CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial to Evaluate the Efficacy and Safety of OCV-501 in Elderly Patients With Acute Myeloid Leukemia

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A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial to Evaluate the Efficacy and Safety of OCV-501 in Elderly Patients With Acute Myeloid Leukemia

Clinical Protocol

Protocol No.: 311-12-001

Confidential

Otsuka Pharmaceutical Co., Ltd.

2-9 Kanda-Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, Japan

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Statement of Confidentiality

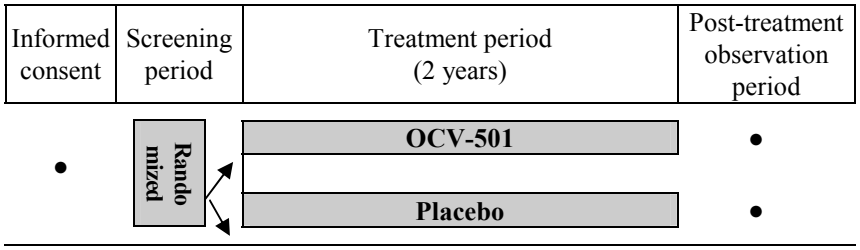
The trial protocol is to be treated as confidential information and is to be made available only to persons involved in the trial. The content of the protocol is not to be disclosed to any third party without the prior written consent of Otsuka Pharmaceutical Co., Ltd., except in the case of its being explained to a candidate trial subject. Disclosure of the results of the trial to academic societies or journals, etc, in part or in whole, will require the prior written approval of Otsuka Pharmaceutical Co., Ltd.

Trial Protocol Synopsis

Name of Test Product	OCV-501
Trial Title	A multicenter, randomized, double-blind, placebo-controlled, phase 2 trial to evaluate the efficacy and safety of OCV-501 in elderly patients with acute myeloid leukemia.
Trial Objectives	Primary: To compare disease-free survival in patients 60 years or older with acute myeloid leukemia (AML) who are randomly assigned to receive either OCV-501 monotherapy or placebo. Secondary: • To compare overall survival between both treatment arms • To compare patient quality of life (European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30) and performance status (Eastern Cooperative Oncology Group performance status [ECOG PS]) between both treatment arms • To characterize and compare safety in the both treatment arms • To assess immunological responses (OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level), immunoglobulin • To assess WT1 mRNA level
Phase of Development	Phase: 2 Type of trial: Exploratory trial
Trial Design	A multinational, multicenter, randomized, double-blind, placebo-controlled trial
Target Disease	Acute myeloid leukemia
Target Number of Subjects	120 patients (60 patients in OCV-501 arm and 60 patients in placebo arm)
Inclusion Criteria	Patients who meet all of the following criteria at the time of enrollment will be selected. 1) Patients with AML (WHO classification 2008) who achieved first complete remission within one or two courses of standard induction therapy*, and completed standard consolidation

	therapy* (one or more courses). * Induction therapy and consolidation therapy are according to the institution's standard of care. • Applicable types of disease for this trial in WHO classification – AML with recurrent genetic abnormalities – AML, myelodysplasia-related changes – AML, not otherwise specified 2) Patients who are 60 years or older at the time of providing informed consent 3) Sex: Male or female 4) Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2 at the time of trial enrollment 5) Patients with no significant impairments in the functions of major organs (as indicated by laboratory values) meeting the following criteria within 3 weeks of investigational medicinal product (IMP) administration: • Hematological functions Patients must not require administration of a blood-derived product or blood transfusion, or granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF). – Neutrophil count: > 1,000/μL, – Platelet count: > 50,000/μL • Hepatic functions – AST and ALT: < 5 × the upper limit of normal (ULN) – Total bilirubin: < 3 × ULN • Renal function – Serum creatinine: < 3 × ULN 6) Patients with a life expectancy of at least 3 months 7) Patients who have provided written informed consent within 90 days from the last dose of consolidation therapy on an informed consent form that has been approved by an institutional review board or independent ethics committee
Exclusion Criteria	Patients who fall under any of the following exclusion criteria at the time of enrollment will be excluded from participation in the trial.

	1) Patients who have acute promyelocytic leukemia (APL) with t(15;17)(q22;q12), (PML/RARA) karyotype abnormalities, and other variant types. 2) Patients who are scheduled for hematopoietic stem cell transplantation 3) Patients who have undergone cancer immunotherapy (eg, cancer vaccine [including OCV-501], lymphocyte or dendric cell transfusional treatment) 4) Patients who have received drugs potentially affecting the immune system within 4 weeks before starting IMP administration or who may receive such drugs after start of the trial (eg, corticosteroid systemic administration, immunosuppressants, immunostimulants, and anti-cancer drugs) 5) Patients who have a history or complication of autoimmune diseases (eg, Hashimoto's disease, idiopathic thrombocytopenic purpura, autoimmune hepatitis, or connective tissue disease) or primary immune deficiency disease 6) Patients who have active infectious diseases 7) Patients who have a history or complication of interstitial pneumonia 8) Patients who have a severe concurrent disease (eg, cardiac failure [NYHA class III or IV], uncontrolled diabetes mellitus, uncontrolled hypertension) or psychiatric illness likely to interfere with participation in this trial 9) Patients who are HIV antibody positive or HBV-DNA positive, or have unrecovered* chronic hepatitis C with positive HCV antibody *: Recovery is determined by sustained virologic response of HCV-RNA. 10) Patients who have cirrhosis 11) Patients who have a history of hypersensitivity or serious adverse drug reaction to any of the components of IMP 12) Patients who have a concurrent second cancer (except carcinoma *in situ*, intramucosal cancers, or malignancies treated at least 5 years previously with no evidence of relapse) 13) Patients who have been administered investigational drugs or individually imported drugs within 12 weeks before starting IMP 14) Women with confirmed or suspected pregnancy, or breast-feeding women

	15) Patients not agreeing to take adequate contraceptive measures during the trial period and until 180 days (for males) or 120 days (for females) after the last IMP administration 16) Patients judged to be ineligible by the investigator (or subinvestigator) for any other reasons
Discontinuation Criteria	If any of the following conditions is met, the investigator or subinvestigator will discontinue administration of the IMP. 1) If the patient wishes to withdraw from the trial 2) If the investigator or subinvestigator judges that it is difficult to continue IMP administration due to occurrence of an adverse event 3) If relapse of the primary disease (AML) is observed 4) If a prohibited concomitant drug or therapy is used 5) If it is later found that the patient did not to meet the eligibility criteria at the time of enrollment 6) If the patient is found to be pregnant 7) If it is not possible to administer the IMP within 21 days after obtaining informed consent 8) If the investigator or subinvestigator judges that it is necessary to discontinue IMP administration for any another reason
Investigational Medicinal Products, Dose and Regimen, and Treatment Period	The trial will be designed as a two-arm trial with patients randomly assigned to one of the following treatment groups: • OCV-501 arm: 3 mg of OCV-501 (0.4 mL), once-weekly up to the 8th administration, and once every two weeks from the 9th administration onward. • Placebo arm: Placebo (0.4 mL), once-weekly up to the 8th administration, and once every two weeks from the 9th administration onward. The IMP will be subcutaneously administered. The administration site will be the axilla or inguinal region. The IMP will be administered at a dose of 0.4 mL per injection site.  Adjustment factors of allocation at the time of randomization:

	・Country/region (by each country/region: Japan, Republic of Korea, Taiwan) ・Age (60 to 64 years, 65 to70 years, and ≥ 71 years)
Prohibited Concomitant Drugs and Therapies	Only the IMP will be used for treating the primary disease, and concomitant use of the drugs (including Chinese herbal medicine) and therapies listed below is prohibited from the time of informed consent to the end of the post-treatment examination. • Other anti-cancer drugs, hormone therapy, antibody therapy, radiation therapy, thermal therapy or other anti-cancer therapies • Systemic administration of corticosteroids (equivalent to > 10 mg/day of prednisolone for 2 weeks or longer) and systemic administration of drugs potentially affecting the immune system, including immunosuppressants and immunostimulants • G-CSF and GM-CSF • Topical application of corticosteroids at the IMP injection sites • Investigational drugs and individually imported drugs
Endpoints	[Efficacy] **Primary endpoint:** Disease-free survival (DFS) **Secondary endpoints:** • Overall survival (OS) • Quality of life (EORTC QLQ-C30) • Performance status (ECOG PS) [Safety] Adverse events, hematology test, blood biochemistry tests, vital signs (blood pressure, pulse rate, body temperature), urinalysis, body weight, and electrocardiogram [Exploratory] OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, and anti-WT1

	antibody level, immunoglobulin, and WT1 mRNA
Scheduled Duration of the Trial	Sep 2013 through Dec 2017

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List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
AE	Adverse event
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
CR	Complete remission
Cr	Creatinine
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
DFS	Disease-free survival
DLT	Dose limiting toxicity
DTH	Delayed-type hypersensitivity
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer QLQ-C30
FAS	Full analysis set
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
GVL	Graft versus leukemia
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IMP	Investigational medicinal product
IVRS	Interactive Voice Response Services
IWRS	Interactive Web Response Services
HR	Hazard ratio
LOCF	Last observation carried forward
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities (The ICH international medical dictionary)
MG	May-Giemsa
MRD	Minimal residual disease
NYHA	New York Heart Association
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
QOL	Quality of life
PPS	Per protocol set

Abbreviation	Expansion
PS	Performance status
QTc	Corrected QT interval
QTcF	QT interval as corrected by Fridericia's formula
RFS	Relapse-free survival
SS	Safety Set
Th1	Type I helper T lymphocytes
ULN	Upper limit of normal
WG	Wright's-Giemsa
WT1	Wilm's tumor gene 1

Definitions of Terms

Term	Definition
Screen failure	A screen failure is a subject from whom written informed consent was obtained, but to whom an investigational medicinal product (IMP) was not allocated
Individual subject trial start date	The day of obtaining the subject's written informed consent
Individual subject withdrawal	A subject who discontinue OCV-501 or placebo treatment before completion of the post-treatment observation period
Individual subject trial withdrawal date	The day of the withdrawal examination of the post-treatment observation period within 7 days after the investigator or subinvestigator judged withdrawal to be necessary
Individual subject completion	A subject who completes 2 years of treatment with OCV-501 or placebo, and completes the post-treatment examination at 11-17 days after the end of IMP administration
Individual subject trial completion date	The day of the completion examination at 11-17 days after the end of the 2-year IMP administration period
Individual subject trial period	The period from the day of obtaining the subject's informed consent to the day of trial completion or the day of the withdrawal examination. Does not include the follow-up period nor the outcome survey.

1 Introduction

1.1 Background of Trial Plan

Acute myeloid leukemia (AML) is a malignant disease derived from myeloid hematopoietic cells. In AML, unregulated proliferation of leukemia cells is associated with inhibition of normal hematopoiesis. AML is a life-threatening disease with various symptoms such as infection, anemia, hemorrhage due to thrombocytopenia, and organ disorders. Although AML occurs in people of all ages, it is known to be more prevalent among the elderly, and the median age of onset is reported to be 62 years in Japan.[1] Treatment of AML is based on the concept of total cell kill. Normally, after complete remission (CR) is achieved by remission induction therapy to reduce leukemia cell count to below 10^9 cells, consolidation therapy is performed to further reduce the number of residual leukemia cells to near zero.[2] However, it is not rare for patients, especially elderly patients, to experience relapse due to proliferation of residual leukemia cells after CR. The prognosis for AML becomes worse as age increases. There are many reasons for this. For one, the deterioration in organ functions (including bone marrow, liver, cardiorespiratory and renal functions) in the elderly constitutes a barrier to adequate AML therapy. Also, AML in elderly patients more frequently arises from antecedent hematologic disorders such as myelodysplastic syndrome (MDS), which is always associated with a worse outcome. Moreover, elderly AML patients have a higher incidence of poor-risk cytogenetics, which is associated with poor outcome. In an investigation involving elderly AML patients (aged 50 to 70 years) not receiving allogeneic hematopoietic cell transplantation, even for those patients who achieved CR, the 3-year relapse-free survival (RFS) was as low as 29% and many patients experienced relapse.[3] When treating elderly patients with antitumor drugs, it may be necessary to reduce the dose. There are a considerable number of limitations and much debate regarding therapeutic regimens in elderly patients with leukemia. Therefore, a new therapy is needed to prevent relapse of AML, and extend survival of elderly patients with AML.

In recent years, investigations have been made into cancer immunotherapy using tumor-specific antigen peptide as a new treatment for cancers, including AML. Tumor-specific antigen peptides are classified as either killer peptide or helper peptide. Killer peptide directly increases cytotoxic T lymphocyte (CTL) count via HLA class I molecules. Helper peptide indirectly increases CTL count by activating Th1 cells via HLA class II molecules. The WT1 gene was isolated as the causal gene of Wilms' tumor, a cancer of

the kidney typically occurring in children,[4,5] and it was initially categorized as a tumor suppressor gene.[6,7] Although WT1 gene is also seen localized in normal tissues such as genitalia, kidneys, hematopoietic progenitor cells, and mesothelial tissues,[8,9] further study has revealed an overexpression of WT1 in various types of solid tumors and hematological malignancies,[10,11,12,13] and also an oncogene-like role.[14,15]

OCV-501, an HLA class II-restricted WT1 helper peptide licensed from International Institute of Cancer Immunology, Inc., consists of 16 amino acid residues derived from the WT1 gene product protein. In in vitro studies, OCV-501 not only induced or activated various HLA class II-restricted OCV-501-specific Th1 cells, but also increased the induction of WT1-specific CTLs, suggesting that it is a promising peptide for use in cancer immunotherapy.[16,17]

1.2 Study Results and Trial Rationale

1.2.1 Nonclinical Study Results

1.2.1.1 Pharmacology

OCV-501 significantly induced OCV-501-specific type 1 T-helper (Th1) cells and cytotoxic T-lymphocytes (CTLs) in peripheral blood mononuclear cells (PBMCs) from healthy adult donors. OCV-501 also significantly induced interferon gamma (IFN-γ) production from the OCV-501-specific T-cells in a dose-dependent manner. In some cases, the IFN-γ production induced by OCV-501 was inhibited by addition of anti-human leukocyte antigen (HLA)-DR antibody, but no inhibition by anti-HLA-DQ antibody was seen. OCV-501 also showed binding to and/or activation of T-cell via the HLA class II molecules HLA-DRB1*01:01, DRB1*04:05, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*13:02, DRB1*14:03, DRB1*14:05, DRB1*15:01, DRB1*15:02, DRB3*02:02, DRB4*01:01, DQB1*04:01, DPB1*05:01, and DPB1*09:01. As one possible mechanism of OCV-501's antitumor effect, OCV-501 increased the number of HLA-A*02:01-restricted WT1-derived killer peptide WT1-126-134 (WT1-126)-specific CTLs in 3 of 3 samples and the number of HLA-A*24:02-restricted WT1-derived modified killer peptide WT1-235-243 (WT1-235mu)-specific CTLs in 6 of 8 samples in the presence of PBMC-derived OCV-501-specific Th1 cells and WT1-killer peptide-specific CTLs. Additionally, 18 of 20 OCV-501-specific Th1 clones displayed significant cytolytic activity.

