2 of the Pharmaceutical Affairs Law.

5.4.2 Emergency Reporting

(1) In the present trial, serious adverse events that meet the following description are subject to the emergency reporting requirement: any event occurring in the study treatment period that is life-threatening, requires emergency intervention, and for which information on whether the administration of betamethasone should be allowed is deemed necessary to review the treatment approach for the participant concerned.

(2) Upon occurrence of an adverse event that is deemed “life-threatening and requiring emergency intervention as well as information on whether the administration of betamethasone should be allowed in order to review the treatment approach,” the attending physician shall promptly notify the investigator. In the event the investigator cannot be contacted, the physician shall assume the responsibility of the investigator.

(3) If an event is deemed “life-threatening and requiring emergency intervention as well as

information on whether the administration of betamethasone should be allowed in order to review the treatment approach," the investigator shall report the event immediately to the director of the hospital facility.

(4) The investigator shall follow the procedures provided in 4.8 for emergency code breaking and reporting.

(5) The investigator (attending physician) shall record what transpired that led to the disclosure of the study drug allocation number and the disclosed information following Procedure 1 of 4.8 (emergency code breaking) or Procedure 2 (contacting the secretariat) on the Emergency Allocation Number Code Breaking Request Reporting Form, send it by email attachment or facsimile transmittal to the secretariat within 72 hours from the day of such a request, and retain the allocation number. The investigator shall also retain the sent file.

5.4.3 Routine Reporting

Adverse events subject to the routine reporting requirement are shown in "5.1 Definition of Adverse Event." If an adverse event subject to the routine reporting requirement occurs, the investigator (attending physician) shall record the required information on the CRF corresponding to the time period during which the event occurred and the Adverse Event Reporting Form and enter the information on the data center's EDC by the deadlines for submitting each survey form.

In addition, wherever possible, the investigator (attending physician) shall follow up and document the outcome of the adverse event during the trial period on the survey form.

5.5 Expected Adverse Events

See the package insert of Betamethasone Tablets (Appendix).

5.5.1 Adverse events that have been reported in association with the terminal-stage use of corticosteroids, particularly during long-term use, include oral candidiasis, subcutaneous hemorrhage, moon face, mood elevation, hyperglycemia, and gastrointestinal hemorrhage. Nevertheless, a wide variety of drugs are used in the terminal stage, making it unclear whether the adverse events are attributable to corticosteroids or other drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs)[37-39].

5.5.2 In a previous study of Decadron®, a 2-week randomized controlled trial with placebo, no significant difference in frequency of adverse events was reported between the active-drug group and the placebo group (41/62 vs. 44/58; P = .14)[20].

6 Endpoints

6.1 Primary Endpoints

Fatigue (FA) score of EORTC QLQ-C15-PAL

The primary endpoint selected is the fatigue (FA) score, which represents a participant's QOL, on the EORTC QLQ-C15-PAL used to evaluate QOL on Day 7 after study commencement.

[Rationale for the choice of primary endpoint]

In the present trial, the subscale fatigue (FA) score as part of the assessment of patient QOL is considered the representative parameter of QOL and selected as the primary endpoint.

Palliative medicine is an approach aimed at improving QOL in patients and their families facing the issues related to a life-threatening disease[2)]. PS2/3 terminal-stage patients with advanced cancer-related fatigue who participate in the present trial share the treatment goal of QOL improvement. Thus, the QOL in participants will be assessed, with the score serving as an endpoint for assessing the efficacy of palliative medicine. The QOL questionnaire, however, is based on a multi-dimensional scale. The subscale fatigue (FA) has the greatest effect on QOL and is considered a representative parameter.

To reduce the load from EORTC on the patients receiving palliative care, the number of questions has been reduced from 30 in the EORTC QLQ-C30 used routinely to assess QOL in cancer patients to 15 in the disease-specific EORTC QLQ-C15-PAL for palliative care patients used to assess QOL in the present trial[33)]. Its Japanese version has been validated, with the validation results published[34)]. Registration with EORTC will take place before use.

