

## Supplementary Online Content

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### **Supplement 1.** Study protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

## Study Protocol

### Study title

“Prospective, randomized, open-label, blinded-endpoint trial to examine the effect of active vitamin D on cardiovascular events in hemodialysis patients: Japan Dialysis Active Vitamin D trial (J-DAVID)”

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### Note

- This is an English translation of the original protocol written in Japanese (translation by Tetsuo Shoji).
- The changes made in the final version (version 2.7) are indicated **in red**, which were made because (1) the principal investigator’s position was changed, and (2) a paragraph “16. How long data is stored” was added. The other parts of the protocol are the same as the version 2.6.

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## 1. Outline of the study

### **Title of the study**

Prospective, randomized, open-label, blinded-endpoint trial to examine the effect of active vitamin D on cardiovascular events in hemodialysis patients: Japan Dialysis Active Vitamin D trial (J-DAVID)

### **Purpose**

The purpose of this study is to examine whether treatment with active vitamin D sterol reduces the risk of cardiovascular events in hemodialysis patients by a randomized controlled trial with prospective, randomized, open-labeled, blinded-endpoint (PROBE) design. This is a multi-center trial including 972 participants (486 participants in the two groups, target numbers) followed-up for 4 years.

### **Study drug**

Alfacalcidol (representative brand name: Alfarol®)

### **Outcome measures**

#### *Primary outcome*

Composite of 1) fatal and nonfatal cardiovascular events including acute myocardial infarction, congestive heart failure requiring hospitalization, stroke, aortic dissection/rupture, amputation of ischemic limb, and cardiac sudden death, 2) coronary intervention (plain old balloon angioplasty, stenting) or bypass grafting, 3) lower limb artery intervention (plain old balloon angioplasty, stenting) or bypass grafting.

#### *Secondary outcome*

All-cause mortality

### **Population**

Patients treated with maintenance hemodialysis

### **Inclusion criteria**

- 1) Patients on maintenance hemodialysis for 90 days or longer
- 2) Men or women aged  $\geq 20$  and  $\leq 80$  years old
- 3) No treatment with VDRA for more than 4 weeks prior to this study
- 4) Serum Ca level  $\leq 10.0$  mg/dL, phosphate level  $\leq 6.0$  mg/dL, and intact PTH level  $\leq 180$  pg/mL

### **Exclusion criteria:**

- 1) History of myocardial infarction, stroke, aortic dissection/rupture, amputation of a lower limb, coronary revascularization or bypass surgery, lower limb revascularization or bypass surgery, within 12 weeks
- 2) Heart failure of NYHA grade III or IV
- 3) Respiratory failure with  $\text{PaO}_2 < 60$  mmHg or  $\text{SpO}_2 < 90\%$

- 4) Life expectancy shorter than 1 year due to known malignant, infectious, or other diseases
- 5) Abnormal liver function tests exceeding x3 upper normal limits
- 6) Pregnant or lactating females or females planning to be pregnant
- 7) History of an allergic reaction to alfacalcidol
- 8) Participation to other interventional studies within 12 weeks prior to this study
- 9) Inappropriate for this study as judged by an attending investigator

### **Discontinuation and drop-out**

#### ***Criteria for completion of study participation***

- 1) When participants have died
- 2) When participants completed the 48 months of follow-up

#### ***Criteria for discontinuation of study participation***

- 1) When a participant or legally acceptable representative withdrew consent
- 2) When participation was discontinued because of the participant's circumstances (change of residence, hospital, etc.)
- 3) When a participant was found not to meet the eligibility criteria after enrollment
- 4) When a participant was found not to follow the instructions by the attending investigator.
- 5) When there was an incidental accident
- 6) When the attending physician decided to discontinue the participation to the study due to adverse events
- 7) When there was a serious violation of the study protocol
- 8) When the investigator or sub investigator made a judgement based on the situation difficult to continue

#### ***Drop-out from the assigned treatment***

- 1) In the intervention group, when a participant is untreated with alfacalcidol for 12 weeks or longer
- 2) In the control group, when a participant is treated with any active vitamin D sterol for 12 weeks or longer

### **Target number of participants**

A total of 972 participants. 486 participants in the intervention group and control group, respectively.

### **Methods**

#### ***(1) Study design***

Prospective, randomized, open-labeled, blinded-endpoint (PROBE) design

#### ***(2) Usage and dosage of study drug***

After obtaining written informed consent, participants shall be randomly assigned to the intervention group or control group. Participants in the intervention group shall be assigned to treatment with oral alfacalcidol at a starting dosage of 0.5 µg per day. Participants in the control arm shall be assigned to treatment without any VDRA.

In accordance with the recommendations by the JSDT clinical practice guideline published in 2006 (JSDT-GL 2006) and the JSDT-GL 2012 after April, 2012, we define the target ranges of serum corrected Ca and P as following; corrected Ca,  $8.4 \leq$  and  $\leq 10.0$  mg/dL; P,  $3.5 \leq$  and  $\leq 6.0$  mg/dL). Serum Ca and P levels shall be monitored twice monthly. In cases with hypercalcemia ( $\geq 10.5$  mg/dL) and/or hyperphosphatemia ( $\geq 7.0$  mg/dL), the patients shall be treated with dietary therapy, and/or dose adjustment of calcium carbonate, sevelamer hydrochloride, and other medications.

If serum calcium and/or phosphate levels are not improved, the dose reduction or temporal cessation of the study drug shall be allowed in the intervention group. The medication shall be re-started, after confirming the recovery of serum Ca and P levels within the target ranges. The dose of alfacalcidol should be in the range between 0.25 and 7  $\mu$ g per week. It shall be 'drop-out' from the assigned treatment, if a participant in the intervention group is kept untreated with alfacalcidol for 12 weeks or longer.

In both groups, intact PTH levels shall be monitored once per 3 months. In the intervention group, if serum phosphate and calcium levels are in the recommended ranges and intact PTH exceeds 180 pg/mL\*, a switch from oral alfacalcidol to another oral or intravenous VDRA shall be allowed. During treatment with intravenous VDRA, intact PTH shall be monitored once a month. When intact PTH is reduced to 180 pg/mL\* or lower, a switch back to treatment with oral alfacalcidol shall be considered.

In the control group, if serum phosphate and calcium levels are in the recommended ranges and intact PTH exceeds 180 pg/mL\*, treatment with oral or intravenous VDRA shall be allowed. During treatment with intravenous VDRA, intact PTH shall be monitored once a month. When intact PTH is reduced to 180 pg/mL\* or lower, cessation of VDRA treatment shall be considered. If treatment with VDRA is done for more than 12 weeks in the control group, it shall be "dropped-out" from the assigned treatment in the control group.

In both groups, if intact PTH exceeds 500 pg/mL, the indication of parathyroid intervention shall be considered.