1.2.1.2 Safety Pharmacology

The effects of OCV-501 on general physical condition and behavior were evaluated by modified Irwin's method and effects on the respiratory system were evaluated by whole body plethysmography as part of a single subcutaneous dose toxicity study in rats. Effects on blood pressure, heart rate, and electrocardiography (ECG) were evaluated as part of a single subcutaneous dose toxicity study in dogs. In addition, effects on blood pressure, heart rate, and ECG were also evaluated as a part of intermittent subcutaneous dose toxicity studies in dogs. No effects on any parameters were observed at a dose of 4.5 mg/kg in the single-dose toxicity studies and at doses of up to 2.5 mg/kg in the intermittent-dose toxicity studies.

Effects on human ether-a-go-go related gene (hERG) currents were not investigated in an in vitro study because the administration route for OCV-501 is subcutaneous, for which systemic exposure is low. Furthermore, effects on ECG were sufficiently evaluated as described above in single- and intermittent-dose studies in dogs and no specific issues were identified that would pose notable risk in AML patients in clinical trials.

1.2.1.3 Non-clinical Pharmacokinetics and Drug Metabolism

OCV-501 was administered subcutaneously at single doses of 0.45, 1.5, and 4.5 mg/kg to fed male rats and at a single dose of 1.5 mg/kg to fed female rats, intradermally at a single dose of 1.5 mg/kg to fed male rats, and intravenously at a single dose of 1.5 mg/kg to fed male rats. Following subcutaneous and intradermal administration, the plasma concentration of OCV-501 was below the lower limit of quantification (LLOQ, 5 ng/mL) at up to 24 hours postdose. Following intravenous administration, the plasma concentration of OCV-501 was below the LLOQ (5 ng/mL) at up to 6 hours postdose.

OCV-501 was administered subcutaneously at single doses of 0.45, 1.5, and 4.5 mg/kg and intravenously at a single dose of 1.5 mg/kg to fed male beagle dogs. Following subcutaneous administration, one animal at a dose 4.5 mg/kg showed a plasma concentration of 12.69 ng/mL at 0.5 hours postdose and 20.21 ng/mL at 1 hour postdose. Following intravenous administration, the plasma concentration in one animal was 8.211 ng/mL at 0.083 hours postdose.

In investigation of the in vitro stability of OCV-501 in fresh rat, dog, and human plasma at 37°C, the half-life ($t_{1/2}$) of OCV-501 was respectively 9.90, 4.15, and 2.30 minutes. Following incubation of OCV-501 (250 μg/mL) in cryopreserved rat, dog, and human plasma at 37°C for 20 minutes, 4 metabolites were detected in the rat and dog plasma and 5 metabolites were detected in human plasma.

1.2.1.4 Toxicology

Single-dose Toxicity: Single subcutaneous dose toxicity studies in rats and dogs showed no systemic toxicity, and the approximate lethal dose was judged to be higher than 4.5 mg/kg.

Intermittent-dose Toxicity: In 4-week intermittent (once weekly) subcutaneous dose toxicity studies in rats and dogs with 4-week recovery tests, the no observed adverse effect level (NOAEL) for systemic toxicity was estimated to be 2.5 mg/kg in both species. As local changes at the administration site, large or small cavity, hemorrhage, edema, fibrosis, granuloma, inflammatory cell infiltration and monocyte infiltration were commonly observed in both the vehicle control group administrated a mixture of Montanide and saline without OCV-501 and the OCV-501-treated groups, and it was considered that these changes were mainly attributable to the irritancy of Montanide used as an adjuvant. The changes at the administration site showed gradual recovery over time in both the vehicle control group and the OCV-501-treated groups. In subsequent 13-week intermittent (once weekly) subcutaneous dose toxicity studies in rats and dogs with 4-week recovery tests, the NOAEL for systemic toxicity was again estimated to be 2.5 mg/kg in both species, and the changes at the administration site were similar to those observed in the 4-week intermittent dose toxicity studies, showing no increase in severity with prolongation of the dosing period.

Genotoxicity: The genotoxicity studies routinely conducted for pharmaceuticals are not applicable to OCV-501, which is a synthetic peptide, and therefore genotoxicity was not investigated.

Local Irritancy: The local irritation potential of OCV-501 emulsion for injection at the intended clinical route was evaluated in intermittent subcutaneous dose toxicity studies in rats and dogs. In addition to those studies, the irritation potential of OCV-501 emulsion for injection was investigated by single intradermal administration in rabbits, since it was considered possible that the intradermal route might also be used for clinical administration of OCV-501 emulsion. Results showed irritant reactions such as acanthosis, hemorrhage, crust, erosion, pseudoeosinophil infiltration, and histiocyte infiltration at the administration site for each OCV-501 emulsion for injection (0%, 0.025%, 0.075%, 0.25%, and 0.75%), as well as for 0% formulation (mixture of Montanide and saline). Some of these changes showed increased frequency or severity at sites treated with 0.25% and 0.75% emulsions for injection compared with the 0% formulation. However, there were only slight differences in any of the findings between OCV-501 emulsions for injection and the 0% formulation. It was therefore considered

that the changes at the administration site were mainly attributable to the irritancy of Montanide used as an adjuvant.

1.2.2 Clinical Trial Results

Trial 311-10-001 (Japan) was a phase 1 trial of OCV-501 to assess the safety and tolerability of OCV-501 subcutaneously administered once a week for 4 weeks at doses of 0.3, 1, and 3 mg in elderly patients with AML who had completed standard consolidation therapy after being judged to have achieved complete remission following an induction regimen. Of 9 subjects enrolled (3 subjects in each cohort: 0.3, 1, and 3 mg), no subject showed relapse after administration of OCV-501. No dose limiting toxicity (DLT) was observed in any of the 3 cohorts, and the maximum tolerated dose was therefore considered to be ≥ 3 mg. There was no evidence of major safety problems in any cohort. In OCV-501-specific delayed-type hypersensitivity reaction (DTH) observation, erythema was observed in all 3 cohorts and induration was observed in one subject each in the 0.3 mg and 3 mg cohorts.

Trial 311-10-002 is ongoing as of the cutoff date (7 May 2013). Trial 311-10-002 is a long-term, open-labeled extension trial to assess the safety of OCV-501 administered once a week in patients with AML who completed Trial 311-10-001 and who desired to continue receiving OCV-501[18,19]. Aggravation of the underlying disease (AML) was reported in 5 subjects (5 incidences) as SAEs, and all of these events were judged by the investigator to be unrelated to the IMP. Drug allergy was reported in one subject, and the event was not judged by the investigator to be an SAE, although the sponsor considered it to be serious.

1.2.3 Trial Rationale

OCV-501 is a drug product containing an HLA class II restricted WT1 derived peptide. In in vitro pharmacology studies, OCV-501 has demonstrated significant induction of OCV-501-specific Th1 cells and CTLs in PBMC from healthy adult donors,[20] and significant induction of interferon (IFN-γ) production from OCV-501-specific T cells in a dose-dependent manner. The activation effect on OCV-501-specific T cells was HLA class II restricted.[20,21] In the presence of OCV-501-specific T cells, the addition of OCV-501 increased the number of co-existing WT1 killer peptide-specific CTLs.[22]

Because WT1 expresses frequently in patients with AML[11,12,23] and AML patients often show an increased number of WT1-specific CTLs in comparison with healthy donors,[24] OCV-501 is being developed as an AML therapy product. It is expected that normal

leucocytes will have recovered and there will be fewer leukemia cells in patients who have completed consolidation therapy. Therefore, AML patients who have completed consolidation therapy were set as the target trial subjects.

In the phase 1 trial (Trial 311-10-001), OCV-501 was subcutaneously administered once a week for 4 times at doses of 0.3 mg, 1 mg, and 3 mg in elderly AML patients and safety and tolerability of OCV-501 were assessed. In this phase 1 trial, no DLTs were reported and the tolerability of OCV-501 treatment up to a dose of 3 mg was confirmed. In addition, OCV-501 specific DTH was observed at each dose. This finding suggests that OCV-501 induces the T cell mediated immune response. See Section 3.2, for the rationale of setting the trial design, dose, regimen, and primary endpoint.

This trial is planned as a randomized placebo-controlled comparative trial, to assess the efficacy and safety of OCV-501 treatment as a maintenance therapy in elderly patients with AML who have completed consolidation therapy after being judged to have achieved CR following an induction regimen. In the ongoing phase 1 extension trial (Trial 311-10-002), drug allergy was observed for one patient and it was considered that a causal relationship between the adverse event (AE) and OCV-501 could not be ruled out. Therefore, in this phase 2 trial, patients' general conditions, including injection site reaction, will have to be observed at the trial site for one hour after IMP administration.

Based on the above, the conduct of this clinical trial, as described in this clinical trial protocol, was considered to be scientifically and ethically justified.

See the investigator's brochure for further details of data mentioned in this protocol and other trial results.

2 Trial Objectives

Primary objective

The primary objective of this trial is to compare disease-free survival (DFS) in patients 60 years or older with AML who are randomly assigned to receive either OCV-501 monotherapy or placebo.

Secondary objectives

The secondary objectives of this trial are:

- to compare overall survival between both treatment arms
- to compare patient quality of life (QOL; The European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30) and performance status (ECOG PS) between both treatment arms
- to characterize and compare safety in the both treatment arms
- to assess immunological responses:
  OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level, and immunoglobulin level
- to assess WT1 mRNA level

3 Trial Plan

3.1 Trial Design

This trial is a multinational, multicenter, randomized, double-blind, placebo-controlled trial in elderly patients with AML, to compare DFS in patients 60 years or older with AML who are randomly assigned to receive either OCV-501 monotherapy or placebo.

This trial consists of the following three periods.

3.1.1 Screening Period

The investigator or subinvestigator will obtain written consent directly from potential subjects prior to the screening examination. Within 3 weeks before IMP administration, bone marrow aspiration and hematology tests will be performed to confirm the continuation of CR. Virus test, chest x-ray, hCG pregnancy test, body height, and PS will be evaluated. A medical interview, blood biochemistry tests, urinalysis, vital signs, body weight, electrocardiogram, AE observation, and a concomitant drug survey will be performed in the screening period.

The eligible patients will be randomly assigned to one of following treatment groups at a ratio of 1:1:

- OCV-501 arm: 3 mg of OCV-501 (0.4 mL)
- Placebo arm: Placebo (0.4 mL)

The patients will be assigned to either treatment group via the Interactive Voice Response Services (IVRS) or the Interactive Web Response Services (IWRS).

Blood sample collection for HLA genotyping, QOL (EORTC QLQ-C30) and measurement of WT1 mRNA expression level, OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody, anti-WT1 antibody, and immunoglobulin will be performed before IMP administration of Day 1.

3.1.2 Treatment period

From Week 1 to Week 104, the IMP will be subcutaneously administered once weekly up to the 8th administration, and every two weeks from the 9th administration onward. The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration, because drug allergy was reported in another trial (Trial 311-10-002) using OCV-501 and it was considered that a causal relationship with OCV-501 could not be ruled out, and the AE was considered to be serious by the sponsor. Hematology tests will be performed at least once every two

weeks. If leukemic blast cells appear in peripheral blood or if there is a reduction in blood cell components, bone marrow aspiration will be performed. Smears will be prepared after hematology tests and bone marrow aspiration at every time point, and smears will be collected by the sponsor for central pathological review. Blood sampling for measurement of WT1 mRNA expression level, anti-OCV-501 antibody, anti-WT1 antibody, and immunoglobulin will be performed at least once every four weeks. OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production will be assessed at Week 5, Week 9, Week 13, and every 12 weeks. QOL and PS will be measured at least once every 4 weeks. A concomitant drug survey will be performed at every scheduled visit. For the safety of the subjects, a medical interview, blood biochemical tests, urinalysis, and AE observation will be performed. Vital signs, body weight, and 12-lead ECG will be measured.

Central Pathological Review

Trial sites will prepare extra smears, other than for evaluation at the trial site, from bone marrow and peripheral blood in all scheduled tests performed during the trial, and prepare a May-Giemsa (MG) staining* or Wright's-Giemsa (WG) staining* sample (to protect subjects' personal information, only subject numbers and the name of the staining method will be written on smears). The sponsor will collect the smears prepared during the trial (from screening period to post-treatment observation period). Retrospective evaluation of samples will be conducted by the central pathological review committee. The central pathological review committee will evaluate the sample used at the judgment of relapse by the trial site and the previous sample from before relapse, and verify the judgment of relapse of the trial site. (If possible, the trial site will prepare a peroxidase-stained smear, a specific esterase-stained smear, and a nonspecific esterase-stained [α-naphthyl-butyrate-esterase-stained and/or α-naphthyl-acetate-esterase-stained] smear from bone marrow and submit them to the sponsor when relapse has been judged at the trial site.)

* Both staining methods are acceptable, but only one method may be used for each subject.

If a subject does not show relapse at the completion examination, or if a patient discontinues treatment for any reason other than relapse, the central pathological review committee will evaluate samples from the completion examination or withdrawal examination and confirm that the patient has not relapsed.

3.1.3 Post-treatment observation period

Subjects will return to the trial site 11 to17 days after the last dose of the 2-year IMP administration period to undergo a completion examination during the post-treatment observation period. If a patient discontinues IMP administration before completion of the 2-year treatment period, the patient will undergo a withdrawal examination within 7 days after the investigator or subinvestigator judged withdrawal to be necessary.

3.2 Rationale for Trial Design

In this trial, the primary endpoint is DFS defined as the time from randomization to AML relapse or death from any cause, whichever comes first within the observation period. This endpoint was set to assess the efficacy of OCV-501 as a maintenance therapy in AML patients who were judged to have achieved CR following an induction regimen. Since DFS is a time-to-event variable, this trial was designed as a randomized comparative study with two treatment arms (the OCV-501 arm and the placebo-control arm). No DLTs were reported and the tolerability of OCV-501 treatment up to a dose of 3 mg was confirmed, and OCV-501 specific DTH was observed at each dose in this phase 1 trial (Trial 311-10-001), and the number of AML patients is not very high. The maximum dose (OCV-501 3 mg) that has been confirmed safe in the phase 1 trials will be used to assess the efficacy and safety of OCV-501 compared with placebo. Since no treatments are administered in patients who complete consolidation therapy, placebo was set as a control.

The DFS rates in maintenance therapy with other drugs[25,26,27] in AML patients 60 years or older are summarized below. As DFS rates were approximately 10 to 30% after 2 years, approximately 70 to 90% of events could be observed within 2 years. Thus, the observation period of DFS in this trial is set from the time of randomization to 2 years after the first IMP administration.

