**Observational Research Study Title:**

**Regional differences in hemodialysis practices, treatment strategies and patient outcomes over time in Turkey:** ***A Multicenter Observational Cohort Study in Turkish Hemodialysis Patients***

Amgen Protocol Number 20150316

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| Study Sponsor: | Amgen Ilac. Tic. Ltd. Sti.<br>Is Kuleleri, Kule 2, Kat:25<br>4. Levent 34330 Besiktas, Istanbul |
| Country: | Turkey |
| Indication: | Patients with chronic kidney disease (CKD) receiving hemodialysis |
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| Date: | 04 April 2016 |
| Study Outline Amendment 1: | 01 December 2016 |

## Table of Contents

## 1. KEY PROJECT DETAILS

- Estimated protocol approval date: 02 May 2016
- Estimated study start date (first data collection): 27 July 2016
- Planned # of sites: 100
- Planned # of subjects/patients: 2500
- Planned Enrollment Period: 1 year
- Study duration (eg, FSE through Last Subject Last Visit [LSLV]): 24 July 2019
- Individual Subject Observation Period: 2 years
- Anticipated database lock: 06 September 2019
- Anticipated final Observational Research Study Report (ORSR) date: 11 March 2020

## 2. BACKGROUND AND RATIONALE

### 2.1 Background

The incidence and prevalence of renal replacement therapy (RRT) for patients with end-stage renal disease (ESRD) is increasing worldwide (1,2). Turkey, with a population of 75 million, has an RRT prevalence of 918 pmp and incidence of 147 pmp as of 2014 (3). By the end of 2014, 55,890 chronic hemodialysis patients were being treated at 847 hemodialysis units in Turkey while 4306 patients were receiving chronic peritoneal dialysis (3). The percentage of patients receiving hemodialysis (HD) treatment in private and chain centers in Turkey is 61,79.

Despite the improvement in dialysis technology and knowledge, the annual mortality of individuals on hemodialysis remains high. Probably the best available comparative data come from the Dialysis Outcomes and Practice Patterns Study (DOPPS), which uses a prospective design and attempts to harmonize data collection across several countries and continents (4). The DOPPS reported that crude 1-year mortality rates from 1996 to 2002 were 6.6% in Japan, 15.6% in Europe, and 21.7% in the United States (5). Dialysis patients have many comorbidities and a high symptom burden affecting their quality of life (6-8). Moreover, many of these problems are associated with increased mortality (9-11)

Since 1990 Turkish Society of Nephrology has been coordinating a national renal registry that collects data on patients receiving RRT. The reports are published annually and they are unique source of information about demographic, epidemiological and

clinical features of ESRD necessitating RRT in Turkey and the status of the therapy methods and the changes in those parameters in years. The National Renal Registry is one of major most referred sources of information in determining national strategy and approaches regarding the control and treatment of ESRD (3). However, the data collected are not patient based and it represents the mean values of the last 3 months of the year of all patients of the centers participating in the registry. Also patient outcomes are not collected and the data is the general overview of Turkish RRT patients lacking the regional differences in demographic and clinical features of ESRD.

In Turkey, there are differences in the distribution of number of HD centers and patients at the geographic regional level. While the number of private centers in Marmara is 115, this numbers falls to 11 in the East Anatolian region. Likewise the number of HD patients being treated in private dialysis centers is 14,870 in Marmara Region and 811 in East Anatolian region (12). It was also shown that the patient profiles and parameters differ between geographical regions in Turkey (13).

Hence in Turkey the relationship between treatment strategies and hemodialysis practices with patient outcomes covering high number of patients is lacking. Also there is very limited data the regional differences in HD practice, treatment strategies and patient outcomes over time. The aim of this study is to show the regional differences in patient outcomes in relation with routine hemodialysis practice and management strategies. Besides the collected data would be able to determine the association of patient outcomes with HD practices, treatment strategies and trends over time in Turkish HD patients. The data generated would help to provide better standardization in HD practices and treatment strategies all over Turkey and determine the most suitable treatment targets for Turkish patients receiving HD.