6.2 Secondary Endpoints

6.2.1 Efficacy Endpoints

(1) QOL-related scores other than the FA score on EORTC QLQ-C15-PAL

The efficacy of the steroid is confirmed if the EORTC QLQ-C15-PAL subscales of physical functioning, emotional functioning, appetite loss, and overall QOL showed improvements on Day 7 after study commencement.

(2) NRS (numeric rating scale)

The efficacy is confirmed if the fatigue NRS on Day 7 after study commencement showed an improvement.

(3) Survival time

Assess time to death with the day of enrollment (randomization) as the starting point. The efficacy is confirmed if the survival time is extended.

[Rationales for the choices of secondary endpoints (efficacy endpoints)]

(1) To assess improvements in the EORTC QLQ-C15-PAL subscales of physical functioning, emotional functioning, appetite loss, and overall QOL that are related to fatigue, in addition to the

fatigue subscale.

(2) To use the fatigue NRS, which is used by NCCN for screening fatigue, as one of the efficacy endpoints in the present trial.

(3) To ascertain in this 1-week study if the corticosteroid has efficacy in extending survival time.

6.2.2 Safety Endpoint

Adverse events

See “5. Adverse Events Assessment and Reporting.”

[Rationale for the choice of secondary endpoint (efficacy endpoints)]

To assess the study drug’s safety by comparing the occurrences of adverse events between the steroid group and the placebo group.

6.3 Exploratory Endpoints

Blood test (CRP, white blood cell count, hemoglobin, platelet count, blood glucose)

To investigate changes in the results of the blood tests (CRP, white blood cell count, hemoglobin, platelet count, blood glucose) between the most recent data on or before Day 0 and the most recent data on or after Day 7.

[Rationale for the choice of exploratory endpoint]

Several potential causes including anemia, psychologic problems, and cytokines have been proposed for the fatigue in terminal-stage cancer patients, but the causes are yet to be elucidated. Comparing CRP, white blood cell count, hemoglobin, platelet count, and blood glucose between the intervention group and the placebo group may provide data that indicate what the causes of fatigue might be.

7 Statistics

7.1 Approach in Analysis of Primary Endpoint

The approach in the analysis of the primary endpoint is to be specified in the statistical analysis plan prepared by a biostatistician before data lock.

The approach in the analysis of endpoints is as follows. The EORTC QLQ-C15-PAL fatigue (FA) subscale, the primary endpoint, will be scored from 0 to 100 in accordance with the scoring algorithm formulated by EORTC; differences between the two groups at baseline and one week post-treatment will be determined; and tests of differences will be carried out. The null-hypothesis is defined as “no difference in change of QLQ-C15-PAL fatigue (FA) score between the steroid-treated group and the placebo group.”

7.2 Analysis Sets

Analysis sets are defined below. Details on handling of cases and procedures for handling missing and excluded cases and abnormal data are provided in the statistical analysis plan prepared before data lock. The efficacy endpoint analyses are to be performed on the full analysis set (FAS) and, for reference purpose, on the per protocol set as well. The safety endpoint analysis is to be performed on the safety analysis set.

(1) Full analysis set (FAS)

The population of participants consisting of all enrolled patients after excluding (1) ineligible patients, (2) patients who were never exposed to the study drug (steroid or placebo) after allocation, and (3) patients for whom the data required for major assessments are not available

(2) Per protocol set (PPS)

The population of participants consisting of those in the FAS who were deemed protocol compliant with no protocol deviations

(3) Safety analysis set

The population of participants who received at least one or more doses of the study drug (steroid or placebo)

7.3 Interim Analysis

No interim analysis will be conducted. However, information on safety will be reported periodically to the independent data monitoring board for review.

8 Data Collection

8.1 Forms and Submission Deadlines

(1) Report data for all participants for whom written informed consent was submitted.
(2) In the present trial, all data are to be collected using the EDC created by the data center.
(3) The deadline for submitting patient enrollment forms is the day of enrollment.
(4) The deadline for submitting the baseline and the end-of-study patient survey forms (CRFs) is two weeks after the end of the study treatment.
(5) The deadline for submitting outcome reporting forms is two weeks after a participant's death.
(6) The deadline for submitting adverse events reporting forms is two weeks after the end of the study treatment.
(7) The deadline for submitting serious adverse events survey forms is within 72 hours of the investigator becoming aware of such an event.