Disease Free Survival Rates			
Publication	**1 year later**	**2 years later**	**3 years later**
Cancer and Leukemia Group B Study 9720 (2008)[25]	29%	10%	5%
Hellstrand et al (2008)[26,*]	44%	32%	27%
Cancer and Leukemia Group B study 9420 (2002)[27,**]	40%	20%	18%
Note: values are round number *Leukemia-free survival: Definition is identical to DFS. Values are estimated by comparing data among all patients and patients less than 60 years of age. ** Results of Interleukin 2 monotherapy			

For overall survival (OS), the cutoff date was set as the date after 728 days (2 years) from the day that the last subject started IMP administration

As mentioned above, no DLTs were reported and the tolerability of OCV-501 treatment up to a dose of 3 mg was confirmed, and OCV-501 specific DTH was observed at each dose in the phase 1 trial. This study will consist of two arms (ie, OCV-501 arm and placebo arm) with consideration of feasibility of patient enrollment.

Once-weekly dosing was set as the administration method because the safety of this administration method was confirmed in the phase 1 trial. Considering that other cancer treatment vaccines were administered 6 to 12 times weekly[28 29 30 31] or once every two weeks,[32 33] the IMP will be administered once a week until the 8th administration and will be administered once every two weeks from the 9th administration onward. The IMP will be administered subcutaneously in the same manner as in the phase 1 trial.

This study protocol was developed based on the results of consultation with the Pharmaceuticals and Medical Devices Agency (PMDA, the regulatory agency of Japan).

3.3 Endpoints

3.3.1 Efficacy

3.3.1.1 Primary Endpoint

Disease-free survival (DFS)

3.3.1.2 Secondary Endpoints

- Overall survival (OS)
- Quality of life (EORTC QLQ-C30)
- Performance status (ECOG PS)

3.3.2 Safety

Adverse events, hematology test, blood biochemistry tests, urinalysis, vital signs (blood pressure, pulse rate, body temperature), body weight, and electrocardiogram

3.3.3 Exploratory

- OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level and immunoglobulin
- WT1 mRNA level

[Rationale for endpoint selection]

[Efficacy]

Primary endpoint

This trial was planned to assess the contribution of OCV-501 to life prognosis through relapse prevention in AML patients who have completed consolidation therapy. Therefore, disease-free survival (DFS: time from randomization to AML relapse or death from any cause, whichever comes first, within the observation period) was set as the primary endpoint.

Secondary Endpoints

Overall survival (OS) was set as a general endpoint relevant to survival in anticancer drug therapy. The representative QOL and performance status surveys, EORTC QLQ-C30 and ECOG PS, were set to assess QOL and PS in subjects.

[Safety]

General tests were set out of consideration for subjects' safety and to assess the safety of OCV-501.

[Exploratory]

Measurements of OCV-501-specific IFN-γ production and WT1-killer peptide specific IFN-γ production were set to measure the helper T cell activation and WT1-killer specific T cell activation induced by OCV-501. Measurements of anti-OCV-501 antibody level and anti-WT1 antibody level were set to confirm antibody induction ability because antibody induction against the WT1 protein has been reported.[34] Immunoglobulin was set to monitor whole immunological changes.

Expressed level of WT1 mRNA was set because it is considered to be useful as a monitoring marker of minimal residual disease (MRD).

3.4 Target Number of Patients

The planned number of patients is 120 in total (60 patients in the OCV-501 arm and 60 patients in placebo arm).

4 Investigational Medicinal Products

4.1 Test Product and Comparator

4.1.1 Test Product

Code Name	OCV-501
Generic Name	None
Molecular Formula	$C_{94}H_{150}N_{32}O_{21}S$
Content and Formulation	OCV-501 for injection is a subcutaneous injection formulation that consists of two vials, one of OCV-501 aqueous solution and one of emulsifier, to be mixed prior to use. OCV-501 aqueous solution for injection 3 mg contains OCV-501. The other components are citric acid monohydrate, sodium chloride, sodium hydroxide, glacial acetic acid and water for injection. The emulsifier contains Montanide™ ISA 51 VG (Montanide).
Storage Conditions	The IMP should be stored under conditions specified in the IMP label.

4.1.2 Comparator

Code Name	Placebo
Generic Name	Not applicable
Molecular Formula	Not applicable
Content and Formulation	The placebo injection is a subcutaneous injection formulation that consists of two vials, one of placebo aqueous solution and one of emulsifier, to be mixed prior to use. Placebo aqueous solution for injection includes citric acid hydrate, sodium chloride, glacial acetic acid, sodium hydroxide and water for injection. The emulsifier contains Montanide.
Storage Conditions	The IMP should be stored under conditions specified in the IMP label.

4.2 Packaging and Labeling

4.2.1 Packaging

The vial of aqueous solution of OCV-501 or placebo is packed in one box, and the vial of emulsifier is packed in another box.

4.2.2 Contents of Label

The following information is written on the labels of IMP(s): specification that the drug is for use in a clinical trial, the code name of the IMP, lot number, expiration date, storage conditions, name and address of the sponsor, etc.

5 Trial Population

5.1 Target Disease

Acute myeloid leukemia

5.2 Inclusion Criteria

Patients who meet all of the following criteria at the time of enrollment will be selected.

1) Patients with AML (WHO classification 2008) patients who achieved first complete remission within one or two courses of standard induction therapy*, and completed standard consolidation therapy* (one or more courses).
   * Induction therapy and consolidation therapy are according to the institution's standard of care.

- Applicable types of disease for this trial in WHO classification
  - AML with recurrent genetic abnormalities
  - AML, myelodysplasia-related changes
  - AML, not otherwise specified

2) Patients who are 60 years or older at the time of providing informed consent
3) Sex: Male or female
4) Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2 at the time of trial enrollment
5) Patients with no significant impairments in the functions of major organs (as indicated by laboratory values) meeting the following criteria within 3 weeks of IMP administration:

- Hematological functions

  Patients must not require administration of a blood-derived product or blood transfusion, or granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF)

  - Neutrophil count: > 1,000/μL
  - Platelet count: > 50,000/μL
- Hepatic functions
  - AST and ALT: < 5 × the upper limit of normal (ULN)
  - Total bilirubin: < 3 × ULN
- Renal function
  - Serum creatinine: < 3 × ULN

6) Patients with a life expectancy of at least 3 months
7) Patients who have provided written informed consent within 90 days from the last dose of consolidation therapy on an informed consent form that has been approved by an institutional review board or independent ethics committee.

[Rationale for Inclusion Criteria]

1) The WHO classification is used for the definition of AML and corresponding types of disease are specified.
   Elderly AML patients with therapy-related myeloid neoplasms have an especially poor prognosis and it is expected that AML will relapse at an early point in those patients. Considering the pharmacological profile of OCV-501 that exerts therapeutic efficiency through boosting immune response, patients with therapy-related myeloid neoplasms were excluded.
   Patients who have not achieved CR within 2 courses of induction therapy are considered to be poor responders and will receive salvage therapy. Therefore, trial subjects were defined as patients who had achieved CR within 2 courses of induction therapy.
2) Elderly AML patients were defined as patients 60 years of age or older. There is no clear definition for elderly AML patients. Patients less than 60 years of age are treated as younger adults in the clinical trials conducted outside Japan. In Japan, patients less than 65 years of age receive strong induction therapy, the same as younger adults. Since this is a multinational trial, subjects to be enrolled in the trial were defined as patients 60 years of age or older.
3) This criterion was set because no differences in safety and efficacy were reported.
4) This criterion was set because outpatients were expected for this trial. Patients with PS of 2 or higher who can walk and are self-sufficing are eligible.
5) This criterion was set to ensure patient safety.
6) This criterion was set to ensure patient safety and to avoid any influence on efficacy.
7) This criterion was set so that all subjects will start OCV-501 therapy within a standard period after completion of consolidation therapy, and was also set for regulatory reasons.

5.3 Exclusion Criteria

Patients who fall under any of the following exclusion criteria at the time of enrollment will be excluded from participation in the trial.

1) Patients who have acute promyelocytic leukemia (APL) with t(15;17)(q22;q12), (PML/RARA) karyotype abnormalities, and other variant types
2) Patients who are scheduled for hematopoietic stem cell transplantation
3) Patients who have undergone cancer immunotherapy (eg, cancer vaccine [including OCV-501], lymphocyte or dendric cell transfusional treatment)
4) Patients who have received drugs potentially affecting the immune system within 4 weeks before starting IMP administration or who may receive such drugs after start of

the trial (eg, corticosteroid systemic administration, immunosuppressants, immunostimulants and anti-cancer drugs)

5) Patients who have a history or complication of autoimmune diseases (eg, Hashimoto's disease, idiopathic thrombocytopenic purpura, autoimmune hepatitis, or connective tissue disease) or primary immune deficiency disease
6) Patients who have active infectious diseases
7) Patients who have a history or complication of interstitial pneumonia
8) Patients who have a severe concurrent disease (eg, cardiac failure [NYHA class III or IV], uncontrolled diabetes mellitus, uncontrolled hypertension) or psychiatric illness likely to interfere with participation in this trial
9) Patients who are HIV antibody positive or HBV-DNA positive, or have unrecovered* chronic hepatitis C with positive HCV antibody
   *: Recovery is determined by sustained virologic response of HCV-RNA.
10) Patients who have cirrhosis
11) Patients who have a history of hypersensitivity or serious adverse drug reaction to any of the components of IMP
12) Patients who have a concurrent second cancer (except carcinoma *in situ*, intramucosal cancers, or malignancies treated at least 5 years previously with no evidence of relapse)
13) Patients who have been administered investigational drugs or individually imported drugs within 12 weeks before starting IMP
14) Women with confirmed or suspected pregnancy, or breast-feeding women
15) Patients not agreeing to take adequate contraceptive measures during the trial period and until 180 days (for males) or 120 days (for females) after the last IMP administration
16) Patients judged to be ineligible by the investigator (or subinvestigator) for any other reasons

[Rationale for Exclusion Criteria]

1) Since a high remission rate is expected with all-trans retinoic acid (ATRA) or arsenic trioxide therapy in patients with APL with t(15;17)(q22;q12) or its variant types. Therefore, patients with APL with t(15;17)(q22;q12) or its variant types are excluded from the trial.
2) This criterion was set to exclude patients who plan to receive existing aggressive therapy.

3), 4) These criteria were set to avoid any influence on efficacy evaluation.

5) - 12) These criteria were set in consideration of the safety of subjects and to avoid any influence on efficacy evaluation.

13) This criterion was set to avoid any influence on efficacy and safety evaluation.

14), 15) These criteria were set because the safety of OCV-501 in regard to

reproductive potential and offspring has not been established.

16) This criterion was set to enable the investigator or subinvestigator to consider factors other than the exclusion criteria in subject selection.

6 Trial Design

6.1 Dose, Regimen, and Treatment Period

This is a two-arm, multi-centre, phase 2 trial with patients randomly assigned to one of the following treatment groups:

- OCV-501 arm: 3 mg of OCV-501 (0.4 mL) once-weekly up to the 8th administration, every two weeks from the 9th administration onward
- Placebo arm: Placebo (0.4 mL) once-weekly up to the 8th administration, every two weeks from the 9th administration onward

The IMP will be subcutaneously administered. The administration site will be the axilla or inguinal region. The IMP will be administered at a dose of 0.4 mL per injection site.

The outline of the trial plan is shown in Figure 6.1-1.

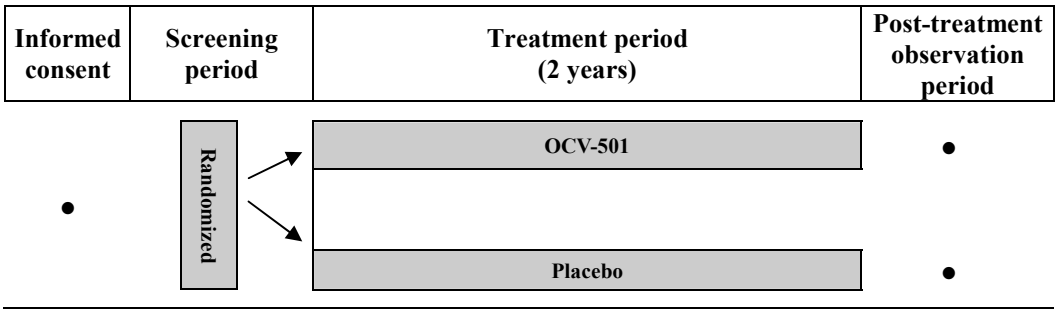

Figure 6.1-1 Trial Design

Adjustment factors of allocation at the time of randomization:

- Country/region (by each country/region: Japan, Republic of Korea, Taiwan)
- Age (60 to 64 years, 65 to 70 years, and ≥ 71 years)

[Rationale for dose, regimen, and treatment period]

[Dose]

In this phase 1 trial, no DLTs were reported and the tolerability of OCV-501 treatment up to a dose of 3 mg was confirmed.[30] Therefore, in consideration of subject safety, and the feasibility of patient enrollment in the trial (given the small number of AML patients), and considering that immunological response was observed at each dose level, the dose for this trial was set to the maximum dose

(OCV-501 3 mg) whose safety was confirmed in the phase 1 trial, to assess the efficacy and safety of OCV-501 compared with the placebo.

[Regimen]

Once-weekly dosing was set as the standard administration method because the safety of this administration method was confirmed in the phase 1 trial (Trial 311-10-001). Considering that other cancer treatment vaccines were administered 6 to 12 times weekly[28 29 30 31] or once every two weeks,[32 33] the IMP will be administered once a week until the 8th administration and will be administered once every two weeks from the 9th administration onward. The IMP will be administered subcutaneously in the same manner as in the phase 1 trial.

[Treatment period]

See Section 3.2, Rationale for Trial Design

6.2 Prior and Concomitant Treatment

If a drug (except for components of water for injection such as a saline or dextrose in water) other than the IMP has been used during the period from 4 weeks before IMP administration to the completion examination or withdrawal examination, the name of the drug, purpose of use, daily dose, route of administration, and dates of start and completion of administration, whether or not prior treatment has been ongoing from 4 weeks before commencement of IMP administration, and whether or not concomitant treatment is continued after the completion examination visit or withdrawal examination visit will be recorded in the case report form (CRF). For non-drug treatments, the name of the treatment, its purpose, the dates of start and completion of the treatment, whether or not prior treatment has been ongoing from 4 weeks before commencement of IMP administration, and whether or not concomitant treatment is continued after the completion examination visit or withdrawal examination visit will be recorded in the CRF.

6.2.1 Prohibited Concomitant Drugs and Therapies

Only the IMP will be used for treating the primary disease (AML), and concomitant use of the drugs (including Chinese herbal medicine) and therapies listed below is prohibited from the time of informed consent to the end of the post-treatment examination. If a subject requires treatment with a prohibited concomitant drug or therapy, the subject

should be withdrawn from the trial according to Section 9.2, Criteria and Procedures for Withdrawal of Individual Subjects.