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### 2.1.1 Disease State Background

Chronic kidney disease (CKD) is a growing health problem worldwide that leads to end-stage kidney failure and cardiovascular complications (1). CKD is defined as kidney damage and/or decreased kidney function expressed as glomerular filtration rate (GFR) for at least 3 months, regardless of the cause (2,3). CKD is classified into five stages based on the severity of the disease (2,3). Incidence and prevalence rates of stage 5 CKD, also known as end-stage renal disease (ESRD), are increasing worldwide (4,5). Turkey, with a population of 75 million, has a prevalence of ESRD requiring RRT 918 pmp and incidence of 147 pmp as of 2014 (6). This data indicates that the prevalence of ESRD has increased 3-fold since 2001 (324 pmp vs. 918 pmp) (6). In Turkey 78,37% of the patients with ESRD requiring RRT is treated with hemodialysis by the end of 2014 (6).

Anemia management is an important aspect of care for HD patients as anemia is a common and debilitating complication of CKD. It results primarily from decreased production of erythropoietin by the kidney (7) and becomes increasingly prevalent and

severe as the kidney function declines; over 90% of patients undergoing RRT are anaemic in the absence of treatment with an erythropoiesis stimulating agent (ESA) (8,9,10).

Low hemoglobin (Hb) levels have been associated with cardiovascular events (11), mortality (12,13), health-related quality of life (14,15) or physical activities (16,17) in many observational studies on HD patients. The management of anemia in HD patients requires attention to variety of factors including ESA dosing, inflammation, iron deficiency from thrice-weekly blood loss during HD or blood loss caused by other conditions, adequacy of dialysis and shortened red blood cell life time, among others. Numerous benefits have been associated with good anemia control in HD patients including lower mortality and hospitalization risks (18-21) and reduced occurrence of left ventricular hypertrophy (22,23).

Secondary HPT is a common and serious disease that develops early in CKD (glomerular filtration rate [GFR] ≤ 60 mL/min) before the initiation of dialysis and progresses as patients reach ESRD (24). The disorder is characterized by persistently elevated levels of parathyroid hormone and complicated by important disturbances in mineral metabolism (25). Bone disease is the most widely recognized consequence of secondary hyperparathyroidism (26). Several reports indicate, however, that alterations in calcium and phosphorus metabolism, as a result of either secondary hyperparathyroidism or the therapeutic measures used to manage it, contribute to soft-tissue and vascular calcification, cardiovasculardisease and the risk of death (27-32). The data from the Turkish Society of Nephrology 2014 annual registry indicates that the proportion of patients with PTH levels over 600 pg/ml is 23.15% and the proportion of patients with phosphorus levels over 5.5 mg/dl is 37% as the end of 2014 (6).

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### 2.1.2 Study Rationale

Turkey has an RRT prevalence of 918 pmp and incidence of 147 pmp as of 2014 and the prevalence of ESRD has increased 3-fold since 2001 (324 pmp vs. 918 pmp) (1). Despite the high number of HD patients there is no patient based data which evaluates the patient outcomes in relation with HD practices and treatment strategies in Turkey. For this reason it is important to determine the factors which are contributing morbiditiy and mortality in this population to improve patient outcomes. This study will be first study in Turkey which will collect patient based data in a large population of HD patients to evaluate regional differences in patient outcomes.

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### 2.1.3 Rationale for Selected Study Type

Data from interventional studies can not necessarily be generalised to the setting of routine clinical practice for the following reasons:

- Selected patient populations are enrolled in interventional studies and the study populations might not represent the true heterogeneity of the dialysis population
- The studies are conducted within limited period of time under controlled conditions and do not reflect changes in therapeutic standards.

Consequently, this study will focus on real-life HD practices, treatment strategies and patient outcomes in the clinical management of Turkish dialysis patients. Knowledge gained from this study will provide insight into current clinical practice and may be used to disseminate information to physicians to help to optimise management of dialysis patients.