\*Since April 2012, the target range (upper limit) of intact PTH has been changed to 240 pg/mL according to the JSDT-GL 2012.

**(3) Prohibited treatment**

- Oral VDRA other than alfacalcidol (as mentioned above)

**(4) Allowed treatment**

- Sevelamer hydrochloride, calcium carbonate, cinacalcet hydrochloride, lanthanum carbonate.
- No restriction in medication for other than CKD-MBD.

**(5) Other management:**

- Encourage dietary phosphate restriction of 800 mg/day or lower.

**Examination schedule**

Data shall be obtained as indicated by the table below. The allowance of date is  $\pm 2$  weeks.

	IC	S	R	0M	3M	6M	12M	18M	24M	30M	36M	42M	48M
Informed consent	X												
Clinical background		X		X									
Laboratory data		X		X	X	X	X	X	X	X	X	X	X
Physical examination				X	X	X	X	X	X	X	X	X	X
Use/nonuse of alfacalcidol		X		X	X	X	X	X	X	X	X	X	X
Other medications				X	X	X	X	X	X	X	X	X	X
Primary & secondary outcomes, SAEs					X	X	X	X	X	X	X	X	X

*The test drug (alfacalcidol) shall be given only to participants in the intervention group. The target ranges of serum phosphate, calcium and intact PTH during the study shall be as recommended by JSDT-GL 2006 and by JSDT-GL 2012 after April 2012. To achieve these targets, management by dietary and/or drug treatment shall be done. The predefined switch of treatment for less than 12 weeks shall be allowed.*

- 1) Clinical background: age, sex, duration of hemodialysis, underlying renal disease, and presence of prior cardiovascular disease.
- 2) Laboratory data: Complete blood counts (WBC, RBC, Hb, Ht, Platelet), biochemistry (Ca, P, intact PTH, albumin, CRP, AST, ALT, ALP, BUN, Cr, Na, K, Cl, TC, TG, HDL-C; (Only for patients with diabetes mellitus, HbA1c and glycoalbumin)
- 3) Physical examination: Height (at screening only), body weight (dry weight), blood pressure and pulse rate (at the start of dialysis session)

Abbreviations: IC, informed consent; S, screening; R, randomization; 0M-48M, predefined observation time points; SAEs, serious adverse events.

## Evaluations

### *Efficacy*

- Primary outcome: Composite of (1) fatal and nonfatal CVD events (acute myocardial infarction, congestive heart failure, stroke, aortic dissection/rupture, amputation of ischemic limb, and cardiac sudden death), (2) coronary intervention (plain old balloon angioplasty, stenting) or bypass grafting, (3) lower limb artery intervention (plain old balloon angioplasty, stenting) or bypass grafting.
- Secondary outcome: All-cause death
- These outcomes shall be adjudicated by the Event Evaluation Committee with treatment groups being masked to the Committee.

### *Safety*

- Because the test drug (alfacalcidol; the representative brand name, Alfarol<sup>®</sup>) is a previously approved drug with its safety profile being known in detail, serious adverse events due to the test drug are preventable by careful monitoring of physical examination and biochemical tests. For the evaluation of

safety, the occurrence of SAEs and changes in laboratory data shall be monitored.

**Study period:**

48 months (per each participant)

**Study sites**

207 institutions included in J-DAVID Research Group (as of April 24, 2012)

## 2. Background

In patients with chronic renal failure treated on hemodialysis, serum  $1\alpha,25(\text{OH})_2$  vitamin D, a bioactive form of vitamin D, is depleted due to impaired activation by  $1\alpha$ -hydroxylase in the kidney. This, in concert with phosphate retention, is one of the main causes of secondary hyperparathyroidism. Active vitamin D sterols, or vitamin D receptor (VDR) activators (VDRAs) have been widely used as a major therapy for secondary hyperparathyroidism [1].

Vitamin D has its physiological roles not only in the mineral metabolism but also in other systems including the heart, arteries, immune cells, endocrine organs, skeletal muscle, liver and neurological systems, because VDR is expressed these tissues and cells [2]. Experimental studies with cultured cells revealed that active vitamin D sterols have suppression [3] (and stimulation at higher concentrations [4]) of vascular smooth muscle cell proliferation, suppression of macrophage scavenger receptor expression [5], suppression of inflammatory response of vascular endothelial cells to endotoxin [6], indicating anti-atherogenic properties of active vitamin D. In contrast, conditions with inhibited vitamin D action, such as VDR knock-out [7] and  $1\alpha$ -hydroxylase knock-out mice [8], are known to cause stimulated rennin production and cardiac hypertrophy.

According to a meta-analysis [9] of 18 randomized studies in humans without renal failure, supplement with  $25(\text{OH})$  vitamin D reduced the risk of all-cause death by 7%.

In observational studies in patients with chronic renal failure treated with hemodialysis, treatment with active vitamin D sterol was associated with improvement of cardiac hypertrophy [10], cardiac function [11], glucose tolerance [12], and immune function [13, 14], and others. Also, in cohort studies of hemodialysis patients, the use of active vitamin D sterol is associated with approx 25% lower risk of death [15-18]. We [19] previously reported that the use of alfacalcidol was associated with lower risk of cardiovascular death (adjusted hazard ratio, 0.377; 95% confidence interval, 0.246–0.578;  $P = 0.022$ ). These studies raise a possibility that treatment with active vitamin D sterol reduces cardiovascular risk, and improves survival of hemodialysis patients.

By contrast, active vitamin D stimulates vascular calcification as shown by experimental studies [20]. Thus, although there is no enough clinical evidence, there is a speculation that active vitamin D may stimulate vascular calcification by increasing serum phosphate and calcium levels.

So far, there is no report of randomized clinical trials which prospectively examined whether treatment with active vitamin D sterol reduces cardiovascular events in hemodialysis patients. At the same



time, there is no evidence showing accelerated vascular calcification by treatment of active vitamin D in hemodialysis patients.

Thus, the purpose of this study is to examine the effect of alfacalcidol, an active vitamin D sterol, on cardiovascular events in a randomized controlled trial.

### 3. Purpose and outcome measures

#### 3.1. Purpose

The purpose of this study is to examine the effect of alfacalcidol on cardiovascular events in a randomized controlled trial with prospective, randomized, open-labeled, blinded-endpoint design.

#### 3.2. Outcomes

##### 3.2.1. Primary outcome

Composite of (1) fatal and nonfatal CVD events (acute myocardial infarction, congestive heart failure, stroke, aortic dissection/rupture, amputation of ischemic limb, and cardiac sudden death), (2) coronary intervention (plain old balloon angioplasty, stenting) or bypass grafting, (3) lower limb artery intervention (plain old balloon angioplasty, stenting) or bypass grafting.