- Other anti-cancer drugs, hormone therapy, antibody therapy, radiation therapy, thermal therapy or other anti-cancer therapies
- Systemic administration of corticosteroids (equivalent to > 10 mg/day of prednisolone for 2 weeks or longer) and systemic administration of drugs potentially affecting the immune system, including immunosuppressants and immunostimulants
- G-CSF and GM-CSF
- Topical application of corticosteroids at the IMP injection sites
- Investigational drugs and individually imported drugs

[Rationale for establishing the prohibited concomitant drugs and therapies]

The above-defined prohibited concomitant drugs and therapies were set because there is a possibility of these drugs or therapies affecting safety and efficacy assessments.

6.3 Method of Minimizing or Avoiding Bias

The treatment allocation code will be double-blinded during the treatment period, meaning neither the investigator nor the subject will know whether the treatment administered is OCV-501 or placebo. The sponsor's trial personnel, such as those involved in monitoring, data management, and data analysis, including personnel belonging to contract research organizations (CROs), will not have access to the treatment allocation code during the conduct of the trial. Only the subject randomization center will have access to the treatment allocation code for this trial, and only if it is needed in an emergency.

OCV-501 vials and placebo vials will be indistinguishable in appearance and shape.

Blinding is critical to the integrity of this trial. However, in the event that a subject experiences a medical emergency in which knowledge of the IMP is critical to the subject's management, the blind may be broken by the investigator. The need to break the blind must first be discussed with the sponsor and the best method to do this will be determined. The treatment allocation code should be kept confidential and revealed only to those individuals that must be informed for medical management of the subject. See Section 8.2.4 for procedural details.

For measurement of the OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, and anti-WT1 antibody level, the results will not be revealed until unblinding at conclusion of the trial. If a medical emergency occurs in a subject and knowledge of his or her IMP randomization code is considered important for treatment, the emergency code will be broken according to Section 8.2.4, Emergency Code Breaking (Procedure for Unblinding During the Trial Period).

The randomization will be stratified by two stratification factors: country/region (Japan, Republic of Korea, Taiwan), and age at the time of providing informed consent (60 to 64 years, 65 to 70 years, and ≥ 71 years) to minimize imbalances between the treatment arms.

7 Trial Procedures

7.1 Schedule and Procedures

The schedule of observations, examinations, and evaluations is shown in Table 7.1-1. The investigator or subinvestigator will perform observations, examinations, and evaluations in accordance with this schedule. Items that trial associates are capable of performing, such as the subject background survey, may be performed by trial associates under the supervision of the investigator or subinvestigator.

Table 7.1-1 Trial Schedule

Procedure (Week) (Day)	Screening period	Treatment period														Post-treatment observation period *1	
		W1 to W8 (once-weekly IMP administration)								W9 to W104 (every two weeks IMP administration)						Completion	Withdrawal
		W1	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W11**	**W13**	**W15**	After Week 17 up to Week 102	**W103**	**W104**	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D71	D85	D99		D715	D722	D729
(Allowance)		1	5 - 11	12 - 18	19 - 25	26 - 32	33 - 39	40 - 46	47 - 53	54 - 60	66 - 76	80 - 90	94 - 104	Same as W11 to W15 (up to Week 102)	710 - 720	-	11 - 17 days after W 103
Written informed consent	●																
Subject Information	□																
Virus test [a)]	□																
Chest x ray	□																
hCG pregnancy test [b)]	□																
Body height	□																
Patient enrollment for this trial		○															
Blood sampling for HLA genotyping		○															
IMP administration [c)]		↓ (1)	↓ (2)	↓ (3)	↓ (4)	↓ (5)	↓ (6)	↓ (7)	↓ (8)	↓ (9)	↓ (10)	↓ (11)	↓ (12)	↓ (every 2 weeks) (13-55)	↓ (56)		
Concomitant drug survey	←———											□		———→			
Adverse event observation	←———											□		———→			
Medical interview by (sub)investigator	□	○	○	○	○	○	○	○	○	○	○	○	○	○ (every 2 weeks)	○		□	□
Body weight	□	▲				□				□		□		□ (every 4 weeks)			□	□
Vital signs [d)]	□	▲				○				○		○		○ (every 4 weeks)			□	□
Hematology test [e) f)]	□	▲		○		○		○		○	○	○	○	○ (every 2 weeks)	○		□	□
Peripheral blood smear preparation	□	▲		□		□		□		□	□	□	□	□ (every 2 weeks)	□		□	□
Blood biochemistry test [g)]	□	▲				○				○		○		○ (every 4 weeks)			□	□
12-Lead electrocardiogram	□					○				○		○					□	□
QOL(EORTC QLQ-C30)		○				□				□		□		□ (every 4 weeks)			□	□
Performance status (ECOG PS)	□	▲				□				□		□		□ (every 4 weeks)			□	□
Bone marrow aspiration [f)]	□																□	
Bone marrow smear preparation [g)]	□																□	
Urinalysis [h)]	□	▲				○				○		○		○ (every 4 weeks)			□	□
Expressed level of WT1 mRNA		○				○				○		○		○ (every 4 weeks)			□	□
IFN-γ production (OCV-501-specific, WT1-killer peptide specific)		○				○				○		○		○ (at Weeks 25, 37, 49, 61, 73, 85, 97)			□	□
Anti-OCV-501 antibody		○				○				○		○		○ (every 4 weeks)			□	□
Anti-WT1 antibody		○				○				○		○					□	□
IImmunoglobulin		○				○				○		○					□	□

●: Obtained before screening examinations.
○: Mandatory (to be performed/collected before IMP administration).
▲: Data from a screening examination can be used if they were obtained within 7 days before the IMP administration (to be performed before IMP administration except peripheral blood smear preparation).
□: Mandatory

[a] HIV antibody, HBV-DNA, HCV antibody.
[b] To be performed only for female subjects who are capable of becoming pregnant (Urine test).
[c] Once-weekly up to the 8th administration, once every two weeks from the 9th administration onward. The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.
[d] Blood pressure, pulse, body temperature
[e] Hb, Hct, RBC, WBC, WBC differential (visual count), PLT.
[f] If leukemic blast cells appear in peripheral blood or if there is a reduction in blood cell components, perform bone marrow aspiration by post-treatment observation period, and prepare smear.
[g] AST, ALT, ALP, LDH, γ-GTP, TP, ALB, T-Bil, BUN,UA, Cr
[h] pH and specific gravity, bilirubin, glucose, ketone bodies, white blood cells, occult blood, protein, urobilinogen

*[1] Even if treatment is discontinued before completion of the 2-year treatment period, patients will still undergo the post-treatment examination.
(If an AE has not resolved by the end of the post-treatment observation period, the investigator or subinvestigator will explain to the subject the need for follow-up investigation and will request the subject's cooperation. The investigator or subinvestigator will conduct a follow-up investigation within 4 weeks after the post-treatment observation period.)

7.1.1 Acquisition of Informed Consent

The investigator or subinvestigator will obtain written consent directly from subjects prior to the screening examination. After giving informed consent, each subject will be registered in either the IVRS or the IWRS and assigned a subject number, which will be recorded. The investigator or subinvestigator will record the subject number (three-digit trial site number + four-digit sequential serial number) and the date of written informed consent on the medical records and CRF.

7.1.2 Screening Examination

7.1.2.1 Screening Examination

After acquisition of informed consent, the following screening examination will be performed and subjects who meet the inclusion criteria and do not fall under any of the exclusion criteria will be selected. The results of tests/assessments and the date of measurement/examination or the date of blood/urine collection will be recorded in the medical records and CRF.

The following items will be performed at a feasible time.

- Virus test (HIV antibody, HBV-DNA, HCV antibody)
  Virus test will be performed at the central laboratory.
- Chest x-ray
  The chest x-ray will be performed according to the institutional standard method. The results will be recorded in the medical records and CRF.
- hCG pregnancy test (urine test)
  The pregnancy test will be performed for female subjects at the trial site. A pregnancy test will not be required for subjects who have undergone bilateral oophorectomy or hysterectomy, or have not experienced menses for at least 12 consecutive months for whatever other medical reasons.
- Body weight / body height
  The measurements will be performed according to the institutional standard method. The results will be recorded in the medical records and CRF.
- Survey of concomitant drugs and therapies
- Survey of AEs
- Medical interview by investigator or subinvestigator
- Vital signs (blood pressure, pulse, and body temperature)
- Hematology test (Hb, Hct, RBC, WBC, WBC differential, PLT)
- Peripheral blood smear preparation
- Bone marrow aspiration and bone marrow smear preparation
  Bone marrow aspiration will be performed. The date of bone marrow aspiration and

result will be recorded in the medical records and CRF.
The measurement parameters will include the following items:
The percentage of myeoblasts/leukemia cells, lymphoblasts, erythroblast, monoblast, promyelocytes, myelocytes, metamyelocytes, neutrophils [Stab cell, segmented cells], basophiles, eosinophils, monocytes, lymphocytes, and atypical lymphocytes.

- Blood biochemistry tests (AST, ALT, ALP, LDH, γ-GTP, TP, ALB, T-Bil, BUN, UA and Cr)
- Urinalysis (pH and specific gravity, bilirubin, glucose, ketone bodies, white blood cells, occult blood, protein, urobilinogen)
- 12-Lead electrocardiography (ECG)
- Performance status (ECOG PS)

7.1.2.2 Subject Information

At the time of obtaining informed consent or at the screening examination, the following subject information will be recorded in the medical records (if necessary) and the CRF.

- Date of informed consent acquisition
- Subject number
- Subject's background information:
  - Sex
  - Date of birth (year, month, day),
  - Country where the trial was conducted
  - Race
- Information of AML and other malignancies:
  - Diagnosis of AML (WHO classification) and date of diagnosis
  - Caryotype or cytogenetic abnormalities of AML at the diagnosis
  - Existence of extranodullary disease
  - Percentage of leukemic blast (bone marrow blast) at the diagnosis
  - Regimen of induction therapy (name of drug, dose) and date of start.
  - Number of courses until CR is achieved
  - Date of CR by induction therapy
  - Regimen of consolidation therapy (name of drug, dose) and date of start.
  - Number of courses of consolidation therapy
  - Last date of administration of consolidation therapy
  - Maximum WT1 mRNA level and date of sample collection at AML diagnosis or at the time of induction therapy or consolidation therapy (if possible).
  - Diagnosis of malignant tumor other than AML and date of diagnosis and date of cure

  - Treatment of malignant tumor other than AML
- Medical history and concomitant disease:
  - Medically significant medical history and date of diagnosis
  - Diagnosis of concomitant disease at the time of obtaining informed consent, and date of diagnosis

7.1.2.3 Allocation of Investigational Medicinal Products to Subjects at Enrollment (Before Week 1 IMP Administration)

From the results of the screening examination, the investigator or subinvestigator will verify that the subject meets the inclusion criteria and does not fall under any of the exclusion criteria, and each subject will be registered in either the IVRS or the IWRS and assigned a treatment allocation code. Date of the enrollment will be recorded in the medical records and CRF.

7.1.3 Observations, Examinations, and Evaluations During the Observation Period

7.1.3.1 Observations, Examinations, and Evaluations From Week 1 to Week 8

7.1.3.1.1 Week 1 (1st Administration [Day 1])

The following observations, examinations, evaluations, and IMP administration will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) A medical interview by investigator or subinvestigator will be performed before IMP administration.
2) Blood sampling for HLA genotyping (HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DPB1, HLA-DQB1, and HLA-A) will be performed.
3) Adverse event observation and a concomitant drug survey will be performed.
4) Subjects will receive the IMP (3 mg of OCV-501 [0.4 mL] or placebo [0.4 mL]) according to the IMP pack number (unique ID No.) provided through the IVRS or the IWRS at each scheduled visit. The IMP pack number (unique ID No.) will be issued according to the treatment allocation code. The IMP will be subcutaneously administered at the axilla or inguinal region.
   (The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.)
5) Blood sampling for measurement of WT1 mRNA expression level will be performed before IMP administration.
6) QOL (EORTC QLQ-C30) self-assessment will be performed by subjects.

7) Blood sampling for measurement of OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti OCV-501 antibody level, anti-WT1 antibody, and immunoglobulin will be performed before IMP administration will be performed.

If the following examinations were conducted within 7 days before IMP administration, the data can be used as the Day 1 examination data.

8) Body weight measurement will be performed before IMP administration.
9) Measurement of vital signs will be measured before IMP administration (blood pressure, pulse, and body temperature).
10) Blood sampling for a hematology test will be performed before IMP administration.
11) Peripheral blood smear preparation will be performed.
12) Blood sampling for a blood biochemistry test will be performed before IMP administration.
13) Performance status (ECOG PS) will be measured.
14) A urine sample for urinalysis will be collected before IMP administration.

7.1.3.1.2 Weeks 2, Week 4, Week 6, and Week 8

The margin of acceptability is ± 3 days. The following observations, examinations, evaluations, and IMP administration will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) The investigator or subinvestigator will perform a medical interview before IMP administration.
2) Subjects will receive the IMP (3 mg of OCV-501 [0.4 mL] or placebo [0.4 mL]) according to the IMP pack number (unique ID No.) provided through the IVRS or the IWRS at each scheduled visit. The IMP pack number (unique ID No.) will be issued according to the treatment allocation code. The IMP will be subcutaneously administered at the axilla or inguinal region.
   (The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.)
3) Adverse event observation and a concomitant drug survey will be performed.

7.1.3.1.3 Week 3 and Week 7

The margin of acceptability is ± 3 days. The following observations, examinations, evaluations, and IMP administration will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) The investigator or subinvestigator will perform a medical interview before IMP administration.
2) Samples will be collected for a hematology test before IMP administration.
3) Peripheral blood smear preparation*.
4) Subjects will receive the IMP (3 mg of OCV-501 [0.4 mL] or placebo [0.4 mL]) according to the IMP pack number (unique ID No.) provided through the IVRS or the IWRS at each scheduled visit. The IMP pack number (unique ID No.) will be issued according to the treatment allocation code. The IMP will be subcutaneously administered at the axilla or inguinal region.
   (The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.)
5) Adverse event observation and a concomitant drug survey will be performed.

*: If leukemic blast cells appear in peripheral blood or if there is a clinically significant reduction in blood cell components, the investigator or subinvestigator will perform bone marrow aspiration and prepare bone marrow smears.

7.1.3.1.4 Week 5

The margin of acceptability is ± 3 days. The following observations, examinations, evaluations, and IMP administration will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) The investigator or subinvestigator will perform a medical interview before IMP administration.
2) Samples for a hematology test will be collected before IMP administration.
3) Peripheral blood smear preparation* will be performed.
4) Samples for a blood biochemistry test will be collected before IMP administration.
5) A urine sample for urinalysis will be collected before IMP administration.
6) Samples for measurement of WT1 mRNA expression level will be collected before IMP administration.
7) Samples for measurement of OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level, and immunoglobulin will be collected before IMP administration.
8) Subjects will receive the IMP (3mg of OCV-501 [0.4 mL] or placebo) according to the IMP pack number (unique ID No.) provided through the IVRS or the IWRS at each scheduled visit. The IMP pack number (unique ID No.) will be issued according to the treatment allocation code. The IMP will be subcutaneously administered at the axilla or inguinal region.
   (The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.)