8.2 Data Entry Preparation

(1) The investigator shall enter the relevant information in the blanks and check the corresponding items provided in the CRF (hard copy)
(2) The information entered by the investigator is to be double-checked by a clinician other than the individual who entered the information.
(3) The clinician who double-checked the information on the CRF shall affix his/her signature and the date in the space for signature.

8.3 Data Entry Procedure

(1) The investigator shall insert the USB flash drive provided by the data center into a computer.
(2) Enter the ID and password provided.
(3) Enter the information on a hard copy of the CRF prepared in advance as instructed in the data entry operating procedure prepared by the data center.

8.4 Data Transmission Procedure

(1) The investigator (attending physician), after entering data into the EDC, shall save, recheck, and then transmit the data to the data center.
(2) The investigator shall retain the original copy of the CRF for a period of five years after study completion.

8.5 Verification of and Inquiries about Information in CRFs

The data center may question the investigator (attending physician) regarding any ambiguities in the report forms.

The secretariat shall inquire about cases for which no outcome survey form has been submitted four

months after all enrollments have been completed in the study. The investigator shall enter information in the EDC as instructed by the data center.

The term “data lock” refers to the finalization of data after the information in the case reports for all participants has been verified.

9 Ethics

9.1 Protection of Study Participants

9.1.1 Compliance

(1) The conduct of the present trial is in compliance with the World Medical Association Declaration of Helsinki[41)42)] and the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare, and the Ministry of Education[43)].

(2) Given that participants in the present trial are PS2/3 terminal-stage patients with advanced cancer-related fatigue, in addition to providing routine palliative care from the time when they become a candidate for enrollment until the study is completed the investigator shall also afford these patients special attention.

9.1.2 Relationship to the Pharmaceutical Affairs Law

The present trial is considered to be consistent with the Pharmaceutical Affairs Law based on the explanation given below.

[Basis for claiming consistency with the Pharmaceutical Affairs Law]

The Compliance and Narcotics Division of the Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare was requested to review a draft protocol of the present trial (office communication dated December 14, 2012). We received an email reply that there are no issues with the conduct of the present trial as the review found the study does not violate the Pharmaceutical Affairs Law, which clinical trials must comply with, because the study is a clinician (investigator)-initiated clinical study that does not involve any pharmaceutical manufacturer (last office communication dated January 7, 2013).

9.2 Preparation and Revision of Written Information and Consent Form

The Written Information (Appendix) is a document written by the investigator (attending physician) or a staff member appointed by the investigator in easy-to-understand language and given to patients. The document contains information about the clinical trial, including background information, significance, objectives, and methodology. It is used when providing explanatory information about the trial to patients and their families.

The Consent Form (Appendix) is a document on which patients and their families express their willingness to participate in and cooperate with the present trial.

[Definition of the term “family”]

The definition of the term “family,” given the diversity in today’s society, is not limited to the so-called blood relationship as defined by laws. The following adopted by WHO in 1990 applies: The term family refers to

individuals related by blood to the patient or other individuals who play an important key role for the patient."

9.2.1 Preparation and Revision

The Written Information and Consent Form is to be prepared by the principal investigator after consultation with the investigators (attending physicians) who will be providing information to patients, and to be used after approvals from the institutional review board (IRB) of Kyoto University and the IRB at each study site. Revisions shall be proposed for review by the steering committee, the independent enrollment supervisory board, or the independent data monitoring board according to the procedures established by the IRB of Kyoto University and the IRB at each study site.

9.2.2 Written Information and Consent Form

The Written Information shall include the following information: study objectives; study methodology including the information that it is a placebo-controlled, randomized, double-blind study; expected benefits and disadvantages of the drug and treatment method; other therapies available; that the study results will be helpful to patients in the future; that refusal to take part will involve no disadvantages to the patient; that the patient may request withdrawal from the study at any time after submitting his/her Consent Form; that the patient's privacy will be protected when the information obtained in the study is published; costs and payment; contact information for inquiries about the study; and the name of the individual who provided the information.