## 2.2 Objectives and Outcomes Measures

### 2.2.1 Primary Objective

- To describe regional differences in patient all cause mortality and cardiovascular morbidity in relation with treatment strategies over time

### 2.2.2 Secondary Objective(s)

- To describe regional differences in patient all cause mortality and cardiovascular morbidity in relation with HD practices
- To describe regional differences in the rate of hospitalizations and infections in HD patients
- To describe the regional differences between incident and prevalent patients regarding Hb levels
- To describe regional differences in the proportion of patients with Hb levels at target, lower and higher than target values
- To describe regional differences in iron status and iron use over time
- To describe Hb concentrations in relation with dialysis vintage, age and gender

- To describe the regional differences in the burden of SHPT as measured by PTH, P, Ca and CaxP levels and the changes in these parameters over time

### 2.2.3 Primary Outcome Measure

- The rate of patient all cause mortality and cardiovascular morbidity in different regions of Turkey in relation with treatment stragies

### 2.2.4 Secondary Outcome Measure(s)

- The rate of patient all cause mortality and cardiovascular morbidity in different regions of Turkey in relation with HD practices
- The rate of hospitalizations and infections in different regions of Turkey
- The difference in Hb levels in incident and prevalent HD patients in different regions of Turkey
- The difference in the proportion of patients with Hb levels at target, lower and higher than target values over time in different regions of Turkey
- The difference in iron status and iron use over time in different regions of Turkey
- Hb concentrations in relation with dialysis vintage, age and gender
- The differences in PTH, P, Ca and CaxP levels and the changes of these parameters over time in different regions of Turkey

## 2.3 Safety Data Collection, Reporting and Recording

### 2.3.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject who is administered a pharmaceutical product(s) and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition

- Events occurring from a medication error or overdose of a product(s), whether accidental or intentional
- Events occurring from abuse of a product(s)
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)
- Any lack or loss of intended effect of the product(s)

### 2.3.2 Adverse Drug Reactions (ADRs)

AEs that are considered related to a specific product(s) are classified as adverse drug reactions (ADRs). It is the Investigator's responsibility to evaluate whether an event is related to a specific product prior to reporting the event to the manufacturer.

### 2.3.3 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that also:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility. "Other significant medical hazards" refers to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

### 2.3.4 Serious Adverse Drug Reactions

SAEs that are considered related to Amgen product(s) are classified as serious adverse drug reactions (SADRs). It is the Investigator's responsibility to evaluate whether an event is related to an Amgen product prior to reporting the event to Amgen.

### 2.3.5 Definition of Other Safety Findings

Other Safety Findings include:

- Medication errors, overdose, misuse, or abuse, whether accidental or intentional, involving an Amgen product, regardless of whether associated with an ADR and/or SADR
- Pregnancy and lactation exposure regardless of whether associated with an ADR and/or SADR
- Transmission of infectious agents regardless of whether associated with an ADR and/or SADR
- Reports of uses outside the terms for authorized use of the product including off label use when associated with an ADR and/or SADR

### 2.3.6 Reporting and Recording Responsibilities

All adverse events related to observed Amgen products (Adverse Drug Reactions [ADRs], Serious Adverse Drug Reactions [SADRs], product complaints, and other safety findings [eg, Serious Adverse Events (SAEs, pregnancy, lactation) in routine clinical practice will be documented in accordance with Amgen requirement documents. Participating physicians will report all adverse events to Turkish Ministry of Health as required in related regulation.

Participating physician is responsible for medical management of subjects who experience Adverse Events from the date of awareness to resolution or stabilization.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study Case Report Forms (CRFs) where safety data may also be recorded (eg, Adverse Event Summary CRF).

## 3. STUDY DESIGN

### 3.1 Design and Assessments

This is a multi-centre, prospective observational cohort study in incident and prevalant patients receiving haemodialysis. Incident patients is described as patients receiving hemodialysis <3 months and prevalant patients is decribed as patients receiving hemodialysis >3 months.