##### 3.2.2. Secondary outcome

All-cause death

#### *Definition of cardiovascular events*

- **Acute myocardial infarction:** Clinical signs and symptoms such as chest pain or cardiogenic shock, associated with abnormalities in biomarkers (creatine kinase, troponin, etc.) and/or electric cardiogram (new abnormal Q-wave, ST elevation, etc.) for myocardial infarction.
- **Congestive heart failure:** Congestive heart failure (NYHA grade III or IV) requiring hospitalization, excluding dyspnea due to non-cardiac causes (bronchial asthma, etc.)
- **Stroke:** Rapidly developing clinical signs of neurological deficit attributable to a focal and/or total brain functions, without clear causes than vascular origin, lasting for more than 24 hours or leading to death (if not interrupted by surgical operations or death). Stroke includes subarachnoidal hemorrhage, intracranial hemorrhage, and cerebral infarction, but excludes transient ischemic attack, cerebrovascular disease due to hematological disorders (leukemia, polycythemia vera, etc.), primary brain tumors, and metastatic brain tumors. Stroke secondary to trauma is also excluded.
- **Aortic dissection/rupture:** Clinical symptom of chest pain and/or abdominal pain, and diagnosed with imaging test such as contrast enhanced computed tomography.
- **Amputation of ischemic limb:** Major amputations at ankle joint or proximal as treatment for patients with symptom and/or signs of lower extremity ischemia.
- **Cardiac sudden death:** Unexpected death from a cardiac cause that occurs within one hour of symptom onset (witnessed) or within 24 hours of last being observed in normal health (unwitnessed).

### ***Rationale***

These outcomes were set based on the purpose of this study. All-cause death was defined as the secondary outcome, because alfacalcidol may have effects on non-cardiovascular systems.

## **4. Target population**

### **4.1. Target population**

Patients treated with maintenance hemodialysis, who gave written informed consent, meeting the following inclusion criteria, and not violating the following exclusion criteria.

### **4.2. Inclusion criteria**

- 1) Patients on maintenance hemodialysis for 90 days or longer
- 2) Men or women aged  $\geq 20$  and  $\leq 80$  years old
- 3) No treatment with VDRA for more than 4 weeks prior to this study
- 4) Serum Ca level  $\leq 10.0$  mg/dL, phosphate level  $\leq 6.0$  mg/dL, and intact PTH level  $\leq 180$  pg/mL

### **4.3. Exclusion criteria**

- 1) History of myocardial infarction, stroke, aortic dissection/rupture, amputation of a lower limb, coronary revascularization or bypass surgery, lower limb revascularization or bypass surgery within 12 weeks
- 2) Heart failure of NYHA grade III or IV
- 3) Respiratory failure with  $\text{PaO}_2 < 60$  mmHg or  $\text{SpO}_2 < 90\%$
- 4) Life expectancy shorter than 1 year due to known malignant, infectious, or other diseases
- 5) Abnormal liver function tests exceeding x3 upper normal limits
- 6) Pregnant or lactating females or females planning to be pregnant
- 7) History of an allergic reaction to alfacalcidol
- 8) Participation to other interventional studies within 12 weeks prior to this study
- 9) Inappropriate for this study as judged by an attending investigator

### ***Rationale***

The above exclusion criteria are set:

- 1)–5), 7), 8) For the safety of participants.
- 6) Because the safety of alfacalcidol is not established for human pregnancy.
- 9) This was set for the safety of participants to allow decision by reasons other than the above

### **4.4. Target number of participants**

A total of 972 participants. 486 participants in the intervention group and control group, respectively.

### ***Rationale***

The sample size was calculated based on the following assumptions:

- (1) 28 % of participants in the control arm will experience the primary outcome during the 4-year period.
- (2) The risk will be reduced by 30 % in the intervention arm.
- (3) 5 % of participants will be lost to follow-up.

The trial requires a minimum of 972 participants to detect difference in proportion of the primary endpoint between the two arms with 80 % power ( $\beta$  level of 0.2) and  $\alpha$  level of 0.05.

## 5. Methods

### 5.1. Study design

- Prospective, randomized, open-labeled, blinded-endpoint (PROBE) design
- Phase IV clinical study

### 5.2. Study drug

#### 5.2.1. Study drug

Generic name: Alfacalcidol (1 $\alpha$ -hydroxyvitamin D<sub>3</sub>)

Representative brand name: Alfarol<sup>®</sup>

Several preparations of alfacalcidol are available and allowed to be used for this study. See the package insert for details.

#### 5.2.2. Usage and dosage

For participants in the intervention group, the starting dose of alfacalcidol shall be 0.5  $\mu$ g, per os, once daily. Serum Ca and P levels are monitored twice monthly. To maintain corrected Ca and P within the target ranges (corrected Ca,  $8.4 \leq$  and  $\leq 10.0$  mg/dL; P,  $3.5 \leq$  and  $\leq 6.0$  mg/dL), dietary therapy shall be encouraged and dose adjustment shall be considered for medications other than the test drug (calcium carbonate, sevelamer hydrochloride, and others). In cases with hypercalcemia ( $\geq 10.5$  mg/dL) and/or hyperphosphatemia ( $\geq 7.0$  mg/dL), the dose reduction or temporal cessation of the study drug shall be allowed. The study drug shall be re-started, after confirming the recovery of serum Ca and P levels within the target ranges. The dose of alfacalcidol should be in the range between 0.25 and 7  $\mu$ g per week. ‘Drop-out’ from the assigned treatment shall be defined when participants in the intervention group are kept untreated with alfacalcidol for 12 weeks or longer.

### ***Rationale***

The usage and dosage was determined according to the package insert of the test drug. The starting dose was set by referring our previous study [19] in which the median dose of alfacalcidol was 0.5 $\mu$ g per day in the Japanese hemodialysis patients. The methods for dose reduction and temporal cessation of alfacalcidol were based on the 2006 [21] and 2012 versions [22] of JSDT guidelines. Assuming that there could be some patients using 0.25  $\mu$ g, once weekly, and some patients using 1  $\mu$ g per day to avoid hypocalcemia, the weekly dose range was set. We defined the “drop-out” from the assigned treatment with alfacalcidol, if the

participants are untreated with alfacalcidol continuously for 12 weeks or longer, because the cessation may be temporal and such participants may be treated again with alfacalcidol.

### **5.2.3. Study period**

48 months (for each participant)

### **Rationale**

This study compares the cardiovascular endpoints. The study period was set according to the purpose of this study.

### **5.2.4. Registration and Allocation of study drug**

Random allocation shall be done to minimize differences in clinical background between groups. We assume that age, sex, dialysis duration, underlying renal disease (diabetic nephropathy or not), prior cardiovascular disease (present or absent), and geographical regions (institutions) are the major factors affecting the rate of the primary outcome. Stratified randomization shall be performed with the above six stratification factors using permuted block method.