The Consent Form, to be prepared in duplicate, shall include the contents of the information presented, the fact that consent was given voluntarily by the patient and his/her family, and a space for the patient and his/her family to sign and date the form.

9.3 Obtaining Permission at Study Sites to Conduct the Study

(1) First, the conduct of the study is subject to approval by the IRB of Kyoto University, which the principal investigator is affiliated with.
(2) Thereafter, it is subject to approval by the IRB at each study site based on the approved protocol and the documents submitted to each study site as required by the rules and regulations set forth at the facility.
(3) Annual renewals of the IRB's approval for the study shall follow the rules and regulations set forth at each study site.

9.4 Protection of Personal Information

Points to consider regarding the participants' personal information are as follows.

(1) Names of participants at study sites shall be anonymized in a linkable fashion within the study site.
(2) In the anonymization process, assign the letter designated by the secretariat for each facility and

a number in the order of enrollment to each participant.

(3) Within a study site, the investigator shall create a list showing the anonymized names of participants and corresponding patient IDs and keep the list in a locked location under strict safeguard.

(4) The data center shall strictly safeguard the transmitted data in a room that is locked at all times.

9.5 Informed Consent

(1) The investigator (attending physician) shall provide the Written Information that has received approval from the institutional review board (IRB) at his/her study site and give a comprehensive oral explanation to a patient and his/her family before his/her participation in the study.

(2) The Written Information shall include the following information: 1) study objectives; 2) information about the drug; 3) information about the treatment method; 4) expected benefits and disadvantages; 5) benefits and disadvantages to the patient (you) personally; 6) whether any other therapies are available and information on such therapies; 7) information on participating in the study; 8) the fact that privacy will be protected; and 9) costs and payment as well as information on making inquiries regarding the study.

(3) After providing the explanatory information, confirm that the patient and his/her family have a good understanding about the study, request participation in the study, and obtain voluntary written consent using the Consent Form (Appendix).

(4) The Consent Form shall include the following information: 1) study objectives; 2) information about the drug; 3) information about the treatment method; 4) expected benefits and disadvantages; 5) benefits and disadvantages to the patient (you) personally; 6) whether any other therapies are available and information on such therapies; 7) information on participating in the study; 8) the fact that privacy will be protected; and 9) costs and payment as well as information on making inquiries regarding the study.

(5) Participation in the study is allowed only if both the patient and his/her family gave consent.

(6) Upon consent to participate in the study, the patient and his/her family shall sign and date the Consent Form. In addition, the investigator (attending physician) who provided the explanatory information and the clinical research coordinator (CRC), among others, who provided supplementary information, if any, shall each sign and date the form at the time such information was given.

(7) The Consent Form shall be prepared in duplicate, with one copy retained by the patient personally while the study site shall strictly safeguard a second copy.

9.6 Independent Enrollment Supervisory Board

(1) Establish an independent enrollment supervisory board to confirm whether consent by participants was voluntary from the administration of informed consent to enrollment and

throughout the trial period. (See 16.6 below)

(2) The independent enrollment supervisory board shall respond to inquiries from patients during the trial period, and its contact information shall be provided in the written information about the study.

10 Quality Control

10.1 Study Monitoring

Study monitoring is carried out to confirm whether the present trial is conducted safely and in accordance with the protocol and whether the data collected are accurate.

Confirm protocol compliance through central monitoring based on the patient enrollment forms, CRFs, outcome report forms, among other records, collected by the data center.

10.2 Data Check

10.2.1 The data center shall check the following data.

(1) The data center shall install a logical check function in advance in the EDC.

(2) Confirm the eligibility and theoretical consistency of the main data.

10.3 Record Retention

The investigator shall retain records related to consent by participants, documents related to patient screening forms, basic data (e.g., laboratory data) used to generate reports, written approvals from the IRB, and archival records generated at his/her medical institution.

Such records shall be retained until at least 10 years have elapsed since publication of the study results.

Such records shall be disposed of by a method that safeguards confidentiality.