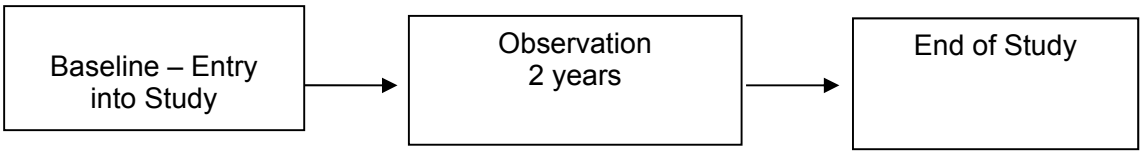
In order to achieve to enroll 2500 patients which is the targeted patient number, study will be conducted at appropriate number of dialysis centers A nationally representative sample of dialysis patients and centers will be enrolled from each geographical region of Turkey. HD patients will be randomly selected within each participating center. To reflect the number of incident and prevalent HD patient distribution in Turkey 435 incident HD patients will be enrolled to the study. Patients who would leave the study for any reason (transfer to different facility, lost to follow up, change in modality, renal transplant) will not be replaced. The expected dropout rate is around 20%. The duration of observation for a patient will be 2 years.

It is aimed to recruit approximately 2500 patients over a period of one year. Patients are considered as having been enrolled once entry of their data into the database has begun, following patient signature of informed consent. The patients will be assessed at baseline and every 3 months for 2 years.

### 3.2 Design Flow Chart and Definitions

Patients are considered as having been enrolled once entry of their data into the database has begun, following patient signature of informed consent.

As this is a noninterventional study it will not alter the clinical management of patients.




### 3.3 Key Inclusion/Exclusion Criteria

#### 3.3.1 Inclusion Criteria

- Patients ≥ 18 years of age
- Incident or prevalent patients with ESRD receiving hemodialysis treatment

- Patient and/or patient's legally accepted representative has provided informed consent

### 3.3.2 Exlusion Criteria

- Patients who do not wish to sign informed consent

## 3.4 Case Report Form (CRF)

Data will be collected through a web-based electronic case report form (eCRF).

***Baseline Assessments***

- Informed consent
- Demographic data (age, gender etc.)
- Medical history
    - Cause of ESRD
    - Duration of ESRD (including different RRTs)
    - Dialysis vintage
    - Glomerular filtration rate (will be collected only for incident dialysis patients)
    - Residual Urine Volume
    - Smoking status
    - Coexisting medical conditions (hypertension, diabetes mellitus, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular disease, revascularization procedures, chronic pulmonary disease, liver disease, malignancies, gastrointestinal bleeding, neurologic disease)
    - Hospitalizations
- Medications
    - Antihypertensives (if applicable)
    - ESA treatment (yes /no)
    - ESA treatment dose
    - ESA treatment administration route (IV, SC)
    - ESA treatment frequency
    - ESA type (epoetin alfa, epoetin beta, darbepoetin alfa epoetin zeta, pegylated EPO,other.
    - The distribution of ESA treatment to 13 dialysis sessions
    - ESA treatment switch
    - Iron treatment administration route (IV, Oral)

  - Iron treatment dose (IV, oral) (per month)
  - Iron treatment type (For IV treatment)
  - Iron treatment frequency (for IV treatment)
  - Blood Transfusions
  - Vitamin C
  - L-carnitine
  - Phosphate binders (calcium based/noncalcium based)
  - Vitamin D (dose and frequency)
  - IV Vitamin D (dose and frequency)
  - Cinacalcet (dose)
  - **Acetylsalicylic Acid**
  - **Statins**
  - Other concomitant medications
- Dialysis prescription
  - Dominant vascular access (fistula/graft/central venous catheter)
  - Number of sessions per week
  - Treatment time
  - Anticoagulation (heparin/low molecular weight heparin)
  - Blood flow rate (pomp rate)
  - Kt/v
  - Type of dialyser
  - Ultrafiltration rate (the last 3 sessions and actual visit)
  - Dialysate flow rate
  - Dialysate sodium, potassium, calcium, bicarbonate
  - Dialyser surface area
- Physical examination
  - Resting blood pressure (predialysis and postdialysis blood pressure measurements will be collected preceding 3 dialysis sessions before the actual visit and at the actual visit )Weight (predialysis and postdialysis weight measurements will be collected preceding 3 dialysis sessions before the actual visit and at the actual visit)
  - Height
  - Resting Heart rate (predialysis and postdialysis heart rate measurements will be collected preceding 3 dialysis sessions before the actual visit and at the actual visit)