- Age: younger than 65 years vs. 65 years or older
  - Sex: Male vs. female
  - Duration of hemodialysis: shorter than 5 years vs. 5 years or longer
  - Underlying renal disease: diabetic nephropathy vs. others
  - Prior cardiovascular disease: presence vs. absence
- 1) The allocation officer shall prepare the computer-generated random sequence beforehand, and keep it properly.
  - 2) When informed consent is obtained, the investigator shall promptly ask the registration office to register and randomize the participant by sending the registration form by FAX.
  - 3) The registration office shall confirm the eligibility of the participant by the faxed information, and registration and random allocation shall be performed. The result of allocation shall be sent back to the investigator by FAX.

The allocation officer: Mitsuru Fukui  
Laboratory of Statistics  
Osaka City University Graduate School of Medicine

The registration office: Hisako Fujii  
Department of Drug and Food Clinical Evaluation  
Osaka City University Graduate School of Medicine  
1-2-7, Asahi-machi, Abeno-ku, Osaka 545-0051, Japan  
Phone 06-6645-3443

FAX 06-6646-3588

Working hours 9:00 to 17:00 on week days (FAX is always available)

Upon sending back the result of random allocation, the registration office shall promptly record the date/time of registration, the date of informed consent, the participant identification code, the institution of the participant, the name of the attending investigator, the registration number, and the allocation group using the allocation record form, and keep it with the FAX sheet sent to the registration office.

Prior to registration of a participant, the investigator shall prepare and keep the participant identification code table for the participant who gave informed consent. The participant identification code table shall include the participant's name, sex, date of informed consent, medical record number at the institution, participant identification code, and date of allocation. Participant identification code is a unique code for a participant determined by each institution, for which the participant's medical record number or patient ID may be used. The investigator shall record the allocation group, which is to be sent by the allocation officer, in the participant identification code table.

### **5.3. Medical costs during the study**

In this trial, the prescription of the test drug, medical examination, and laboratory tests shall be done using the usual health insurance. In case of health damage in participants of this study, the needed and appropriate treatments shall be provided with health insurance.

### **5.4. Prohibited/allowed drugs before and during the study**

The medications for complications used at the predefined time points (before, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M, and 48M) shall be recorded in case report forms (name of drug, route of administration). In particular, regarding drugs affecting Ca, P, and PTH such as VDRA, phosphate binders, and calcimimetics, the dose and the administration period shall also be recorded.

#### ***5.4.1. Prohibited treatment***

In principle, no VDRA shall be given to participants in the control group. VDRA include not only the study drug oral alfacalcidol, but calcitriol (oral, intravenous), falecalcitriol (oral), and maxacalcitol (intravenous). However, these may be allowed if clinically needed. The participant shall be "drop-out" from the assigned treatment if a VDRA is used for 12 weeks or longer in the control group (the follow-up shall be continued). Regarding these drugs, the use or not shall be recorded. If used, the drug name, dose, route of administration, and period of administration shall be recorded.

#### ***5.4.2. Allowed treatment***

During the study, when serum P is increased, the use of sevelamer hydrochloride and/or calcium carbonate, as phosphate-binder, shall be initiated or the dose shall be increased. After lanthanum carbonate (a new phosphate binder) and cinacalcet hydrochloride (calcimimetics to reduce PTH) become available, these drugs

shall be allowed to use. If these drugs are used, the drug name, dose, administration route, and administration period shall be recorded in the case report forms. There is no restriction of medications for conditions other than abnormalities in serum P, Ca, and PTH.

#### 5.4.3. Other medical management

Restriction of phosphate intake (800 mg/day or lower) shall be encouraged for hyperphosphatemia during the study.

#### 5.5. Treatment after the study

There is no restriction in treatment after completion of the study.

### 6. Study variables of and time schedule

Data shall be obtained as indicated by the table below. The allowance of date is  $\pm 2$  weeks.

	IC	S	R	0M	3M	6M	12M	18M	24M	30M	36M	42M	48M
Informed consent	X												
Clinical background		X		X									
Laboratory data		X		X	X	X	X	X	X	X	X	X	X
Physical examination				X	X	X	X	X	X	X	X	X	X
Use/nonuse of alfacalcidol		X		X	X	X	X	X	X	X	X	X	X
Other medications				X	X	X	X	X	X	X	X	X	X
Primary & secondary outcomes, SAEs					X	X	X	X	X	X	X	X	X

*The test drug (alfacalcidol) shall be given only to participants in the intervention group. The target ranges of serum phosphate, calcium and intact PTH during the study shall be as recommended by JSDT-GL 2006 and by JSDT-GL 2012 after April 2012. To achieve these targets, management by dietary and/or drug treatment shall be done. The predefined switch of treatment for less than 12 weeks shall be allowed.*

- 1) Clinical background: age, sex, duration of hemodialysis, underlying renal disease, and presence of prior cardiovascular disease.
- 2) Laboratory data: Complete blood counts (WBC, RBC, Hb, Ht, Platelet), biochemistry (Ca, P, intact PTH, albumin, CRP, AST, ALT, ALP, BUN, Cr, Na, K, Cl, TC, TG, HDL-C; (Only for patients with diabetes mellitus, HbA1c and glycoalbumin)
- 3) Physical examination: Height (at screening only), body weight (dry weight), blood pressure and pulse rate (at the start of dialysis session)

Abbreviations: IC, informed consent; S, screening; R, randomization; 0M-48M, predefined observation time points; SAEs, serious adverse events.

#### 6.1. Screening for eligibility

After obtaining informed consent from a study participant, the investigator or sub investigator shall perform screening of the participant for eligibility. Based on the inclusion and exclusion criteria, the investigator shall judge the participant's overall eligibility, which shall be recorded in the registration form.

### **6.1.1. Background of participants**

Before enrollment, the investigator shall check the following information, and record them in the registration form:

- Participant identification code: A unique code for the participant determined by each institution, such as medical record number.
- Clinical background: Age, sex, underlying renal disease (diabetic nephropathy or others)
- Informed consent: Date of informed consent
- Duration of hemodialysis: Shorter than 5 years or 5 years or longer
- Medical history: Allergy to the study drug; History of myocardial infarction, stroke, aortic dissection/rupture, amputation of a lower limb, coronary revascularization or bypass surgery, lower limb revascularization or bypass surgery, within 12 weeks.
- Comorbidity: Heart failure of NYHA grade III or IV; Respiratory failure with PaO<sub>2</sub> <60 mmHg or SpO<sub>2</sub> < 90%; Malignancy, serious infectious disease, pregnancy, lactating, and others.
- Others: Treatment with VDRA within 4 weeks; Participation to interventional studies other than this study within 12 weeks.