9) QOL (EORTC QLQ-C30) self-assessment by subjects will be performed.
10) Performance status (ECOG PS) will be measured.
11) Vital signs will be measured before IMP administration.
12) 12-Lead ECG will be performed before IMP administration.
13) Body weight will be measured.
14) Adverse event observation and a concomitant drug survey will be performed.

*: If leukemic blast cells appear in peripheral blood or if there is a clinically significant reduction in blood cell components, the investigator or subinvestigator will perform bone marrow aspiration and prepare bone marrow smears.

7.1.3.2 Observations, Examinations, and Evaluations From Week 9 to Week 104

7.1.3.2.1 Week 9

The margin of acceptability is ± 3 days. The following observations, examinations, evaluations, and IMP administration will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) The investigator or subinvestigator will perform a medical interview before IMP administration.
2) Samples for a hematology test will be collected before IMP administration.
3) Peripheral blood smear preparation* will be performed.
4) Samples for a blood biochemistry test will be collected before IMP administration.
5) A urine sample for urinalysis will be collected before IMP administration.
6) Samples for measurement of WT1 mRNA expression level will be collected before IMP administration.
7) Samples for measurement of OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level, and immunoglobulin will be collected before IMP administration.
8) Subjects will receive the IMP (3 mg of OCV-501 [0.4 mL] or placebo) according to the IMP pack number (unique ID No.) provided through the IVRS or the IWRS at each scheduled visit. The IMP pack number (unique ID No.) will be issued according to the treatment allocation code. The IMP will be subcutaneously administered at the axilla or inguinal region.
   (The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.)
9) QOL (EORTC QLQ-C30) self-assessment by subjects will be performed.
10) Performance status (ECOG PS) will be measured.
11) Vital signs will be measured before IMP administration.

12) 12-Lead ECG will be performed before IMP administration.
13) Body weight will be measured.
14) Adverse event observation and a concomitant drug survey will be performed.

*: If leukemic blast cells appear in peripheral blood or if there is a clinically significant reduction in blood cell components, the investigator or subinvestigator will perform bone marrow aspiration, and prepare bone marrow smears.

7.1.3.2.2 From Week 11 to Week 104

The margin of acceptability is ± 5 days. The following observations, examinations, evaluations, and OCV-501 administration will be performed on odd numbered weeks (Week 11, 13, 15, 17, 19, 21, etc). The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) The investigator or subinvestigator will perform a medical interview before IMP administration.
2) Samples for a hematology test will be collected before IMP administration.
3) Peripheral blood smear preparation* will be performed.
4) Subjects will receive IMP (3 mg of OCV-501 [0.4 mL] or placebo) according to the IMP pack number (unique ID No.) provided through the IVRS or the IWRS at each scheduled visit. The IMP pack number (unique ID No.) will be issued according to the treatment allocation code. The IMP will be subcutaneously administered at the axilla or inguinal region.
   (The subject's general conditions, including injection site reaction, must be observed at the trial site for one hour after IMP administration.)
5) Adverse event observation and a concomitant drug survey will be performed.

*: If leukemic blast cells appear in peripheral blood or if there is a clinically significant reduction in blood cell components, the investigator or subinvestigator will perform bone marrow aspiration by post-treatment observation period, and prepare bone marrow smears.

The following observations, examinations, and evaluations will be performed every 4 weeks (Week 13, 17, 21, etc).

- Samples for a blood biochemistry test will be collected before IMP administration.
- A urine sample for urinalysis will be collected before IMP administration.
- Samples for measurement of WT1 mRNA expression level will be collected before IMP administration.

- Samples for measurement of anti-OCV-501 antibody level, anti-WT1 antibody level, and immunoglobulin will be collected before IMP administration.
- QOL (EORTC QLQ-C30) self-assessment by subjects and performance status (ECOG PS) measurement will be performed, and body weight will be measured.
- Vital signs will be measured and 12-Lead ECG will be performed before the IMP administration.

The following blood collection will be performed every 12 weeks (Week 13, 25, 37, 49, 61, 73, 85, and 97).

- Samples for measurement of OCV-501-specific IFN-γ production, and WT1-killer peptide specific IFN-γ production will be collected before IMP administration.

7.1.4 Observations, Examinations, and Evaluations During the Post-Treatment Observation Period

7.1.4.1 Observations, Examinations, and Evaluations at 11 to 17 days After Week 103 (Completion Examination)

For the completion examination, the following examinations and observations will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) The investigator or subinvestigator will perform a medical interview.
2) Samples will be collected for a hematology test and peripheral blood smear preparation.
3) Samples will be collected for a blood biochemistry test.
4) A urine sample for urinalysis will be collected.
5) 12-Lead ECG will be performed.
6) Vital signs (blood pressure, pulse rate, and body temperature) will be measured.
7) Body weight will be measured.
8) Adverse event observation and a concomitant drug survey will be performed.
9) QOL (EORTC QLQ-C30) self-assessment by subjects will be performed.
10) Performance status (ECOG PS) will be measured.
11) Samples will be collected for measurement of WT1 mRNA expression level.
12) Samples will be collected for measurement of OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level, and immunoglobulin.
13) Bone marrow aspiration and bone marrow smear preparation will be performed.

7.1.4.2 Time of Withdrawal and Withdrawal Examination

At the time of withdrawal, the following examinations, observations, and evaluations will be performed within 7 days from the day on which withdrawal was judged to be necessary. If the subject refuses to undergo any examinations at the time of withdrawal, or if the investigator or subinvestigator judges that any examinations cannot be performed due to an emergency or other circumstances (eg, SAE or relapse of AML), of the examination items specified for the time of withdrawal, only those items that can be performed will be performed. The date and results of observations, examinations, and evaluations, and the date of blood samplings will be recorded in the medical records and CRF.

1) Adverse event observation and a concomitant drug survey will be performed.
2) The investigator or subinvestigator will perform a medical interview.
3) Body weight will be measured.
4) Vital signs (blood pressure, pulse rate, and body temperature) will be measured.
5) 12-Lead ECG will be performed.
6) Blood sampling for a hematology test and peripheral blood smear preparation* will be performed.
7) Blood sampling for a blood biochemistry test will be performed.
8) A urine sample for urinalysis will be collected.
9) QOL (EORTC QLQ-C30) self-assessment by subjects will be performed.
10) Performance status (ECOG PS) will be measured.
11) Samples will be collected for measurement of WT1 mRNA expression level.
12) Blood sampling for measurement of OCV-501-specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level, and immunoglobulin will be performed.

*: If leukemic blast cells appear in peripheral blood or if there is a clinically significant reduction in blood cell components, the investigator or subinvestigator will perform bone marrow aspiration, and prepare bone marrow smears.

7.1.5 Follow-up Investigation

7.1.5.1 Adverse Events

If an AE has not resolved by the end of the post-treatment observation period, additional investigations will be performed in accordance with Section 8.4, Follow-up Investigation of Adverse Events.

7.1.6 Outcome Observation

7.1.6.1 Overall Survival

All patients will be surveyed for survival by the date of cutoff.

The cutoff date was set as the date after 728 days (2 years) from the day that the last subject started IMP administration. The outcome and dates of any events or reason for censoring (if censored) will be recorded in the CRF.

7.1.6.2 Post Treatment for AML

Post treatment (drugs or therapies) for AML after this trial will be surveyed from the last dose of the IMP until the cutoff date for the overall survival for all patients. The start date and regimen of post treatment will be recorded in the medical records and CRF.

If relapse is observed after the post-treatment examination period in any patients who did not show any relapse up to the post-observation period, the date of relapse will also be surveyed up to the cutoff date of OS. The data will be recorded in the medical records and CRF.

7.2 Method of Evaluation

7.2.1 Efficacy Evaluation

7.2.1.1 Relapse of AML Based on the Response Criteria of the International Working Group

Hematology tests will be performed in the screening period and every two weeks during the treatment period. If leukemic blast cells appear in peripheral blood or if there is a clinically significant reduction in blood cell components, bone marrow aspiration will be performed. The results will be assessed according to the response criteria of the International Working Group shown in Table 7.2.1.1-1 and the assessment will be recorded in the medical records and CRF. Trial sites will prepare extra smears other than for evaluation in the trial site from bone marrow and peripheral blood in all scheduled tests performed during the trial (from screening period to post-treatment observation period), and prepare the MG staining* or WG staining* sample according to the procedures of the trial site (to protect subjects' personal information, only subject numbers and the name of staining method will be written on smears). The percentage of leukemic blast cells and other differential white blood cell counts in the prepared specimen will be measured at the trial site and the result along with the date of blood collection will be recorded in the medical records and the CRF.

* Both staining methods are acceptable, but only one method may be used for each subject.

The sponsor will collect the smears prepared during the trial (from screening period to post-treatment observation period) and retrospective evaluation of samples will be conducted by the central pathological review committee. The central pathological review committee will evaluate samples used at the judgment of relapse by the trial site and the previous sample from before relapse, and verify the judgment of relapse of the trial site. (If possible, the trial site will prepare a peroxidase-stained smear, a specific esterase-stained smear, and a nonspecific esterase-stained [α-naphthyl-butyrate-esterase-stained and/or α-naphthyl-acetate-esterase-stained] smear from bone marrow and submit them to the sponsor when relapse has been judged at the trial site.)

If a subject does not show relapse at the completion examination, or if a patient discontinues treatment without relapse before the end of the post-treatment observation period, the central pathological review committee will evaluate samples at the completion examination or withdrawal examination and confirm that the patient has no relapse.

The investigator or subinvestigator will assess the DFS, and will record the outcome and dates of any events or reason for censoring (if censored) in the medical record and CRF.

Table 7.2.1.1-1 Assessment of Therapeutic Response by Response Criteria[35]

Complete Remission	A case that meets all of the following criteria will be designated as complete remission. 1. The bone marrow contains less than 5% blast cells and no Auer rods. 2. The patient has an absolute neutrophil count of > 1,000/μL 3. The patient has a platelet count of ≥ 100,000/μL. 4. The patient is independent of transfusion. 5. There is no residual evidence of extramedullary leukemia.
Relapse (morphologic relapse)	A case will be designated as relapse if any of the following occur. Reappearance of leukemic blast cells in the peripheral blood or ≥ 5% blast cells in the bone marrow after CR

(If chromosome analysis is conducted during the trial period, any cases that show reappearance of leukemia cells with chromosomal aberrations [cytogenetic relapse] or appearance of extranodullary disease will be handled as cases of relapse)

7.2.1.2 Quality of Life (QOL) (The European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30)

At the specified times, each subject will assess his/her own QOL status according to the criteria of the EORTC QLQ-C30. The investigator or subinvestigator will record the date

and the results of assessment in the CRF. The original survey slip filled out by each subject will be stored in the medical records.

7.2.1.3 Performance Status (The Eastern Cooperative Oncology Group performance status [ECOG PS])

The investigator or subinvestigator will assess performance status according to the criteria of ECOG PS and record the date and results of evaluation in the medical records and CRF.

ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982 .

7.2.2 Safety Evaluation

7.2.2.1 Body Weight

Body weight will be measured according to the procedure specified by the trial site, and the date and the results of measurement will be recorded in the medical records and CRF. If body weight is measured to the second decimal place, the value will be rounded to the first decimal place.

7.2.2.2 Vital Signs (Body Temperature, Blood Pressure, and Pulse Rate)

Systolic and diastolic blood pressures, pulse rate, and body temperature will be measured at rest according to the procedures specified by the trial site, and the date of evaluation and the result will be recorded in the medical records and CRF.

7.2.2.3 Clinical Laboratory Tests (Hematology test, Blood Biochemistry Test) and Urinalysis

The central laboratory will measure the endpoints listed in Table 7.2.2.3-1. The volume of blood sampling is shown in Annex 3.

The investigator or subinvestigator will review the analysis report from the central laboratory, and date and sign the analysis report.

Table 7.2.2.3-1 Clinical Laboratory Tests (Central Laboratory)- Listing

Hematology Test	Blood Biochemistry Test
Hemoglobin (Hb)	Aspartate transaminase (AST)
Hematocrit (Hct)	Alanine transaminase (ALT)
Red blood cell count (RBC)	Alkaline phosphatase (ALP)
White blood cell count (WBC)	Lactate dehydrogenase (LDH)
Platelet count (PLT)	γ - glutamyltransferase (γ-GTP)
	Total protein (TP)
	Albumin (ALB)
	Total bilirubin (T-BIL)
	Blood urea nitrogen (BUN)
	Uric acid (UA)
	Creatinine (Cr)

Differential leukocyte count (myeloblasts/leukemia cells, lymphoblasts, erythroblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, neutrophils [Stab cell, segmented cells], basophiles, eosinophils, monocytes, lymphocytes, and atypical lymphocytes) and urinalysis (pH and specific gravity, bilirubin, glucose, ketone bodies, white blood cells, occult blood, protein, urobilinogen) will be measured by each trial site. The date of sampling and the result will be recorded in the medical records and the CRF. For urine collection, the information on whether collection was performed in a fasting state or not will be recorded in the medical records and the CRF.

7.2.2.4 12-Lead Electrocardiography

The investigator or subinvestigator will measure 12-lead ECG parameters according to the procedures of the trial site in the screening period and at least once every four weeks in the treatment period. The central ECG laboratory will electronically collect 12-lead ECG data and determine heart rate, PR interval, QRS complex, QT interval and QTc interval (QTcF= QT interval/[R-R interval]$^{1/3}$). The central ECG laboratory will report the analysis results to the investigator or subinvestigator. The investigator or subinvestigator will then review the results, and date and sign the analysis report. The investigator or subinvestigator will also reconfirm the normality/abnormality judgment by

referring to the analysis report provided by the central ECG laboratory, and record the reconfirmation date in the medical records and CRF, along with the date and time of the ECG measurement. Any clinically significant findings will be evaluated as AEs.

7.2.2.5 Medical Interview

The investigator or subinvestigator will conduct medical interview at every scheduled visit and will record the results of the medical interview in the medical records and will evaluate any clinically significant events as AEs. AEs will be recorded in the CRF.

7.2.2.6 Adverse Events

The investigator or subinvestigator will assess the nature and severity of AEs and record the results in the CRF (see Section 8, Adverse Events).

7.2.2.7 Concomitant Drug Survey

The investigator or subinvestigator will conduct concomitant drug survey and record the results in the CRF (see Section 6.2, Prior and Concomitant Treatment).

7.2.3 Evaluation of Exploratory Items

The volume of blood sampling is shown in Annex 3.