10.4 Data Lock Declaration

The term “data lock declaration” refers to a declaration by the principal investigator, after receiving a communication from the data center of data check completion, that all data in the present trial have been locked; the declaration shall include the date of data lock. (4.14)

11 Support for Costs and Study-related Injuries to Study Participants

11.1 Costs to Study Participants

The medical care provided in the present trial, as in normal practice, is to be covered by the participant's health insurance plan and co-payments.

In the present trial, no insurance claims will be filed for reimbursement of the cost of the study drug used in the study period; instead the cost will be covered by the budget for the study.

There will be no monetary compensation provided to participants for participation and cooperating in the present trial.

11.2 Support in the Event of Study-related Injuries

Treatments for any injury to health attributable to the study will be provided using the participant's health insurance plan just as in routine medical care.

Four insurance companies were asked to provide quotes for clinical study insurance coverage, but all four companies "declined" to provide a quote. Thus, there will be no subscription for insurance coverage. Given that the study drug is an approved drug, any study-related injuries to the participants and any necessary compensation arising from a causal relationship to the study treatment will be covered by the Adverse Drug Reaction Relief System[40] of the Pharmaceuticals and Medical Devices Agency.

12 Conflict of Interest and Research Funding Sources

12.1 Conflict of Interest

The conflict of interest will be properly reviewed and managed by the “Kyoto University Conflict of Interest Review Committee” in accordance with the “Kyoto University Conflict of Interest Policy” and “Kyoto University Regulations for Conflict of Interest Management.”

12.2 Research Funding Sources

The present trial will be funded by a scientific research grant, Basic Research (B) “Research with a New Perspective on Palliative Care: Clinical Practice Guidelines and Patients’ Perception of Value/QOL Challenges,” and “Standardization of treatment for advanced-cancer fatigue,” department administrative budgets, and donations.

13 Publication of Research Results and Assignment of Rights

13.1 Clinical Trial Registry

The present trial will be registered with UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), where information will be publicly disclosed. The principal investigator shall complete the task of clinical trial registration before the first participant is enrolled.

13.2 Publication of Research Results

In accordance with the authorship qualification requirements[46)] provided in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors, the principal investigator and the person responsible for writing the protocol shall determine the authorship of papers and presentations at academic conference.

A group of authors appointed by the principal investigator and the person responsible for writing the protocol shall write the manuscripts. Individuals who are not in the group of authors but meet the authorship qualification requirements[46)] will be credited as an author by group name, with a note indicating that group members meet the authorship qualification. Names of individuals in such a group will be mentioned in an acknowledgement.

Individuals who publish the trial results shall seek a review and approval by the principal investigator, the person responsible for writing the protocol, and the steering committee before doing so.

13.3 Assignment of Data and Access Rights

Data collected in the present trial shall be assigned to the principal investigator and the person responsible for writing the protocol. The principal investigator, the person responsible for writing the protocol, the steering committee, the data center, and the statistical analysis manager in the present trial may access the collected data for the purpose of conducting the present trial.

14 Protocol Revision

14.1 Revision of This Protocol

Revisions shall be carried out by the person responsible for writing the protocol, and applications for change shall be filed in accordance with the procedure set forth by the IRB at each site.

14.2 Record Keeping and Reporting of Revisions

The principal investigator shall record the history of revisions in writing and report to the investigators.

14.3 Reporting Revisions

The investigator shall report revisions to the person responsible at his/her medical institution and proceed with the process of revisions. For minor changes, follow the rules and regulations set forth by each medical institution.

If a proposed revision will affect the patient enrollment form or the CRF and EDC forms, the principal investigator shall ask the data center to revise the patient enrollment form or the CRF and EDC forms.

15 Study Completion and Premature Termination

15.1 Study Completion

This study is complete when the deaths of all enrolled participants have been confirmed or when 16 weeks (four months) have elapsed since the last enrollment, whichever is earlier. Upon study completion, the investigator shall check the quantity of the leftover study drug that had been distributed and its allocation number and return the leftover study drug promptly to the study drug manager.