### **6.1.2. Laboratory tests**

Complete blood counts (WBC, RBC, Hb, Ht, Platelet), biochemistry (Ca, P, intact PTH, albumin, CRP, AST, ALT, ALP, BUN, Cr, Na, K, Cl, TC, TG, HDL-C; (Only for patients with diabetes mellitus, HbA1c and glycoalbumin)

## **6.2. Observation variables before starting the assigned treatment**

### **6.2.1. Clinical background of participants**

In addition to the information obtained at screening, the investigator shall record the following information; (1) date of birth, (2) underlying renal disease in detail, (3) history of prior cardiovascular diseases in detail, (4) history of parathyroid intervention (PTX, PEIT, and others), (5) conditions for hemodialysis (dialysis session number per week, hours of dialysis per session, dialysis membrane, dialysate calcium concentration, single pool Kt/V).

### **6.2.2. Laboratory tests**

The items are the same as indicated in 6.1.2. Laboratory tests. If the assigned treatment is started within 2 weeks after registration, the data at screening may be used as the data here.

### **6.2.3. Physical examination**

Height, weight (dry weight), blood pressure and pulse rate at the start of dialysis session

#### 6.2.4. Concomitant drugs

Concomitant drugs shall be recorded with drug name and administration route by the following categories. In particular, regarding drugs for abnormal mineral metabolism and hyperparathyroidism, the dose and the administration period shall also be recorded:

- 1) Drugs for abnormal mineral metabolism and hyperparathyroidism (calcium carbonate, sevelamer hydrochloride, cinacalcet hydrochloride, lanthanum carbonate, intravenous VDRA, and others)
- 2) Antihypertensive drugs (calcium channel blocker, ACE inhibitor, Angiotensin receptor blocker,  $\beta$ -blocker,  $\alpha$ -blocker, loop diuretics, and others)
- 3) Other cardiovascular drugs (digitalis, anti-arrhythmic drug, coronary vasodilator, and others)
- 4) Anti-platelet drugs (aspirin, ticlopidine hydrochloride, cilostazol, and others)
- 5) Anti-coagulants (warfarin potassium)
- 6) Anti-diabetic drugs (insulin injection, sulfonyl urea, rapid-acting insulin secretagogue,  $\alpha$ -glucosidase inhibitor, and others)
- 7) Lipid-lowering drugs (statin)
- 8) ESAs (recombinant human erythropoietin, long-acting ESA)
- 9) Iron preparations (oral, intravenous)

#### 6.3. Dosage of study drug

For participants in the intervention group, the starting dose of alfacalcidol shall be 0.5  $\mu\text{g}$ , per os, once daily. Serum Ca and P levels shall be monitored twice monthly. To maintain corrected Ca and P within the target ranges (corrected Ca,  $8.4 \leq$  and  $\leq 10.0$  mg/dL; P,  $3.5 \leq$  and  $\leq 6.0$  mg/dL), dietary therapy shall be encouraged and dose adjustment shall be considered for medications other than the test drug (calcium carbonate, sevelamer hydrochloride, and others). In cases with hypercalcemia ( $\geq 10.5$  mg/dL) and/or hyperphosphatemia ( $\geq 7.0$  mg/dL), the dose reduction or temporal cessation of the study drug shall be allowed. The study drug shall be re-started, after confirming the recovery of serum Ca and P levels within the target ranges. The dose of alfacalcidol should be in the range between 0.25 and 7  $\mu\text{g}$  per week. ‘Drop-out’ from the assigned treatment shall be defined when participants in the intervention group are kept untreated with alfacalcidol for 12 weeks or longer. In the control group, participants shall be followed up without administering alfacalcidol.

In both groups, the development of secondary hyperparathyroidism shall be monitored by measuring intact PTH once per three months, and treatment shall be considered according to the JSDT clinical practice guideline. In the intervention group, if the assigned treatment with alfacalcidol is changed to treatment with another oral or intravenous VDRA, and it is continued for 12 weeks or longer, it shall be judged as “drop-out” from the assigned treatment participants. In the control group, if the assigned treatment without any VDRA is changed to treatment with any oral or intravenous VDRA, and it is continued for 12 weeks or longer, it shall be judged as “drop-out” from the assigned treatment.

#### 6.4. Observation variables during the study



During study, the following variables shall be examined on the first session of the week (Monday or Tuesday) in principle.

#### **6.4.1. Time points**

3M, 6M, 12M, 18M, 24M, 30M, 36M, 42M, 48M, and at the time of discontinuation

#### **6.4.2. Observation variables**

- 1) **Primary outcome:** Incidence and recurrence of fatal and nonfatal cardiovascular events, and its date (acute myocardial infarction, congestive heart failure, stroke, aortic dissection/rupture, amputation of ischemic limb, and cardiac sudden death, coronary intervention or bypass grafting, lower limb artery intervention or bypass grafting)
- 2) **Secondary outcome:** All-cause death, date of death, cause of death  
*In case of the primary or secondary outcome, detailed information shall be written in the event report form, with the participant's assigned treatment group being blinded.*
- 3) **Adverse events:** All serious adverse events, causal relationship with the study drug
- 4) **Physical examination:** Body weight (dry weight), blood pressure (at the start of dialysis session)
- 5) **Complete blood count:** WBC, RBC, Hb, Ht, Platelet
- 6) **Blood biochemistry:** Ca, P, intact PTH, albumin, CRP, AST, ALT, ALP, BUN, Cr, Na, K, Cl, TC, TG, HDL-C. (Only for patients with diabetes mellitus, HbA1c and glycoalbumin.)
- 7) **Concomitant drugs:** Name of drug, administration route, reason for use. (For some specified drugs, dosage and administration period shall also be recorded).

#### **6.5. Collection and management of data**

- 1) Investigators or sub investigators shall record the data (observations, examinations, and tests) in the report forms, send them to the registration office by FAX, and keep the original.
- 2) The registration center shall keep the faxed information, and its copy shall be handed to the data manager.
- 3) The data manager shall enter the data to the database and also check the validity of the data. If needed, queries shall be sent to the investigator or sub investigator via the registration office.
- 4) When the incidence of the primary or secondary outcome is reported to the registration office, its validity shall be checked by the event evaluation committee on a regular basis.

### **7. Completion of follow-up, discontinuation, and drop-out**

#### **7.1. Criteria for completion of study participation**

- 1) When participants have died
- 2) When participants completed the 48 months of follow-up

#### **7.2. Criteria for discontinuation of study participation**

- 1) When a participant or legally acceptable representative withdrew consent
- 2) When participation was discontinued because of the participant's circumstances (change of residence, hospital, etc.)