7.2.3.1 WT1 mRNA Expression Level

1) A blood sample will be collected using a blood-collection tube containing EDTA and the date will be recorded in the medical records, in CRF and on the test request form.
2) Immediately after collection, the blood will be mixed by gently inverting the tube several times and will then be stored refrigerated. After the necessary items in the test request form have been filled out, a request for sample collection will be made to the test laboratory.
3) The central laboratory will measure the level of expression of WT1 mRNA of all subjects and will submit the inspection report to the trial site and to the sponsor. The investigator or subinvestigator will then review the results, and date and sign the inspection report.

7.2.3.2 OCV-501-Specific IFN-γ Production and WT1-killer Peptide Specific IFN-γ Production

1) A blood sample will be collected using a vacuum blood collection tube provided by the sponsor and the date and time will be recorded in the medical records, in the CRF and on the test request form. (The planned sampling date and time should be previously notified to the central laboratory to permit the central laboratory to treat the sample within 24 hours after sampling. After the necessary items in the test request

form have been filled out, a request for sample collection will be made to the central laboratory.)

2) Immediately after collection, the blood will be mixed by gently inverting the tube several times and will then be left at room temperature until the central laboratory collects the sample.
3) The central laboratory will measure the amount of OCV-501-specific IFN-γ and WT1-killer peptide specific IFN-γ production of all subjects after preparing peripheral-blood mononuclear cells (PBMC) and will keep the inspection report under lock and key until unblinding.
4) After unblinding, the central laboratory will submit the inspection report to the sponsor.
5) The residual sample will be cryopreserved at or below − 65°C until completion of the clinical study report for this trial and, then will be discarded.

7.2.3.3 Anti-OCV-501 Antibody and Anti-WT1 Antibody

1) A blood sample will be collected using a blood-collection tube containing a procoagulant agent and the date will be recorded in the medical records and CRF and on the test request form.
2) Immediately after collection, the blood will be mixed by gently inverting the tube several times and will then be left at room temperature for about 30 minutes. The serum specimen obtained after centrifuging the tube at 1800 × G for 10 minutes at about 4°C will be divided into sample stock tubes in duplicate. The specimen will be immediately cryopreserved at or below − 65°C and after the necessary items in the test request form have been filled out, a request for sample collection will be made to the central laboratory.
3) The central laboratory will measure anti-OCV-501 antibody level and anti-WT1 antibody level of all subjects and will keep the inspection report under lock and key until unblinding.
4) After unblinding, the central laboratory will submit the inspection report to the sponsor.
5) The residual sample will be cryopreserved at or below − 65°C until completion of the clinical study report for this trial and then will be discarded.

7.2.3.4 Immunoglobulin

1) A blood sample will be collected using a blood-collection tube containing a procoagulant agent and the date will be recorded in the medical records and CRF and on the test request form.
2) Immediately after collection, the blood will be mixed by gently inverting the tube several times and will then be left at room temperature for about 30 minutes. The serum specimen obtained after centrifuging the tube at 1800 × G for 10 minutes at

room temperature will be divided into sample stock tubes. The specimen will be immediately refrigerated and after the necessary items in the test request form have been filled out, a request for sample collection will be made to the central laboratory.

3) The central laboratory will measure an immunoglobulin of all subjects and will keep the inspection report under lock and key until unblinding.
4) After unblinding, the central laboratory will submit the inspection report to the sponsor.

7.2.4 Evaluation of Other Items

7.2.4.1 HLA Genotyping

HLA genotyping (HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DPB1, HLA-DQB1, and HLA-A) will be performed according to the procedures of the central test laboratory. The genotyping results will not be disclosed to subjects.

1) A blood sample will be collected using a blood-collection tube containing EDTA, and the date will be recorded in the medical records and CRF and on the test request form.
2) Immediately after collection, the blood will be mixed by gently inverting the tube several times and will then be refrigerated. After the necessary items in the test request form have been filled out, a request for sample collection will be made to the central test laboratory.
3) The central test laboratory will identify the genotype by the method of polymerase chain reaction sequence-based typing, etc. and submit the measurement report to the sponsor. Any remaining samples used in the genotyping will be disposed according to the procedures of the central test laboratory.

7.2.5 Investigational Medicinal Product Compliance

The investigator or subinvestigator will record in the medical records and CRF the date and time of IMP administration. If the IMP is not administered at the time specified in the trial protocol even just once, or if IMP administration was judged to be infeasible, the investigator or subinvestigator will record the details in the CRF. Drug accountability will be checked by vials.

7.3 Measures to Be Taken for Subjects Visiting or Planning to Visit Other Hospitals or Departments

At the time of obtaining informed consent, the investigator or subinvestigator will confirm whether or not the subject is receiving treatment at another hospital or department. If the subject is receiving treatment at another hospital or department, the investigator or subinvestigator will inform the attending physician of that hospital or

department about the subject's participation in the clinical trial and the IMP being used, with the subject's consent. The investigator or subinvestigator will also obtain and record in the medical records and CRF information on the treatment that the subject is receiving at the other hospital or department (name of disease being treated and information on the type of treatment or measures being implemented) and judge whether or not the subject should continue to participate in the trial.

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

[ICH E2A guideline: Definition]

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
>
> An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[a]

For this trial, the term "medical product" is regarded as "IMP," and to secure the safety of subjects, AEs occurring from consent to the start of IMP administration are included in the definition of AEs in addition to the definition given by ICH.

If an event, symptom, or sign existing at the time of acquisition of informed consent worsens after acquisition of informed consent, or if an AE occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be treated as a new AE.

In this trial, relapse of AML without any related comorbidity will not be handled as an AE. In the case that a comorbidity with AML associated with clinical symptoms meets the definition of an AE, it will be reported as an AE.

8.1.2 Serious Adverse Event

A serious AE is defined as an AE corresponding to one of the events listed in 1) to 6) below.[a]

The seriousness of AEs occurring during the period from consent to the start of IMP administration will also be judged.

1) An event resulting in death

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[a] "Clinical Safety Data Management", Notification No. 227 of the Examination Division, Pharmaceutical Affairs Bureau dated 20 Mar 1995 (ICH E2A).

2) A life-threatening event
   The term "life-threatening" refers to an event in which the subject was at a risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, had it been more severe.
3) An event requiring in-patient hospitalization or prolongation of existing hospitalization for treatment
4) An event resulting in persistent or significant disability/incapacity
5) An event causing a congenital anomaly/birth defect
6) A major event resulting in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in 1) to 5) above. Examples of such events are intensive treatment in an emergency room for bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Explanation of hospitalization for treatment of an SAE:

Hospitalization for treatment means that the subject must be hospitalized at a medical institution for treatment of an AE, typically for at least one night. This includes hospitalization for treatment of the AE in which no particular medical procedures are carried out (rest therapy). However, it does not include hospitalization for undergoing tests or treatment for an underlying disease or complication that has not worsened since the subject's entry into the trial, hospitalization for social reasons or convenience not intended for treatment of the AE, or hospitalization for treatment or tests scheduled prior to participation in the trial.

8.2 Response to Occurrence of Adverse Events

8.2.1 Actions to Be Taken for Subjects

The investigator or subinvestigator will provide adequate medical care for all clinically significant, trial-related AEs throughout the period of subject participation in the trial as well as thereafter. If treatment for an AE is necessary, the subject will be informed of this.

8.2.2 Expedited Reporting of Serious Adverse Events and Events Specified by the Sponsor

(1) Serious Adverse Events Requiring Expedited Reporting

1) Any SAEs occurring during the trial period regardless of causal relationship with the IMP

2) SAEs occurring during the follow-up period (see Section 8.4, Follow-up Investigation of Adverse Events), if a follow-up investigation is performed, for which a causal relationship with the IMP cannot be ruled out, or AEs that become serious during the follow-up period for which a causal relationship with the IMP cannot be ruled out
3) Among SAEs occurring after completion of the trial (after the follow-up investigation, if a follow-up investigation is performed) and reported by subjects to the investigator or subinvestigator, those for which the investigator or subinvestigator cannot rule out a causal relationship with the IMP

(2) Procedures for Expedited Reporting

Countries/Regions other than Japan:

1) When an AE falling under any of the above items (1) 1) to 3) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) by facsimile (refer to Annex 1, Emergency Contact).

   The notification to the sponsor must include at least the following information. Subject's date of birth, sex, starting date of IMP, information of AE, causal relationship with the IMP
2) The investigator or subinvestigator will then promptly submit a detailed report on any SAEs occurring after the start of IMP administration to the head of the trial site and the sponsor within the period specified by the applicable regional requirements after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours) by facsimile, and additional reporting will be performed if necessary.
3) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the IRB to prepare additional information (autopsy report, terminal care report, or other required information) on a reported SAE, the investigator or subinvestigator will respond to the request.

Japan:

1) When an AE falling under any of the above items (1) 1) to 3) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) by facsimile (refer to Annex 1, Emergency Contact).
   The notification to the sponsor must include at least the following information. Subject's date of birth, sex, starting date of IMP, information of AE, causal relationship with the IMP
2) The investigator or subinvestigator will then promptly submit a detailed report on any SAEs occurring after the start of IMP administration to the head of the trial site and the sponsor within 10 days after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours) by facsimile, and additional reporting will be performed if necessary.

3) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the IRB to prepare additional information (autopsy report, terminal care report, or other required information) on a reported SAE, the investigator or subinvestigator will respond to the request.

8.2.3 Expedited Reporting of Non-serious Adverse Events Resulting in Discontinuation of IMP Administration

When a non-serious AE occurs for which the investigator or subinvestigator judges that IMP administration should be discontinued (but not when IMP administration is merely temporarily interrupted), the investigator or subinvestigator will notify the sponsor within 3 working days in principle after their judgment by facsimile (refer to Annex 1, Emergency Contact).

8.2.4 Emergency Code Breaking (Procedure for Unblinding During the Trial Period)

The investigator will not open the treatment allocation code UNLESS knowledge of the subject's treatment is required for the subject's clinical care and safety. The investigator or subinvestigator will contact the sponsor by any means available, including by telephone, with an explanation of the need for opening the treatment allocation code before opening the code or within 24 hours of opening the code, and shall confer with the sponsor regarding the decision to break the blind if he/she can contact the sponsor before opening the code.

Documentation of breaking the blind will be recorded in the subject's medical records with the date and time the blind was broken and the names of the personnel involved. IMP administration will be discontinued, and the data obtained will be promptly fixed and evaluated within one week.

8.3 Assessment of Adverse Events

The investigator or subinvestigator will assess AEs for the following items.

8.3.1 Terms for Adverse Events

If the disease responsible for an AE can be specified, the name of the diagnosed disease will be recorded in the CRF and not the individual symptoms.

8.3.2 Date of Onset and Recovery

(1) Date of onset:

The date of onset of an AE or date of confirmation of an AE will be recorded in the medical records and CRF. If an event, symptom, or sign existing at the time of acquisition of informed consent worsens, the date of exacerbation will be recorded in the CRF as "date of onset of AE." Also, if an AE occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be recorded in the CRF as a new AE with the date of exacerbation recorded as "date of onset of exacerbated AE."

(2) Date of recovery:

The date of recovery of an AE or date of confirmation of recovery of an AE will be recorded in the medical records and CRF.

8.3.3 Severity

Severity of AEs will be classified using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 into five categories (Grade 1 to Grade 5).

8.3.4 Causal Relationship With Investigational Medicinal Product

The causal relationship between the IMP and AEs occurring after the start of IMP administration will be judged according to the following five categories. The causal relationship with the IMP will be recorded in the CRF.

1) Definitely related:
There is a reasonable causal relationship between the IMP and the AE, when the event responds to withdrawal of the IMP (dechallenge), and recurs with rechallenge by administration of the IMP.

2) Probably related:
There is a reasonable causal relationship between the IMP and the AE. The event responds to dechallenge. Rechallenge not required.

3) Possibly related:
There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear.

4) Unlikely related:
There is a temporal relationship to IMP administration, but there is not a reasonable causal relationship between the IMP and the AE.

5) Not related:
There is no temporal or causal relationship to IMP administration.

The five categories described above will be considered as follows: "definitely related", "probably related", and "possibly relate" will be taken to mean "relationship with the IMP cannot be ruled out" and will be reported as an "adverse drug reaction"; "unlikely related" and "not related" will be taken to mean "relationship to the IMP can be ruled out."

8.3.5 Actions to Be Taken Regarding IMP Administration

Actions to be taken regarding IMP administration following the occurrence of an AE after initiation of IMP administration will be selected from among the following. Actions to be taken regarding IMP administration will be recorded in the CRF.

- No change
- Discontinuation of IMP administration
- Interruption of IMP administration
- Unknown
- Not applicable

8.3.6 Actions to Be Taken for Adverse Events

The performance of medical treatments (medications and/or other treatments) for AEs and details of the treatments will be described in the medical records and CRF.

In addition, the information in case of discontinuation, withdrawal or change of concomitant drugs in response to occurrence of an AE will be described in the CRF.

8.3.7 Outcome

The outcome of an AE will be selected from the following six categories (one only).

If the subject died, the date of death will be recorded in the CRF; if the subject's condition was recovering/resolving, not recovered/not resolved, or unknown, the date of outcome confirmation will be recorded in the CRF.

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown (for some reason, a follow-up investigation could not be performed even once)

8.4 Follow-up Investigation of Adverse Events

The term "recovered" used below means that a subject who had an AE prior to the start of IMP administration returned to his or her original condition, or a subject who had an AE after the start of IMP administration returned to his or her condition before the start of IMP administration.

1) If an AE has not resolved by the end of the post-treatment examination, the investigator or subinvestigator will explain to the subject the need for follow-up investigation and will request the subject's cooperation. The investigator or subinvestigator will conduct a follow-up investigation within 4 weeks after the end of the post-treatment examination and record information regarding the AE in the subject's medical records. If an AE has not resolved by the end of the end of the post-treatment examination, the investigator or subinvestigator will record the outcome in the CRF as "recovering/resolving", "not recovered/not resolved", or as otherwise appropriate.
2) If an AE has not resolved by the end of the post-treatment examination and a causal relationship with the IMP cannot be ruled out, follow-up investigation will be continued until the event resolves or becomes stable and information regarding the AE will be recorded in the subject's medical records. If a causal relationship between the AE and the IMP can be ruled out, no further follow-up will be made beyond the day of the initial follow-up investigation.
3) If, between the end of the post-treatment examination and the day of the follow-up investigation, a new SAE for which a causal relationship with the IMP cannot be ruled out occurs, or if an AE that has not resolved by the end of the post-treatment examination period and for which a causal relationship with the IMP cannot be ruled out becomes serious, follow-up investigation will be conducted until the AE resolves or becomes stable and information regarding the AE will be recorded in the subject's medical records.
4) If an SAE for which a relationship with the IMP cannot be ruled out is discovered after the end of the post-treatment examination, or after the day of the initial follow-up investigation (if performed), follow-up investigation will be conducted until the AE resolves or becomes stable or until follow-up of the subject becomes impossible and information regarding the AE will be recorded in the subject's medical records.
5) If post treatment of AML is started after the end of the post-treatment observation period and the investigator or subinvestigator considers it difficult to confirm the outcome because of the effect of the post treatment, AEs will not be followed up even if the AE has not been resolved by the end of the post-treatment examination.