- Laboratory investigations
    - Hb, iron, transferrin saturation, ferritin
    - PTH, total calcium, phosphor
    - HbA1c (diabetic patients)
    - Total cholesterol, LDL-C, HDL-C, triglyserid
    - Serological parameters (HbsAg, HBsAb, Anti-HCV)
    - Urea , serum total protein, serum creatitine, albumin, uric acid, alkaline phosphatase, ALT
    - Number of red blood cells, white blood cells, platelets
    - C-reactive protein (CRP)
    - Venous bicarbonate
    - Residual urine volume

After baseline medications, dialysis prescription, resting blood pressure, weight, coexisting medical conditions, laboratory investigations and clinical outcomes will be recorded every 3 months.

- Clinical outcomes
    - Mortality (all cause mortality, cardiovascular death, sudden death, death due to infection, malignancy)
    - Hospitalizations (all cause hospitalizations, hospitalizations due to cardiovascular events, hospitalizations due to cerebrovascular events, congestive heart failure, fluied overload, infections, vascular access problems, other causes) and average duration of hospitalization
    - Cardiovascular outcome (new onset documented acute myocardial infarction, new onset atrial fibrillation, heart failure, revascularization procedures, stroke, peripheral arterial disease)
    - Vascular access problems
    - Amputations due to diabetic foot
    - Infections
    - Tranplantation

No laboratory or diagnostic tests, other than those currently performed as part of the patient's routine care will be collected.

### 3.5 Local Regulations and Legal Aspects

Observational study will be submitted to Ethics Committee and Ministry of Health for review and approval. Written informed consent will be obtained from each patient prior to enrolment and collection of any study-related data.

Participating physician must ensure that the patient's confidentiality is maintained. Only the patient's study identification number should be used to identify forms or other documents submitted to Amgen. Documents that are not for submission to Amgen (eg signed informed consent forms) should be kept in strict confidence by the participating physician.

### 3.6 Statistical Considerations

#### 3.6.1 Sample Size

The planned number of patients is 2500 which reflects nearly the 4% of the incident and prevalent patient population in Turkey. The total patient number and the number of incident and prevalent patients will reflect the distribution of patients per geographic region and also the distribution of prevalent and incident HD patients by the end of 2014.

Note that approximately 435 of the enrolled subjects will be incident HD subjects (HD < 3 months). Subgroup analyses by geographic region will have smaller sample sizes. The levels of precision provided by the overall population of 2500 and the possible smaller sample sizes is provided in Table 1 for various proportions. The annual dropout rate (transfer to different facility, lost to follow up, change in modality, renal transplant) is expected to be around 20%. The sample size and duration of the study will enable to address the primary objective of the study.

**Table 1 Half width of 95% Confidence Intervals for Various Proportions and Sample Sizes**

| | N | | | | |
|---|---|---|---|---|---|
| p | 100 | 250 | 500 | 1000 | 2500 |
| 0.1 | 5.9% | 3.7% | 2.6% | 1.9% | 1.2% |
| 0.15 | 7.0% | 4.4% | 3.1% | 2.2% | 1.4% |
| 0.2 | 7.8% | 5.0% | 3.5% | 2.5% | 1.6% |
| 0.25 | 8.5% | 5.4% | 3.8% | 2.7% | 1.7% |
| 0.3 | 9.0% | 5.7% | 4.0% | 2.8% | 1.8% |
| 0.35 | 9.3% | 5.9% | 4.2% | 3.0% | 1.9% |
| 0.4 | 9.6% | 6.1% | 4.3% | 3.0% | 1.9% |
| 0.45 | 9.8% | 6.2% | 4.4% | 3.1% | 2.0% |
| 0.5 | 9.8% | 6.2% | 4.4% | 3.1% | 2.0% |

### 3.6.2 Bias Minimization

To be eligible for study participation the total number of patients treated per week in a dialysis unit must be at least ≥25 patients. This minimum facility size is chosen to provide a sufficient patient sample size to obtain accurate estimates of facility practices and outcomes. The number of selected HD centers will be representative of HD center dialysis distribution per geopraphical region. Study patient population at selected HD centers will reflect the actual real life HD patient population distribution in different geographical regions of Turkey based on the latest Annual of Dialysis Statistics 2015 (1).