- 3) When a participant was found not to meet the eligibility criteria after enrollment
- 4) When a participant was found not to follow the instructions by the attending investigator.
- 5) When there was an incidental accident
- 6) When the attending physician decided to discontinue the participation to the study due to adverse events
- 7) When there was a serious violation of the study protocol
- 8) When the investigator or sub investigator made a judgement based on the situation difficult to continue

**7.3. Criteria for drop-out from the assigned treatment** (*Follow-up shall be continued for ITT analysis*)

- 1) In the intervention group, when a participant is untreated with alfacalcidol for 12 weeks or longer
- 2) In the control group, when a participant is treated with any active vitamin D sterol for 12 weeks or longer

**7.4. Investigation and treatment after discontinuation**

At the discontinuation of study participation of a participant, the investigator or sub investigator shall perform investigation and treatment following the procedures below:

- 1) At the discontinuation, all the observations and evaluations at the discontinuation shall be done. The date of discontinuation, reasons, treatment and the clinical course shall be recorded in the case report form.
- 2) If the discontinuation is due to safety issue such as an adverse event and worsening of comorbidity, the investigator or sub investigator shall give necessary treatment. When the investigator or sub investigator confirms safety, the follow-up shall be continued until the follow-up is judged to be unnecessary, excluding when the participant is not cooperative.
- 3) If a participant is going to discontinue or has decided to discontinue during the study, it is not mandatory for the participant to disclose the reason. The investigator or sub investigator shall try to identify the reason to the extent it is possible with full respect for the right of the participant.
- 4) If a participant misses an appointment because of the participant's inconvenience, the investigator, sub investigator, or test collaborator shall take a follow-up investigation by a letter, telephone, and others. The method of contact, the date of contact, the reason for missing an appointment, and the details shall be recorded in the case report form.

**8. Ethical considerations**

This trial shall be conducted in accordance with the principles of the Declaration of Helsinki, and the Ethical Guidelines for Clinical Studies by Ministry of Health, Labor and Welfare, Japan (the original version in 2003 which was modified in 2004 and 2008), and adhering to this protocol.

**8.1. Evaluation and approval by institutional review board (or ethics committee)**

Prior to implementation of this trial, institutional review board (or ethics committee) shall evaluate the contents of this protocol, informed consent document, and other documents required by the institutional review board (or ethics committee) from the point of view of ethical, scientific and medical validity, and the eligibility of investigators and sub investigators. This trial shall be conducted after approval. Similar

evaluation shall be performed if addition, update, and/or revision (excluding minor addition, update, and/or revision) are made on these documents.

## **8.2. Selection of participants and informed consent**

### ***8.2.1. Selection of participants***

In selection of participants, investigators or sub investigators carefully examine the appropriateness for participation to this trial, from the point of view of human right protection, and based on the inclusion and exclusion criteria of this trial, considering such factors as health status, symptoms, age, sex, competency for giving consent. Those who are not competent for giving consent due to comorbidity (psychological disorders, severe dementia, etc.) shall be excluded from the participants of this trial.

### ***8.2.2. Creation of informed consent document***

In order to obtain informed consent to this trial, investigators shall create, and if necessary revise, the informed consent document. In creation or revision, the investigators shall adhere to the principles of the Declaration of Helsinki, and the Ethical Guidelines for Clinical Studies by Ministry of Health, Labor and Welfare, Japan. The created or revised informed consent documents shall be evaluated for approval by the institutional review board (or ethics committee). The informed consent document shall contain the following 14 items as indicated by the Ethical Guidelines:

- 1) The fact that the participation to this research is voluntary.
- 2) The fact that the refusal to participate does not cause any disbenefit to the research subject.
- 3) The fact that research subjects or legally acceptable representatives may withdraw their consent at any time without causing any disbenefit to such research subjects.
- 4) Reasons why asked to be enrolled in the research.
- 5) Significance, objectives, methods, and time period of the research
- 6) Names and positions of investigators etc.
- 7) Expected research results, expected benefits, predictable risks, and inevitable uncomfortable conditions to be caused on the research subjects
- 8) The fact that research subjects can request and obtain or read the research protocol and documents concerning method of the research, to the extent it does not interfere the protection of personal information of other research subjects, or the originality of the research.
- 9) Handling of personal information and privacy
- 10) The fact that this research can result in intellectual property right, and the holder of the right
- 11) The fact that the results may be published in the way research subjects are not identifiable.
- 12) Funding source of the research, potential conflict of interest, and the relationship between the investigators and related organizations
- 13) Whether or not compensation shall be offered for research-related health damage and details of such compensation
- 14) Information on contact address for inquiry and complaint

### ***8.2.3. Informed consent***

The investigator or sub investigator shall provide sufficient information on this research, prior to enrollment, with the informed consent document which has been approved by the institutional review board (or ethics committee). The research subject shall be given the opportunities for question and sufficient time to consider whether to participate or not. The research subject shall give voluntary consent in writing to participate to this research prior to enrollment after understanding the content of this research.

The investigator or sub investigator and the research subject shall put their signatures and date on the informed consent document. The consent form shall be copied, with the original being kept in the medical record, and the copy being kept by the research subject.

### ***8.2.4. Provision of new information to participants***

When the investigator obtains new and important information that may affect the participants' consent or the participants' intention to continue the participation, the investigator shall promptly revise the informed consent document etc. and get the approval of the institutional review board (or ethics committee). The investigator or sub investigator shall promptly provide the information to the participant, obtain anew voluntary consent of continued participation to this research, and give to the participant the copy of the consent form and the revised informed consent document.

### ***8.3. Protection of participant's privacy***

In recording in case report forms and in handling with data of participants, protection of the privacy of the participants shall be considered. Namely, participants shall be identified with their participant identification codes, without using their names or initials. The investigator shall prepare a participant identification code table indicating participant identification codes generated at each institution and corresponding medical record numbers, participants' names, and dates of birth. The participant identification code table shall be kept by the investigator. At the Center for Drug and Food Evaluation, Osaka City University Hospital, the case registration forms and the allocation record forms, made during the process of case registration and allocation, shall be kept in an appropriate manner.

### ***8.4. Response to health damage***

In case health damage occurs while carrying out this research, the investigator and sub investigators shall provide sufficient treatment, take other appropriate measures, and make an effort to investigate the cause. Treatment of the adverse event shall be provided, in principle, by usual medical insurance. When it is necessary to communicate with the regulatory body, in applying to the Relief Systems for Adverse Drug Reactions etc., the investigator and sub investigators shall do so, and have sufficient discussion with the related persons.

### ***8.5. Communication to attending physician***

The investigator and sub investigator shall confirm whether the participant has the attending physician other than themselves. And if so, they shall inform the attending physician about the participant's enrollment to

this research, and record the result.

#### ***8.6. Deviation from protocol and change of protocol***

Investigators and sub investigators must not deviate from the protocol or revise it without prior evaluation and written approval by institutional review board (or ethics committee). However, this shall not apply to unavoidable circumstances in medical care such as to avoid emergent danger of the participant, or to minor modifications in administrative processes of the research. Such cases shall be reported to the principal investigator via the data center.