15.2 Premature Termination of Study

The term “premature termination of study” refers to termination of the study earlier than scheduled due to any of the reasons below. Under the following circumstances, the independent data monitoring board shall advise the principal investigator to terminate the study prematurely.

(1) When the study treatment is deemed to have safety issues based on any report of serious adverse events or any safety information including information available outside of the study

(2) When completion of the study is deemed difficult due to delays in patient enrollment or frequent protocol deviations, among other reasons

16 Organizational Structure of the Trial

The present trial is an investigator-initiated clinical trial conducted by the principal investigator and the steering committee.

The organizational structure of the trial is as described below.

16.1 Principal Investigator

The principal investigator shall oversee the trial.

Kikuko Miyazaki
Kyoto University School of Public Health, Department of Health Informatics
Yoshidakonoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan
Phone: 090-2421-6077
E-mail: miy@plum.ocn.ne.jp

16.2 Vice Principal Investigator

The vice principal investigator shall play the role of assisting the principal investigator and be appointed by the principal investigator as necessary.

Takeo Nakayama
Kyoto University School of Public Health, Department of Health Informatics
Yoshidakonoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan
Phone: 080-1432-5322、075-753-9477
FAX: 075-753-9478
E-mail: nakayama.takeo.4a@kyoto-u.ac.jp

16.3 Trial Secretariat

The trial secretariat shall be responsible for clerical work related to the operation and management of the present trial.

(1) Responsible for clerical work related to the operation and management of the present trial
(2) To liaise with relevant departments and study sites
(3) To send documents to relevant parties as requested by the principal investigator or the steering committee
(4) To sort and retain documents related to the present trial
(5) To make preparation for and manage the convening of meetings

Secretary Office
Kyoto University School of Public Health, Department of Health Informatics
Yoshidakonoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan
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FAX: 075-753-9478
E-mail: pasqol@hi.med.kyoto-u.ac.jp

16.4 Steering Committee

(1) The steering committee shall convene upon the call of the principal investigator.
(2) The steering committee shall support the principal investigator to oversee the trial and, upon her request, shall hold consultations over the planning, implementation, and operation of the trial, interpretation of results, coordination with publications, and ascertaining issues related to the conduct of the trial and countermeasures.
(3) The principal investigator shall take and maintain minutes of the steering committee meetings.

Masayuki Ikenaga	Yodogawa Christian Hospital
Kenji Ueshima	Kyoto University Hospital, Patient Support Center
Hiroi Kasai	Kyoto University Hospital, Institute for Advancement of Clinical and Translational Science
Takashi Kawamura	Kyoto University Health Service
Tosiya Sato	Kyoto University School of Public Health
Yoshimi Suzukamo	Tohoku University Graduate School of Medicine
Takahiro Horimatsu	Kyoto University School of Medicine

16.5 Independent Data Monitoring Board

(1) The independent data monitoring board shall assess the progress and safety of the present trial at appropriate intervals and advise the principal investigator whether to continue the trial, modify the protocol, or discontinue the trial, according to the provisions of the independent data monitoring board.
(2) Upon receiving a report from the secretariat on the occurrence of a serious adverse event, the board shall determine the relationship of the event to the study treatment and examine countermeasures.
(3) The board shall make a decision on and respond to the secretariat’s request for emergency code breaking.
(4) The principal investigator shall take and maintain minutes of the independent data monitoring board meetings.

Shinya Saito	Okayama University Graduate School of Health Sciences
Fumihiko Wakao	National Cancer Center, Center for Cancer Control and Information Service
Mariko Naito	Hiroshima University School of Dentistry

16.6 Independent Enrollment Supervisory Board

(1) The independent enrollment supervisory board shall verify on an ongoing basis the proper administration of informed consent (see 4.3), the eligibility of enrolled participants, and the participation in the trial by participants during the trial period, according to the provisions of the independent enrollment supervisory board.

(2) The chairperson of the independent enrollment supervisory board shall elect independent enrollment supervisory board members; however, the opinions of cancer patients should be reflected, and the board members shall include at least one individual who has had cancer.

(3) The chairperson of the independent enrollment supervisory board shall take and maintain minutes of the board meetings.