8.5 Pregnancy

If women of childbearing potential or male subjects whose partners are capable of becoming pregnant participate in the trial, the investigator or subinvestigator will attend to the following.

- Information on reproductive and developmental toxicity of the IMP
- Information regarding pregnancy in the ICF
- Explanation of contraceptive methods
- Reporting and follow-up of cases of pregnancy

8.5.1 Guidance to Subjects Including Contraceptive Methods

1) Before the start of the trial, the investigator or subinvestigator will explain to the subjects the importance of using contraception and the risks associated with pregnancy of a female subject or partner of a male subject and, after subjects have read the written information for subjects and understood it, the investigator or subinvestigator will have subjects sign the ICF.
2) If women of childbearing potential or male subjects whose partners are capable of becoming pregnant wish to participate in the trial, the investigator or subinvestigator will instruct them to practice contraception during the period specified in the trial protocol.
3) Contraceptive methods include condoms, pills, pessaries, IUD, implantable contraceptive devices, spermicide, vasectomy, and tubal ligation. However, if a female subject or male subject's partner is without question unable to become pregnant (ie, has undergone bilateral ovariectomy or hysterectomy or has not experienced menses for at least 12 consecutive months for whatever other medical reasons, or the male subject/partner has undergone bilateral orchidectomy), or if the subject and his/her partner remain abstinent, use of contraception is unnecessary.
4) The investigator or subinvestigator will instruct the subjects that if the contraceptive measures fail and evidence of pregnancy of the female subject or male subject's partner such as delay in menstruation is observed, this should be promptly reported to the investigator or subinvestigator.

8.5.2 Actions to Be Taken by the Investigator or Subinvestigator When Pregnancy Is Suspected

If the investigator or subinvestigator or a subject suspects that the subject has become pregnant before initiation of IMP administration, initiation of IMP administration will be withheld and a pregnancy test will be performed. If the test result is positive, the trial subject will be withdrawn without receiving IMP administration. If a pregnancy is

suspected after initiation of IMP administration, IMP administration will be discontinued (refer to Section 9.2, Criteria and Procedures for Withdrawal of Individual Subjects).

The timing of reporting to the sponsor will be same as for the reporting of SAEs to the sponsor.

8.5.3 Actions to Be Taken by the Investigator or Subinvestigator When a Subject Is Discovered to Be Pregnant

When a female subject is found to be pregnant, the investigator or subinvestigator will withdraw the subject from the trial and perform follow-up investigation until delivery or end of pregnancy, and report this in writing to the sponsor.

After discontinuation of IMP administration, the investigator or subinvestigator will perform the withdrawal examinations and follow-up observation stipulated in the protocol, in so far as they do not affect the pregnancy.

8.5.4 Expedited Reporting of Pregnancy

When a female subject or a partner of a male subject is found to be pregnant during the trial, the investigator or subinvestigator will promptly report this to the sponsor orally or by telephone or e-mail (refer to Annex 1, Emergency Contact). The investigator or subinvestigator will then provide any additional information requested by the sponsor.

The notification to the sponsor must include at least the following information:
Subject's date of birth, sex, starting date of IMP, the date and result of the pregnancy test.

8.5.5 Follow-up Investigation of Pregnancy

If a female subject becomes pregnant, the investigator or subinvestigator will perform follow-up investigation of the pregnancy up to delivery or the end of pregnancy and report the results of follow-up in writing to the sponsor. When a subject or subject's partner has delivered, it is best that the neonate be observed for at least six months after delivery.

9 Withdrawal of Individual Subjects From the Trial

Any subject may discontinue participation in the trial at any time without medical disadvantage. The investigator or subinvestigator may withdraw a subject from the trial at any time if it is considered necessary for medical treatment of that subject.

9.1 Screen Failure

If a subject is a screen failure, the following information should be recorded in the medical records and CRF:
date of investigation (the start date of the screening examination), date of informed consent acquisition, date of birth, sex, country where the trial was conducted, race, and reason for screen failure.

9.2 Criteria and Procedures for Withdrawal of Individual Subjects

In any of the events listed below, the investigator or subinvestigator will discontinue IMP administration, perform the tests to be performed at withdrawal stipulated in Section 7.1, Schedule and Procedures of the Trial, and promptly inform the sponsor of the withdrawal (Annex 1, Emergency Contact). The investigator or subinvestigator will record the date and reason for withdrawal in the CRF.

If withdrawal is necessitated by problems with safety, such as the occurrence of an AE or aggravation of the underlying disease, the investigator or subinvestigator will promptly take appropriate measures and perform follow-up if necessary (refer to Section 8.4, Follow-up Investigation of Adverse Events).

1) If the patient wishes to withdraw from the trial
2) If the investigator or subinvestigator judges that it is difficult to continue IMP administration due to occurrence of an AE
3) If relapse of the primary disease (AML) is observed
4) If a prohibited concomitant drug or therapy is used
5) If it is later found that the patient did not to meet the eligibility criteria at the time of enrollment
6) If the patient is found to be pregnant
7) If it is not possible to administer the IMP within 21 days after obtaining informed consent
8) If the investigator or subinvestigator judges that it is necessary to discontinue IMP administration for any another reason

9.3 Follow-up Investigation of Subjects Who Do not Visit the Trial Site

When a subject stops visiting the trial site for unknown reasons, the investigator or subinvestigator will promptly contact the subject or subject's family by phone or other means to check for AEs and to ask the subject to visit.

1) When the subject has visited
   A withdrawal examination will be performed (see Section 7.1.4.2 Time of Withdrawal).

2) When the subject has not visited
   The following items will be recorded in the medical records and CRF.
   1. The date of investigation
   2. The method of investigation
   3. Whether or not the subject was contacted
   4. The reason why the subject does not (or cannot) visit the trial site
   5. Occurrence or non-occurrence of AEs. If an AE has occurred: name of the event, date of onset and date of recovery, severity, relationship to the IMP, measures taken regarding IMP administration, treatment of AE, outcome
   6. If follow-up investigation is impossible: the reason why

10 Collection of Case Report Form Data and Specification of Source Data

10.1 Collection of Case Report Form Data

1) Electronic Data Capture (EDC) will be used in the trial.
2) Subject data will be entered directly into the database from the trial site via a Web browser. These data collected by EDC will constitute the CRF. The results obtained from the clinical laboratory test performed by the central laboratory will be transferred from the central laboratory directly to the sites, except for the results of immunological monitoring of exploratory endpoints, HLA genotyping, and central pathological review, which are to be transferred to the sponsor.
3) Regarding quality assurance of CRFs, the guidelines specified in FDA 21CFR Part11 will be observed.
4) For every subject who provides consent to participate in the trial, a CRF will be created on an EDC data entry screen that conforms to the items of CRF data collection described in the trial protocol.
5) The investigator, subinvestigator, or trial associate will create CRFs according to the manual provided by the sponsor. If source documents are available and the objectivity of the data can be ensured, then the data may be recorded in a CRF by a trial associate.
6) When entering data into CRFs from the trial site, a predetermined check will be automatically performed. The investigator, subinvestigator, or a trial associate will make corrections as necessary.
7) The sponsor will verify CRFs in comparison to source documents and conduct data reviews. If additional query is necessary, the sponsor will issue an intra-system query and the investigator, subinvestigator, or a trial associate will perform data correction or provide a response to the sponsor's query as necessary.
8) A history of all revisions made after the initial data entry is saved on the server will be automatically recorded within the system (date and time of revision, name of person making revision, pre- and post-revision data, reason for revision, date and time of query, name of person issuing query, details of query, etc).
9) After completion of all CRF data entry and confirmation that the content is correct and complete, including confirmation of the audit trail, the investigator will attach an electronic signature.
10) Details concerning data collection will be specified in a separate manual prepared in advance.

10.2 Source Documents

1) Source documents are defined as those documents that are the source of data transcribed into CRFs as trial results.
   Medical records and other records (eg, nursing records, prescription records),

registration verification forms, subject screening list, ICFs, clinical laboratory test and other measurement reports, ECG charts, IMP management records, and other documents

2) The investigator or the trial site will retain all trial-related documents and records except CRFs in such a manner that enables the sponsor or the regulatory authority to have direct access to the documents and records.
3) The original ICFs will be retained according to the method specified by each trial site.
4) After completion of the trial, the sponsor will retain the original CRFs on CD-ROM or some other appropriate electronic medium and the investigator or the trial site will retain copies.

10.3 Case Report Form Items to Be Treated as Source Data

Of the data recorded in the CRF, the following items will be treated as CRF-based source data.

- Signature of investigator and date of confirmation
- Content of investigator or subinvestigator comment
- Adverse event name, severity, seriousness, actions to be taken regarding IMP administration, outcome, causal relationship with IMP.
- Reason for withdrawal
- Concomitant therapy or drug , dosage, route of administration, and reason (purpose)
- Reason for patient death after the post-treatment examination
- Reason for screen failure

10.4 Data to Be Collected by the Sponsor

1) CRFs (data following acquisition of informed consent)
2) Clinical laboratory results including immunological monitoring and standard values (if available)
3) Copies of 12-lead ECG charts
4) 12-Lead ECG analysis report

11 Statistical Analysis

More specific details of the statistical analyses are described in the statistical analysis plan. The statistical analyses will be fixed prior to unblinding.

11.1 Statistical Analysis Sets

11.1.1 Safety Analysis Set (SS)

The SS includes all subjects who received the IMP at least once and from whom data on at least one safety endpoint was obtained after the start of IMP administration.

11.1.2 Full Analysis Set (FAS)

The FAS includes all subjects who received the IMP at least once and from whom data on at least one efficacy endpoint was obtained after the start of IMP administration.

11.1.3 Per Protocol Set (PPS)

The PPS includes all FAS subjects except those who have major protocol deviations or those who have withdrawn from the trial within 8 weeks from start of IMP administration. However, if a subject withdrew due to any reason other than an event (relapse or death) within 8 weeks from start of IMP administration, the subject will still be included in the PPS.

11.1.4 Immune Response Set (IRS)

The IRS includes all subjects who received the IMP at least once and from whom data on at least one immune response endpoint were obtained after the start of IMP administration.

11.2 Handling of Data

Baseline is defined as the last available screening or pre-treatment assessment.

If a problematic subject or data are encountered, the sponsor will decide how to handle the subject or data, with advice from the medical expert, as necessary.

11.3 Analysis Items and Method

11.3.1 Efficacy Analysis

FAS will be used as the primary analysis population and PPS will be used as the secondary analysis population to assess the stability.

Regarding the judgment of relapse which will be used in the primary endpoint, the percentage of leukemic blast cells and other differential white blood cell counts in the prepared specimen will be measured at the trial site and the central pathological review committee will evaluate and verify the judgment of relapse by the trial site. The final judgment from the central pathological review committee will be taken as the main evaluation criteria.

11.3.1.1 Primary Endpoint

1) Definition

- Disease-free survival (DFS)
  - Observation period: For each subject, the time from randomization to the DFS-cutoff date. The DFS-cutoff date was set as the completion date of each subject.
  - Definition: The time from randomization until relapse or death from any cause, whichever comes first by the DFS-cutoff date.
  - Event: Relapse or death from any cause by the DFS- cutoff date.
  - Censoring:
    - If an event has not been observed by the DFS-cutoff date, then the last confirmed non-relapse date will be used as the censoring date.
    - For subjects who have withdrawn from this trial before the completion date for reasons other than relapses or deaths, if non-relapse has been confirmed on the withdrawal date, then the withdrawal date will be used as the censoring date.

2) Analysis Set

FAS, PPS

3) Analysis Method

Primary method: Kaplan-Meier curve, log-rank test

The Kaplan-Meier method will be carried out to estimate DFS functions and plot the DFS curve by treatment arm.

- The log-rank test will be used to determine whether there are differences at the 5% significance level in DFS between the OCV-501 treatment arm and the placebo arm.
- The hazard ratio (OCV-501 vs. placebo) and its 95% confidence interval will be calculated using the wald test.
- The 2-year survival rate and median survival time will be calculated and 95% CI of survival rate will be calculated using the Greenwood formula.

Exploratory method:

- Harrington-Fleming Test: applying the weight 1-S(t), where S(t) is calculated from Kaplan Meier survival estimate.
- HR and its 95% CI will be calculated at every 3-month interval. The hazard rate will be calculated using the person-year method by treatment arm.
- The Cox PH (Proportional Hazards) model will be used to adjust treatment comparison for a set of covariates which are set to be country (each country) and age (60 to 64 years, 65 to 70 years, and ≥ 71 years) on the time-to-event variable. Also, the assumption that the hazard ratio is constant over time will be graphically assessed by looking at the log-minus-log survival plots with stratification of covariates.

11.3.1.2 Secondary Endpoints

1) Definition:

- Overall survival (OS)
  - Observation period: For all subjects, the time from randomization to OS-cutoff date. The OS-cutoff date was set as the date after 728 days (2 years) from the day that the last subject started IMP administration without consideration of withdrawal by the OS-cutoff date.
  - Definition: The time from randomization until death from any cause by the OS-cutoff date.
  - Event: Death from any cause by the OS-cutoff date.
  - Censoring:
    - If an event has not been observed by the OS-cutoff date, then the last confirmed survival date will be used as the censoring date.
- Quality of life (QOL)

Global health status
Functional Scale: Physical Role Cognitive Emotional Social
Symptom Scale: Fatigue Pain Nausea/vomiting
Single Items: Dyspnea Sleep disturbance Appetite loss Constipation Diarrhea Financial impact

- Performance status (PS)

2) Analysis Set

FAS, PPS

3) Analysis Method:

- Overall survival (OS)

Primary method: Kaplan-Meier curve, log-rank test

The Kaplan-Meier method will be carried out to estimate the OS function and plot the OS curve of each treatment arm.

- The log-rank test is used to determine whether there are differences at the 5% significance level in OS between the OCV-501 arm and the placebo arm.
- The hazard ratio (OCV-501 vs. placebo) and its 95% confidence interval will be calculated using the wald test.
- The 2-year survival rate and median survival time will be calculated and 95% CI of survival rate will be calculated using the Greenwood formula.

Exploratory method:

- Harrington-Fleming Test: applying the weight 1-S(t), where S(t) is calculated from Kaplan Meier survival estimate.
- HR and its 95% CI will be calculated at every 3-month interval. The hazard rate will be calculated using the person-year method by treatment arm.
- The Cox PH (Proportional Hazards) model will be used to adjust treatment comparison for a set of covariates which are set to be country (each country) and age (60 to 64 years, 65 to 70 years, and ≥ 71 years) on the time-to-event variable. Also, the assumption that the hazard ratio is constant over time will be graphically assessed by looking at the log-minus-log survival plots with stratification of covariates.

- Quality of Life (QOL)

At each time point, the scores and changes from baseline will be summarized using descriptive statistics by treatment arm. Changes from baseline at each time point will be plotted by trend diagram.