#### ***8.7. Discontinuation/interruption of the trial***

While carrying out this research, if it becomes necessary to discontinue/interrupt this research or to revise the protocol etc., the principal investigator shall promptly notify it with the reason to all the investigators. The investigators shall promptly report the information to the institutional review board (or ethics committee) with a written document, and to all sub investigators and collaborators.

- 1) When the principal investigator becomes aware of important information regarding safety and efficacy of the study drug
- 2) When the principal investigator has decided to revise the protocol because of incidence of serious adverse event
- 3) When it is judged quite difficult to achieve the target number of participants because of difficulty in recruiting participants

### **9. Adverse events**

Investigators and sub investigators shall record all the serious adverse events, whether observed or reported by participants during the study, regardless of the causality with study drug, in the serious adverse event report form. Serious adverse events to be reported in the report form also include serious disease occurring during the study and the worsening of comorbidities which were already present before enrollment to the study.

#### **9.1. Predictable side effects**

The following is the list of predictable side effects of the study drug alfacalcidol extracted from the package insert of Alfarol<sup>®</sup> capsule (version 5, October 2005):

##### **Serious side effects**

- **Acute renal failure (frequency unknown)**

Because acute renal failure with elevated serum calcium level may occur, monitor serum calcium and renal function on a regular basis, and if abnormality is found, take appropriate measures such as cessation etc.

- **Liver dysfunction, jaundice (frequency unknown)**

Because liver dysfunction with elevated AST (GOT), ALT (GPT), or ALP or jaundice may occur, observe carefully, and if abnormality is found, take appropriate measures.

## Other side effects

Take appropriate measures including dose reduction and cessation etc., if the following side effects are noticed:

- **Digestive system:** Frequency lower than 0.1–5%, loss of appetite, nausea, diarrhea, constipation, and stomachache; Frequency lower than 0.1%, vomit, sense of abdomen distension, discomfort of stomach, dyspepsia, oral discomfort, thirst, etc.
- **Psycho-neurological system:** Frequency lower than 0.1%, headache, dull headache, insomnia, irritation, weakness, feeling of fatigue, dizziness, numbness, sleepiness, hypomnesia, memory disturbance, tinnitus, presbycusis, back pain, stiff neck, leg cramp, chest pain, etc.
- **Cardiovascular system:** Frequency lower than 0.1%, slight elevation of blood pressure, palpitation.
- **Liver:** Frequency lower than 0.1–5%, elevation in AST (GOT), ALT (GPT); Frequency lower than 0.1%, elevation in LDH,  $\gamma$ GTP.
- **Kidney:** Frequency lower than 0.1–5%, elevation in BUN, creatinine (decreased renal function); Frequency lower than 0.1%, renal stone.
- **Skin:** Frequency lower than 0.1–5%, itch sensation; Frequency lower than 0.1%, eruption, heat sensation.
- **Eye:** Frequency lower than 0.1–5%, conjunctival injection.
- **Bone:** Frequency lower than 0.1%, periarticular calcification (ossification)
- **Others:** Frequency lower than 0.1%, hoarseness, edema

## 9.2. Drug interactions

Listed below are from the package insert of Alfarol<sup>®</sup> capsule (version 5, October 2005)

### 9.2.1. Magnesium-containing preparations (*magnesium oxide, magnesium carbonate*)

Symptoms and treatment: There was a report of hypermagnesemia.

Mechanism and risk factors: unknown

### 9.2.2. Digitalis preparations (*digoxin, etc.*)

Symptoms and treatment: Arrhythmia may occur.

Mechanism and risk factors: The action of digitalis is intensified if hypercalcemia develops by this drug.

### 9.2.3. Calcium-containing preparations (*Calcium lactate, calcium carbonate, etc.*)

Symptoms and treatment: Hypercalcemia may occur.

Mechanism and risk factors: This drug facilitates intestinal calcium absorption.

### 9.2.4. Vitamin D and its derivatives (*calcitriol, etc.*)

Symptoms and treatment: Hypercalcemia may occur.

Mechanism and risk factors: Additive effect.

### **9.3. Treatment to predictable side effect**

Predictable adverse effects are nonspecific. In case of adverse effects, investigators or sub investigators shall take appropriate measures, and the administration of study drug shall be stopped if it is judged difficult to continue the study. In such occasion, the name, dosage of the drug, and the date of administration shall be recorded in the case report form.

### **9.4. Monitoring of adverse events**

For all the serious adverse events, investigators and sub investigators shall obtain sufficient information to evaluate the causality (for example, it is attributable to the study drug, other disease, etc.), and the evaluation shall be recorded in the case report form.

### **9.5. Definitions of terms related to adverse event**

#### ***9.5.1. Adverse event***

Adverse event is defined as any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or illness caused to research subjects, regardless of causal relation with the study drug.

#### ***9.5.2. Side effect***

Side effect is defined as adverse event which has reasonable causal relation (refer 9.5.4) with the study drug and the causality cannot be excluded (namely “1. Related” or “2. Possibly related” to the study drug).

#### ***9.5.3. Serious adverse event***

Serious adverse event is defined as any undesirable experience during the study when the patient outcome is one of the following regardless of the dosage:

- 1) death,
- 2) life-threatening,
- 3) hospitalization (initial or prolonged),
- 4) disability or permanent damage,
- 5) congenital anomaly/birth defect,
- 6) other important medical events.

#### ***9.5.4. Causal relation with study drug***

Side effects are judged by the following criteria, excluding adverse event that is reported “3. Not related”:

1. Related: Adverse event which cannot be explained by other reasons, or the relation is strongly suggested by the time association.
2. Possibly related: Adverse event which may be due to the use of the study drug. Namely, the relation cannot be excluded because other reasons are not definite or the time association is reasonable.
3. Not related: The adverse event is not reasonably attributed to the study drug.

#### ***9.5.5. Severity of adverse events***

- 1) Slight: Usually transient. The degree not to cause impairment of daily living, and not to require treatment (able to live a normal life)
- 2) Moderate: The degree to cause some impairment of daily living, to cause sufficient discomfort, and to require treatment (activity is accompanied with discomfort)
- 3) High-degree: The degree to cause significant impairment of daily living, and to require treatment (difficult to live a normal life)

#### **9.6. Record of serious adverse events**

Regarding serious adverse events which occurred after starting the assigned treatment, investigators or sub investigators shall record what happened, severity, date of occurrence/worsening, date of confirmation, date of disappearance, treatment, outcome, and date of outcome, and relation with the study drug, in the case report form.

Investigators or sub investigators shall record abnormalities in laboratory tests in the case report form if judged as being clinically important.

#### **9.7. Report of serious adverse events**

In case of a serious adverse event which is related or possibly related to the study drug (side effect), the investigator or sub investigator shall give first priority to safety of the participant, take prompt and appropriate measures, and then promptly report it to the head of the institute and the principle investigator. The principal investigator shall consult the event evaluation committee about the reported serious adverse event, and if needed, report to the heads of other institutes and other investigators.