Shigemi Matsumoto	Kyoto University Graduate School of Medicine
Keiko Sato	Kyoto University Hospital, Patient Safety Unit
Ikuko Yamaguti	Non-Profit Organization, COML

16.7 Person Responsible for Writing the Protocol

This person shall be responsible for writing and revising Protocol v1.0.

Kikuko Miyazaki	Kyoto University School of Public Health

16.8 Statistical Analysis Manager

As a statistician, the statistical analysis manager shall be responsible for overseeing statistics in the present trial, creating a statistical analysis plan, and performing data analyses.

Tosiya Sato	Kyoto University School of Public Health
Yoshimi Suzukamo	Tohoku University School of Medicine

16.9 Study Drug Manager

The study drug manager shall create an operating procedure for preparation of the study drug and an operating procedure for delivery and acceptance of the study drug, and control the preparation of the study drug (betamethasone and placebo).

Shuichi Nawata	Showa University Northern Yokohama Hospital

16.10 Allocation Manager

The allocation manager shall create specifications for preparing allocation schedules, generate an allocation schedule based on the specifications, and keep it under seal until the data lock declaration. Furthermore, the allocation manager shall also create an operating procedure for allocation and verify whether the study drug was properly allocated based on the operating procedure. In addition, the allocation manager shall review the blinding after the data lock declaration.

Takashi Kawamura	Kyoto University Health Service
Keiichi Matsuzaki	Kyoto University Health Service

16.11 Data Center

Kyoto University Hospital, Institute for Advancement of Clinical and Translational Science
54, Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan
Phone: 075-751-4760
Fax: 075-761-
E-mail: pasqol@mail2.adm.kyoto-u.ac.jp

16.11.1 EDC System

(1) The data center shall construct an EDC system for data collection.
(2) The data center shall create an EDC manual.
(3) The data center shall be responsible for the maintenance of the EDC.

16.11.2 Enrollment Reception

(1) The data center, upon receiving a patient enrollment form transmitted by the investigator (attending physician), shall verify eligibility criteria.
(2) The center shall communicate the enrollment status to the secretariat twice monthly.

16.11.3 Data Management

The data center shall compile data, process the compiled data, and generate a dataset for statistical analysis.

(1) The data center shall compile only clinical information that has been anonymized using identification codes.
(2) It shall check for inconsistencies in the eligibility of enrolled patients and perform the operation of enrollment.
(3) It shall check the eligibility of the data collected.
(4) It shall properly retain the anonymized data and keep the anonymized clinical information on the CRFs in the form of electronic data strictly safeguarded in a server.
(5) It shall generate a dataset for statistical analysis.

17 Study Sites

Study Site	Investigator
Yodogawa Christian Hospital	Masayuki Ikenaga
Yokohama University City Medical Center	Mari Saito
Kyoto University Hospital	Taro Funakoshi
Yokohama Municipal Citizen's Hospital	Hirotsugu Kunikane
Toho University Ohashi Medical Center	Yoichi Nakamura
Kumamoto University Hospital	Atushi Yoshitake
Japan Baptist Hospital	Tetsuya Yamagiwa
Tokai Central Hospital	Kunihiro Kawabata
Kyoto Min-iren Chuo Hospital	Akira Nozaki
Tokyo Medical and Dental University Medical Hospital	Satoshi Miyake
Suzuki Clinic of Internal Medicine	Hiroshi Suzuki
National Hospital Organization Kinki Chuo Chest Center	Akihiro Tokoro
Okayama University Hospital	Naruto Taira
Kyoto City Hospital	Toshihiko Kirishima
Kyoto Okamoto Memorial Hospital	Yoshihiro Shimizu
Mitsubishi Kyoto Hospital	Akira Yoshioka
National Hospital Organization Kyoto Medical Center	Akira Nozaki
Kishiwada City Hospital	Masahiro Kawashima
Momotaro Home Visit Clinic	Eisaku Komori
Kitano Hospital	Yuko Katayama
Kaedenokaze Home Visit Clinic	Hiroshi Miyaki
Kansai Electric Power Hospital	Tooru Kajiyama
Watanabe Home Visit Clinic	Tsuyoshi Watanabe

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