In order to show the whole picture of dialysis care in private centers in Turkey two main chain dialysis centers (Diaverum and FMC) are also included to the study.

1. DİADER 2014 Diyaliz İstatistik Yıllığı 2015

### 3.6.3 Enrollment Rate

It's expected that enrollment of 2500 patients will be completed in 2 years.

### 3.6.4 Key Analysis

The primary analysis will be conducted once all enrolled subjects have had the opportunity to complete 2 years of followup. This study is descriptive. Only summary statistics and interval estimates will be provided.

The primary outcome will be assessed by calculating the proportion of subjects who die or develop a clinical outcome as defined in section 3.4 . The number of clinical outcomes per subject will be tallied. Normal approximation 95% confidence intervals (CI) will be computed around the proportion estimates. The rate of mortality and morbidity will be calculated as the number of clinical outcomes or death divided by the duration on study. Poisson CI will be computed around the rate estimate. The proportions, rates and CI will be computed for the whole study population and for subgroups defined by treatment.

The secondary outcomes will assess the proportions and rates from the primary outcome by geographic regions. Regions will be defined both by HD practice and by SHPT parameters.

Laboratory analytes Hb, iron, PTH, P, Cas and CaxP will be summarized by mean, median, standard deviation, minimum, maximum and first and third quartiles at each

timepoint. Proportion of patients with Hb < 10 g/dL and ≥ 12 g/dL will be summarized at each timepoint for the different regions. Hb will also be summarized by subgroups of dialysis vintage ( 0-5 years, 6-10 years, 11-15 years, 16-20 years and >20years), age (<65 and ≥65), gender and whether a subject was incident or prevalent at study entry.

The number of transfusions will be tallied per subject over the duration of follow up with the rate calculated as the number of transfusion episodes divided by total subject years of followup as well as the number of units of blood transfused divided by the total subject years of follow up. These estimates will include 95% CI estimates.

The proportion of subjects using iron (IV only) will be estimated at each timepoint as well as at anytime while in follow up.

The primary outcome and secondary outcomes will be analysed by the following subgroups:

- Region by HD practice
- Region by SHPT parameter
- Incident versus prevalent HD
- Treatment strategy.

Hb will be summarized by additional subgroups Hb will also be summarized by subgroups of dialysis vintage ( 0-5 years, 6-10 years, 11-15 years, 16-20 years and >20years), age (<65 and ≥65) and gender.

Two annual interim analysis after enrollment is completed is planned to be conducted in addition to the final analysis.

The first interim analysis will be conducted once enrollment is complete. The analysis will include baseline subject and disease characteristics. The purpose of the first interim is for publication. No safety data or post baseline outcomes will be included in the first interim.

The second interim analysis will be conducted once all enrolled subjects have had the opportunity to complete 12 months ±4weeks of followup. The primary outcomes and secondary outcomes will included in the second interim analysis for publication purposes. No safety data will be included in the second interim.

### 3.6.5 Study Limitations/Operational Risks

A limitation of the study is its observational nature. As the investigators are not blinded this may influence or bias the selection of study subjects. Besides if the drop out rate would be too higher than expected this may reduce the internal validity of the study.

Operational risks would include drop out of study sites, noncompliance to study plan and missing data.

## 4. STUDY OUTCOME

The findings of this study will help to determine the relationship between patient outcomes and HD practices, treatment strageties and treatment trends in Turkish HD patients and will help to improve the patient outcomes. Also by determining the regional differences in patient outcomes the findings would provide better standardization in HD practices and treatment strategies all over Turkey and determine the most suitable treatment targets for Turkish patients receiving HD.

### 4.1 Report and Potential Publications

☐ ORSR or ORSR Abstract

☒ Abstract National Nephrology, Hypertension, Dialysis and Transplantation Congress, ERA/EDTA Congress

☒ Manuscript: Turkish Nephrology, Dialysis and Transplantation Journal, Nephrology Dialysis Transplantation Journal

### 4.2 Team Endorsement

☒ Team confirms to follow Amgen process regarding clinical pricing thus locally the investigator payments are within fair market value (FMV).