The principal investigator shall report the adverse events, if needed, to the manufacturer of the study drug (person in charge of medicine information).

Upon receipt of the report from the principal investigator, the manufacturer shall report to the regulatory body within the specified period as necessary (among serious adverse events, “side effects causing death”, “side effects which may cause death”, “serious and unpredictable side effects” should be reported to the regulatory body).

### **10. Handling of cases and statistical analysis**

- 1) In per-protocol analysis, participants who “dropped-out” from the assigned treatment shall be censored according to the criteria above. In intention-to-treat (ITT) analysis, no participants shall be censored at the time of “drop-out”. ITT analysis shall be the primary analysis.
- 2) Event-free curves shall be constructed by the Kaplan-Meier method, and the difference between the two groups shall be evaluated by log-rank test. Cox proportional hazard model shall be used to calculate the hazard ratio (95% confidence interval).
- 3) As an additional analysis, the effect of treatment shall also be calculated with multivariate Cox model adjusted for age, sex, duration of hemodialysis, diabetic nephropathy or not, the presence of prior cardiovascular disease.
- 4) As mentioned in 1), the population for ITT analysis shall be the all participants who were randomized



(full analysis set, FAS), without censoring at the time of “drop-out” from the assigned treatment. In per-protocol analysis, the population for analysis shall be the all participants who were randomized, but participants who “dropped-out” from the assigned treatment shall be censored at the time of “drop-out” (per-protocol set, PPS). As an additional analysis, we shall perform a similar analysis with the modified per-protocol set (modified PPS). The modified PPS consists of the all participants who were randomized, but participants in the intervention group shall not be censored at the time of “drou-out”, if the participants were kept treated with any VDRA other than alfacalcidol, because the participants were kept treated with VRDA. The details shall be written in the statistical analysis plan.

## **11. Case report forms**

Investigators or sub investigators shall fill in the case report form with date and signature for all participants who gave consent. Case report forms shall be filled for the specified time points (before starting, 3M, 6M, 12M, 18M, 24M, 30M, 36M, 48M, and at the time of discontinuation), and send them to the data center promptly. Data in the case report forms should be consistent with the source data.

## **12. Completion of the study**

Investigators shall submit the final report to institutional review board (or ethics committee) promptly after completion of the study.

## **13. Agreement of Publication**

The results of this multi-center study shall belong to the study group indicated in “14. Implementation system of this trial”. Matters related to the publication of the results shall be discussed and decided by the members of the study group. In publication, confidentiality of the research subjects shall be kept.

## **14. Implementation system of this trial**

The implementation body of this research is The J-DAVID Research Group including the principal investigator, investigators, and sub investigators nominated by the investigators, consisting of 207 facilities all over Japan. The registration center, allocation officer, data manager, and biostatistician shall support this study. Also, this study has the event evaluation committee and the independent data monitoring committee, which are independent of the implementation body of this study.

- The principal investigator shall be responsible for the study.
- The principal investigator and his advisors shall organize the steering committee which is in charge of the idea, planning and steering of the study.
- The executive committee shall consist of the main members of the J-DAVID Research Group, and the committee shall be in charge of planning of the study and promoting the implementation of this study.
- Data manager shall be responsible for data management, representing the data center. The data center shall compile accurate data and assure the data quality.
- The event evaluation committee shall evaluate the reports of the primary and secondary outcomes from investigators based on the criteria of the protocol, with the assigned treatment group being masked. This

committee shall assure the scientific validity by keeping the consistency and objectiveness of event evaluation. In this study, this committee shall also evaluate serious adverse events and the reasons for discontinuation, which may be closely related to the primary and secondary outcomes.

- The independent data monitoring committee shall evaluate data of this study. Based on the data the committee shall give appropriate advice to the principal investigator for the safety of participants and to assure the integrity of the clinical trial as far as possible. This committee shall give an advice in the neutral standpoint by understanding and considering the influences on the society, organization, and market, and by taking the findings which may be obtained or lost by interrupting the study or by revising the protocol. Details shall be written in the manual of this committee. In this study, this committee shall also serve as audit.

#### **14.1. Investigators and study sites**

Principal investigator

Tetsuo Shoji, Associate Professor,  
Department of Vascular Medicine, Osaka City University Graduate School of Medicine

Investigators at study sites

Listed in the attached document #8

#### **14.2. Data center (Data manager)**

Yuichi Kato, Chief  
Center for Drug and Food Clinical Evaluation, Osaka City University Hospital

#### **14.3. Statistical analysis**

Mitsuru Fukui, Associate Professor  
Laboratory of statistics, Osaka City University Graduate School of Medicine

#### **14.4. Registration office**

Hisako Fujii  
Osaka City University Graduate School of Medicine

#### **14.5. Allocation officer**

Mitsuru Fukui, Associate Professor  
Laboratory of statistics, Osaka City University Graduate School of Medicine

#### **14.6. Event evaluation committee**

Hiroki Hase, Professor,  
Department of Nephrology, Toho Medical Center Ohashi Hospital  
Yuji Ikari, Professor  
Department of Cardiology, Tokai University School of Medicine

Minoru Yoshiyama, Professor

Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine

#### **14.7. Independent data monitoring committee**

Shinichiro Ueda, Professor

Department of Clinical Pharmacology & Therapeutics, University of the Ryukyus Graduate School of Medicine

Toyoaki Murohara, Professor

Department of Cardiology, Nagoya University Graduate School of Medicine

Sinichi Nishi, Professor

Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine

#### **15. Period of the research**

Case recruitment period: After approval – To December 28, 2010

Follow-up period: After approval – To April 30, 2015

Data analysis period: After approval – To April 30, 2017

#### **16. How long data is stored**

Data of this research shall be kept appropriately until the later one of the following two dates:

- The day after 5 years since the final report of this study is made
- The day after 5 years since the final results are published

#### **17. Funding source**

The funding source of this research is the research grant to the J-DAVID Research Group from The Kidney Foundation, Japan.

#### **18. Disclosure of conflict of interest of investigators**

Masaaki Inaba, the representative of the J-DAVID Research Group, received lecture fees and research grant unrelated to the J-DAVID trial from Chugai Pharmaceutical Co. Ltd., but the expenditure of the research grant is managed by the finance and accounting system of Osaka City University. Fairness is assured by reporting the conflict of interest to the committee for the management of conflict of interest at Osaka City University.

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## **20. Attached documents**

- #1 Package insert of Alfarol®
- #2 Informed consent document
- #3 Case registration form
- #4 Allocation record form
- #5 Participant identification code table
- #6 Case report forms
- #7 Compliance sheet for alfacalcidol
- #8 List of study sites of J-DAVID trial

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