At each time point, the treatment effect will be estimated using the difference of change between the least squares means (adjusted means) of each treatment arm.

- Performance Status (PS)

Frequency distributions at each time point will be calculated in the OCV-501 arm and the placebo arm.

11.3.2 Safety Analysis

1) Definition:
AEs, clinical laboratory tests, vital signs (blood pressure, pulse rate, body temperature), urinalysis, body weight, and electrocardiogram.

2) Analysis Set:
SS

3) Analysis Method
The analysis will be performed by each treatment arm.

Descriptive statistics will be calculated for continuous variables and frequency distributions at each time point will be calculated for categorical variables.

The object of analysis is AE occurrence after the start of IMP administration. AEs will be categorized using the terminology of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT), with PT substituted for verbatim terms. The number of subjects and number of incidence of the following events will be tabulated per arm. A summary of SAEs will be provided by severity.

- Adverse events
- Adverse drug reactions
- Serious adverse events by severity
- Adverse events leading to withdrawal

Severity will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

4) Safety Interim Analysis
For the purpose of data safety monitoring, the safety interim analysis will be conducted regularly on all subjects to provide AE tables, SAE lists, etc, while the level of blinding is being maintained.

11.3.3 Exploratory Items Analysis

1) Definition:
OCV-501 specific IFN-γ production, WT1-killer peptide specific IFN-γ production, anti-OCV-501 antibody level, anti-WT1 antibody level, WT1 mRNA level and immunoglobulin.

2) Analysis Set:
IRS

3) Analysis Method:
Generally, a summary will be provided in terms of the mean, geometric mean, standard deviation, median, minimum, maximum and number of patients, unless otherwise stated. Trend diagrams will be plotted by subject.

For WT1 mRNA item, the change from baseline at each time point will be log-transformed and t-test will be conducted between two treatment arms. At each time point, a summary of descriptive statistics will be provided and trend diagrams will be plotted by subject.

11.3.4 Demographic and Other Baseline Characteristics

1) Definition:
Age, sex, height, body weight, diagnosis of AML (WHO classification), regimen of induction therapy, regimen of consolidation therapy, duration from the last dose of consolidation therapy to randomization, maximum WT1 mRNA level at AML diagnosis or at the time of induction therapy or consolidation therapy, and country where the trial was conducted.

2) Analysis Set:
FAS, PPS, SS

3) Analysis Method:
Frequency distribution or descriptive statistics for each variable will be calculated according to the nature of the data (continuous or discrete).

11.3.5 Extent of Exposure

1) Definition:
Duration of exposure to treatment (days), full dose, total number of doses

2) Analysis Set:
SS

3) Analysis Method:
A summary of the duration of exposure to treatment and total dose will be provided. The descriptive statistics will be calculated by treatment arm.

Duration of exposure to treatment will be calculated in days as follows:

IMP administration end date- IMP administration start date+1

11.3.6 Significance Level and Confidence Interval

Two-sided statistical tests will be conducted at the 5% significance level and 95% confidence interval will be provided.

11.3.7 Subgroup Analysis

1) Definition:
The primary endpoint DFS and secondary endpoint OS will be examined for the following subgroups.

Factor	Categories
Country/ region	Japan, Republic of Korea, and Taiwan
Age	60 to 64 years, 65 to 70 years, ≥ 71 years

2) Analysis Set:
FAS

3) Analysis Method:
For each subgroup, summaries and statistical analysis will be conducted by treatment arm as follows.

- The Kaplan-Meier method will be carried out to estimate the survivor function and plot the survival curve by treatment arm.
- The hazard ratio (OCV-501 vs. placebo) and its 95% confidence interval will be calculated using the wald test
- The 2-year survival rate and median survival time will be calculated and 95% CI of survival rate will be calculated using the Greenwood formula.

11.4 Procedures for Reporting Deviations From the Original Statistical Analysis Plan

If there is any need for a change in the statistical analysis plan, the timing, details and reasons of the change will be included in the clinical trial report.

11.5 Rationale for Target Number of Patients

The number of AML patients is not very high, and is estimated to be approximately 7000 in Japan[36]. From the fact that in the previous clinical trial (JALSG GML200) in elderly AML patients, it has been forecast that the possible enrollment in Japan is to be at most 70 in one year. Also, from the preliminary trial feasibility survey, it is known that around 50 subjects could be recruited in one year in Republic of Korea and Taiwan. Through a global trial in Japan, Republic of Korea and Taiwan, it is considered possible to enroll 120 subjects in one year to assess the efficacy of OCV-501.

Within the limitation of the past experiences with regard to IMP administration, the target sample size will be considered with reference to following publications[25,26,27,37] With reference to disease-free survival which has been reported from trials in AML subjects 60 years or older who have received the consolidation therapy followed by the maintenance therapy, the 2-year DFS rate of placebo arm has been estimated to be around 20%.[25,26,27] On the other hand, considering the so-called graft-versus-leukemia (GVL) effect associated with a lower relapse risk after the allogeneic hematopoietic stem cell transplantation, OCV-501 is basically expected to have the same benefits. With reference to the findings of Kurosawa et al,[37] which have reported a 30% higher 2 or 3-year DFS in elderly AML subjects who have received the allogeneic hematopoietic stem cell transplantation compared with those without transplantation, OCV-501 is expected to have a 15% - 20% higher 2-year DFS. Under the assumption of exponential distribution of DFS time, the hazard ratio (placebo vs. OCV-501) has been set to 0.57 - 0.65, and with a two-sided log-rank test at the 5% significance level, 60 or more subjects in each treatment group can achieve a power of 53 to 75% or more to detect the difference between placebo and OCV-501 groups.

12 Quality Control and Quality Assurance for the Trial

To ensure the quality of the trial, trial sites, contract research organizations, laboratories performing clinical tests, and the sponsor will perform quality control for the trial according to their respective Standard Operating Procedures.

The audit division of the sponsor company will carry out audits within the company and, as necessary, at the trial site and contract research organizations or organizations entrusted to perform related activities, and check whether quality control of the trial is appropriately performed according to the Standard Operating Procedures.

13 General Items of Caution Pertaining to the Trial

13.1 Ethics and GCP Compliance

This trial must be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki, the ICH-GCP Guideline,[b] all applicable regional regulatory requirements (eg, Pharmaceutical Affairs Law, Standards for the Conduct of Clinical Studies [Ordinance No. 28, GCP dated 27 Mar 1997] and related notifications in Japan), and the protocol.

13.2 Institutional Review Board

Each trial site will seek approval from an IRB/IEC according to regional regulations. The IRB/IEC will investigate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRFs, the investigator, subinvestigator, and their staff must take measures to ensure adequate care in protecting subject privacy.

13.3 Subject Consent

13.3.1 Procedures for Obtaining Consent

1) Prior to the start of the screening examination, the investigator or subinvestigator will fully explain the matters listed in Section 13.3.2 to each subject who will be included in the trial, using the ICF, and give the ICF to the subject. The subject will be provided sufficient time to make a decision regarding participation. After confirming that the subject has properly understood the explanation, the investigator or subinvestigator will obtain written voluntary consent for participation in the trial from the subject.
2) The investigator or subinvestigator who has provided the explanation and the subject will each put their printed name and personal seal or signature on the ICF, and write the date on which they sign or stamp the form. If a trial associate has provided a supplemental explanation of the trial, he/she will also put his/her printed name and personal seal or signature on the form and write the date on which he/she signs or stamps the form.
3) The original of the ICF that was signed or stamped and dated will be retained by the investigator or subinvestigator according to the regulations of the trial site. A copy of the original ICF will be given to the subject.
4) After obtaining informed consent from a subject, the investigator or subinvestigator will write the date of informed consent acquisition and subject number in the documents for enrolled subjects (list of screened subjects and list of enrolled subjects).

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[b] International Conference on Harmonization (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized May 1996, corrected Jun 1996; cited 2005 Dec 06]. Available from: http://www.ich.org/cache/compo/276-254-1.html.

5) If new information becomes available that may influence the willingness of the subject to continue participation in the trial, the investigator or subinvestigator will promptly inform the subject of such information and confirm the willingness of the subject to continue participation in the trial, and then record the result in the subject's medical records. If there is guidance regarding the recording of re-consent stipulated by the trial site, it will be followed.

13.3.2 Contents of Informed Consent Form

The informed consent form must explain the following:

1) That the trial involves research
2) The purpose of the trial
3) The trial treatment(s) and the probability for random assignment to each treatment
4) The trial procedures to be followed, including all invasive procedures
5) The characteristics of HLA genotyping
6) The subject's responsibilities
7) Those aspects of the trial that are experimental
8) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant
9) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
10) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks
11) The compensation and/or treatment available to the subject in the event of trial-related injury
12) The anticipated prorated payment, if any, to the subject for participating in the trial
13) The anticipated expenses, if any, to the subject for participating in the trial.
14) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
15) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
16) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

17) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial
18) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury
19) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated
20) The expected duration of the subject's participation in the trial.
21) The approximate number of subjects involved in the trial

13.3.3 Amendments to the Informed Consent Form

If revision of the ICF becomes necessary due to newly obtained information, the investigator will promptly revise the ICF to include that information after conferring with the sponsor.

The investigator, when revising the ICF, will report this to the head of the trial site and submit the revised document to the IRB designated by the trial site to obtain its approval.

If new information becomes available that may influence the willingness of subjects to continue participation in the trial and the ICF has been revised according to the new information, the investigator or subinvestigator will again obtain subjects' written informed consent to continue participation in the trial.

13.4 Management of Investigational Medicinal Products

1) The sponsor will issue the "Procedures for Handling of Investigational Medicinal Products" to the head of the trial site and the IMP manager designated by the head of the trial site (referred to as the IMP manager hereinafter).
2) The sponsor will issue the "Document on Investigational Medicinal Products Storage Conditions" to the investigator or subinvestigator, trial associates, and IMP manager.
3) The sponsor will deliver the IMPs to the trial site following the start of the trial period contracted with the trial site.
4) The IMP manager will manage the IMPs appropriately according to the "Procedures for Handling of Investigational Medicinal Products" prepared by the sponsor.
5) The IMP manager will prepare and retain the "Record of Management and Storage of Investigational Medicinal Products."

13.5 Direct Access to Source Documents and Monitoring

13.5.1 Direct Access to Source Documents

The head of the trial site and the investigator must accept monitoring and audits to be performed by the sponsor and inspection by the IRB and Japanese and foreign regulatory authorities, and must make source documents and all other trial-related records available to these agencies for direct access (including copying). Subjects authorize such direct access by signing the written ICF.

13.5.2 Monitoring

The sponsor bears responsibility for ethical, legal, and scientific conduct of the trial. The sponsor will perform monitoring according to the "Procedures for monitoring" specified for this trial. Monitoring includes periodic visits, phone calls, or other contact with the trial site for the provision, obtaining, and recording of updated trial-related information by monitors designated by the sponsor.

The sponsor may entrust a portion of monitoring activity to a contract research organization.

13.5.3 Documents to Be Retained by the Investigator

The trial-related documents to be retained by the investigator will be kept in the investigator's file, which will be managed by the investigator.

13.6 Deviations From and Changes or Amendments to the Trial Protocol

13.6.1 Deviations From the Trial Protocol

1) The investigator or subinvestigator should not deviate from the protocol or change it without prior written agreement between the investigator and the sponsor and the written approval of the IRB of the trial site based on prior review.
2) In unavoidable medical circumstances such as the need to avoid emergent risk to a subject, the investigator or subinvestigator may deviate from the protocol or change the protocol without prior written agreement from the sponsor and prior approval of the IRB. In such an event, the investigator will promptly submit a document providing the details of and reason for the deviation or change to the sponsor and the head of the trial site and obtain approval from the IRB. In addition, the investigator will obtain written approval from the head of the trial site and the written agreement of the sponsor by way of the head of the trial site.
3) The investigator or subinvestigator will record all deviations from the protocol.

13.6.2 Amendments to the Trial Protocol

1) The investigator will promptly submit to the sponsor, the head of the trial site, and the IRB by way of the head of the trial site, a written report on any changes in the trial that may significantly affect conduct of the trial or increase risks to the trial subjects.
2) The sponsor, after conferring with the investigator, will agree with the investigator on the contents of the revised protocol and compliance with the revised protocol.
3) The sponsor will promptly submit the revised protocol to the head of the trial site.

13.7 Archiving of Records

1) The investigator and the trial site will retain all the trial-related documents and records for the period of time indicated in a) or b) below, whichever is longer. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.
   a) A period of at least 3 years following the manufacturing and marketing approval of OCV-501; or, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
   b) The date 3 years after termination or completion of the trial.
2) The investigator will retain the trial-related documents and records as directed by the head of the trial site.
3) If it becomes no longer necessary to retain the trial-related documents and records at the trial site, the sponsor will notify the head of the trial site.

13.8 Termination or Interruption of Part or All of the Trial

13.8.1 Termination or Interruption of the Trial at Individual Trial Sites

1) In the event of termination or interruption of the trial, the investigator will promptly provide the head of the trial site with written notification and a written explanation of the details of the termination or interruption of the trial.
2) When the sponsor has been informed by the head of a trial site that the investigator has terminated or interrupted the trial, the sponsor will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site.

13.8.2 Termination or Interruption of the Entire Trial

1) When the entire trial is to be terminated or interrupted by the sponsor, the sponsor will promptly provide the heads of all trial sites involved in the trial and the

regulatory authority with written notification and a detailed written explanation of the reason for the termination or interruption of the trial.

2) When the investigator has received notification of termination or interruption of the entire trial by the sponsor from the head of the trial site, the investigator will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site, promptly notify the trial subjects currently receiving IMP administration, and take necessary measures such as switching to appropriate alternative treatment(s).
3) When development of the IMP is terminated by the sponsor, the sponsor will promptly provide the heads and the investigators of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination of development.

13.9 Protection of Subjects' Personal Information

In completion and handling of CRFs, the investigator and subinvestigator will take adequate care to ensure protection of the personal information of subjects. Individual subjects will be identified by subject numbers. The sponsor will not provide the information obtained to any third party.

As this trial will involve HLA genotyping, genetic information will be handled carefully and appropriately in consideration of the particularity of the information, even if it is not categorized as personal information due to being coded.

13.10 Compensation for Injury to Health

Trial subjects will be compensated for health damages according to the criteria established by the trial sponsor with reference to applicable regional regulatory requirement(s) for this trial will comprise medical costs and medical benefits.

13.11 Agreement on Publication

The sponsor may use the findings obtained from this trial for purposes such as an "Application for Approval of a Pharmaceutical Product" for the IMP.

When the results of this trial and relevant data are to be published in scientific journals or at academic meetings, the investigator will obtain prior written approval from the sponsor.

14 Trial Administrative Structure

The administrative structure of this trial is shown in Annex 1, and Annex 2.

15 Scheduled Duration of the Trial

Sep 2013 through Dec 2017

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